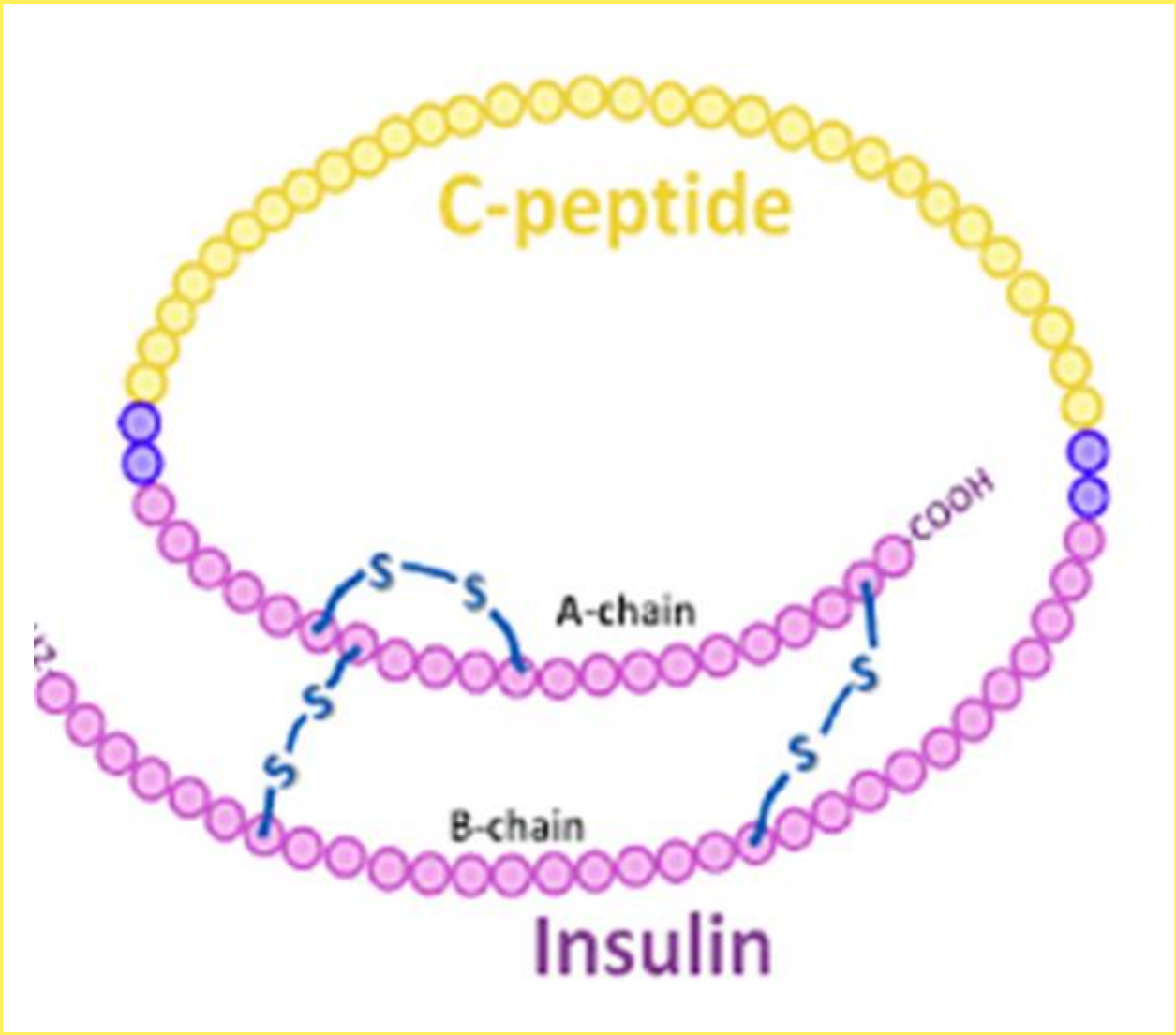

Insulin Therapy

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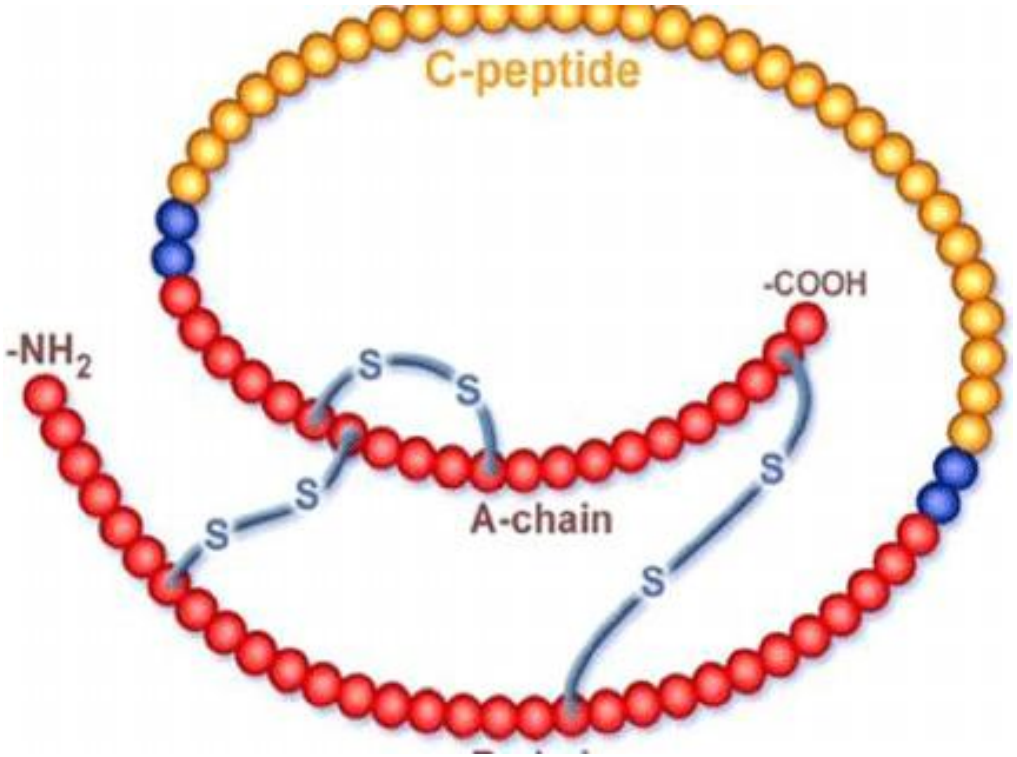
King Abdulaziz University Hospital
Website: http://aagha.kau.edu.sa

Overview

- Human insulin.
- Discovery of insulin.
- Revolution of insulin industry.
- Various insulin types.
- Factors affecting insulin type.
- How to calculate correcting insulin dose.
- Conclusion.

Insulin

- composed of 51 amino acids arranged in two chains, α chain (21 amino acids) and B chain (30 amino acids) that are linked by two disulfide bonds.
- Proinsulin, single-chain 86 amino acid peptide, is cleaved into insulin and C-peptide (a connecting peptide); both are secreted in equimolar portions from the beta cell upon stimulation from glucose and other insulin secretagogues.
- While C-peptide has no known physiologic function, it can be measured to provide an estimate of endogenous insulin secretion.

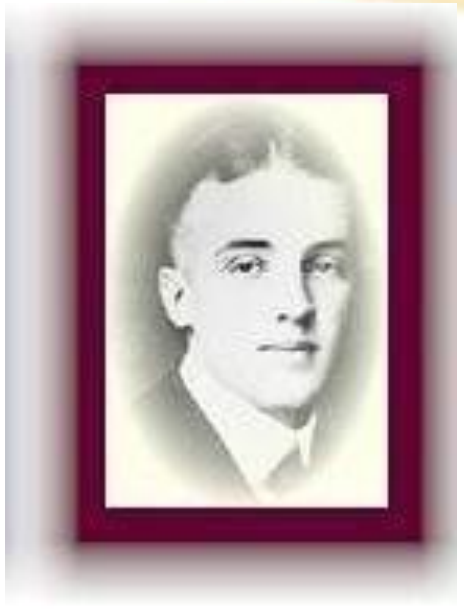


- In 1922, professor Banting & co-worker, were the first to demonstrate a physiologic response to injected animal insulin in a patient with type 1 diabetes.
- Since the introduction of insulin analogs in 1996, insulin therapy options for type 1 and type 2 diabetics have expanded.
- Insulin therapies are now able to more closely mimic physiologic insulin secretion and thus achieve better glycaemic control in patients with diabetes.

Discovery of Insulin

1921

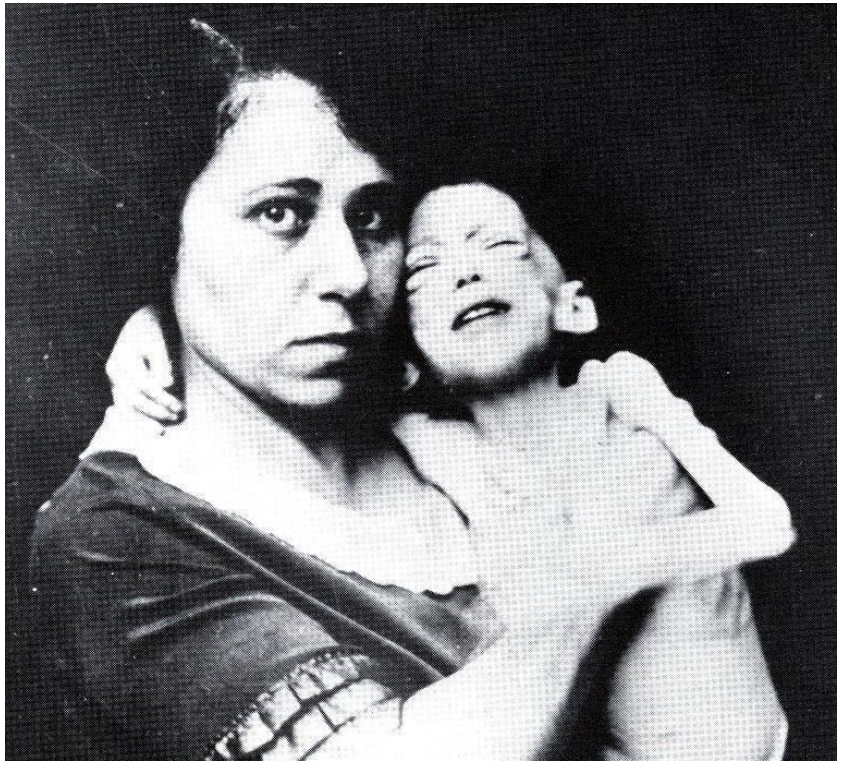
Banting



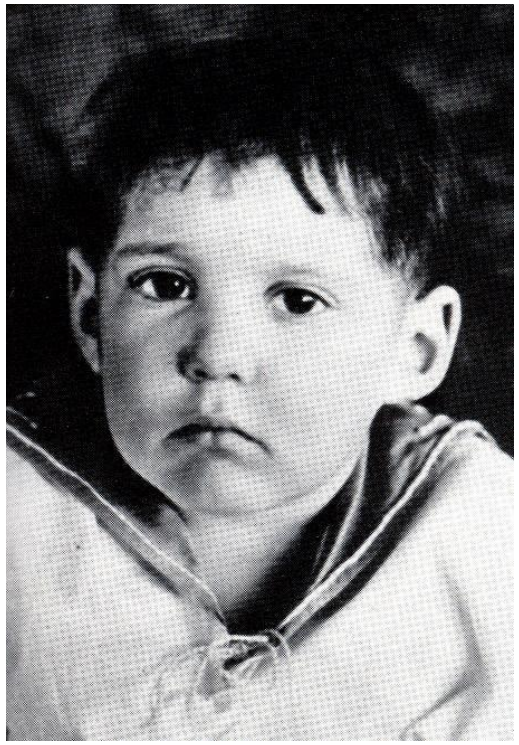
Best

Insulin was the first discovered (late 1920's) which won the doctor and medical student who discovered it the Nobel Prize (Banting and Best)

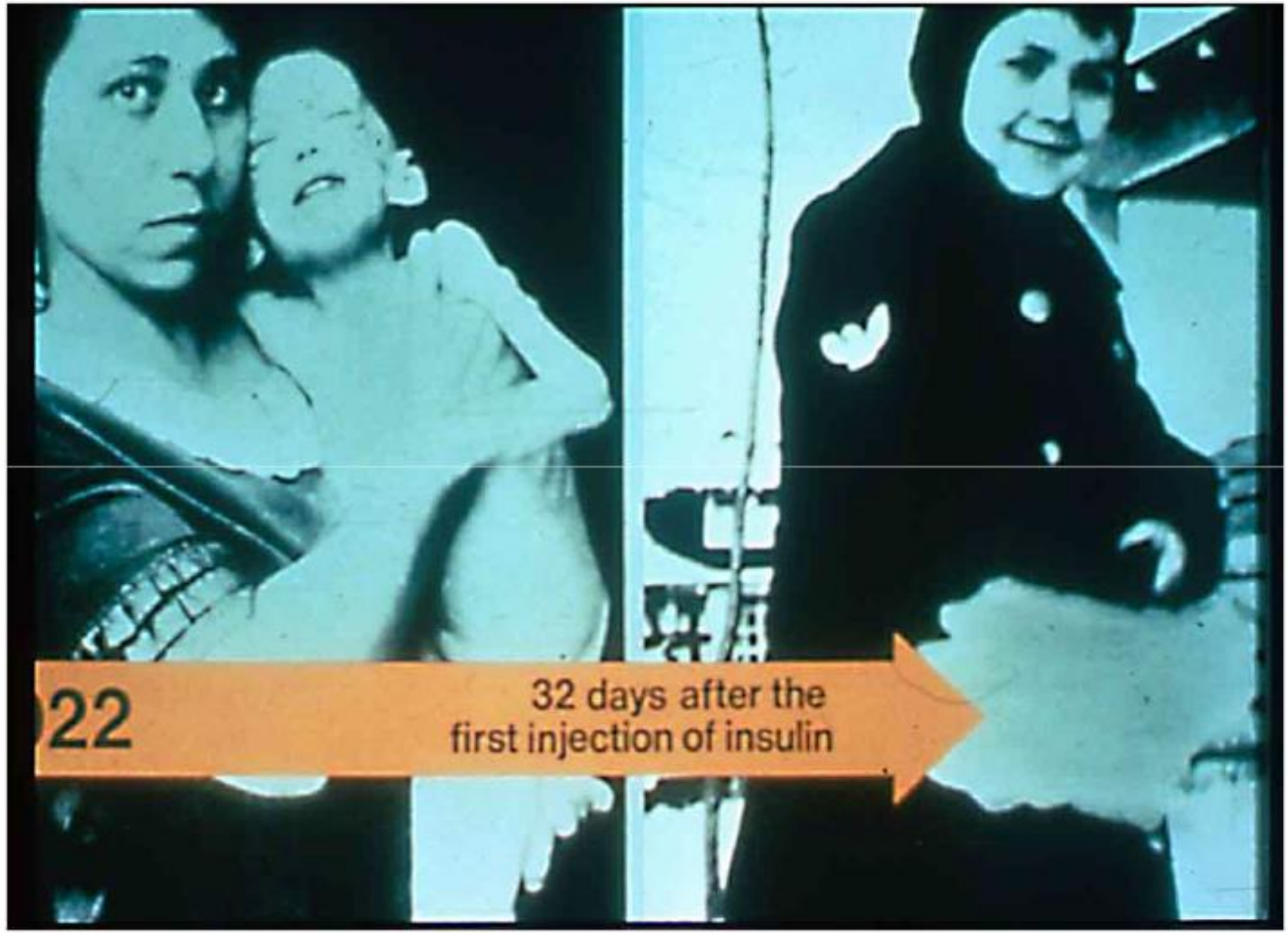
The Miracle of Insulin



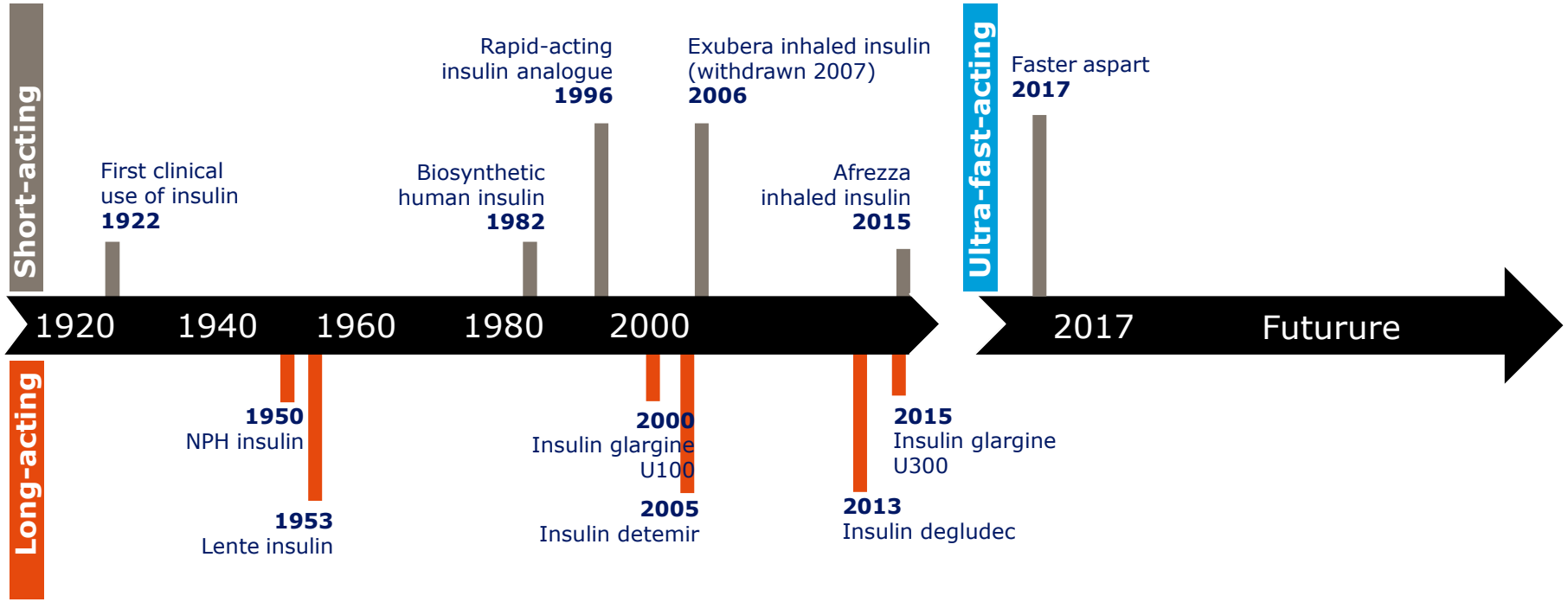
Patient J.L., December 1922 ,15



February 15, 1923


22
32 days after the
first injection of insulin

Evolution of insulin therapy since 1922

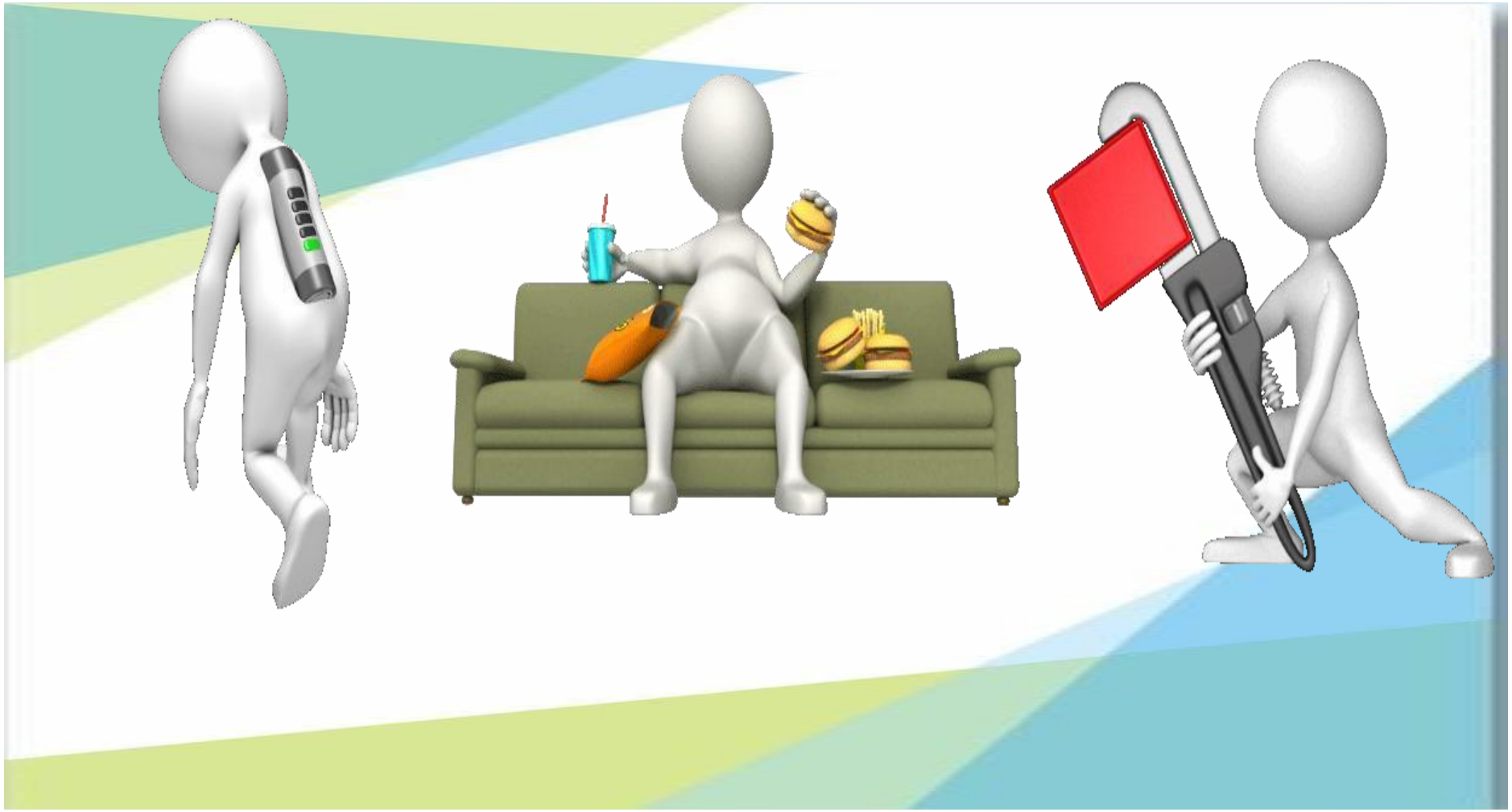


Adapted from Cahn *et al. Lancet Diabetes Endocrinol* 2015;3:638–52; Eli Lilly. Patent application, 12 November 2015; Eli Lilly. Press release, 4 December 2015; Novo Nordisk. Capital Markets Day R&D update, 19 November 2015

Faster aspart, fast-acting insulin aspart; NPH, neutral protamine Hagedorn

The most important fact is Everyone has different needs!

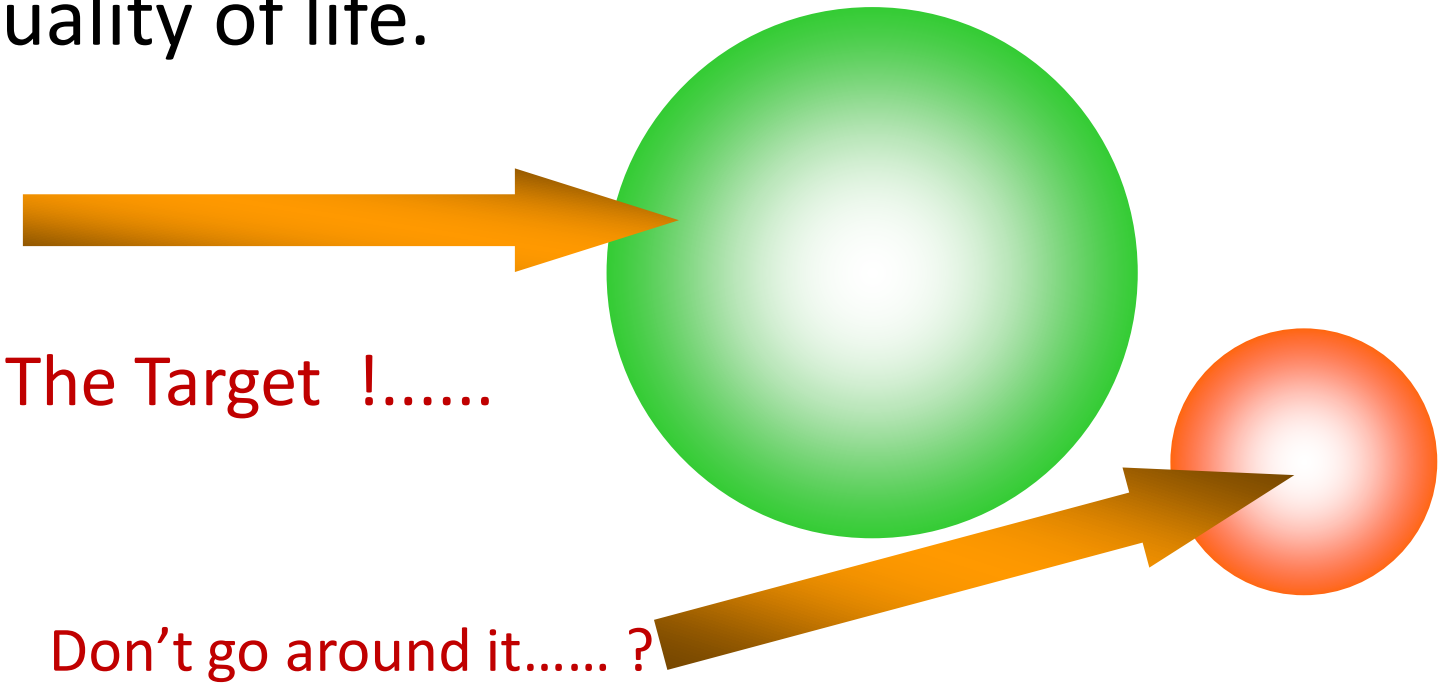
Managing pediatric patients with type 1 DM is challenging!!



Barriers to the use insulin in children

Goals of insulin therapy

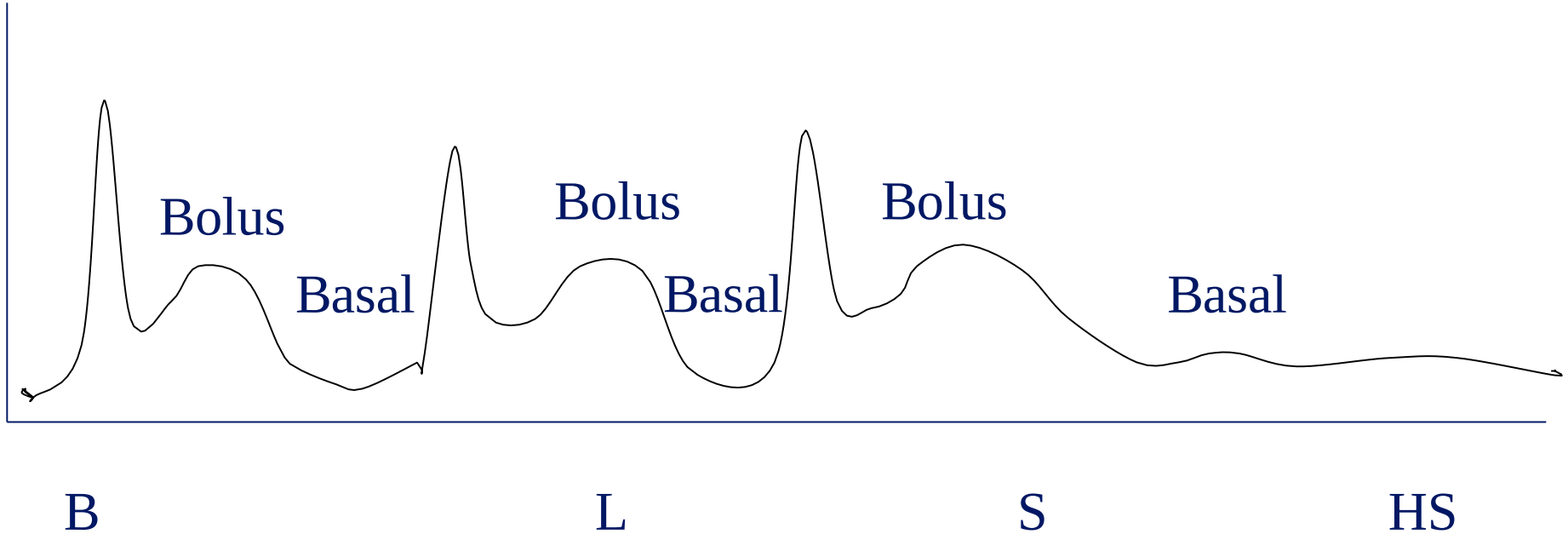
- Maintain near-normal glycaemia.
- Avoid short-term crisis.
- Minimize long-term complications.
- Improve quality of life.



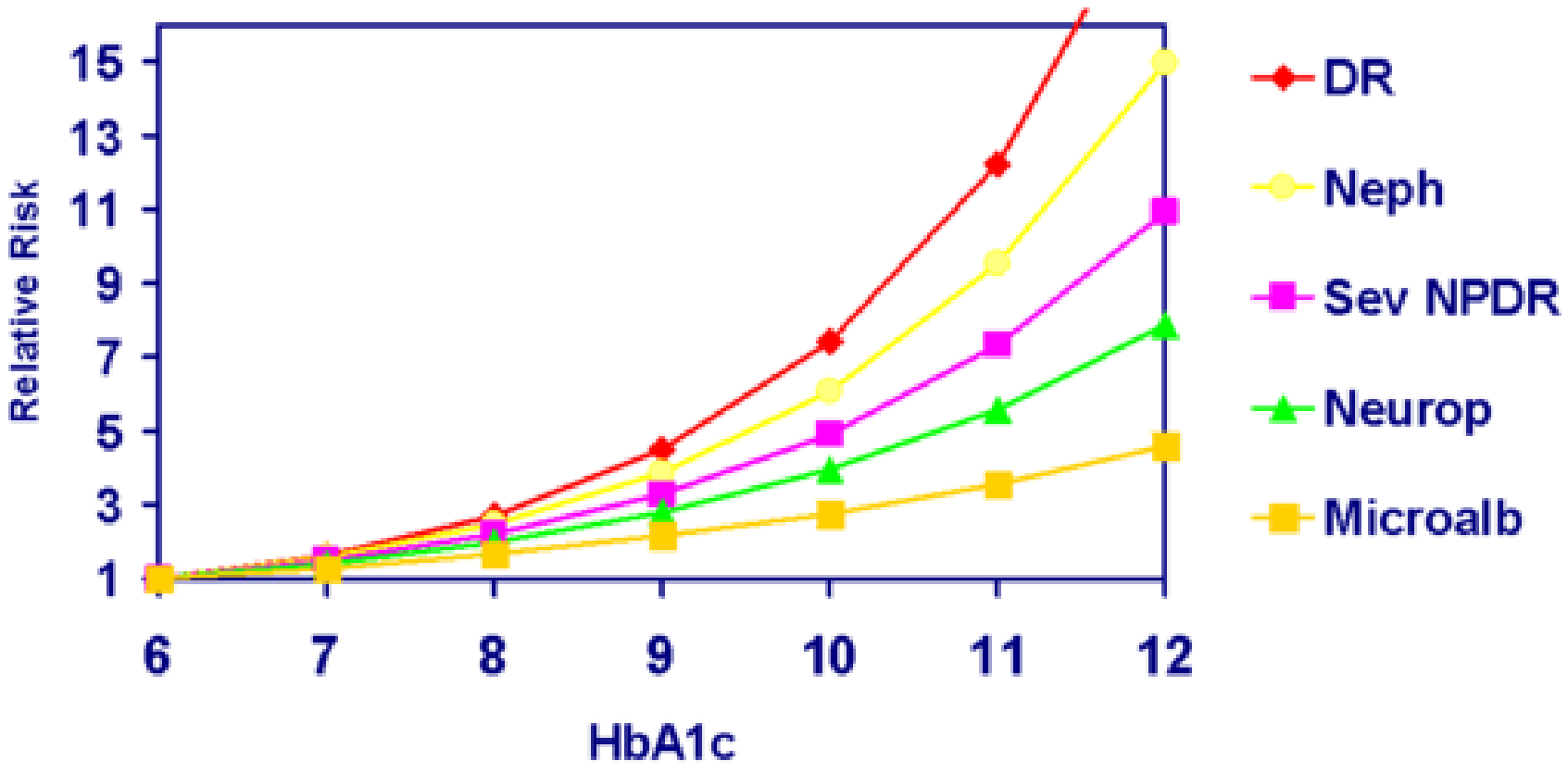
Physiologic Insulin Replacement

- A functioning pancreas releases insulin continuously, to supply a basal amount to suppress hepatic glucose output and prevent ketogenesis between meals and overnight and releases a bolus of insulin prandially to promote glucose utilization after eating.
- Replacing insulin in a manner that attempts to mimic physiologic insulin release is commonly referred to as basal/bolus insulin therapy.
- Physiologic replacement requires multiple daily injections (3 or more) or use of an insulin pump.
- Basal insulin requirements are approximately 50% of the total daily amount.
- Prandial insulin is 50-60% of the total daily insulin requirement administered before meals.
- Providing basal-bolus insulin regimens allows patients to have flexibility in their mealtimes and achieve better glycaemic control.

Basal – bolus insulin therapy



DCCT: Relative Risk of Progression of Diabetic Complications by Mean HbA1c

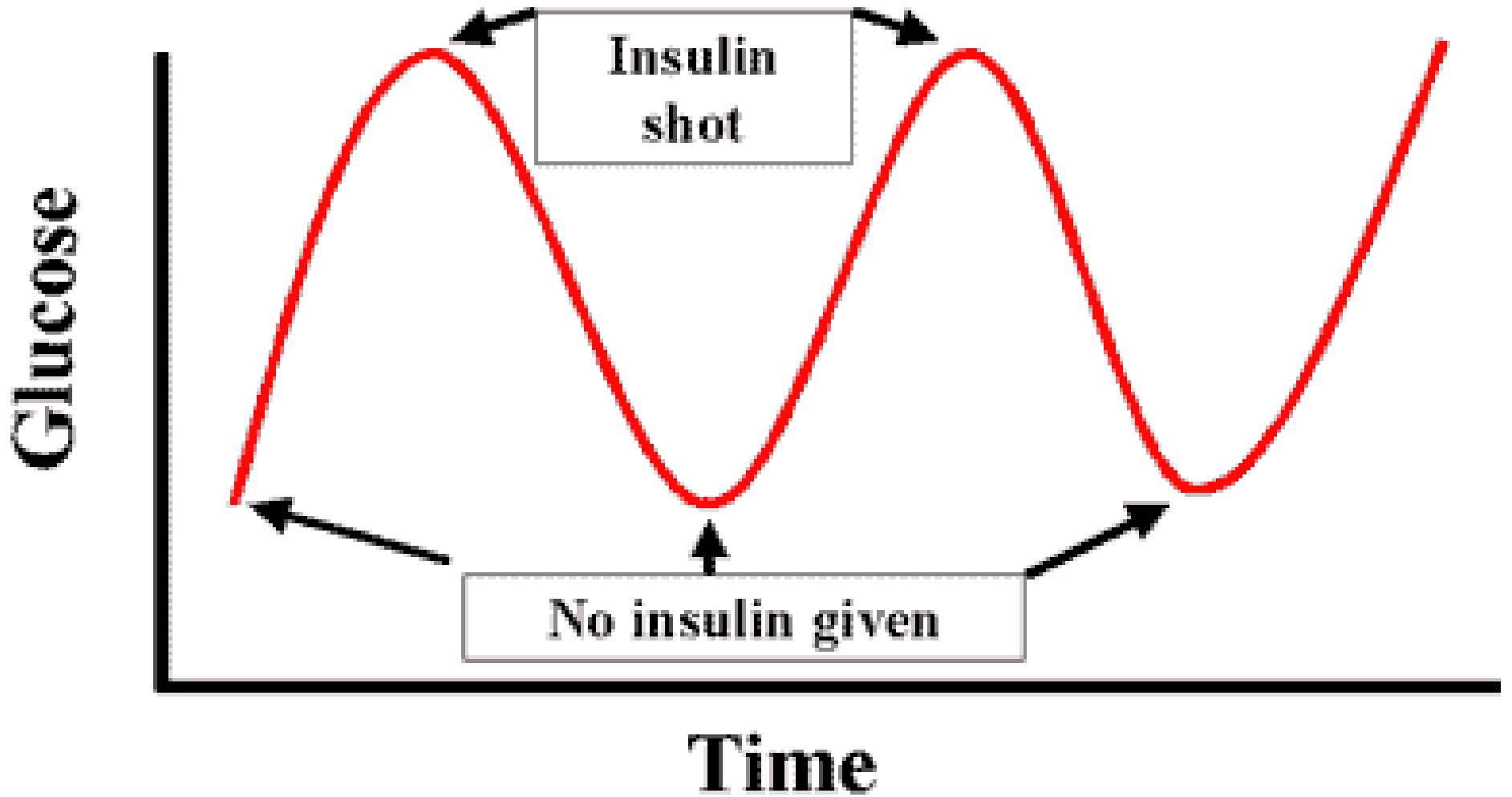


Skyler JS: Endocrin Metab Clin N Am 1996; 25:243-254

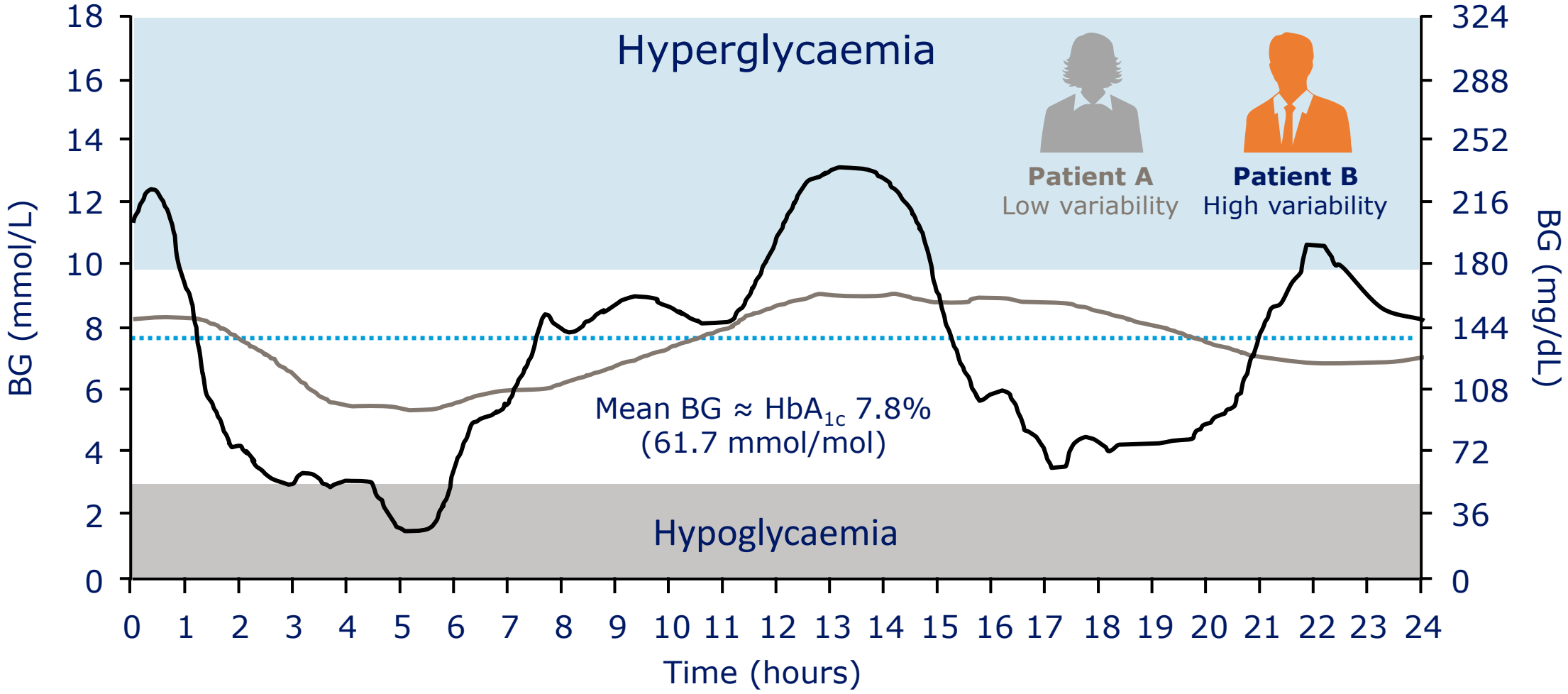
Glycemic control

- HbA1C should be measured in every 3-month intervals to assess their overall glycemic control.
- An A1C target of 7.5% should be considered in children and adolescents with type 1 diabetes.
- With increasing use of CGM devices, outcomes other than A1C, such as “time with glucose in target range” and frequency of hypoglycemia/ hyperglycemia” should be considered in the overall assessment of glycemic control.

Roller Coaster Effect of Insulin Sliding Scale

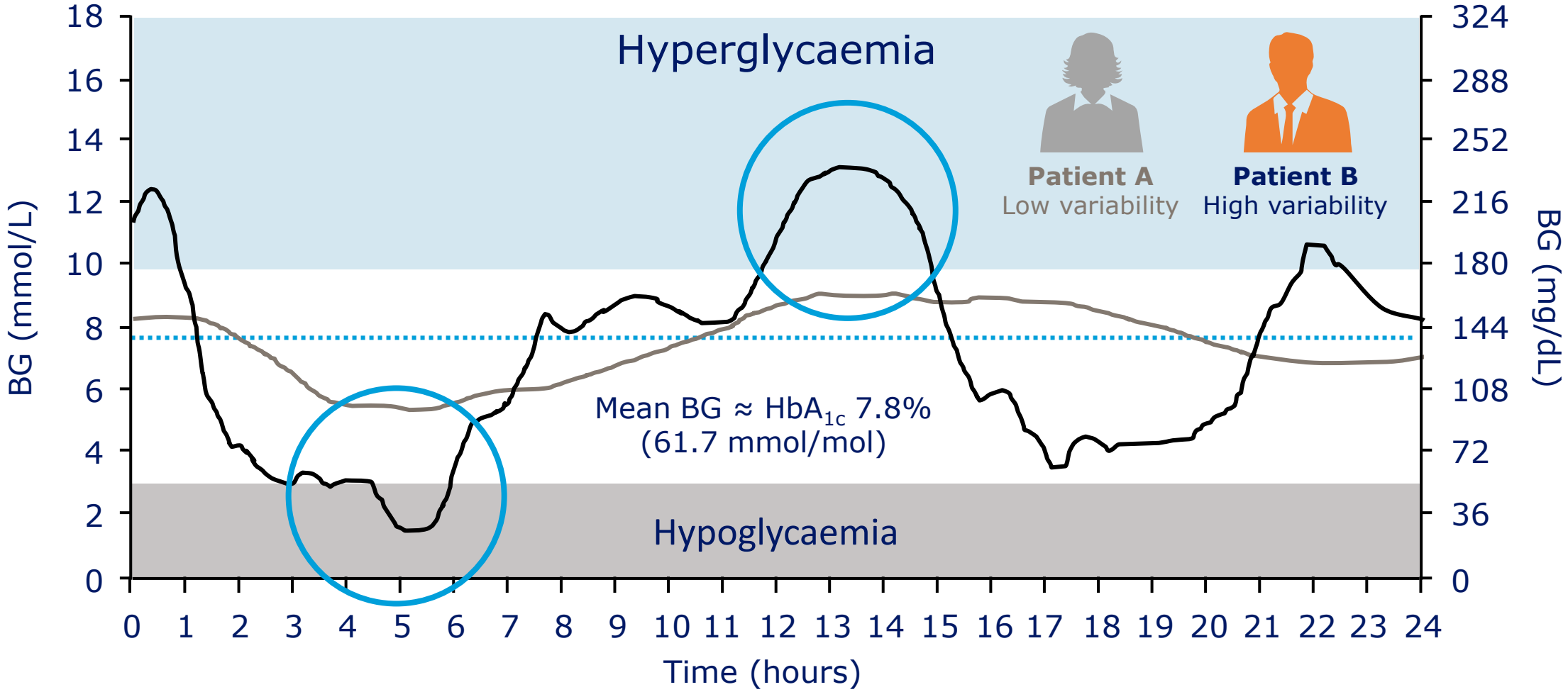


Glycaemic control: variability



BG, blood glucose; HbA_{1c}, glycated haemoglobin.
Image adapted from Penckofer S et al. *Diabetes Techno Ther* 2012;14:303–10; Vora J & Heise T. *Diabetes Obes Metab* 2013;15:701–12.

Glycaemic control: similar HbA_{1c}, different profile



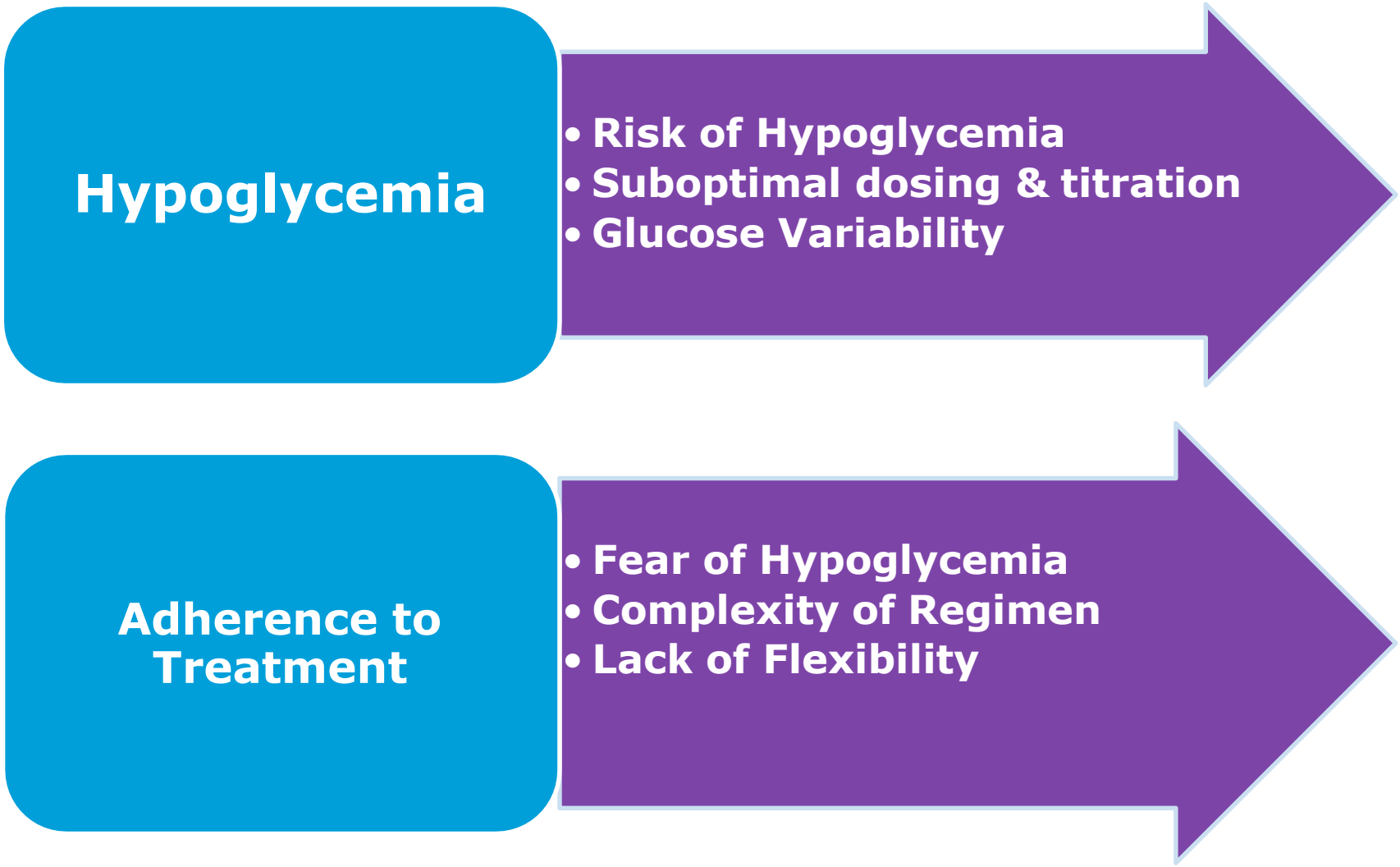
BG, blood glucose; HbA_{1c}, glycated haemoglobin.
Image adapted from Penckofer S et al. *Diabetes Techno Ther* 2012;14:303–10; Vora J & Heise T. *Diabetes Obes Metab* 2013;15:701–12.

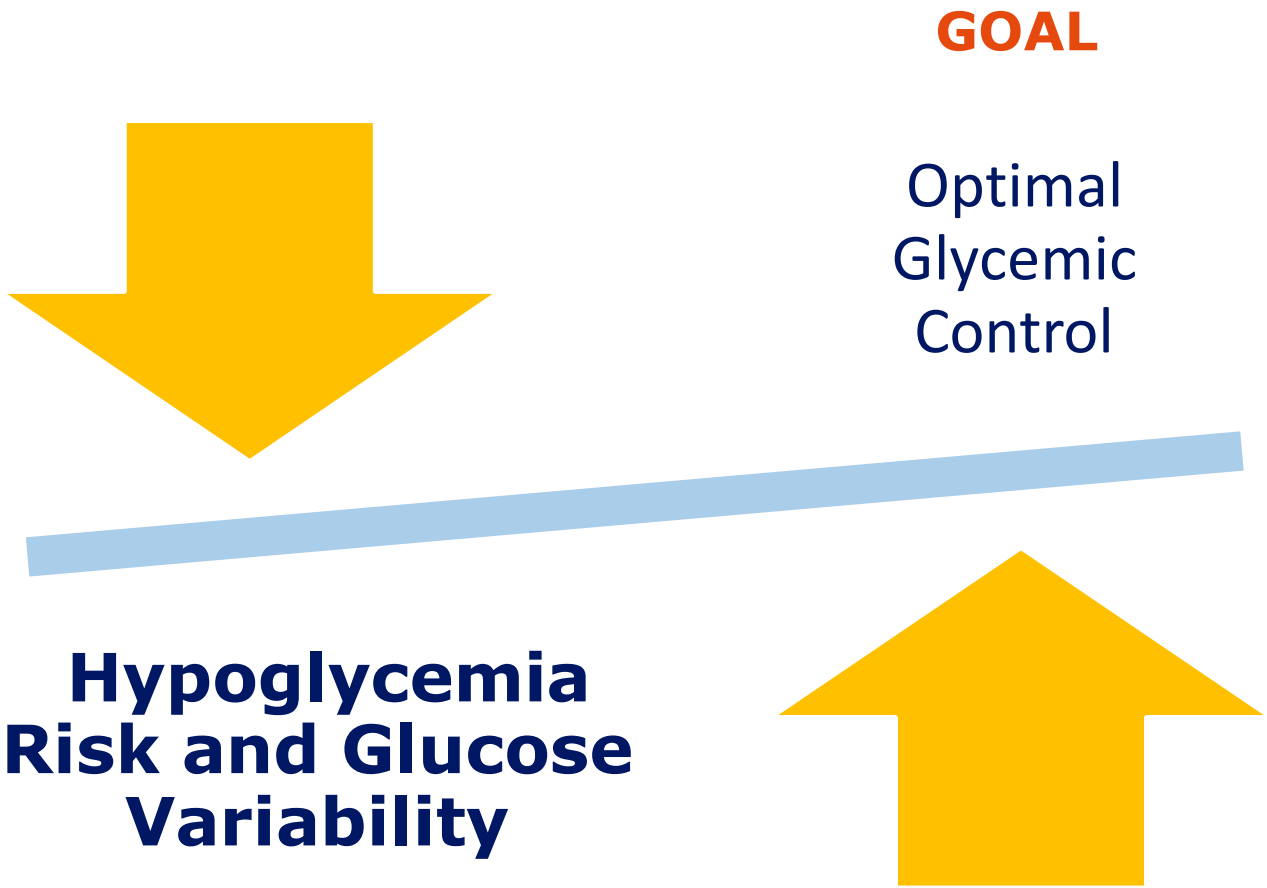
Factors Affecting Insulin Absorption

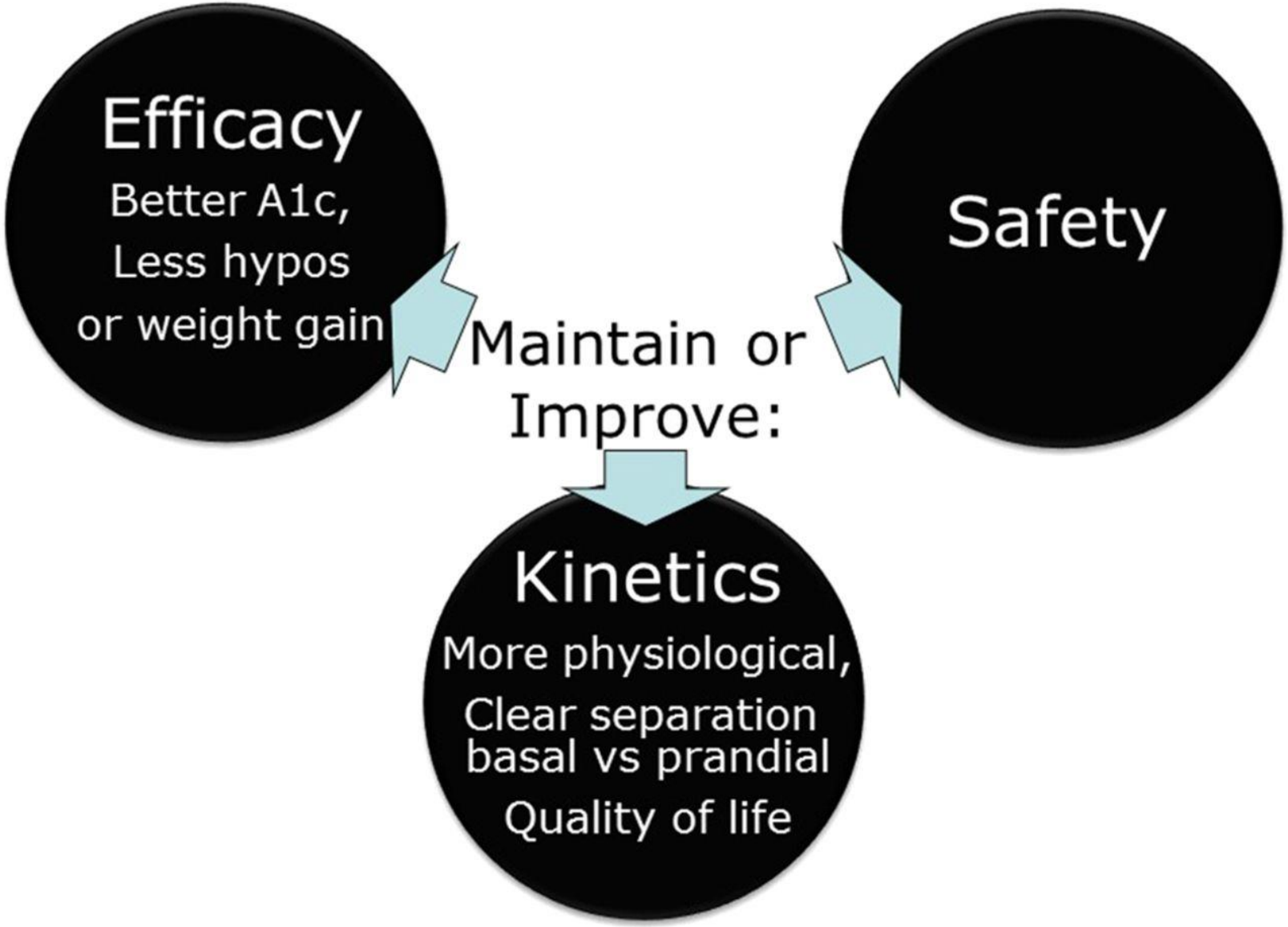
Factors	
Exercise of injected area	Strenuous exercise of a limb within 1 hour of injection will speed insulin absorption. Clinically significant for regular insulin analogs.
Local massage	Vigorously rubbing or massaging the injection site will speed absorption.
Temperature	Heat can increase absorption rate, including use of a sauna, shower, or hot bath soon after injection. Cold has the opposite effect.
Site of injection	Insulin is absorbed faster from the abdomen. Less clinically relevant with rapid-acting insulins, insulin glargine, and insulin detemir.
Lipohypertrophy	Injection into hypertrophied areas delays insulin absorption.
Jet injectors	Increase absorption rate.
Insulin mixtures	Absorption rates are unpredictable when suspension insulins are not mixed adequately (i.e., they need to be resuspended).
Insulin dose	Larger doses delay insulin action and prolong duration
Physical status (soluble vs. suspension)	Suspension insulins must be sufficiently resuspended prior to injection to reduce variability.

Various insulin preparations

Barriers to achieving optimal glycemic control



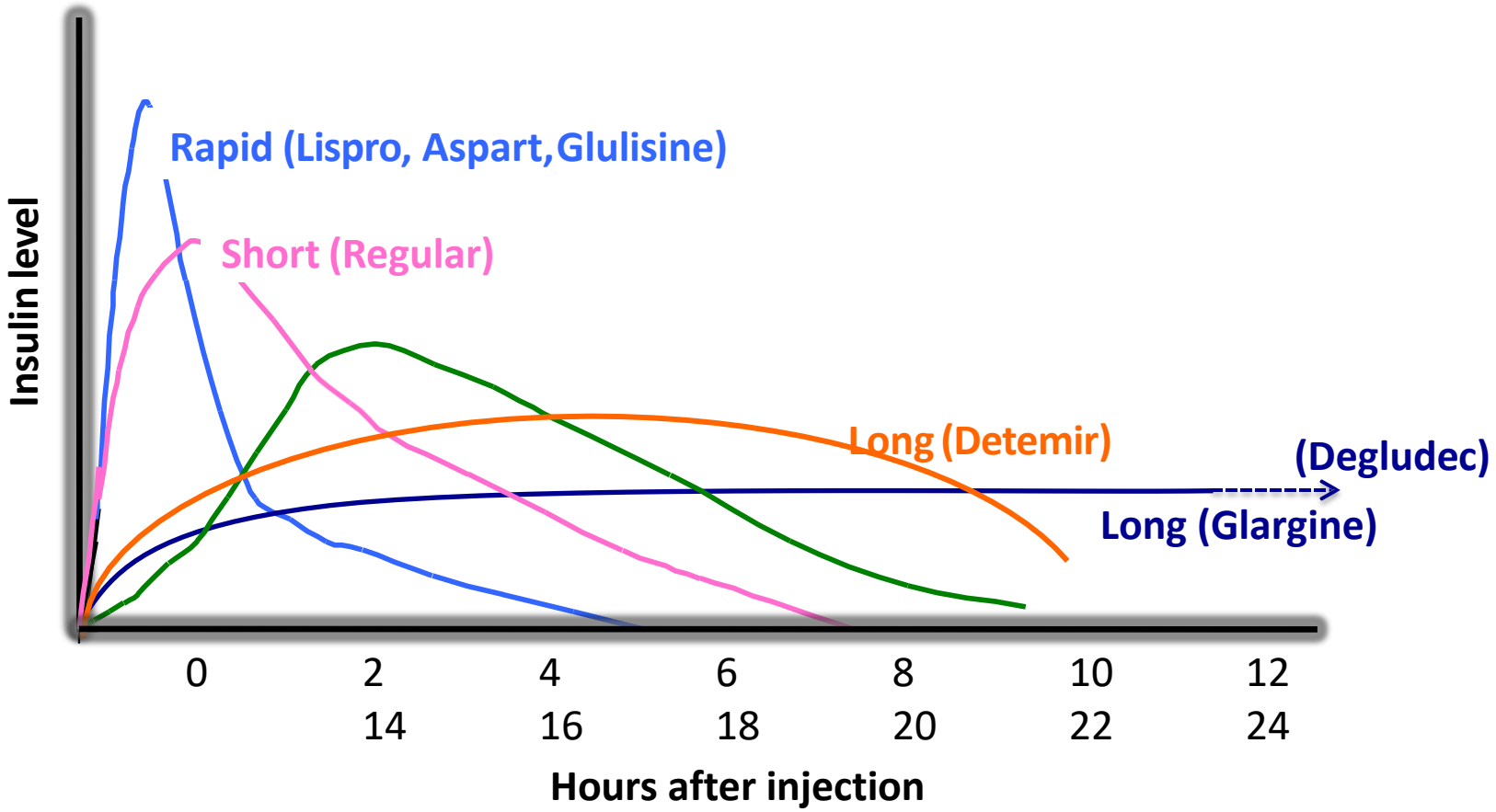

GOAL
Optimal Glycemic Control
Hypoglycemia Risk and Glucose Variability
BARRIERS


Efficacy
Better A1c,
Less hypos
or weight gain
Safety
Maintain or
Improve:
Kinetics
More physiological,
Clear separation
basal vs prandial
Quality of life

Types of insulins

- There are 5 main groups of insulins:
  - Ultra fast - acting insulin.
  - Rapid - acting insulin.
  - Short - acting insulin.
  - Intermediate - acting insulin.
  - Long - acting insulin.
  - Ultra- long acting insulin.

Various insulin preparations available so far as basal – bolus insulin therapy



Various types of insulin preparations

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid-acting analogs			
Aspart (Novolog)	0.25–0.5	1–3	3–5
Lispro (Humalog)	0.25–0.5	1–3	3–5
Glulisine (Apidra)	0.25–0.5	1–3	3–5
Regular insulin	0.5–1	2–4	5–8
Intermediate-acting			
NPH	2–4	4–8	12–18
Long-acting analogs			
Detemir (Levemir)	2–4	none	12–24
Glargine (Lantus, Basaglar, Toujeo)	2–4	none	up to 24
Degludec (Tresiba)	2–4	none	>24

Short-Acting (Prandial or Bolus) Regular Insulin

- It forms hexamers after injection into the SQ space slowing its absorption.
- Hexametric insulin progressively dissociates into absorbable insulin dimers and monomers.
- Regular insulin has a delayed onset of action of 30-60 minutes and should be injected approximately 30 minutes before the meal to blunt the postprandial rise in blood glucose.
- Adherence to a 30-minute pre-meal schedule is inconvenient and difficult for many patients.

Rapid-Acting (Prandial or Bolus) Insulin Analogs

- Rapid-acting analogs result from changes to the amino acid structure of human insulin which lead to decreases in hexameric insulin formation after injection into the SQ space.
- This leads to more rapid dissolution of insulin into monomers, more rapid insulin absorption into the bloodstream, and a shorter duration of action.
- While on a molar basis rapid-acting insulin analogs have identical in vivo potency compared to regular human insulin, higher peak concentrations are achieved.
- For this reason, when converting from regular to a rapid-acting insulin analog, the dose of insulin may need to be reduced.
- When compared to regular insulin, the rapid-acting insulin analogs lead to less postprandial hyperglycaemia and less late postprandial hypoglycaemia.
- Injection of rapid-acting insulin analogs 15-20 minutes pre-meal leads to maximal reduction of postprandial glucose excursions, as compared to 30 or more minutes pre-meal for regular insulin.

Insulin analogues

- Recombinant DNA technology has allowed for the development and production of analogs to human insulin.
- With analogs, the insulin molecule structure is modified slightly to alter the pharmacokinetic properties of insulin, primarily affecting the absorption of the drug from the subcutaneous tissue.
- The B26-B30 region of the insulin molecule is not critical for insulin receptor recognition and it is in this region that amino acids are general
- The structures of three rapid-acting insulin analogs are (insulin aspart, lispro and glulisine) and the structures of three long-acting insulin analogs are (insulin glargine, detemir, and degludec).

Difference between short & Rapid acting insulins

Short acting insulins:

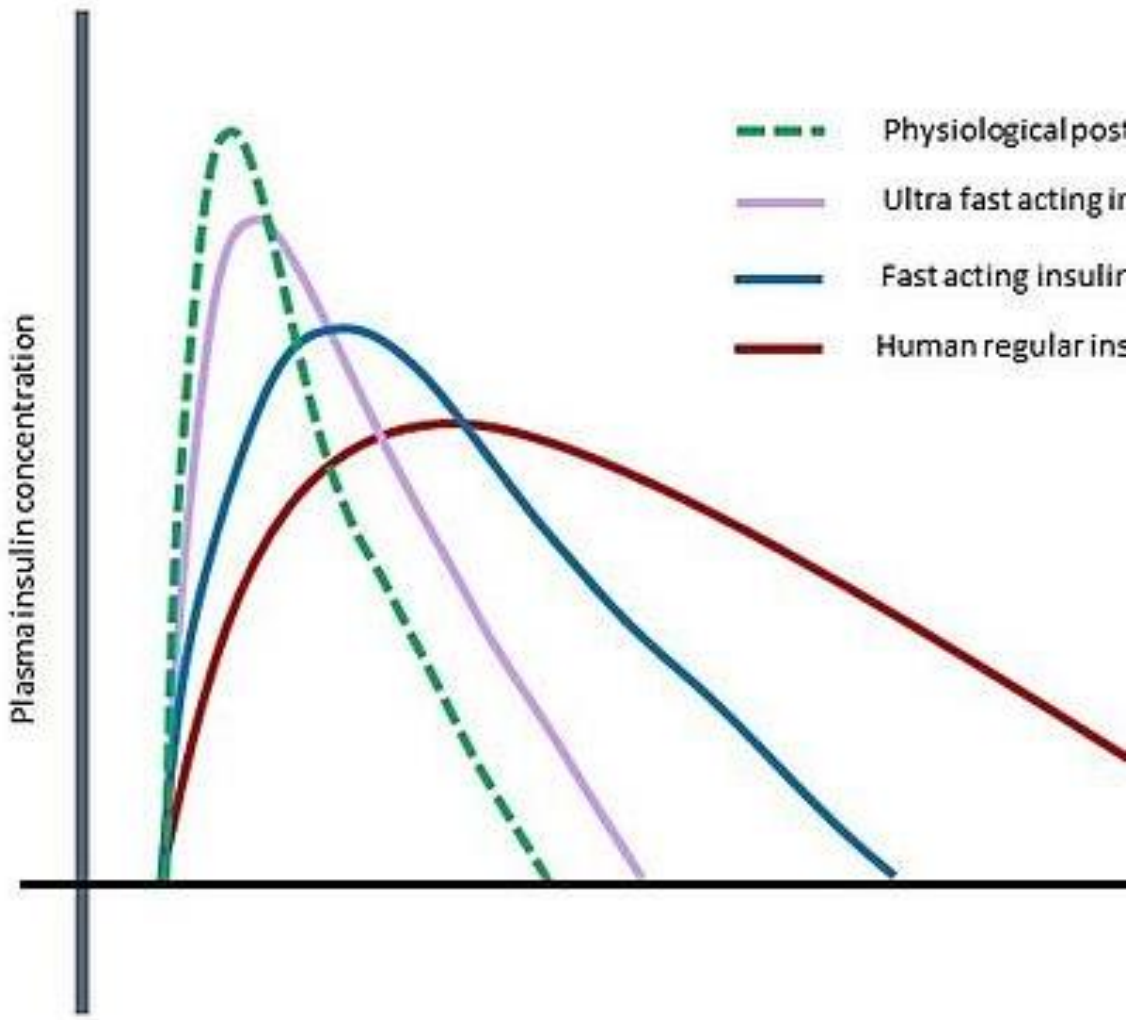
- Has onset of action of 30-60 minutes, peak effect in 2 to 4 hours, and duration of action of 6 to 8 hours.
- The larger the dose of regular the faster the onset of action, but the longer the time to peak effect and the longer the duration of the effect.

Rapid acting insulins:

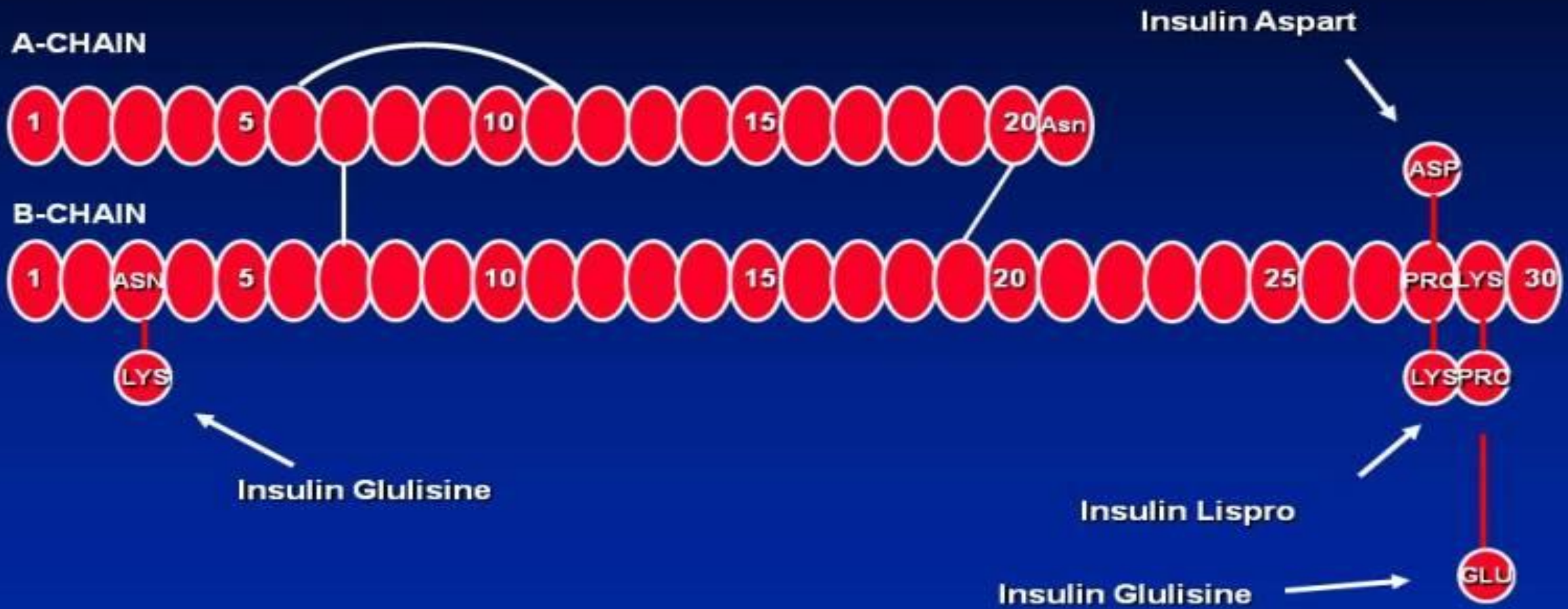
- Insulin Aspart, insulin Lyspro, Insulin Glulisine which have an onset of action of 5 to 15 minutes, peak effect in 1 to 2 hours and duration of action that lasts 3-4 hours.
- With all doses, large and small, the onset of action and the time to peak effect is similar,
- The duration of insulin action is, however, affected by the dose .
- As a general rule, assume that these insulins have duration of action of 3-4 hours.

Ultra fast insulin

- Insulin at mealtimes, rather than before them!
- Optimal coverage of prandial insulin requirements remains an elusive goal.
- Reducing postprandial glycaemic excursions in patients with diabetes in comparison with using regular human insulin; however, even with these, the physiological situation cannot be adequately mimicked.



Insulin Aspart, Lispro, & Glulisine Structure




Fiasp


Apidra® SoloStar®
Insulin glulisine
100 IU/mL
Injection solution for s.c. use

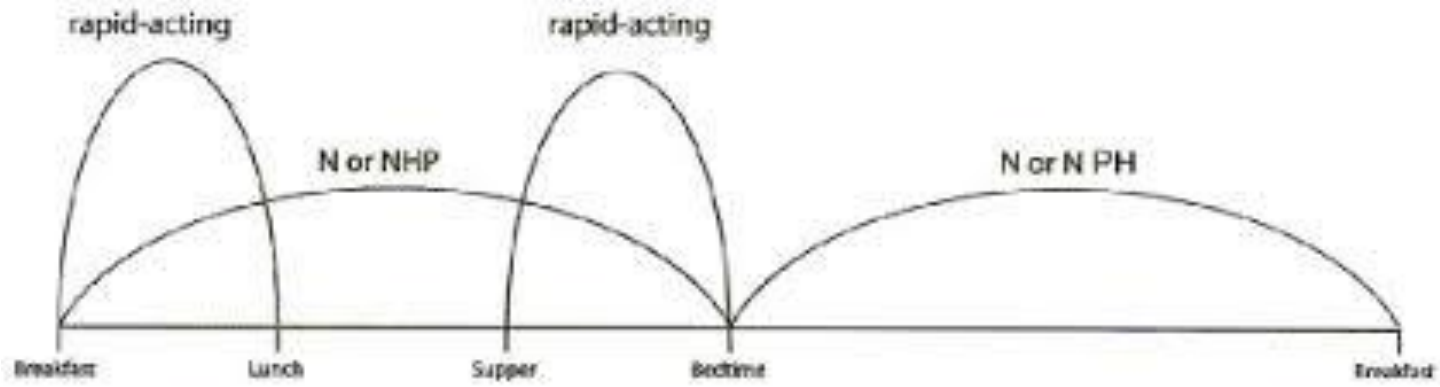

NovoRapid®
FlexPen®
5 x 3 ml

Does it differ one analogue from other?

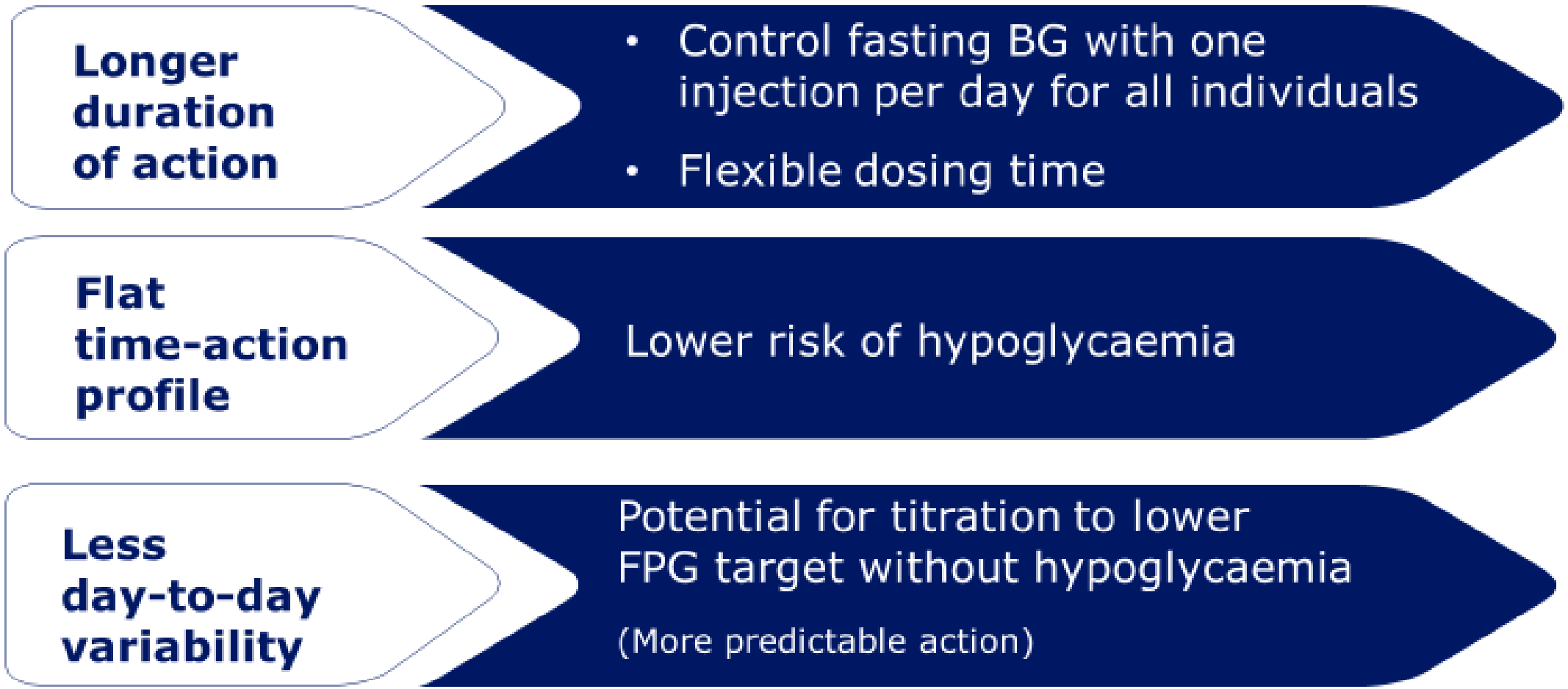
- No significant differences in glycaemic control have been observed in most studies comparing insulin aspart, insulin lispro, and insulin glulisine. Although insulin glulisine exhibits a more rapid onset of action than either insulin lispro or insulin aspart, this does not translate to meaningful clinical differences between these short-acting analog insulins.
- Faster aspart results in a more rapid onset of action and more glucose lowering within 30 minutes of administration than insulin aspart. However, no significant difference between faster aspart and insulin aspart has been observed in total glucose lowering

Intermediate-Acting Insulins (NPH)

- NPH (Neutral Protamine Hagedorn) insulin, was created in 1936 after it was discovered that the effects of subcutaneously injected insulin could be prolonged by the addition of the protein protamine.
- NPH insulin is intermediate-acting insulin, whose onset of action is approximately 2 hours, peak effect is 6-14 hours, and duration of action of 8-12 hours (depending on the size of the dose).
- Because of its broad peak and long duration of action, NPH can serve as a basal insulin only when dosed at bedtime, or a basal and prandial insulin when dosed in the morning.
- NPH insulin is available in various combinations with either regular insulin or rapid-acting insulins
- Very small doses will have an earlier peak effect and shorter duration of action, while higher doses will have a longer time to peak effect and prolonged duration.

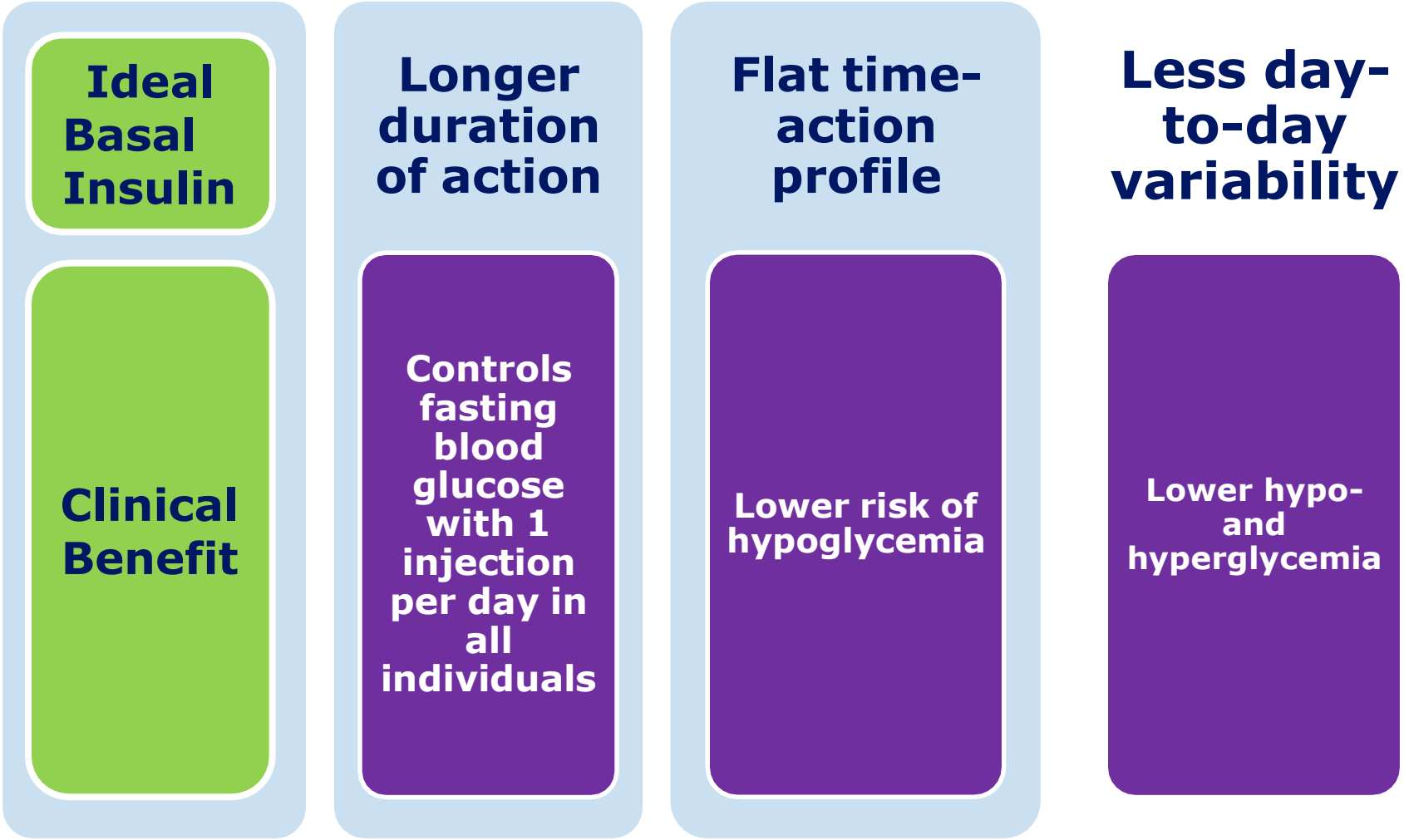


Objectives of developing a new basal insulin

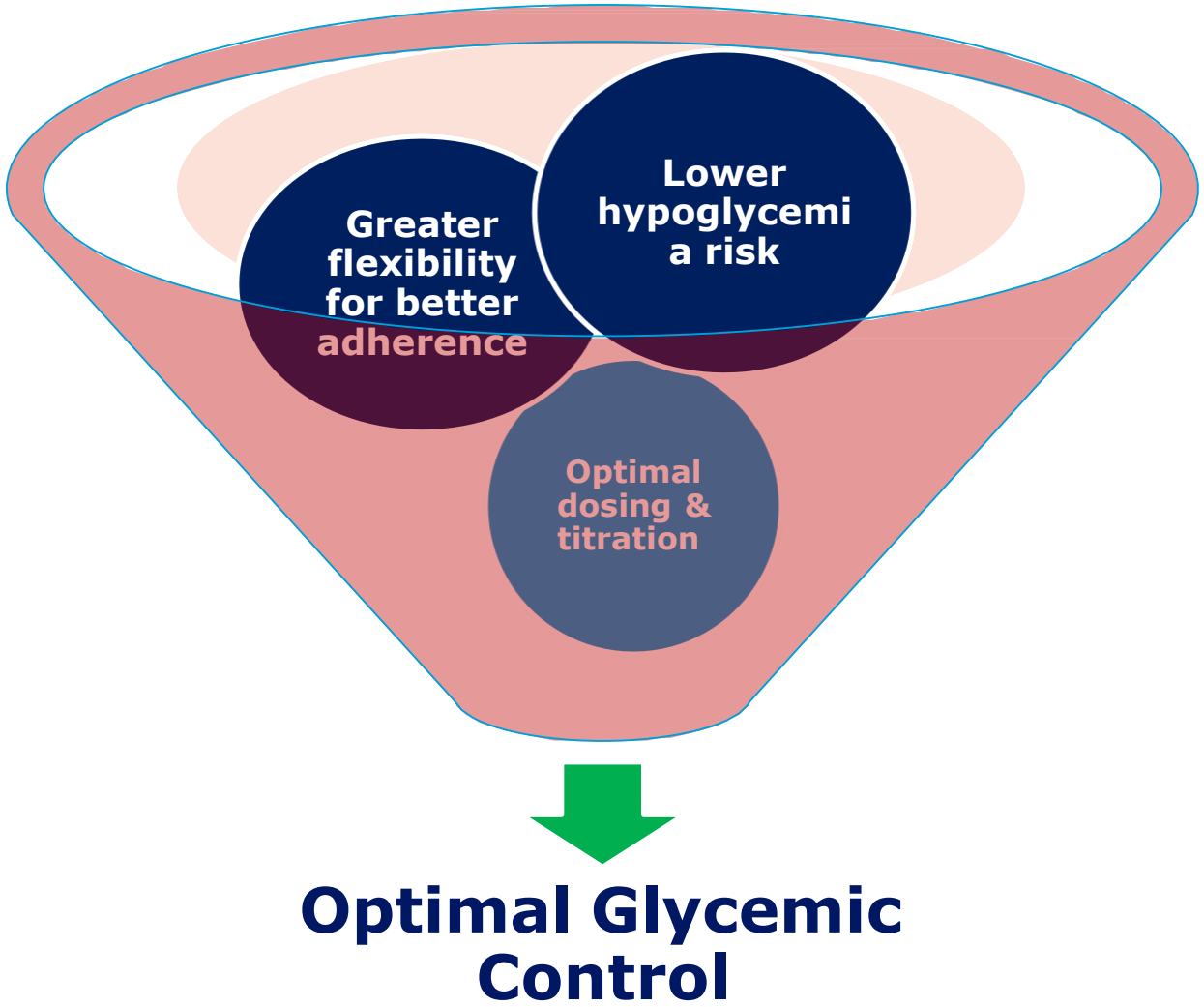


BG, blood glucose; FPG, fasting plasma glucose

Development of an ideal basal insulin to meet these challenges



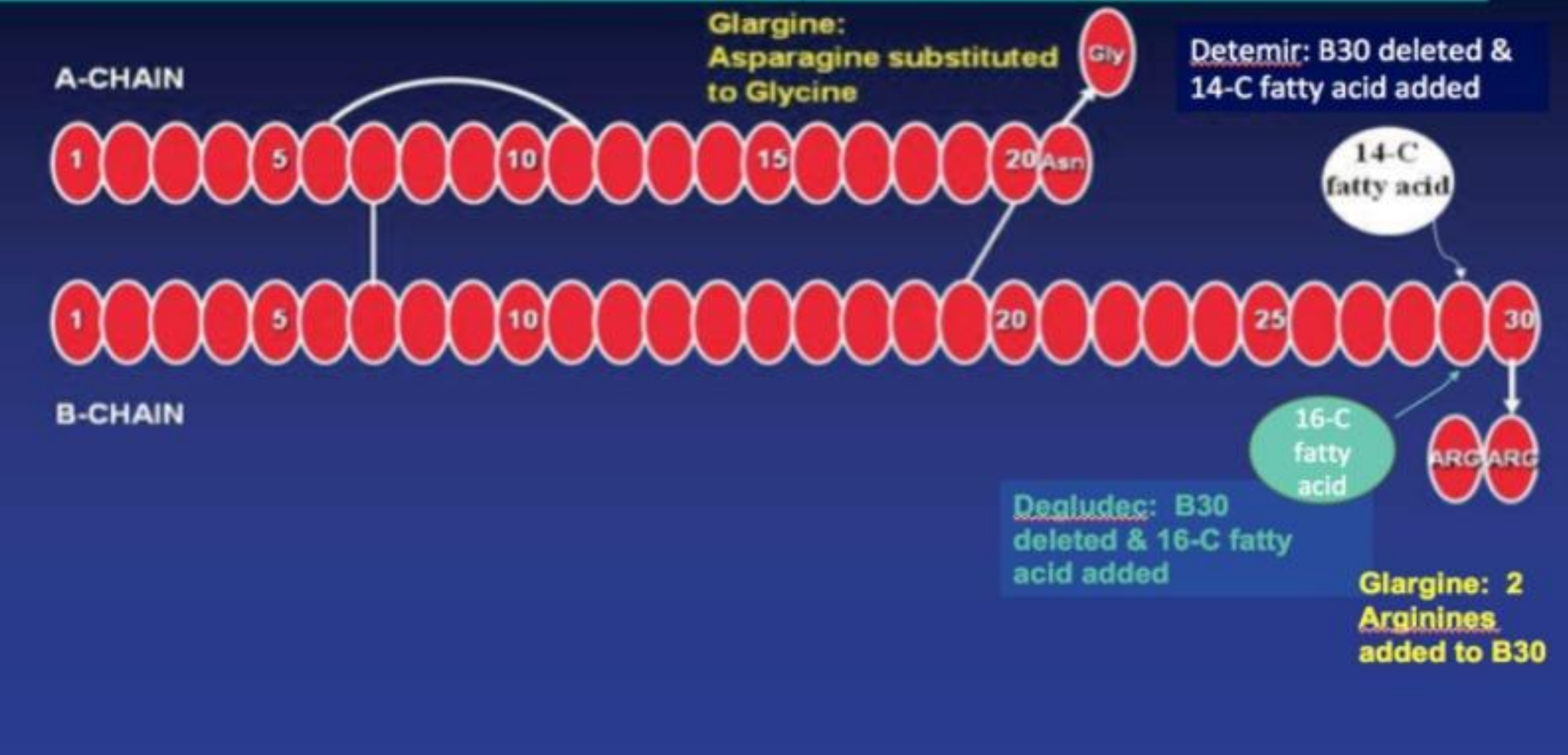
Novel agent to address insulin barriers



Long-Acting (Basal) Insulin Analogs

- Long-acting insulins provide basal insulin coverage.
- Basal insulins suppress hepatic gluconeogenesis, in order to prevent glucose levels from rising during the fasting state in insulin-deficient patients.
- Among patients with type 1 diabetes, basal insulins additionally prevent ketogenesis.
- Is absorbed slowly, has a minimal peak effect, and a stable plateau effect that lasts most of the day.
- Is used to control the blood glucose overnight, while fasting and between meals
- Long- acting insulin analogs (Insulin Glargine, Insulin Detemir) which have an onset of insulin effect in 2 hours.
- The insulin effect plateaus over the next few hours and is followed by a relatively flat duration of action that lasts 12-24 hours for insulin detemir and 24 hours for insulin glargine, 36 hours for Toujeo and 42 hours for Tresiba insulin.

Insulin Glargine, Detemir, and Degludec Structures



Insulin	NPH (Not truly basal)	Glargine	Detemir	Degludec
Structure	Crystalline suspension of human insulin with protamine and zinc	Addition of two and substitution of one amino acid	Addition of accylated fatty acid chain at B	Deletion of B30, addition of glutamic acid spacer and diacylated fatty acid chain at B29
Number of amino acids	51	53	51	50
Carbon in side chain	0	0	14	16
Mechanism of protraction	Less solubility in the extracellular fluid leads to slower absorption and a prolonged effect	Precipitation at acidic pH	Binding to albumin	Multihexamer chain formation
Terminal half life	Variable	12.5 hrs	12.5 hrs	25.1-25.4 hrs
Duration of action	13-20 hrs	Upto 24 hrs	Upto 18-23 hrs	Upto 42 hrs
Intra-patient glycemic variability	High	High	Low	Lowest
Exposure ratio: first 12 hrs to second 12 hrs after injection		60:40	50:50	50:50
Timing of administration	Once or twice or thrice daily	At the same time everyday	Once or twice daily	At any time, every day

Insulin	NPH	Glargine	Detemir	Degludec
Risk of hypoglycemia	Present	Low	Low	Least
Risk of nocturnal hypoglycemia	Present	Low	Low	Least
Risk of severe hypoglycemia	Present	Low	Low	Least
Injection site reactions	Lesser than glargine	Possible, because of acidic pH	Rare	Rare
Weight gain	Yes	Yes	No	Yes
Binding of IGF-1R (human insulin 100)		641±51	18±2	2
Binding affinity to insulin receptor (human insulin 100)		86±3	16±1	13-15
Use in renal impairment	Dose needs to be adjusted	Safe	Safe	Safe
Use in hepatic impairment	Dose needs to be adjusted	Safe	Safe	Safe
Miscibility with regular/rapid acting insulin	Can be mixed with soluble insulin without affecting absorption kinetics of either insulin	No	No	Yes
Miscibility with Glucagon like peptide – 1 receptor agonists		Yes	No	Yes

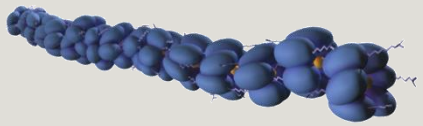
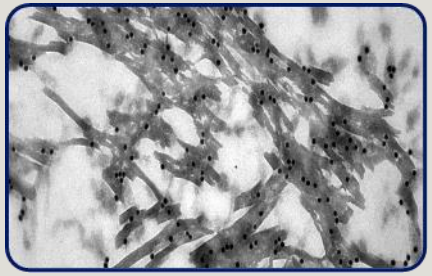
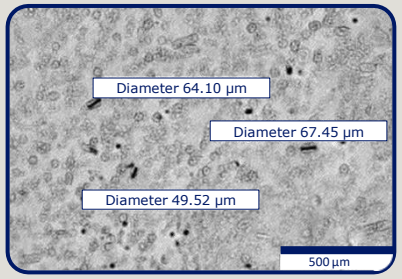
Ultra-long acting basal insulin
Degludec

Tresiba® (insulin degludec injection) 100 U/mL, 200 U/mL

Insulin Degludec

- Novel ultra long-acting insulin analogue.
- Insulin Degludec provides basal insulin coverage for more than 42 hours and achieves similar glycemic control with less overnight hypoglycemia than glargine.
- Half life is about 25 hours.
- FDA approved (September 2015).
- Degludec is approved for use in Europe, Saudi Arabia& Gulf countries.

Degludec and glargine U100 and U300

	Degludec	Glargine U100	Glargine U300
Type of insulin	New-generation long-acting basal insulin analogue	First-generation basal insulin analogue	Up-concentrated formulation of first-generation basal insulin analogue
Mode of protraction	Forms soluble multihexamers 	Precipitates as microcrystals 	Precipitates as microcrystals 
Half life	~25 hours	~12 hours	~19 hours

Glargine U100, insulin glargine 100 units/mL; glargine U300, insulin glargine 300 units/mL
Glargine U100 image data on file; glargine U300 optical microscopy images obtained from European patent application
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=EP&NR=2387989A2&KC=A2&date=&FT=D&locale=en_EP
Jonassen *et al. Pharm Res* 2012;29:2104–14; Heise *et al. Expert Opin Drug Metab Toxicol* 2015;11:1193–201; Heise *et al. Diabetes Obes Metab* 2012;14:859–64

Biologic “biosimilar ”Insulins

- On March 23, 2020 insulin was officially moved to the biologic regulatory framework.
- This exciting step means that all insulins on the market have officially been labelled as biologics by the FDA—paving the way for biosimilar and interchangeable insulins.
- Relative to the production of other medications, the production of a biologically similar insulin is a more complicated process, which contributes to reduced cost savings in purchasing insulin.
- Although not termed a biosimilar insulin, Basaglar, a “follow-on biologic” insulin of Lantus or insulin glargine, was approved by the FDA in 2015
- Similarly, Admelog is a follow-on insulin of Humalog, or insulin lispro.

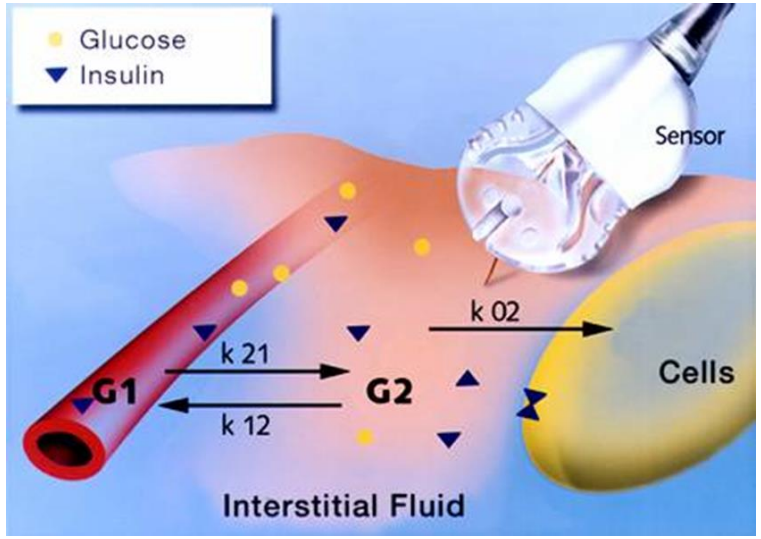
Correction Dose

Self-monitoring of blood glucose levels (SMBG)

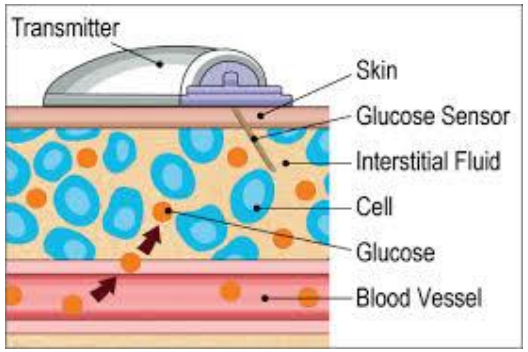
- Is essential component of treatment of type 1 diabetes in children.
- All children and adolescents with type 1 diabetes should have blood glucose levels monitored multiple times daily (up to 6–10 times/day), including:
  - pre-meals.
  - pre-bedtime.
  - as needed for safety in specific situations such as exercise, driving, illness, or the presence of symptoms of hypoglycemia.
- SMBG is necessary for determination of insulin dose (e.g., mealtime), assessment of safety (e.g., corrective action for or prevention of hyper- or hypoglycemia), and longer-term adjustment in insulin dosing regimens based on blood glucose patterns and trends.

Real-time CGM

- Is increasingly used for routine diabetes care in children & adolescents with type 1 diabetes.
- Should be considered in all children & adolescents with type 1 diabetes, whether using injections or insulin pump therapy, as an additional tool to help improve glycemic control.
- Benefits of CGM correlate with adherence to ongoing use of the device.
- For most CGM systems, confirmatory SMBG is required to make treatment decisions.



Availability of various CGMS



How to calculate insulin sensitivity factor

- Health-care professionals use the “1500 rule” to calculate insulin sensitivity factor for people who use Regular (short-acting) insulin.

- Health-care professionals use the “1800 rule” to calculate insulin sensitivity factor for people who use the rapid-acting insulin analogs lispro (brand name Humalog), aspart (NovoLog), and glulisine (Apidra).

Supplemental Insulin for Correction of Hyperglycaemia

- Regular insulin, or the rapid-acting insulins aspart/glulisine/lispro can be used to correct high glucose levels.
- A commonly used correction insulin regimen which targets a glucose of 100 mg/dl pre-meal and 150 mg/dl at bedtime
- The rule of 1800 can be used to approximate the amount that 1 unit of supplemental insulin will lower the glucose, also termed the insulin sensitivity factor (ISF), using the total daily dose (TDD) of insulin:
- Calculation of the insulin sensitivity factor (ISF): ISF= 1800/TDD
- For example, if this person's pre-meal glucose was 280 mg/dl, 6 units of supplemental insulin would be added to their usual dose of pre-meal insulin to decrease glucose by 180mg/dl.

Thank you
or your kind
attention!