Comments on “Comparative Efficacy and Safety of Intermediate-acting, Long-acting and Biosimilar insulins for Type 1 Diabetes Mellitus: A Systematic Review and Network Meta-Analysis” by Tricco et al (Dec 2018)

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1. **Background**

Tricco et al (1) prepared a comprehensive, systematic review on a comparison between intermediate-acting insulins and (ultra)long acting insulins with focus on effectiveness (HbA1c and fasting plasma glucose) and safety (mortality, vascular complications, hypoglycemia, weight changes and quality of life). The review focuses on Type 1 diabetes in older children (> 16 years) and adults.

The authors conclude that “for basal insulin classes, our results suggest that long-acting insulin was superior to intermediate-acting insulin across the A1c, fasting plasma glucose, weight change, major or serious hypoglycemic, and nocturnal hypoglycemic outcomes. As well, ultra-long-acting insulin was superior to intermediate-acting insulin across the fasting blood glucose and nocturnal hypoglycemic episodes outcomes” (P26).

Practically, the insulins that are considered are animal/human intermediate-acting insulins (NPH and lente) and (ultra)long-acting analogues of insulin (glargine, detemir and degludec).

2. **Objectives**

The objective of this commentary is to discuss the results of the review in the context of special populations (resource-limited settings and children).

3. **Characteristics of the insulins included in the review**

The differences between the various types of human and analogue insulins (intermediate-acting, long-acting and ultralong-acting) considered in the review are highlighted below. All these insulins are used as basal insulins, meaning that they aim at providing the basal insulin concentrations that all non-diabetic subjects continuously secrete even when sick or fasting.

**NPH insulin** (ATC code: A10AC) is made by mixing regular insulin and protamine in exact proportions with zinc and phenol such that a neutral-pH is maintained and crystals form. There were human- and pig-insulin based versions although to my knowledge it is presently only available as a human insulin. Its duration of action ranges from 12-16 hours, making it a twice-daily basal insulin. Importantly, it has a clear peak of action 5-7 hours after injection (see figure), which explains why it is associated with hypoglycemia, its major side-effect (2).
Lente insulin was similar to NPH but differed in size of crystals, content of protamine and zinc, and often in species composition, since lente always contained beef insulin. To my knowledge, insulin “lente” is not marketed anymore and the studies thus reflect a historical comparison.

**Insulin glargine** (ATC code: A10AE04) is a long-acting insulin with a duration of action of 18 to 26 hours, making it a once-daily basal insulin. It is an analogue of insulin that differs from human insulin by replacing asparagine with glycine in position 21 of the A-chain and by a carboxy-terminal extension of B-chain by 2 arginine residues (3).

**Insulin detemir** (ATC code: A10AE05) is also an insulin analogue that has a similar duration of action (although clinically perceived as slightly shorter (4)) of 18-26 hours. As a consequence, it is used as a once daily or a twice daily basal insulin. The aminoacid sequence is identical to human insulin but a fatty acid (myristic acid) is bound to the lysine amino acid at position B29, allowing it to bind to albumin (5).

**Insulin degludec** (ATC code: A10AE06) is an ultralong-acting basal insulin analogue. It has a duration of action that lasts up to 42 hours. Insulin degludec has one single amino acid deleted in comparison to human insulin and is conjugated to hexadecanedioic acid via gamma-L-glutamyl spacer at the amino acid lysine at position B29. Degludec is considered as a biosimilar by the authors but is in reality the first analogue insulin in its category. I do not believe that it should be considered as a biosimilar, despite the confusion and variable definitions of what “biosimilar” means (6, 7).

Practically, there are two clinically relevant advantages of using (ultra)long-acting analogues of insulin compared to NPH:
- First, the existence of a significant peak of insulin with NPH, contrasting with a virtual absence of peak for long- and ultralong-acting insulins. As discussed below, this has major implications for meal organisation and for prevention and treatment of hypoglycemias in particular in resource-limited settings {, 2018 #48

**Figure 1:** Comparison of the duration of action and profile for several types of insulins, including NPH, detemir and glargine.
(from: http://tmedweb.tulane.edu/pharmwiki/doku.php/insulin_regimens)

- A lower day-to-day variability in the concentrations of basal insulin achieved with glargine/detemir/degludec compared to NPH (8).

**Figure 2:** Comparison of the day to day variability of basal insulin concentrations following NPH, glargine and detemir administration

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4. **Practical use of basal insulins**

Many different regimens that use subcutaneous injections of insulin are proposed for Type 1 diabetes. All include the use of a basal insulin. Two classical regimens are described below to facilitate the discussion on the relevance of basal insulin analogues to the treatment of Type 1 diabetes in low resource settings.

When NPH is used, a typical regimen is the “2 injection system” (a mixture of NPH and rapid-acting insulin before breakfast and before supper). Breakfast and supper are covered by the rapid acting insulin while lunch is covered by the morning injection of NPH. In addition, snacks are usually needed in particular before bedtime because of the peak of NPH. It requires less injections of insulin but is less flexible. Lunch and often snacks cannot be skipped.

When a long acting analogue is used, a typical regimen is the “multiple daily injection system” or “basal-bolus” (one injection of glargine/detemir or 2 injections of detemir per day to cover the basal needs and one injection of rapid acting insulin to cover each meal). It provides greater flexibility in terms of timing and number of meals eaten (“skip a meal, skip an injection”) but requires more injections. The risk of hypoglycemia is also lower than with the “2 injections system”.

**Figure 3:** Examples of insulin regimens in Type 1 diabetes (9)
5. **Basal insulins and the WHO Model List of Essential Medicines (EML)**

The only type of insulin that is included in the most recent version of the EMLs and that can be used as a basal insulin is:

WHO Model List of Essential Medicines 20th List (March 2017, Amended August 2017)
*Intermediate-acting insulin (Injection: 40 IU/mL in 10- mL vial; 100 IU/mL in 10- mL vial (as compound insulin zinc suspension or isophane insulin) (Section 18.5)*

WHO Model List of Essential Medicines for Children, 6th List (March 2017, Amended August 2017)
*Intermediate-acting insulin. Injection: 100 IU/mL in 10-mL vial (as compound insulin zinc suspension or isophane insulin) (Section 18.5).*

This corresponds primarily to NPH insulin. To the best of my knowledge, there is no more intermediate-acting insulin that is available at a concentration of 40 U/ml (Adult EML).

It is important to recognize that the vast majority of patients affected by diabetes around the world suffer from Type 2 diabetes, while this review focuses on Type 1 diabetes. The EMLs do not presently distinguish between the use of insulins in Type 1 and Type 2 diabetes.

6. **Relevance of the review by Tricco et al to special populations (low-resource settings and pediatric age-group)**

   a. **Low resource-settings**
   
   First, please note that the concept of differences in the quality of diabetes care is not only relevant to low-income countries, but also to low-income settings in many high-income countries.

   Second, management of Type 1 diabetes is complex and insulin administration is only one aspect of the care. The figure below, chosen among many, illustrates the need for comprehensive care. Most of the data that underlies clinical models for the management of Type 1 diabetes come from high-resource settings and it is known that comprehensive care is suboptimal in many low-resource settings (10).
   
   Figure 4: Components of organised diabetes care
   (From: http://advanceddiabetescentre.com/organised-diabetes-care/)
Third, the pace of the transition from human insulin to analogues of insulins has been much slower in low- and middle-income countries compared to high-income countries (Figure 5) and as such there is little published experience on long-acting-analogues of insulin in low-income countries.

**Figure 5:** Transition from human to analogue insulin by insulin type and country-income groupings (1999–2009) (11)

Several topics that are relevant to the use of basal insulin in low-resource settings need to be addressed, recognizing that the expert opinion presented below is not consistently backed by evidence:

- Availability of regular meals
Published studies largely assume/require that patients have access to regular meals.

When NPH is used, 3 meals + 3 snacks are usually recommended. In addition, short-acting insulin is given to cover breakfast and dinner. Indeed, administration of NPH in the morning (which peaks 4-6 hours after injection) provides a peak of insulin at lunch time but also implies that a meal needs to be taken at lunch time. Administration of NPH at dinner time requires a bedtime snack, whether or not one is hungry. Failure to do so puts the patient at high risk for hypoglycemia, in particular at midday or during the night. In contrast, (ultra)long acting analogues of insulin only provide a basal concentration of insulin and, as a consequence, allow for flexibility in the number and timing of meals.

The use of analogues of insulin such as glargine, detemir or degludec is clearly associated with a decrease in the number of severity of daytime and night time hypoglycemia (1). Thus, in settings where food security is not reliable, (ultra)long acting analogues of insulin have an additional advantage over NPH.

- Treatment of severe hypoglycemia

Administration of glucagon in case of severe hypoglycemia is a key aspect of diabetes education. However, despite being included in the EML and EMLc (Section 18.5), availability of glucagon is very low in many low-resource settings (12). This is due to one or more factors: unavailability/absence of registration of glucagon in the country, high cost of glucagon and lack of coverage by the health system, relatively short shelf-life and poor education of the patient (13).

Thus, the decrease of severe and nocturnal hypoglycemia associated with the use of (ultra)long-acting analogues of insulin is even more important in low-compared to high-resource settings.

- Prevention of long-term complications (HbA1c)

The quarterly measure of glycosylated hemoglobin (HbA1c) is widely accepted as a marker of diabetes control and is included in most, if not all, adult and pediatric international guidelines (14, 15). A lower HbA1c is consistently associated with a decrease in short- and long-term complications of diabetes.

In many of the studies reviewed by Tricco et al (1), the mean baseline HbA1c of the participants was below 8%, reflecting acceptable or good diabetes control (See P 53-54 of the review). The results of the review show that in these patients, long-acting analogues of insulin are associated with a small but statistically significantly lower HbA1c and fasting glucose levels compared to NPH. However, in low-resource settings, and in particular in rural areas of low-resource countries where overall diabetes care is poor, the average HbA1c of the patients is expected to be much higher. Whether the results reported in the review can be extended to low-income settings is unknown. Intuitively, it is felt that achieving a stable level of basal insulin (provided by once daily long-acting insulins) would be of even greater benefit in patients with poor diabetes care by decreasing day to day variability of insulin concentrations and by making compliance better (once daily administration of long acting insulin compared to twice daily administration of NPH) but this remains to be demonstrated.
- **Risk of diabetes keto acidosis**

Considering the longer duration of action of glargine, detemir and degludec, it was hypothesized that long-acting analogues of insulin could help decrease the incidence of diabetes ketoacidosis. This was not found to be the case with detemir and glargine (compared to NPH) in children (16). In contrast, in children, administration of degludec (compared to detemir 1 or 2/day) was associated with a decrease in the number of episodes of hyperglycemia with ketosis (17). I could not find similar data in adults. However, it was shown in adults that, thanks to its longer duration of action, degludec could be injected in a fixed schedule (with minimum 8 and maximum 40 hours between doses) without loss of safety or efficacy compared to degludec or glargine once a day at the same time (18). This added flexibility of degludec may be particularly relevant to populations less able to follow a regular injection schedule.

**b. Pediatric age group**

The EMLc includes children from 0-12 years. The long-acting analogues of insulin have been investigated extensively in the pediatric age-group in low and high resource settings and were found to be safe and effective (16, 17, 19-21). They are approved in children from age 2 years (glargine and detemir) or one year (degludec) (22).

Long-acting analogues have also been successfully used in infants and has shown positive effects on glucose control and on hypoglycemia, However, the evidence is based on case reports (23, 24)

**c. Conclusions**

The WHO EMLs for adults and for children presently only include NPH as a basal insulin. Although data specific to low-income settings and in particular to low-income countries are lacking, (ultra)long acting insulins such as glargine, detemir and degludec, compared to NPH, are expected to be of greater benefit for patients with Type 1 diabetes in settings where food security is poor and where glucagon is not available. Whether these insulin analogues will also be of greater benefit in poorly-controlled compared to well-controlled patients remains to be demonstrated. (Ultra)long-acting of insulin have also been shown to be safe and effective in infants and children.

I personally recommend to replace intermediate-acting insulin (NPH) with long-acting analogues of insulins (as a class of medicines) in the core list of EML for both adults and children for the management of Type 1 diabetes. This would need to be followed by strong advocacy in order to make analogue insulins available and affordable in low- and middle-income countries (LMICs) where recent data show that both availability and affordability remain very poor (11, 25, 26). NPH remains an important second choice when (ultra) long-acting analogues are not available.
References