

REVIEW OF THE EVIDENCE ON INSULIN AND ITS USE IN DIABETES

April 2018

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March 2018

Published by

Health Action International
Overtoom 60 (2) | 1054 HK Amsterdam
The Netherlands | +31 20 412 4523
www.haiweb.org

Disclaimer

The ACCISS Study is supported by The Leona M. and Harry B. Helmsley Charitable Trust and Stichting ICF. The analysis included in this report is that of the authors alone and does not necessarily reflect the views of the Helmsley Charitable Trust or Stichting ICF. All references and conclusions are intended for educational and informative purposes and do

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Acknowledgements

The authors would like to thank the ACCISS Study members who reviewed the paper and provided helpful comments. The authors would also like to acknowledge Dr. Justin Echouffo-Tcheugui at Brigham and Women's Hospital for his assistance with data analysis, as well as Paul Bain, librarian at the Countway Library of Medicine of Harvard Medical School, for his help with the extensive literature searches. Their help has been invaluable and we are deeply grateful.

Acronyms

AACE	American Association of Clinical Endocrinologists
ACCISS	Addressing the Challenge and Constraints of Insulin Sources and Supply
ACCORD	Addressing the Challenge and Constraints of Insulin Sources and Supply
ADA	American Diabetes Association
CI	Confidence interval
DCCT	Diabetes Control and Complications Trial
EMA	European Medicines Agency
FDA	Food and Drug Administration
HbA1c	Hemoglobin A1c
LANCELOT	Least One Oral Antidiabetic Drug Treatment
LMICs	Low- and middle-income countries
MHRA	Medicines and Healthcare Products Regulatory Agency
NPH	Neutral Protamine Hagedorn
OR	Odds ratio
PHARMAC	Pharmaceutical Management Agency
RCT	Randomized controlled trial
RR	Risk reduction
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
WHO	World Health Organization

Executive Summary

The *Addressing the Challenge and Constraints of Insulin Sources and Supply* (ACCISS) Study was launched to identify and address barriers to insulin access on a global level. Insufficient access to insulin is a worldwide health crisis with underpinnings that extend from price, an expanding market and, perhaps most importantly, limited available guidance for nations on how and when to provide this necessary medication to individuals living with diabetes. The consequences of poor insulin access around the globe include expedited death in type 1 diabetes, early disability and death due to advanced microvascular disease leading to blindness, amputations and kidney failure. In this evidence review, four clinical topics were explored in detail and from a clinical perspective, namely the clinical outcomes of human vs. analogue insulin and pen delivery systems vs. syringe and vial; the use of insulin in type 2 diabetes; and the interchangeability of common insulins. *Our four key conclusions* which will be discussed in this document are summarised as follows:

1. For people living with diabetes requiring insulin in low resource settings, *human insulin should remain first line therapy*. Analogue insulin, particularly basal insulin, should be available for a small subset of people with severe insulin deficiency for whom all risk factors for hypoglycaemia have been addressed but continue to exhibit recurrent severe hypoglycaemia.
2. Although pen devices appear to be preferable in terms of treatment adherence and persistence, as well as quality of life, the data to support improved clinical outcomes is lacking. Therefore, *in settings where resources are limited, the use of the more affordable vial and syringe is encouraged and justified*.
3. The decision to use insulin in non-type 1 diabetes depends on the degree of insulin deficiency of the individual and the effectiveness (or lack thereof) of non-insulin agents. The decision when to add insulin to non-insulin agent(s) depends on the individual glycaemic target, hypoglycaemia risk, and individual/ system-level affordability. To assist with this decision-making, we have developed a conceptual framework to guide the use of insulin in type 2 diabetes using medications included in the 2017 World Health Organization (WHO) Essential Medicines List (EML).
4. Given the variation in manufacturing process and complexity of insulin production, current guidelines state that *biosimilarity and interchangeability are not the same*. Therefore, *caution is needed when switching from one insulin to another*. Glucose monitoring, follow-up, and comprehensive diabetes education (for both patients and clinicians) remain the cornerstones of safe and effective management of people requiring insulin.

The goal of this document is to provide guidance to the health sectors of the global community on the use of insulin in low resource settings, with an emphasis on optimising benefit and minimising risk based on the currently available evidence.

1. Introduction

Diabetes has been described as one of the largest global health emergencies of the 21st century, with an estimated 415 million people currently affected worldwide (1). This number is expected to rise to 642 million by 2040. Reports suggest that 77 percent of individuals living with diabetes live in low- and middle-income countries (LMICs) and 90 percent of new cases of diabetes will occur in these countries. Africa has the highest percentage of undiagnosed people (~67 percent) and 1 in 10 people in the Middle East and North Africa have diabetes (9.1 percent prevalence) (1). Moreover, in developing countries those affected are most frequently between the ages of 35 and 64, their most economically productive years (2) and more than half a million children under the age of 14 are living with type 1 diabetes (1). Sobering reports suggest that children in Sub-Saharan Africa with newly diagnosed type 1 diabetes often have a life expectancy of less than one year (3).

Despite these striking statistics, little has been done to address access to insulin, which is essential for the survival of people with type 1 diabetes and is often required for optimal management of type 2 diabetes over a lifetime to avoid devastating consequences (4). Considering this, an innovative global study, Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS), was launched to study the supply and barriers to access of insulin on a global level. It is managed by Health Action International, in collaboration with the University of Geneva and Boston University School of Public Health. The ACCISS Study aims to further characterize the inequities and inefficiencies in the global insulin market with the goal of developing a scientific approach to address these challenges (5).

In keeping with the ACCISS Study's goals, this evidence review addresses a key barrier to global access to insulin, specifically the limited available guidance for nations on how and when to provide insulin to individuals suffering from diabetes. Four clinical topics are explored in detail and from a clinical perspective, namely the outcomes of human vs. analogue insulin and pen delivery systems vs. syringe and vial; the use of insulin in type 2 diabetes; and the interchangeability of common insulins. With this guidance directed to the health care sectors of the global community, *the goal is to reduce barriers to increasing insulin and insulin supplies to people with diabetes who have the greatest need for the medication worldwide.*

2. Comparing Clinical Outcomes of Human and Analogue Insulin

2.1 Overview

Key Conclusions: Human vs. Analogue Insulin

Human insulins should remain first line therapy for patients with diabetes requiring insulin (all those with type 1 diabetes and other insulin deficient types) in low resource settings.

Analogue insulin (particularly basal insulin) should be available for a subset of people for whom all risk factors for hypoglycaemia have been addressed and who still exhibit the following characteristics:

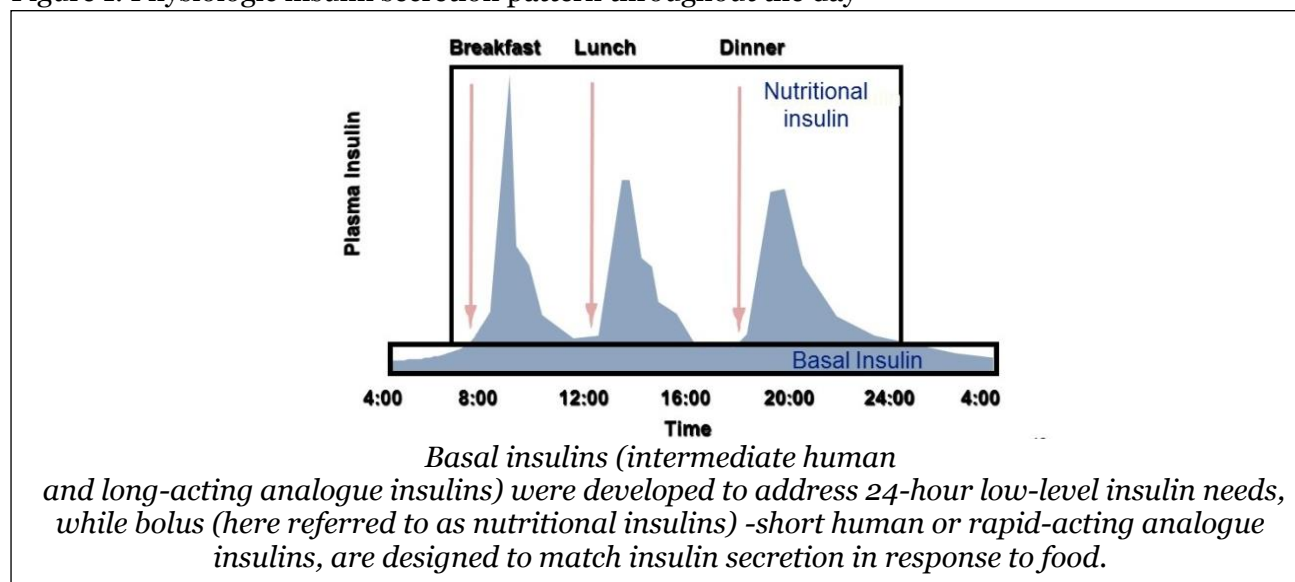
- recurrent severe hypoglycaemia
- severely limited productivity due to recurrent symptomatic hypoglycaemic episodes

Analogue basal insulin could also be considered in the following cases:

- significant intellectual disability who cannot be closely monitored or self-monitor
- type 1 diabetes with significant food insecurity
- type 1 diabetes who are unable to inject insulin twice daily (i.e. due to physical disability)

The current understanding of the impact of insulin therapy on clinical outcomes is still mostly derived from two studies published over a decade ago which relied solely on human insulins, namely the Diabetes Control and Complications Trial (DCCT)(6) in type 1 diabetes and United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes (7). Since these studies showed for the first time that glycaemic control to targets under 200 mg/dl and an HbA1c of ~7 percent had substantial clinical benefits, insulin usage in both type 1 and type 2 diabetes has increased substantially. Over time with this expanding market, chemically modified human insulins, or analogues, have mostly been developed and studied to meet non-inferiority criteria to prior insulins to achieve glucose targets. Expanded outcomes to other clinical realms have included absorption characteristics, glycaemic variability, and most importantly, the risk of low blood glucose, or hypoglycaemia. From a therapeutic perspective, there are two basic functions of insulin products, namely to support a 24-hour steady requirement of insulin (basal insulin; generally long or intermediate-acting insulin) and to support the short-term requirement following a meal or to correct a high blood sugar (bolus insulin; generally short- or rapid-acting insulin) (Figure 1). While basal insulin is the more essential insulin in type 1 diabetes, bolus insulin is also required in this state of absolute insulin deficiency to control symptoms of hyperglycaemia, avoid complications such as ketoacidosis and to consistently achieve individualised glucose targets over time. In type 2 diabetes, basal insulin use without nutritional insulin is the most evidence-based practice and is often sufficient to achieve durable disease control. In both conditions, bolus insulin, while often required, increases the risk of hypoglycaemia due mainly to the challenge of matching food intake, both in terms of timing and quantity, to the insulin dose.

Figure 1. Physiologic insulin secretion pattern throughout the day



Only short and intermediate-acting human insulins have been included in the World Health Organization (WHO) Essential Medicines List (EML). However, newer analogue insulins have gained popularity over the past years and now dominate the market in many high-income countries (8). There has been controversy about their benefit relative to human insulins, particularly considering their high cost. For the most recent review and update of the EML in 2017, an application was submitted to the WHO Expert Committee for the addition of long-acting analogue

insulin to the list, citing mostly the reduced hypoglycaemia risk with long-acting analogue insulins (9). However, after their review of the evidence, the WHO Expert Committee recommended against the addition of analogue insulins to the list of essential medicines (10). They concluded that the modest advantages of analogue insulin, such as reduced risk of hypoglycaemia, given its high cost, did not justify the inclusion on the list (9).

Table 1. Common Types of Insulin

Type of Insulin	Name	Type: Human/Analogue	Type: Basal/Nutritional	WHO Essential med list Yes/No
Rapid Acting	Aspart (Novolog®) Lispro (Humalog®) Glulisine (Apidra®)	Analogue	Nutritional	No
Short Acting	Regular (Humulin R®, Novolin R®)	Human	Nutritional	Yes
Intermediate Acting	NPH (Humulin N®, Novolin N®)	Human	Basal	Yes
Long Acting	Glargine (Lantus®) Detemir (Levemir®)	Analogue	Basal	No
	Glargine (Toujeo®) Degludec (Tresiba®)	Analogue	Basal	No
Pre-Mixed Insulin	NPH/regular (Humulin® 70/30, Novolin® 70/30)	Human	Basal + Nutritional	No
	Lispro protamine/lispro (Humalog® 75/25, Humalog® 50/50)	Analogue	Basal + Nutritional	No
	Aspart Protamine/Aspart (Novolog® 70/30)	Analogue	Basal + Nutritional	No

Hypoglycaemia risk differences between insulin products is an important consideration. Most sources agree that a blood glucose level of less than 70 mg/dl (<3.9 mmol/l) is excessively low and can produce symptoms that range from sweating/shaking to loss of consciousness.¹¹ Low blood glucose is an expected side effect of insulin therapy and hence all insulin users are advised to receive education on hypoglycaemia avoidance and proper treatment at the time of insulin initiation. Hypoglycaemia has long been categorised as either *severe* or *non-severe* based not on the glycaemia level but on the acute consequence of the episode and whether an individual can self-administer glucose. Severe hypoglycaemia was described in the DCCT (6) and this definition has been used in subsequent studies. To qualify as severe hypoglycaemia, an episode had to require assistance from another and included coma or seizures or episodes requiring glucagon, intravenous dextrose, or oral carbohydrate administered by another person (11). While studies vary in terms of identified associations between non-severe hypoglycaemia and outcomes, severe hypoglycaemia has been consistently shown in numerous studies to be associated with negative outcomes, including reduced

productivity, cardiovascular disease and mortality (12).

One of the main responsibilities of a health system is to ensure access to essential medicines that are of assured quality, safety, and efficacy, and used in a scientifically sound and cost-effective way. ⁴ Given the recent decision by the WHO Expert Committee to omit analogue insulin from the EML and the ongoing debate about the benefits of analogue insulin in both type 1 and type 2 diabetes, we performed a comprehensive literature review to summarise the most recent data. The current review focused on updating the evidence for *both* long and short acting analogue insulin since the systematic review and meta-analysis of analogue insulin by Tricco et al. in 2014 (13).

2.2 Methods

Eligibility Criteria

A systematic review by Tricco et al. was conducted on 8 January 2013, published in 2014 (13) and was included in the evidence on long-acting insulin analogues for the WHO Model List of Essential Medicines in 2017. Building on this work, we searched for new studies from 1 January 2013 through 5 January 2017. Since randomised controlled trials (RCTs) and systematic reviews of RCTs are the gold standard tools for evaluating interventions, only systematic reviews, meta-analyses and RCTs directly comparing human to analogue insulin were evaluated. Of note, since the newer insulins, such as degludec, U500 and glulisine, have generally not been studied compared to human insulin and are not intensively marketed in LMICs, they are not included in this review.

Studies involving children and adults with type 1 diabetes or type 2 diabetes who were not pregnant were included. Only peer-reviewed, full-text outcome studies written in English were included. Unpublished data and lone abstracts were not included in the analysis. Only studies in ambulatory humans, not animals or cell culture were included. Studies involving insulin infusions, high dose glucocorticoids, cancer or critically ill patients were excluded. Studies excluded were reviews, case studies, decision models, news, correspondence, commentaries, conference abstracts, posters or those noted only in books or trade journals.

Literature Search

A PubMed search on articles about insulin lispro, aspart, glulisine, lente, ultralente, glargine, detemir, degludec regardless of dose or schedule, if insulin was injected subcutaneously via syringe, pen or pump published since 2013, regardless of study design or the controls, was done on 5 January 2017, as follows:

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("Insulins"[mesh:noexp] OR "Insulin Lispro"[Mesh] OR "Insulin Aspart"[Mesh] OR "insulin glulisine" [Supplementary Concept] OR "Insulin, Lente"[Mesh] OR "Insulin, Ultralente"[Mesh] OR "Insulin Glargine"[Mesh] OR "Insulin Detemir"[Mesh] OR "insulin degludec" [Supplementary Concept] OR "insulin degludec, insulin aspart drug combination" [Supplementary Concept] OR "Biphasic Insulins"[Mesh] OR lispro[tiab] OR lyspro[tiab] OR lysb28[tiab] OR lys b28[tiab] OR humalog[tiab] OR aspart[tiab] OR b28asp[tiab] OR b28 asp[tiab] OR novolog[tiab] OR novorapid[tiab] OR glulisine[tiab] OR lysB3[tiab] OR gluB29[tiab] OR lente[tiab] OR monotard[tiab] OR ultralente[tiab] OR glargine OR glyA21[tiab] OR lantus[tiab] OR basaglar[tiab] OR hoe 901[tiab] OR hoe901[tiab] OR detemir[tiab] OR nn304[tiab] OR nn 304[tiab] OR biphasic insulin[tiab] OR insulin analog*[tiab] OR short acting insulin*[tiab] OR fast acting insulin*[tiab] OR rapid acting insulin*[tiab] OR long acting insulin*[tiab] OR ultralong acting insulin*[tiab] OR ultra long acting insulin*[tiab])
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AND

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("Diabetes Mellitus"[Mesh] OR diabetes[tiab] OR diabetic*[tiab])
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AND

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("2013/01/01"[PDAT] : "3000/12/31"[PDAT])
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NOT

("Animals"[mesh] NOT "Humans"[mesh])

The search terms and syntax were created with the assistance of a librarian at the Countway Library of Medicine of Harvard University.

Meta-analysis

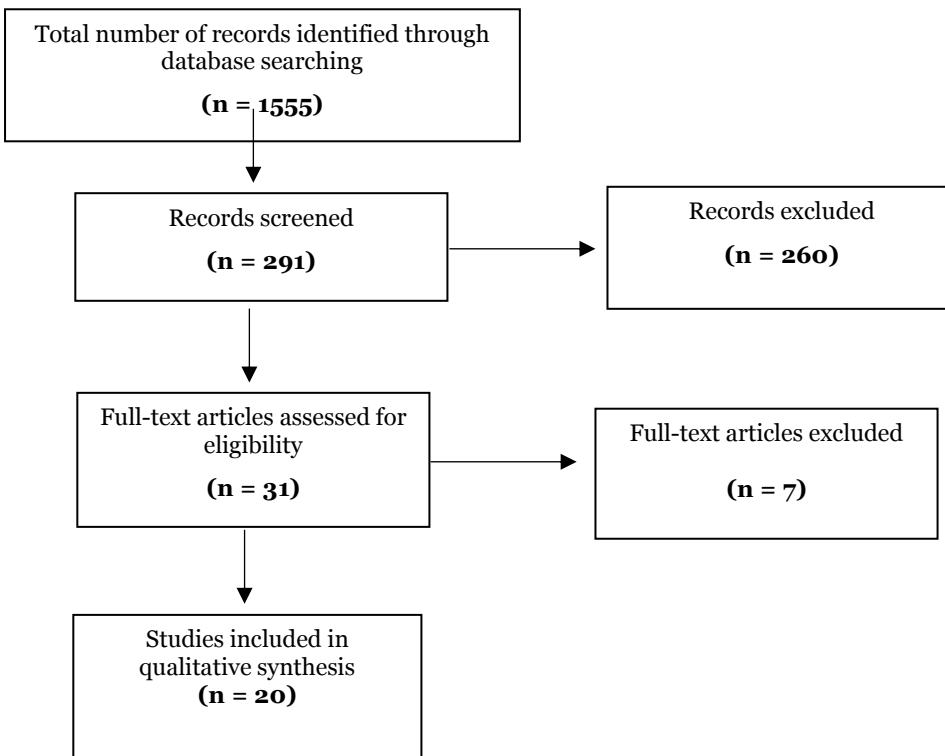
We sought to incorporate into the systematic review recently published meta-analyses that included studies specifically addressing severe hypoglycaemia. There were insufficient data to perform a formal meta-analysis on specific populations (i.e. type 1 or type 2 diabetes, long and rapid acting insulin). We therefore employed meta-analysis technique to assess the overall effect of analogue insulin on severe hypoglycaemia. We pooled the study-specific relative risk estimates using random-effects model meta-analysis to provide a single summary estimate. Random-effects model meta-analysis makes an allowance for between-study heterogeneity. We provided pooled estimates along with their 95 percent confidence intervals (CI), alpha level set at 0.05. We assessed heterogeneity between studies using the I² statistic.

2.3 Results

Literature Search

The literature search yielded a total of 1,555 records. References captured and included in the most recent systematic review in 2016 by Fullerton et al. (14) was used as a control for our search. All relevant references captured by their review were also captured by our search. Twenty studies fulfilled eligibility criteria, including *seven* systematic reviews (four with meta-analyses), *one* retrospective meta-analysis and 12 randomised controlled trials (see Figure 2).

Figure 2. Results of the screening process



Characteristics of Studies

Of the systematic reviews, four only included people with type 1 diabetes, one study only included people with type 2 diabetes and two included both type 1 and 2 diabetes. The meta-analysis included both types of diabetes. Of the RCTs, three studies examined people with type 1 diabetes and nine studied type 2 diabetes. A number of significant limitations and potential sources of bias were evident and need to be taken into consideration when interpreting the below results: Sixteen of the 23 (70 percent) studies were sponsored by pharmaceutical companies. In most of these studies the definition of severe hypoglycaemia was not consistent or defined. Moreover, the type of insulin therapy (such as intensified or conventional insulin therapy) and degree of patient education/participation in diabetes management programs were not always described, but would likely impact metabolic control and hypoglycaemia risk. Many of the included studies are of low quality evidence and all of them were done in high-income countries, which may be a source of selection bias.

Type 1 Diabetes: Systematic Reviews and Meta-Analyses

Tricco et al. (13) performed a systematic review with meta-analysis which examined the safety, efficacy and cost-effectiveness of long-acting analogues in both children and adults with type 1 diabetes. The authors performed a meta-analysis using HbA1c as the primary outcome and included 26 randomised controlled trials and 6,776 people. The analysis showed that glargine once daily (mean difference -0.39 percent, -0.59 percent to -0.19 percent), detemir once daily (-0.26 percent, -0.48 percent to -0.03 percent), and detemir once or twice daily (-0.3 percent, -0.65 percent to -0.08 percent) resulted in significantly reduced HbA1c compared with NPH (Neutral Protamine Hagedorn) once daily after 20 weeks of treatment. However, none of these were statistically significant when the network meta-analysis included predictive intervals, which estimate the likely effect in an individual setting (15). Moreover, once daily long acting analogues are typically compared with twice daily NPH, which is required to achieve a 24-hour basal insulin profile, pointing to a weakness of the analysis.

A network meta-analysis was also done on the number of patients experiencing severe hypoglycaemia (16 randomised controlled trials and 5697 patients were included). While the definition of severe hypoglycaemia varied across the studies, patients receiving detemir once or twice daily experienced significantly less severe hypoglycaemia than those receiving NPH once or twice daily (odds ratio 0.62, 95 percent confidence interval 0.42 to 0.91) after a median of 24 weeks (13). However, this was no longer statistically significant when predictive intervals were included in the network meta-analysis. This study also commented on all-cause mortality, which showed no significant difference between detemir and twice daily NPH after a median 24-week follow-up (two randomised controlled trials; odds ratio 0.97, 0.10 to 9.44; $I^2=0$ percent).

Caires de Souza et al. (16) published a systematic review (no meta-analysis) assessing the efficacy and safety of insulin glargine analogue compared with NPH in people with type 1 diabetes. Their review included eight randomised controlled studies and showed no therapeutic benefit of insulin glargine over other insulin formulations studied when analysing together glycaemic control and the frequency and severity of hypoglycaemia.

The systematic review with meta-analysis by Marra et al. (17) evaluated the effectiveness and safety of analogue insulin glargine compared to recombinant DNA human insulin in people with type 1 diabetes in observational studies. The primary outcomes were HbA1c, weight gain, and hypoglycaemia. Eleven observational studies were included in which they report a high level of heterogeneity and potential conflict of interest. They reported evidence of improved effectiveness with the analogues. The mean difference in glycated hemoglobin was -0.33 percent (CI -0.54 , -0.12 ; $p=0.002$). However, when a subgroup of studies was separately analysed in which there was no conflict of interest, no significant statistical difference was noted regarding HbA1c between groups. Conversely, in the subgroup that reported conflicts of interest, the findings were favorable for insulin glargine. Severe hypoglycaemia risk showed a mean difference of -0.58 (CI -0.99 , -0.16) $p=0.007$, favoring glargine, although severe hypoglycaemia was not defined.

A recent Cochrane review by Fullerton et al. (14) assessed the effects of rapid-acting insulin analogues compared to the short-acting regular human insulin in adults with type 1 diabetes. The

authors describe the studies included as being of low or very low-quality evidence. The mean difference HbA1c was -0.15 percent (95 percent CI -0.2 percent to -0.1 percent; P value < 0.00001) in favor of insulin analogues. The risk of severe hypoglycaemia between the two treatment groups was not significantly different (OR 0.89; 95 percent CI 0.71 to 1.12; P value = 0.31), nor was there an overall hypoglycaemia difference between groups. Two trials reported statistically significant effects on nocturnal severe hypoglycaemic episodes in favor of insulin aspart. However, the authors comment that the validity of these results is questionable due to inconsistent reporting in publications and trial reports. Therefore, the report concluded that there was only a potentially minor benefit of short-acting insulin analogues on glucose control in individuals with type 1 diabetes.

Wojciechowski et al. (18) compared the effects of insulin aspart and regular insulin separately in both type 1 diabetes and type 2 diabetes. Eleven studies involved patients with type 1 diabetes. They concluded that aspart provided a greater reduction in HbA1c (-0.11 percent; 95 percent confidence interval [CI], -0.16 to -0.05) with a reduced risk in nocturnal hypoglycaemia. However, no difference was observed for severe hypoglycaemia (RR, 0.85 [0.66-1.08]). The results for type 2 diabetes are presented below.

Overall the five systematic reviews comparing the effect of analogue vs human insulin HbA1c show no benefit for HbA1c lowering, but possible lower risk of severe hypoglycaemia in type 1 diabetes.

Type 1 Diabetes: Recent RCTs

The HypoAna trial by Pedersen-Bjergaard et al. (19) was a two-year prospective, randomised, open-label, blinded-endpoint crossover trial sponsored by NovoNordisk in Denmark that investigated the rates of severe hypoglycaemia in patients with hypoglycaemia-prone type 1 diabetes with rapid-acting and long-acting insulin analogues compared to their human insulins counterparts. Patients ≥ 18 years of age with type 1 diabetes (diagnosed for >5 years) who had reported two or more episodes of severe hypoglycaemia in the preceding year were randomised to treatment with either analogue insulin (detemir and aspart) or human insulin (human NPH and human regular). The primary endpoint was the number of validated episodes of severe hypoglycaemia (defined by need for treatment assistance from others) reported during the maintenance periods. Their results showed a clinically significant reduction in severe hypoglycaemic episodes in the selected population on the analogue insulin regimen. The absolute rate reduction was 0.5 episodes per patient-year (relative rate reduction of 29 percent) with insulin detemir and aspart, which corresponds to a number of patients needed to treat of two in one year to avoid one episode of severe hypoglycaemia. A post-hoc analysis of the HypoAna trial (20) analysing the outcomes at a single-patient level, reported fewer episodes of severe hypoglycaemia during treatment with analogue insulin in 42 patients (37 percent, 95 percent CI: 28-46 percent) and 23 patients with human insulin (20 percent (13-29 percent). 49 patients (43 percent (34-53 percent) reported a similar number of severe hypoglycaemic events in both treatment arms.

Non-severe hypoglycaemia appeared to be less impacted by analogue insulin in the HypoAna trial. A follow-up analysis (21) showed a six percent relative risk reduction (2-10 percent, $p= 0.0025$) of non-severe hypoglycaemia, defined according to the American Diabetes Association with a plasma glucose concentration ≤ 3.9 mmol/l, but not requiring assistance from others. Interestingly, analogue treatment was associated with a 13 percent increased rate of asymptomatic daytime hypoglycaemia (95 percent CI: 4-23 percent; $p= 0.005$). Non-severe nocturnal hypoglycaemia was lower in those treated with analogue insulin compared with human insulin (10.6 vs. 6.4 events/patient year, 39 percent RRR (95 percent CI 32-46 percent; $p<0.0001$). Interestingly, a short-term cost-effectiveness analysis of the HypoAna trial subsequently showed that despite the higher costs of analogue regimens, the costs for corrective actions for hypoglycaemic events were lower, presumably mostly due to severe and nocturnal hypoglycaemia (22).

Two studies compared analogue vs human insulin in an exclusively pediatric population. Similar to HypoAna, Petit-Bibal et al. (23) combined analogues (basal and bolus) in the comparison with human insulin. They found that children on aspart and detemir had a significantly lower rate of severe ($p=0.025$) and symptomatic hypoglycaemia ($p<0.001$), which is a near two-fold decrease in symptomatic hypoglycaemia. There was no difference in HbA1c between groups. However, it should be noted that the aspart/detemir group used a free-mix insulin combination while the aspart/NPH group used a pre-mixed fixed-ratio formulation.

Thalange et al. (24) looked specifically at analogue basal insulins, comparing the efficacy and safety of detemir vs. NPH in a randomised, multinational, open-label, parallel-group, non-inferiority trial including children with type 1 diabetes aged 2–16 years. After 52 weeks, total hypoglycaemic events and nocturnal events were significantly lower with insulin detemir than with NPH insulin (rate ratio 0.76, 95 percent CI 0.60–0.97, $P=0.028$ and 0.62, 95 percent CI 0.47–0.84, $P=0.002$, respectively). No severe nocturnal hypoglycaemic episodes were reported in the insulin detemir group, while five episodes took place in the NPH group.

In summary, recent RCTs suggest that analogue insulin may have benefit with regard to severe and nocturnal hypoglycaemia in type 1 diabetes, in particular in patients at risk for hypoglycaemia. Of note, two out of the three studies above were sponsored by the pharmaceutical industry.

Type 2 Diabetes: Systematic reviews and Meta-Analyses

One systematic review was done in individuals with type 2 diabetes. Rys et al. (25) analysed 28 RCTs that compared the efficacy and safety of insulin glargine added to oral drugs (OAD) or/and in combination with bolus insulin, NPH or premixed insulin in the same regimen. The studies did not indicate an overall difference in HbA1c lowering but two RCTs demonstrated a favorable effect of glargine over NPH with respect to achieving a target HbA1c without nocturnal hypoglycaemia (RR = 1.32 [1.09, 1.59]). In addition, in a meta-analysis of five studies assessing glargine in comparison with NPH, both added to oral hypoglycaemic agents, revealed that glargine significantly reduced the number of symptomatic (6 RCTs; RR = 0.89 [0.83, 0.96]) and nocturnal hypoglycaemic events (6 RCTs; RR = 0.63 [0.51; 0.77]). However, the risk of severe hypoglycaemia was similar between interventions (5 RCTs; RR = 0.76 [0.47, 1.23]).

The systematic review by Wojciechowski et al. (18) compared the effects of insulin aspart and regular insulin. Five studies examined individuals with type 2 diabetes. The results showed that aspart led to a greater reduction in HbA1c (WMD, -0.22 percent; 95 percent CI, -0.39 to -0.05). However, the risk of overall hypoglycaemia and severe adverse effects was comparable between the groups (RR, 1.00 [0.70, 1.44]).

Overall the two systematic reviews comparing the effect of analogue vs human insulin the effects on HbA1c were variable, but neither study showed a difference in severe hypoglycaemia in type 2 diabetes.

Type 2 Diabetes: Recent RCTs

Four small studies published between 2013 and 2016 reported no difference in HbA1c and/or hypoglycaemia between analogue and human insulin groups (26 – 29). Ridderstrale et al. (30) reported lower *non-severe* hypoglycaemia rates with insulin detemir compared to NPH in insulin-naïve patients with type 2 diabetes with no difference in HbA1c between groups.

In a five-year randomised open-label study, Rosenstock et al. (31) compared twice-daily NPH with once-daily glargine in adults with type 2 diabetes. Although the HbA1c was slightly lower in the NPH group compared to glargine group, those treated with glargine had a significantly lower adjusted

odds ratios (OR) for all daytime hypoglycaemia (OR 0.74; $p = 0.030$) or any severe event (OR 0.64; $p = 0.035$), representing a 26 percent and 36 percent reduction in the odds of daytime and severe hypoglycaemia, respectively. Notably, people taking glargine had less hypoglycaemia despite more subjects in that group being on sulfonylureas (20.3 percent and 15.7 percent in the glargine and NPH groups; respectively).

Berard et al. (32) single-site, open-label, randomised, six-month comparative study of 66 patients from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Randomization was 1:1 to receive insulin glargine or NPH. Rates of symptomatic hypoglycaemia did not differ significantly between groups, however, patients treated with NPH insulin had higher frequencies of severe hypoglycaemia (6.1 ± 0.9) compared to those on glargine (2.7 ± 0.6).

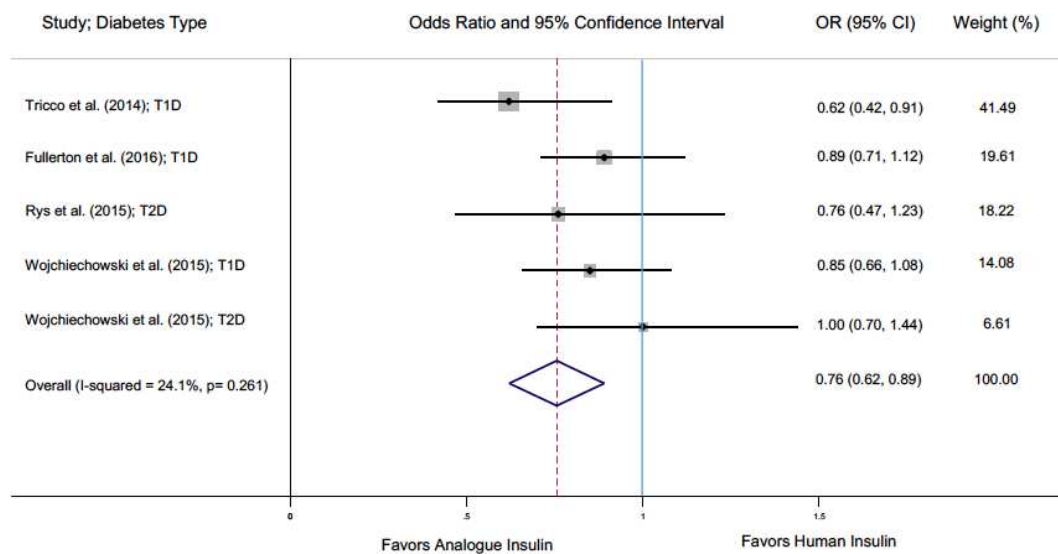
Farshchi et al. (33) published a single-center, parallel-group, randomised, clinical trial looking at 174 patients with poorly controlled type 2 diabetes ($HbA_{1c} \geq 8$ percent) who were randomly assigned biphasic aspart vs NPH and regular insulin and followed for 48 weeks. Therapies were prescribed by a single physician. Glycaemic control did not differ between groups, however, severe hypoglycaemia was lower in the biphasic aspart compared to NPH/regular insulin group. Notably, in this study the insulin was prescribed by one physician who was not blinded.

The Least One Oral Antidiabetic Drug Treatment (LANCELOT) Study by Home et al., (34) was an international 36-week, randomised, open-label, parallel-arm study in which participants were randomized (1:1) to begin glargine or NPH on the background of metformin with glimepiride. At treatment end, HbA_{1c} values and the proportion of participants with $HbA_{1c} < 7.0$ percent were not significantly different for glargine and NPH. There was no difference between groups in the proportion of participants who reported ≥ 1 hypoglycaemic event at any time (36.4 percent for glargine vs 36.0 percent for NPH). Three participants in the glargine group and one participant in the NPH group had severe hypoglycaemic events. However, the rate of symptomatic nocturnal hypoglycaemia, confirmed by plasma glucose ≤ 3.1 mmol/l, was 48 percent less with glargine than with NPH insulin, which was significantly different. The nine studies on type 2 diabetes were sponsored by the pharmaceutical industry.

In summary, the study results vary with the majority showing no significant differences in severe hypoglycaemia between human and analogue insulin. Three studies did show significant reductions in severe hypoglycaemia. However, all three studies were sponsored by pharmaceutical companies and in one study insulin was prescribed by a single physician who was not blinded.

Figure 3. Forest plot of meta-analyses comparing severe hypoglycemic episodes between analogue and human insulin in patients with type 1 diabetes and type 2 diabetes. Abbreviations: OR, odds ratio

Figure 2. Severe hypoglycemia risk with analogue vs. human insulin



2.4 Discussion

To date, the added benefit of analogue insulin over human insulin has been controversial due to inconsistent findings in the literature, as illustrated above. Although analogue insulin is widely used in high income countries, the data has not supported any significant advantage of these insulins over human insulin, particularly given their substantially higher cost. Prior studies and our review of the recent literature shows no consistent or clinical reduction in HbA1c (defined as a reduction in HbA1c by at least 0.5 percent) with analogue insulin, compared to human insulin in both type 1 diabetes and type 2 diabetes. However, the greatest concern with the use of insulin is the risk of severe hypoglycaemia, which has consistently been shown to be associated with negative outcomes, including mortality, in numerous studies (12). Therefore, this review focused on the risk of hypoglycaemia, especially severe hypoglycaemia, comparing human to analogue insulin.

A major challenge in determining the potential benefits of analogue insulins over human insulins is the dramatic variation in study inclusion criteria (type 1, type 2 or both and adults vs. children), the outcomes of interest, and definitions of severe hypoglycaemia. As shown in Figure 3, pooling results from several meta-analyses illustrates a potential “population” advantage of analogue insulins over human insulin specifically to reduce severe hypoglycaemia risk. However, this must be interpreted with caution since individual studies do not have consistent results nor are there consistently identifiable factors that could explain discrepancies. In general, however, these factors include differences in, or lack of, definitions of severe hypoglycaemia, a high level of subject heterogeneity and potential conflict of interest through industry funding.

In contrast, recent RCTs in type 1 diabetes have added some clarity, most notably the HypoAna trial (19). There was a clinically significant reduction in severe hypoglycaemic episodes in those on the analogue insulin regimen with an absolute rate reduction of 0.5 episodes per patient-year (relative rate reduction of 29 percent). However, in a post-hoc analysis evaluating outcomes at a single-patient level, 43 percent reported a similar number of severe hypoglycaemic events in both

treatment arms (20). Despite the concern about how best to compare hypoglycaemia burden between groups, the analogue regimen appeared to have been more cost-effective (22).

Overall, studies in children and adults known to be at risk of hypoglycaemia are consistent with the finding that nocturnal and symptomatic hypoglycaemia are lower with the use of analogue insulin, with best evidence for analogue basals (23, 24). The type 2 diabetes literature is less consistent, with only four of nine recent studies showing reduced rates of severe hypoglycaemia with analogue insulins. This may well be related to differences in patient-level characteristics that would typically distinguish patients in clinic, for example a non-obese patient with non-classical type 2 diabetes who may have features that resemble type 1 diabetes.

2.5 Conclusions

Analogue insulins have similar clinical outcomes compared to human insulin in published trials. However, newer data suggests that long-acting analogue insulins may provide benefit in reducing the risk of severe hypoglycaemia in high-risk patients with type 1 diabetes. Given the high heterogeneity of the studies, the discrete value presented by the estimated effect on effectiveness and safety, potential conflicts of interest of the studies, and the appreciable higher cost of insulin analogues, there is still no support for recommending first-line therapy with analogues.¹⁷ The role of analogues in the treatment of type 1 diabetes could be better determined by further observational studies of good methodological quality to assess their long-term effectiveness and safety, as well as their cost-effectiveness. However, the argument can be made that long-acting analogue insulin should be considered in a small percentage of patients that experience *frequent, severe or nocturnal hypoglycaemia*. Patients who cannot achieve optimal metabolic control on human insulin due to recurrent episodes of hypoglycaemia are more likely to benefit from a long-acting analogue insulin.

Indeed, this approach is reflected by Pharmaceutical Management Agency (PHARMAC) in New Zealand, who have recommended human insulins as first line therapy, with insulin analogues reserved for the subset of patients with type 1 diabetes whose lifestyle is significantly impaired by recurrent symptomatic hypoglycaemia (35). The UK National Institute for Health and Care Excellence suggests prescribing long-acting insulin analogues for patients with type 1 diabetes (36). The American Diabetes Association (ADA) likewise supports the use of long-acting analogue insulin in type 1 diabetes to avoid the risk of hypoglycaemia and for patients with type 2 diabetes with a high risk of hypoglycaemia (37).

3. Comparing Clinical Outcomes of Insulin Pen Devices and Insulin Vial and Syringe

Key Conclusions: Clinical Outcomes of Insulin Pen Devices and Insulin Vial and Syringe

- Pen devices appear to be preferable in terms of treatment adherence and persistence, as well as quality of life.
- Data to support improved clinical outcomes with pens compared to vial and syringe are lacking.
- The use of the more affordable vial and syringe in settings where resources are limited, is encouraged and justified.
 - Exceptions to this are patients with visual impairment who are likely to benefit from pen devices.

3.1 Overview

As described in prior ACCISS reports, affordability is a major barrier in the long-term treatment of diabetes (8). Not only is the cost of insulin itself high, but the additional supply costs, such as insulin delivery devices, further add to the financial strain of diabetes care (38). At present the two most common methods of insulin delivery are insulin vial and syringe vs. pen devices (including both reusable pens with insulin cartridges and disposable pens). For many, insulin pens are preferred for convenience and comfort, and are increasingly being used in higher-income countries. In addition, they are preferred for visually impaired individuals who do not have social support to help with injections. Insulin pens produce an audible “click” during dosing which allows for the visually impaired to dose accurately. However, pens are the higher priced delivery device, further increasing the cost of diabetes care (38). Importantly, most of the newest insulins to enter the market, including concentrated formulations, are only produced in pen form. Rapid and short-acting insulins supplied by vial are still necessary for insulin pump therapy and intravenous infusion when used in critical care inpatient settings and cannot entirely be replaced by pen devices. Moreover, an advantage of classical syringes is that regular and NPH insulin can be mixed in various ratios and given as one injection.

Given the price differential, particularly in lower resource settings, it is crucial to critically examine the clinical outcomes of insulin pen devices compared to syringes and insulin vials. Therefore, we performed a comprehensive literature review to summarise the most recent data assessing the clinical outcomes of insulin pens compared vials with syringes. Since micro- and macrovascular complications and hypoglycaemia contribute most significantly to diabetes-related death and morbidity, the impact of both insulin delivery devices on HbA1c and hypoglycaemia were evaluated.

3.2 Methods

Literature Search

A systematic review and meta-analysis on the subject was recently done by Lasalvia P et al. (39). The corresponding author of the study was contacted to determine the date of their literature search, which was 7 November 2014. To update the literature search since their search was done, we performed a search in PubMed and Embase for the dates 1 November 2014 through 13 February 2017, and Web of Science and Cochrane Central for year 2015 through 13 February 2017. The following syntax was used for each database:

1. *PubMed*

("Diabetes Mellitus"[Mesh] OR "Insulins"[mesh] OR diabetes[tiab] OR diabetic*[tiab] OR insulin*[tiab])

AND

(pen[tiab] OR pens[tiab])

AND

("2014/11/01"[PDAT] : "3000/12/31"[PDAT])

2. *Embase*

('diabetes mellitus'/exp OR 'insulin derivative'/exp OR diabetes:ab,ti OR diabetic*:ab,ti OR insulin*:ab,ti)

AND

('insulin injection pen'/exp OR pen:ab,ti OR pens:ab,ti)

AND

[1-11-2014]/sd AND [embase]/lim

3. *Web of Science*

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2015-2017

TS=(("diabetes" OR "diabetic*" OR "insulin*") AND ("pen" OR "pens"))

4. *Cochrane Central*

Limit to 2015 - 2017

((("diabetes" OR "diabetic*" OR "insulin*") AND ("pen" OR "pens")))

The search terms and syntax were created with the assistance of a librarian at the Countway Library of Medicine of Harvard University.

Only studies directly comparing insulin pen devices to insulin vials with syringes were evaluated. Inpatient settings and studies evaluating nursing preference were excluded.

3.3 Results

Literature Search

The literature search resulted in a total of 656 references. After removing duplicates 415 references remained. Of these, six studies were included for data extraction: One systematic review with meta-analysis, three retrospective studies and two observational studies. No randomised controlled trials were found.

Study Characteristics and Results

Lasalvia et al. (39) performed a systematic review on the efficacy of pen devices compared with vial and syringe in eight databases. 17 studies were included in their analysis. Meta-analyses were done for HbA1c, hypoglycaemia, adherence, and persistence. There was a statistically significant difference for the mean change in HbA1c level favoring pen devices (-0.28 [95 percent CI -0.49, -0.07]), but it did not reach the clinical significance threshold, which is generally between -0.3 to -1 percent. Seven studies examined hypoglycaemia rates. Three showed no difference between pen and vial/syringes. A meta-analysis was performed on four studies with reported hypoglycaemia results at 12 months which showed a favorable effect with pen devices. However, the study which carried ~50 percent of the weight in the meta-analysis was a retrospective cohort study of a large national claims database. The pen users in the study showed less hypoglycaemia, but also had more endocrinologist office visits for unclear reasons, which may potentially confound the results. Two

studies reported hypoglycaemia-related hospital admissions. One was a claims database review which showed reduced numbers of hospitalisations for hypoglycaemia. In the second study the rate of hypoglycaemia-related hospital admissions did not reach significance.

None of the other five studies included in our literature review showed a difference in HbA1c or hypoglycaemia comparing pen devices to vials and syringe. The studies examined are few and do not include randomised controlled trials (40 – 44).

3.4 Discussion

Insulin pen devices are growing in popularity and use in high-income countries given their ease of use and patient preference. These newer insulin delivery devices come at a higher price than the traditional use of syringes and vials. However, the price of syringes are also substantial, and can cost an average of ~ US\$0.20 per syringe in lower income countries (45), and government provision of insulin syringes in many LMICs remains poor. Therefore, many families buy their insulin syringes privately, which is a significant financial burden given the chronicity of diabetes (45). Although insulin pen devices have their advantages, the current literature does not suggest significant differences in quality outcomes between insulin syringe and vials compared to insulin pens. Therefore, particularly in LMICs with limited funds, the priority should be improved access and universal coverage of insulin syringes/vials, before investing in higher priced pen devices. However, evidence and clinical experience support reserving insulin pens for a small subset of insulin users with visual impairment who are unable to use insulin syringes safely.

3.5 Conclusion

Although pen devices appear to be preferable in terms of adherence and persistence, as well as quality of life, the data to support improved clinical outcomes is lacking. Therefore, in settings where resources are limited, the use of the more affordable vial and syringe is encouraged and justified. Exceptions to this are insulin users with visual impairment who are likely to benefit from pen devices.

4. Necessary Insulin Use in Type 2 Diabetes

Key Conclusions: Necessary Insulin Use in type 2 diabetes

- Insulin is necessary for the following situations in type 2 diabetes:
 - Marked hyperglycaemia with symptomatic insulin deficiency (may be transient)
 - Failure of oral agents to achieve individualised glucose targets
- A conceptual framework for the pharmacologic management of type 2 diabetes including only WHO Essential Medicines List is provided

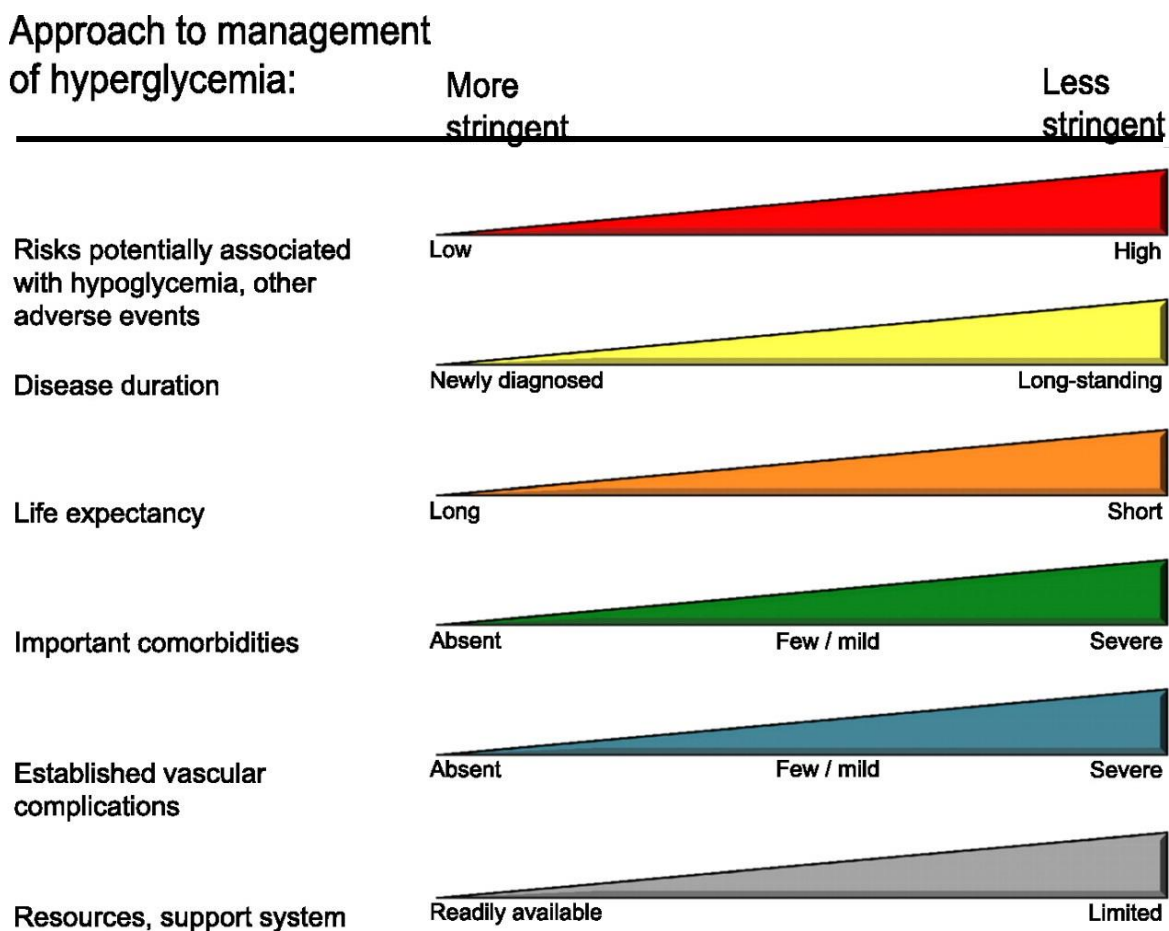
4.1 Overview

Insulin is the mainstay of treatment for all individuals with type 1 diabetes. However, the use of insulin in type 2 diabetes is more complex and practices surrounding the initiation and management of insulin in type 2 diabetes vary. As part of the ACCISS Study, a systematic literature review of published data characterising insulin consumption in type 2 diabetes was done (8). The results show widely varying insulin consumption rates in type 2 diabetes, ranging from 2.4 percent in Taiwan to 23.5 percent in the United States (US). The review demonstrates lacking consensus regarding best practices for insulin treatment in patients with type 2 diabetes. How and when to initiate insulin as monotherapy or in combination with oral hypoglycaemic agents remains ambiguous. Therefore, the following section seeks to review the current guidelines and evidence on insulin use and initiation in type 2 diabetes to help achieve glycaemic targets in a safe and cost-effective manner, particularly in low resource settings.

4.2 Glycaemic Targets in Type 2 Diabetes

The goal of glycaemic control in any person living with diabetes is to avoid long-term micro- and macrovascular complications. Hemoglobin HbA_{1c} targets of <7 percent (53 mmol/mol) have been shown to reduce microvascular complications of diabetes. Epidemiological analyses of the DCCT (6) and UKPDS (46, 7), demonstrate a curvilinear relationship between HbA_{1c} and microvascular complications. Long-term follow up of the UKPDS study (>10 years) suggest that glucose control may also reduce cardiovascular events, although this remains less certain (47). However, subsequent trials (including the ACCORD Trial (48)), showed increased rates of severe hypoglycaemia and mortality in the intensively controlled arm. Therefore, numerous aspects must be considered when setting glycaemic targets. The American Diabetes Association (ADA) (11) and European Association for the Study of Diabetes (EASD) (49) propose that each target be individualised to the needs of each person. The joint ADA and EASD recommendations suggest that an HbA_{1c} goal of <7 percent (53 mmol/mol) is reasonable for many non-pregnant adults (49). More stringent HbA_{1c} goals can be considered (such as <6.5 percent [48 mmol/mol]), if this can be achieved without significant hypoglycaemia, in selected individual patients, such as those with short duration of diabetes, long life expectancy, or no significant cardiovascular disease. Conversely, for people with a history of severe hypoglycaemia, advanced micro- and macrovascular complications or extensive comorbid conditions, and limited life expectancy, less stringent HbA_{1c} goals (such as <8 percent [64 mmol/mol]) may be prudent (11). Figure 4 demonstrates the criteria to consider when determining glycaemic targets in an individual patient.

Figure 4. Approach to Management of Hyperglycaemia¹



It is important to note that the risk of diabetes-related complications is associated independently and additively with hyperglycaemia and hypertension (50). A long-term observational analysis of UKPDS patients found that the risk of any diabetes-related endpoint was decreased by 21 percent and diabetes-related death by 22 percent for every one percent reduction in updated HbA1c. Moreover, *the risk of microvascular disease was reduced by 37 percent for every one percent decrease in HbA1c (50)*. This is particularly important to consider in settings where the above-specified glycaemic targets are difficult to achieve. Individualised approaches to each patient and small reductions in HbA1c and blood pressure have potentially great implications for long-term diabetes complications.

4.3 Pharmacologic Management of Type 2 Diabetes

The main goal of diabetes treatment is to control the plasma glucose level to reduce the risk of macro- and microvascular complications and relieve symptoms of hyperglycaemia, such as polyuria and weight loss, when present. In the landmark UKPDS trial published in 1998, 5,102 patients from 23 centres were randomised to intensive glycaemic control (fasting glucose <6mmol/l/108 mg/dl) vs. conventional control (fasting glucose <15mmol/l/ 270mg/dl). The intensive arm included three main strategies: insulin alone, sulfonylurea, and metformin (overweight only). Over the 10-year study, monotherapy failed at a rate of 5-10 percent per year across both groups and only

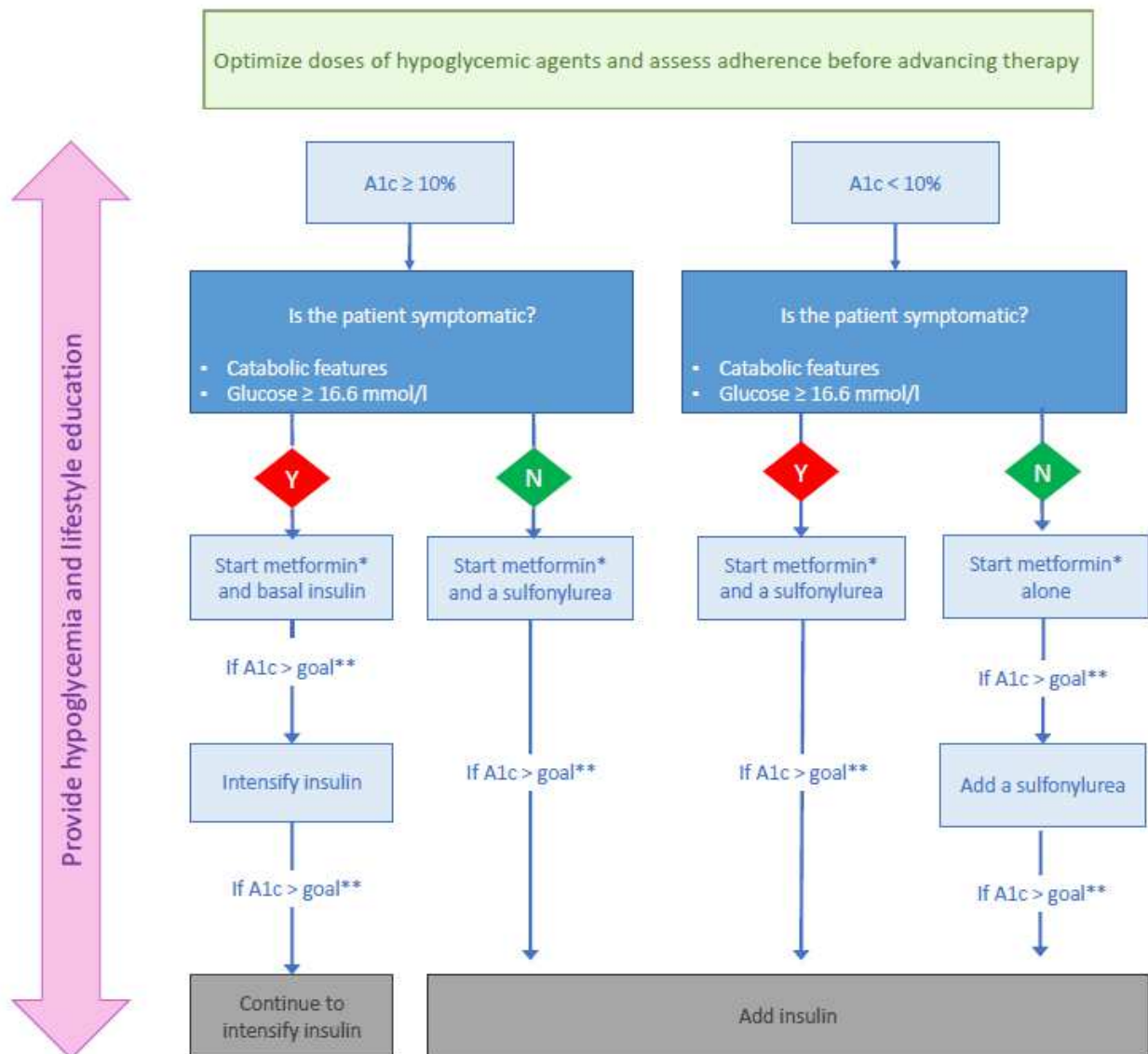
¹ From Annals of Internal Medicine, Ismail-Beigi F, et al., Individualizing Glycemic Targets in Type 2 Diabetes Mellitus: Implications of Recent Clinical Trials, 154, 8, Figure 1, 554. Copyright © 2011. American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

approximately 20 percent of patients were maintained on a single drug by the end of the trial; consequently, it is now standard practice to combine oral agents with insulin to achieve glycaemic control. Indeed, at the end of the original UKPDS about 60 percent of patients in the intensive arm and 50 percent in the conventional arm required insulin to maintain the glucose target. The final median HbA1c was 7.9 percent on conventional therapy and 7.0 percent on intensified therapy, and this was associated with a 25 percent reduction in the rates of retinopathy, nephropathy and (possibly) neuropathy. Results were even stronger in the epidemiological arm (which compared achieved HbA1c rather than treatment arm), and no glycaemic threshold for complications was observed. There was a non-significant 16 percent reduction in myocardial infarction or sudden death with intensified therapy, and a 25 percent reduction in the risk of death for every one percent drop in HbA1c. Of importance, antihypertensive therapy markedly reduced all end-points, microvascular as well as arterial (7).

Non-insulin hypoglycaemic agents have been shown to each lower HbA1c by about 0.5-1.5 percent. Adding a second agent from a different class lowers HbA1c by about another 1.0 percent. Sulfonylureas and metformin have been on the market for many years and generic versions are available. Therefore, their monthly cost is extremely low compared to the newer diabetic agents which can be up to 65 times higher priced than generic sulfonylureas and metformin (51). For most patients with type 2 diabetes, metformin is the best therapeutic choice as initial therapy given its therapeutic profile, relative safety, and low cost (52). There is international consensus in clinical practice guidelines that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first-line agent, which is supported by results from UKPDS and other studies (37,49,53). Sulfonylureas are still widely used and are on the WHO List of Essential Medicines (10). However, studies have repeatedly shown significant hypoglycaemia risk and increased cardiovascular and mortality risk with sulfonylureas, particularly with tolbutamide and glibenclamide (also known as glyburide) (54). These effects were most pronounced with glibenclamide, and less so with gliclazide, glipizide and glimepiride (55). Gliclazide is listed on the WHO List of Essential Medicines, however, glibenclamide likewise still appears on the list (10). The argument has been made that, given the safety concerns with glibenclamide, this agent should no longer be used (55). The verdict on the safety of the newer sulfonylureas, gliclazide, glipizide, and glimepiride, is still out and further studies are needed to address this question (56). Therefore, at present, when sulfonylureas are prescribed choosing a newer agent is preferable.

A framework for the management of type 2 diabetes for settings with access only to the WHO EML can be found in Figure 5 under Section 4.4. If the patient's HbA1c level is below 10 percent at diagnosis, one can start metformin and then add a second non-insulin agent if HbA1c goals are not met in three months. Before advancing the regimen, the recommendation is to titrate the existing medication(s) to their optimal doses and inquire about adherence. Many seemingly 'inadequate' regimens may be subject to patients not taking the regimen correctly. Which agent is chosen next can be based on a person's risk of hypoglycaemia. A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycaemia risk, impact on weight, potential side effects, cost, and user preferences. For those who are not having acute symptoms of hyperglycaemia, if the risk of hypoglycaemia is a major clinical concern (e.g. in a frail older patient or one prone to falls), an appropriate second agent can be a DPP-4 inhibitor. However, if hypoglycaemia is less of a concern, a good second-line agent is a sulfonylurea. The use a shorter half-life agent, such as glipizide, is recommended especially in older patients. Avoid longer-acting sulfonylureas such as glyburide and chlorpropamide. If the patient still cannot reach the target HbA1c goal with either dual-therapy mode, insulin or a third non-insulin agent can be added. If the HbA1c is above 10 percent at diagnosis and the patient is symptomatic (e.g., polydipsia, polyuria, weight loss), we recommend starting metformin and basal insulin therapy. If the HbA1c goal is still not met, intensify the insulin therapy until the goal is met. Ultimately, given the natural progression of the disease, many patients will require insulin therapy (usually in combination with other agents) to maintain good glucose control.

Figure 5. Treatment Algorithm for the Management of type 2 diabetes Using the Current WHO Model List of Essential Medicines, 20th Edition 2017



* If contraindicated or not tolerated, start sulfonylurea (preferentially gliclazide)

** Recommend monitoring every 3 months until target A1c is attained, then every 3-6 months thereafter

These recommendations are based on the diabetes medications currently on the WHO Model List of Essential Medicines, 20th Edition (2017)

4.4 Conclusion

The main goal of diabetes treatment is to control the plasma glucose level to reduce the risk of macro- and microvascular complications and relieve symptoms of hyperglycaemia, such as polyuria and weight loss, when present. HbA1c targets of <7 percent (53 mmol/mol) have been shown to reduce microvascular complications of diabetes. Additionally, the risk of microvascular disease has shown to be reduced by 37 percent for every one percent decrease in HbA1c. However, the benefits of HbA1c lowering must be carefully weighed with the risk of hypoglycaemia, which can lead to increased morbidity and mortality. Hypoglycaemia is preventable and manageable in the vast majority of insulin users and every effort should be made to avoid it completely. Therefore, the

decision to use insulin in type 2 diabetes depends on the degree of insulin deficiency of the individual, the effectiveness of non-insulin agents, hypoglycaemia risk, and cost. In low resource settings where close monitoring and support is challenging, the use of non-insulin agents may be more cost-effective and preferred in asymptomatic patients before starting insulin. In cases where adding insulin would cost less to the person than non-insulin agents, clinicians need to balance the risk and benefit.

5. Interchangeability of Insulin Formulations

Key Conclusions: Interchangeability of Insulin Formulations

- Newer biosimilar insulins are emerging on the global market
- Clinical experience with biosimilar insulin is just starting and the optimal way to supervise patients during these changes is unclear.
- As with any medication adjustment or change, close glucose monitoring, follow-up, and comprehensive education remain the cornerstones of safe and effective insulin management.
- When these key elements are in place, switching an insulin user from an originator product to a lower priced biosimilar is generally reasonable.

5.1 Overview

As described in detail in previous ACCISS reports (5, 8), two of the main barriers to insulin access globally are availability and affordability. Most of the global insulin supply comes from three insulin manufacturers which held an 88.7 percent value share in the global insulin market in 2012: Novo Nordisk, Sanofi and Eli Lilly and Company (8). While initial ACCISS reports identified 42 potentially independent insulin manufacturers worldwide, interviews with companies and others revealed there is likely only about ten, most of them being local manufacturers selling only to their local markets(8). The persistently high cost of insulin is likely due, at least in part, to the market dominance of the three large insulin manufacturers. Over the past few years, biosimilar analogue insulins have emerged on the market (57). Other names for biosimilars include follow-on biologics (US) and subsequent entry biologics (Canada). Biosimilar products are biologic products that are highly similar to a previously approved biologic product (reference product) with no clinically meaningful differences in safety and effectiveness when compared to the reference product (58). Thus, alternative suppliers of insulin for people with diabetes are becoming available, potentially at a lower cost. However, price and accessibility depend in part on the interchangeability of these newer agents.

All people receiving insulin require close monitoring due to the need to maintain the patient in a narrow range for their blood glucose to avoid hypo or hyperglycaemia. Blood glucose levels may be affected by changes in diet, exercise, life style or concomitant illness. The question in this review is whether a change in insulin from an originator to a biosimilar should be treated with routine monitoring of blood glucose levels or whether enhanced monitoring and follow-up are indicated.

5.2. Biosimilar Insulin

With analogue insulin patents expiring, an increasing number of biosimilar products are being developed. As discussed previously in the ACCISS report from 2015 (5), it is estimated that biosimilars in Europe could offer savings of 20 to 30 percent in comparison with the originator medicines and decreases in prices from 12 to 51 percent have been seen on the originator product once a biosimilar is introduced. Unlike the production of generic small molecule medicines, the manufacturing process of biosimilars is critical and each step has great impact on the end-product.

These products are more susceptible to minor variations during the manufacturing process and hence are not considered inherently interchangeable (59). Because of their large size and complexity, it may be impossible to produce an exact copy of the original biologic product. Indeed, clinical and regulatory requirements for biosimilar insulin are more complicated than with smaller molecule generic medicines and their interchangeability remains a debated topic.

It is important to note that hormones such as insulin are not currently regulated as biologics in the US. Therefore, follow-on insulin product(s) approved in the US are also not subject to “biosimilar” regulations by the FDA (60). However, much of this confusion is likely to clear up in 2020. On March 23, 2020, an approved application for a biological product under section 505 of the FDC Act “shall be deemed to be a license for the biological product under section 351 of the PHS Act (61).” In contrast, the EMA does consider insulin a biologic medical product. The reason for this difference is in part a historical one. In the US, analogue insulins such as Lantus® were originally approved as small molecule drugs (New Drug Application) by the FDA (under section 505 of the US Food, Drug, and Cosmetic Act), rather than as biologic products through the BPCI Act (Biologics License Application) (60). Therefore, generic manufacturers seeking marketing authorisation for follow-on insulin products can only submit abbreviated new drug applications using the data associated with the originally approved reference product – in this case, “small-molecule” drugs. Therefore, in the US, biosimilar insulins are referred to as “follow-on” insulin products and may not be subject to the same concerns about biosimilarity and interchangeability. At publication, only two biosimilar insulin analogues have been approved by the EMA for use in the European Union: Abasaglar®, insulin glargine and Lusdana Nexvue®, insulin glargine (62). The FDA recently approved Basaglar® (insulin glargine), although not as a biosimilar, but as a “follow-on biological” agent through an abbreviated FDA approval pathway meant for small molecules (505(b)2). Abasaglar, an insulin glargine biosimilar, was studied in two classic, parallel design, phase III studies, ELEMENT 1 in type 1 diabetes and ELEMENT 2 in type 2 diabetes. However, no switching studies comparing it to the originator insulin glargine were performed and thus no studies were designed to address interchangeability (63).

More biosimilar medicines are currently being developed. Merck’s Lusdana Nexvue®, insulin glargine received tentative approval by the FDA in June. Sanofi is studying an insulin lispro biosimilar that is in phase III trials at present (65). Moreover, Basalog®, an insulin glargine biosimilar manufactured by Biocon, has recently been approved in Japan (66). Therefore, given the number of manufacturers and new biosimilar insulins under development, guidelines for the clinical use of these agents, including where interchangeability remains a grey area, are needed (62).

5.3. Interchangeability

As defined by the EMA, “interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another (67).” In the US an interchangeable medication can be substituted for another equivalent (reference) medication by a pharmacist without the prescriber’s knowledge (59, 68, 69). However, since biosimilarity does not imply interchangeability, further evidence is needed to obtain an interchangeable designation in the US. The regulations around interchangeability are somewhat different in the EU. In another ACCISS report, Dr. Thijs Geizen discusses the topic of interchangeability and biosimilars in the EU (68). Therefore, this article will focus on the perspective in US, where there is a lack of clarity from existing laws about interchangeability of biosimilars.

In the US, a law was signed in 2010 that created an abbreviated licensure pathway for biosimilars established two types of biosimilars: regular biosimilars and interchangeable biosimilars (71). Biosimilar drugs are currently approved through the BPCI Act. According to FDA regulations, interchangeable biosimilars require a higher regulatory standard, but may be safely substituted. Unfortunately, FDA regulations do not provide guidance to individual states or state governments on how to enact or modify their mandatory generic substitution laws. Similarly, the EMA allows member countries to decide whether to designate a biosimilar as interchangeable (59). The

Medicines and Healthcare Products Regulatory Agency (MHRA) of the UK, like the US, discourages the automatic substitution of biosimilar products for the reference product (70).

So far, none of the four FDA approved biosimilar medicines (filrastrim-sndz, infliximab-dyyb, adalimumab-atto, and etanercept-szszs) have met the higher evidentiary standard required to be considered an interchangeable biosimilar product. For example, in addition to proving that the interchangeable product will produce the same clinical result as the reference product for all approved uses, the biosimilar manufacturer must also demonstrate that the “risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch”(68).

5.4 Clinical Relevance/Perspective

With the increase of insulin manufacturers globally, development of biosimilar insulins, differences in global purchasing power and insulin purchases from different vendors (such as locally from wholesalers versus international tenders), the question of interchangeability between insulins arises. Moreover, significant challenges in maintaining the quality and consistency between manufacturers of these biosimilar products exist (72). There are currently no clear guidelines for clinical practice, for example switching an insulin user from brand name Lantus® (insulin glargine) to biosimilar or follow-on drugs Basaglar®/Abasaglar® or Basalog®. The EMA advises that Abasaglar® should only be initiated in those new to insulin glargine or in those who require a review of their therapy due to poor control. Since their effects may not be identical, it has been recommended by the UK's National Institute for Clinical Excellence that patients who have been stable on Lantus not be switched to Abasaglar® (63).

Basaglar's FDA prescribing information recommends continuing the same dose when changing from another insulin glargine product, 100 units/mL, to Basaglar® (73). The time of day for administration should be determined by the physician. A 20 percent dose reduction is recommended if changing an insulin user from a once-daily insulin glargine product, 300 units/mL, to once-daily Basaglar® to avoid hypoglycaemia, although it is not yet clear that this is required in practice. Similarly, a 20 percent total daily dose reduction is encouraged if switching patients from twice-daily NPH to once-daily Basaglar®. If changing from a treatment regimen with an intermediate- or long-acting insulin (other than an insulin glargine product, 100 units/mL) to a regimen with Basaglar®, a change in the dose of the basal insulin may be required and the amount and timing of shorter-acting insulins and doses of any anti-diabetic drugs may need to be adjusted (73).

It is reasonable to state that switching between biosimilar insulins poses very different risks than switching insulin users between insulins with different time-action profiles, i.e. duration of action and timing of peak effect. Clinical judgement and past experiences, such as with those who changed from NPH insulin to long-acting insulin analogues, insulin detemir to insulin glargine, or human regular insulin to rapid-acting insulin analogues, demonstrate that switching insulin users from one insulin to another can be safe if the clinician is both knowledgeable about the differences in the insulins action and can provide close medical supervision (70). This may include written instructions on how to self-adjust depending on glucose testing results or frequent contact for a limited time until a reasonably safe and effective dose is determined. However, until the global community understands the real risks (if any) of interchanging biosimilar insulins produced by different manufacturers, it is impossible to provide solid guidance on the optimal way to supervise insulin users during these changes. Comprehensive insulin user education regarding glucose self-monitoring, diet, and symptoms/management of hypoglycaemia are critically important in any patient using insulin and should always be the foundation of their medical management (11).

5.5 Conclusions

Availability and affordability are great barriers to insulin access globally. Gradually, newer biosimilar insulins are emerging on the global market. Clinical experience with biosimilar insulin is just starting and the regulatory landscape for biosimilar insulins is evolving. Given the variation in

manufacturing process and complexity of insulin production, current guidelines state that biosimilarity and interchangeability are not exactly the same. Therefore, caution is needed when switching from one insulin to a different or biosimilar insulin. Vigilant glucose monitoring as available, follow-up, and comprehensive patient education regarding glucose self-monitoring, diet, and hypoglycaemia remain the cornerstones in safely and effectively managing patients requiring insulin. When these key elements are in place and especially when major affordability differences exist, switching a patient from an originator product to a biosimilar is reasonable.

6. References

1. International Diabetes Federation Diabetes Atlas 7th Edition: International Diabetes Federation; 2015.
2. Diabetes Action Now: World Health Organization and International Diabetes Federation; 2004.
3. The Africa Diabetes Care Initiative 2010-2012: International Diabetes Federation.
4. Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. *The Lancet Diabetes & Endocrinology* 2016;4:275-85.
5. Beran D EM, Laing R. Access to insulin: Current Challenges and Constraints. Amsterdam: Health Action International; 2015.
6. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *The New England Journal of Medicine* 1993;329:977-86.
7. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet (London, England)* 1998;352:837-53.
8. Wirtz V. Insulin Market Profile. Report: Health Action International; 2016.
9. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2017; 2017.
10. WHO Model List of Essential Medicines. World Health Organization, 2017. at http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1.
11. Glycemic Targets. *Diabetes Care* 2017;40:S48-S56.
12. Minimizing Hypoglycaemia in Diabetes. *Diabetes Care* 2015;38:1583-91.
13. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ (Clinical research ed)* 2014;349:g5459.
14. Fullerton B, Siebenhofer A, Jeitler K, et al. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. *The Cochrane Database of Systematic Reviews* 2016:Cd012161.
15. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ (Clinical research ed)* 2011;342.
16. Caires de Souza AL, de Assis Acurcio F, Guerra Junior AA, Rezende Macedo do Nascimento RC, Godman B, Diniz LM. Insulin glargine in a Brazilian state: should the government disinvest? An assessment based on a systematic review. *Applied health economics and health policy* 2014;12:19-32.
17. Marra LP, Araujo VE, Silva TB, et al. Clinical Effectiveness and Safety of Analog Glargine in Type 1 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes therapy : research, treatment and education of diabetes and related disorders* 2016;7:241-58.

18. Wojciechowski P, Niemczyk-Szechowska P, Olewinska E, et al. Clinical efficacy and safety of insulin aspart compared with regular human insulin in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis. *Polskie Archiwum Medycyny Wewnętrznej* 2015;125:141-51.
19. 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. *The Lancet Diabetes & endocrinology* 2014;2:553-61.
20. Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, et al. The potential for improvement of outcomes by personalized insulin treatment of type 1 diabetes as assessed by analysis of single-patient data from a randomized controlled cross-over insulin trial. *Diabetes research and clinical practice* 2016;123:143-8.
21. Agesen RM, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type 1 diabetes prone to severe hypoglycaemia: The HypoAna trial. *Diabetes & metabolism* 2016;42:249-55.
22. Pedersen-Bjergaard U, Kristensen PL, Norgaard K, et al. Short-term cost-effectiveness of insulin detemir and insulin aspart in people with type 1 diabetes who are prone to recurrent severe hypoglycaemia. *Current medical research and opinion* 2016:1-7.
23. Petit-Bibal C, Rothenbuhler A, Lucchini P, et al. Decrease in clinical hypoglycaemia in young children with type 1 diabetes treated with free-mixed aspart and detemir insulin: an open labeled randomized trial. *Pediatric diabetes* 2015;16:345-53.
24. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Insulin analogues in children with Type 1 diabetes: a 52-week randomized clinical trial. *Diabetic medicine : a journal of the British Diabetic Association* 2013;30:216-25.
25. Rys P, Wojciechowski P, Rogoz-Sitek A, et al. Systematic review and meta-analysis of randomized clinical trials comparing efficacy and safety outcomes of insulin glargine with NPH insulin, premixed insulin preparations or with insulin detemir in type 2 diabetes mellitus. *Acta diabetologica* 2015;52:649-62.
26. von Bibra H, Siegmund T, Kingreen I, Riemer M, Schuster T, Schumm-Draeger PM. Effects of analogue insulin in multiple daily injection therapy of type 2 diabetes on postprandial glucose control and cardiac function compared to human insulin: a randomized controlled long-term study. *Cardiovascular Diabetology* 2016;15:7.
27. Sun Y, Shao L, Niu X, et al. Clinical effectiveness of Novolin(R) 30R versus Lantus(R) combined with Glucobay(R) treatment in elderly patients with type 2 diabetes mellitus controlled by oral hypoglycaemic agents: A randomized study. *The Journal of International Medical Research* 2014;42:993-1001.
28. Hermanns N, Kulzer B, Kohlmann T, et al. Treatment satisfaction and quality-of-life between type 2 diabetes patients initiating long- vs. intermediate-acting basal insulin therapy in combination with oral hypoglycemic agents--a randomized, prospective, crossover, open clinical trial. *Health and quality of life outcomes* 2015;13:77.
29. Herrmann BL, Kasser C, Keuthage W, Huptas M, Dette H, Klute A. Comparison of insulin aspart vs. regular human insulin with or without insulin detemir concerning adipozytokines and metabolic effects in patients with type 2 diabetes mellitus. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association* 2013;121:210-3.
30. Ridderstrale M, Jensen MM, Gjesing RP, Niskanen L. Cost-effectiveness of insulin detemir compared with NPH insulin in people with type 2 diabetes in Denmark, Finland, Norway, and Sweden. *Journal of Medical Economics* 2013;16:468-78.
31. Rosenstock J, Fonseca V, Schinzel S, Dain MP, Mullins P, Riddle M. Reduced risk of hypoglycaemia with once-daily glargine versus twice-daily NPH and number needed to harm with

NPH to demonstrate the risk of one additional hypoglycemic event in type 2 diabetes: Evidence from a long-term controlled trial. *Journal of Diabetes and its Complications* 2014;28:742-9.

32. Berard L, Cameron B, Woo V, 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, Hypoglycaemia and Patient Satisfaction. *Canadian Journal of Diabetes* 2015;39:296-301.

33. Farshchi A, Aghili R, Oskuee M, et al. Biphasic insulin Aspart 30 vs. NPH plus regular human insulin in type 2 diabetes patients; a cost-effectiveness study. *BMC endocrine disorders* 2016;16:35.

34. Home PD, Bolli GB, Mathieu C, et al. Modulation of insulin dose titration using a hypoglycaemia-sensitive algorithm: insulin glargine versus neutral protamine Hagedorn insulin in insulin-naive people with type 2 diabetes. *Diabetes, obesity & metabolism* 2015;17:15-22.

35. Moodie P. More from PHARMAC on long-acting insulin analogues: insulin glargine now funded. *The New Zealand Medical Journal* 2006;119:U2040.

36. Type 1 Diabetes in Adults: Diagnosis and Management. UK National Institute for Health and Care Excellence (NICE), 2015. at <https://www.nice.org.uk/guidance/ng17/chapter/1-Recommendations-insulin-therapy-2>.

37. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017;40:S64-S74.

38. Ogle GD, Kim H, Middlehurst AC, Silink M, Jenkins AJ. Financial costs for families of children with Type 1 diabetes in lower-income countries. *Diabetic medicine : a journal of the British Diabetic Association* 2016;33:820-6.

39. Lasalvia P, Barahona-Correa JE, Romero-Alvernia DM, et al. Pen Devices for Insulin Self-Administration Compared With Needle and Vial: Systematic Review of the Literature and Meta-Analysis. *Journal of Diabetes Science and Technology* 2016;10:959-66.

40. Moorman Spangler CM, Greck BD, Killian JH. Analysis of a Delivery Device Conversion for Insulin Aspart: Potential Clinical Impact in Veterans. *Clinical diabetes : a publication of the American Diabetes Association* 2016;34:92-6.

41. Ramadan WH, Khreis NA, Kabbara WK. Simplicity, safety, and acceptability of insulin pen use versus the conventional vial/syringe device in patients with type 1 and type 2 diabetes mellitus in Lebanon. *Patient preference and adherence* 2015;9:517-28.

42. Reynolds SL, Zhou S, Uribe C, Li Y. Impact of insulin delivery systems in elderly patients with type 2 diabetes. *American Journal of Pharmacy Benefits* 2015;7:222-31.

43. Slabaugh SL, Bouchard JR, Li Y, Baltz JC, Meah YA, Moretz DC. Characteristics Relating to Adherence and Persistence to Basal Insulin Regimens Among Elderly Insulin-Naive Patients with Type 2 Diabetes: Pre-Filled Pens versus Vials/Syringes. *Advances in therapy* 2015;32:1206-21.

44. Smallwood C, Lamarche D, Chevrier A. Examining Factors That Impact Inpatient Management of Diabetes and the Role of Insulin Pen Devices. *Canadian Journal of Diabetes* 2017;41:102-7.

45. Ogle GD, Middlehurst AC, Silink M. The IDF Life for a Child Program Index of diabetes care for children and youth. *Pediatric diabetes* 2016;17:374-84.

46. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ (Clinical research ed)* 2000;321:405-12.

47. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *The New England journal of medicine* 2008;359:1577-89.

48. Gerstein H.C. MME, Byington R.P., Goff D.C. Jr., Bigger J.T., Buse J.B., Cushman W.C., Genuth S., Ismail-Beigi F., Grimm R.H. Jr., Probstfield J.L., Simons-Morton D.G., Friedewald W.T.

Effects of Intensive Glucose Lowering in Type 2 Diabetes. *New England Journal of Medicine* 2008;358:2545-59.

49. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycaemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364-79.

50. Stratton IM, Cull, C. A., Adler, A. I., Matthews, D. R., Neil, H. A. W., Holman, R. R. Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75). *Diabetologia* 2006;49:1761-9.

51. Just a spoonful of medicine helps the sugar go down: Improving the management of type 2 diabetes: Alosa Health; 2016.

52. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycaemia in Type 2 Diabetes: A Patient-Centered Approach. Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) 2012;35:1364-79.

53. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2017 executive summary *Endocrine practice* : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2017;23:207-38.

54. Azoulay L, Suissa S. Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies. *Diabetes Care* 2017;40:706-14.

55. Riddle MC. More reasons to say goodbye to glyburide. *The Journal of Clinical Endocrinology and Metabolism* 2010;95:4867-70.

56. Riddle MC. Modern Sulfonylureas: Dangerous or Wrongly Accused? *Diabetes Care* 2017;40:629-31.

57. Heinemann L, Hompesch M. Biosimilar Insulins: Basic Considerations. *Journal of Diabetes Science and Technology* 2014;8:6-13.

58. Information on Biosimilars. U.S. Food and Drug Administration, 2017. (Accessed May 2, 2017, at [https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/.](https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/))

59. Hakim A, Ross JS. Obstacles to the Adoption of Biosimilars for Chronic Diseases. *Jama* 2017.

60. FDA approves Basaglar, the first “follow-on” insulin glargine product to treat diabetes. 2015. at [https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm477734.htm.](https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm477734.htm))

61. Implementation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry. 2016. (Accessed August 12, 2017, at [https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf.](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf))

62. Llano A FM, McKay G. Biosimilar insulin: the current landscape. *Practical Diabetes* 2017;34:51-4.

63. Evidence Summary: Diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar). National Institute for Health and Care Excellence (NICE), 2015. at [https://www.nice.org.uk/guidance/esnm64/resources/diabetes-mellitus-type-1-and-type-2-insulin-glargine-biosimilar-abasaglar-1502681105222341.](https://www.nice.org.uk/guidance/esnm64/resources/diabetes-mellitus-type-1-and-type-2-insulin-glargine-biosimilar-abasaglar-1502681105222341))

64. GaBI Online. Insulin biosimilar meets primary endpoint in phase III studies. (Accessed 5/8/2017, at [http://www.gabionline.net/Biosimilars/Research/Insulin-biosimilar-meets-primary-endpoint-in-phase-III-studies.](http://www.gabionline.net/Biosimilars/Research/Insulin-biosimilar-meets-primary-endpoint-in-phase-III-studies))

65. Clinical Trials.gov. Comparison of SAR342434 to Humalog as the rapid acting insulin in adult patients with type 1 diabetes mellitus also using insulin glargine (SORELLA 1). (Accessed 5/8/2017, at <https://clinicaltrials.gov/ct2/show/NCT02273180>.)
66. Biocon's press release. 2016. at http://www.biocon.com/biocon_press_releases_260416.asp.)
67. Biosimilars in the EU - Information guide for healthcare professionals. (Accessed August 12, 2017, at http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf.)
68. Giezen, T. Interchangeability of Biosimilars in the European Union. Health Action International, 2017
69. Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration, 2017. at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.)
70. Sarpatwari A, Avorn J, Kesselheim AS. Progress and Hurdles for Follow-on Biologics. *The New England journal of medicine* 2015;372:2380-2.
71. Dowlat HA, Kuhlmann MK, Khatami H, Ampudia-Blasco FJ. Interchangeability among reference insulin analogues and their biosimilars: regulatory framework, study design and clinical implications. *Diabetes, obesity & metabolism* 2016;18:737-46.
72. Luo J, Kesselheim AS. Insulin patents and market exclusivities: unresolved issues – Authors' reply. *The Lancet Diabetes & Endocrinology* 2016;4:98-9.
73. Carter AW. FDA-approved biosimilar insulin: good enough for critical care, adulterated, or counterfeit? How can we tell? *Journal of diabetes science and technology* 2014;8:1052-4.
74. Basaglar Prescribing Information U.S. Food and Drug Administration, 2015. at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205692lbl.pdf.)