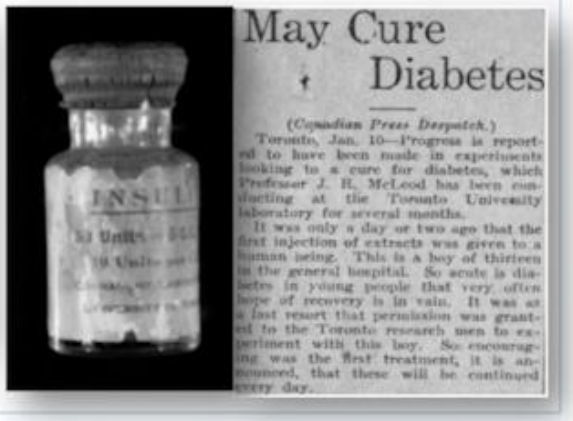
Insulin innovations – the past: journey so far

1920: Diagnosis of T1D was a likely death sentence

Life before insulin

Leonard Thompson in December 1921

Months later



May Cure Diabetes

(*Canadian Press Despatch.*)

Toronto, Jan. 10—Progress is reported to have been made in experiments looking to a cure for diabetes, which Professor J. R. McLeod has been conducting at the Toronto University laboratory for several months.

It was only a day or two ago that the first injection of extracts was given to a human being. This is a boy of thirteen in the general hospital. So acute is diabetes in young people that very often hope of recovery is in vain. It was as a last resort that permission was granted to the Toronto research men to experiment with this boy. So encouraging was the first treatment, it is announced, that these will be continued every day.

The discovery of insulin revolutionised the treatment of diabetes and is one of the greatest achievements in medical history

T1D, type 1 diabetes.

1. Hegele et al. Lancet Diabetes Endocrinol. 2020;8:971–7; 2. Harvard Health Blog: Available here. Accessed August 2021.

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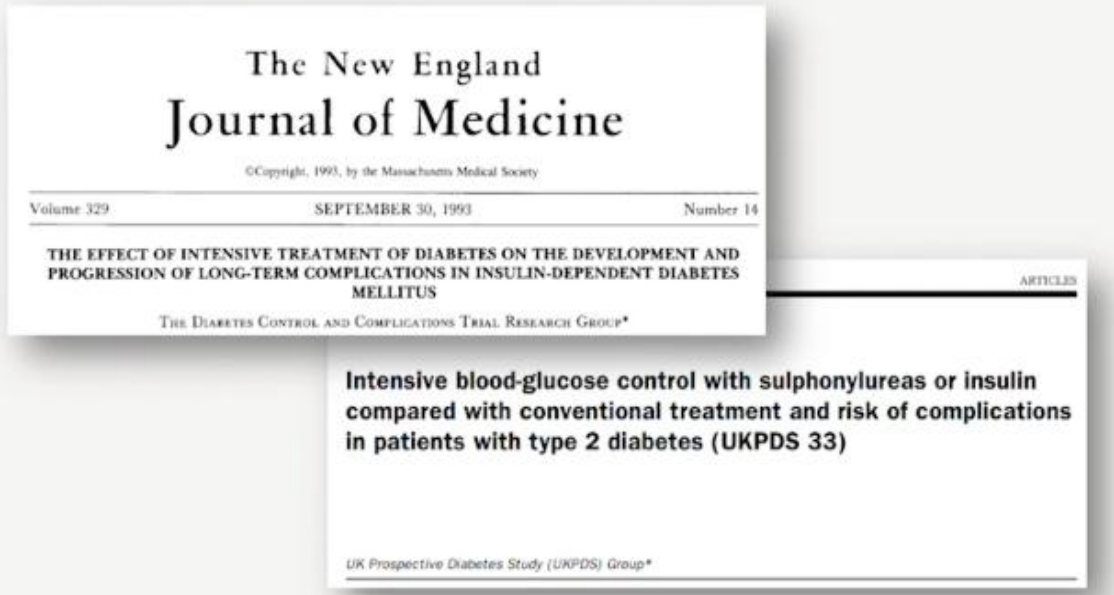
The drive for better glucose control required better insulins

Benefit of tight glycaemic control on microvascular outcomes[1,2]



The New England
Journal of Medicine

Volume 329 SEPTEMBER 30, 1993 Number 14

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*

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*

1.0% ↓
HbA_{1c} reduction

14% ↓
Myocardial infarction

37% ↓
Microvascular disease

**Other hallmark trials include ACCORD; ADVANCE; VADT. HbA_{1c} glycated haemoglobin.*

1. UK Prospective Diabetes Study (UKPDS) Group. The Lancet. 1998;352:837–53; 2. DCCT. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329:977–86.

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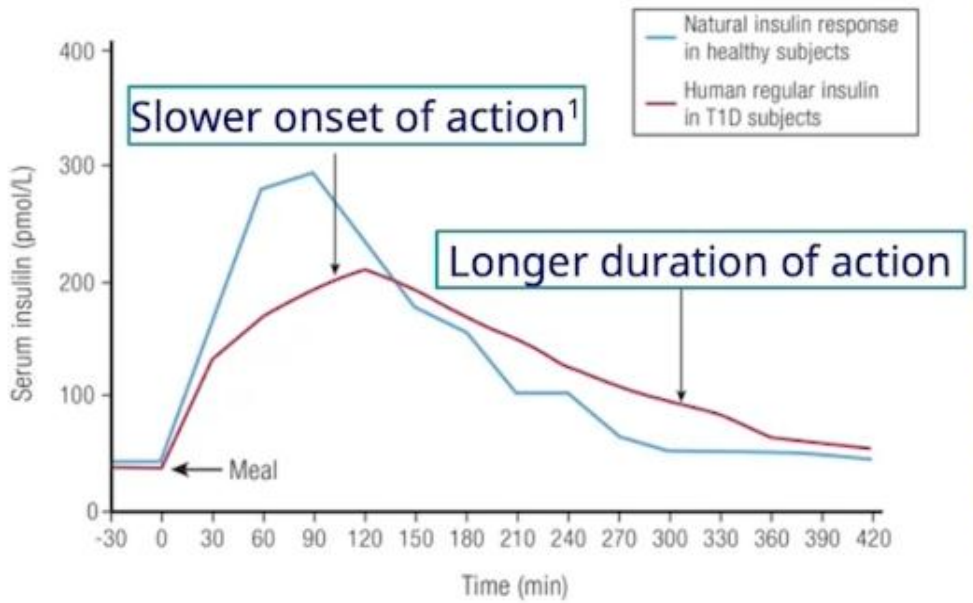
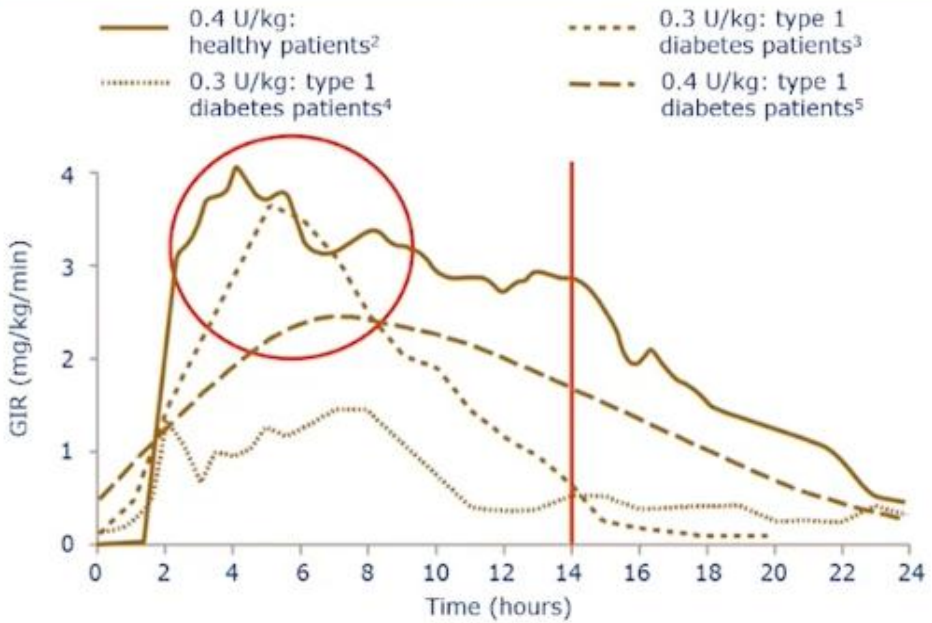
Early insulin formulations were inconvenient for patients and increased the risk of hypoglycaemia



NPH: a relatively short action profile with a peak[2–5]



GIR, glucose infusion rate; GIR curves adapted from references; NPH, Neutral Protamine Hagedorn; T1D, type 1 diabetes.

1. Hirsch et al. Endocr Rev. 2020;41:733–55; 2. Scholtz et al. Diabetologia 2005;48:1988–95; 3. Plank et al. Diabetes Care 2005;28:1107–12; 4. Lepore et al. Diabetes 2000;49:2142–8; 5. Heise et al. Diabetes 2004;53:1614–20.

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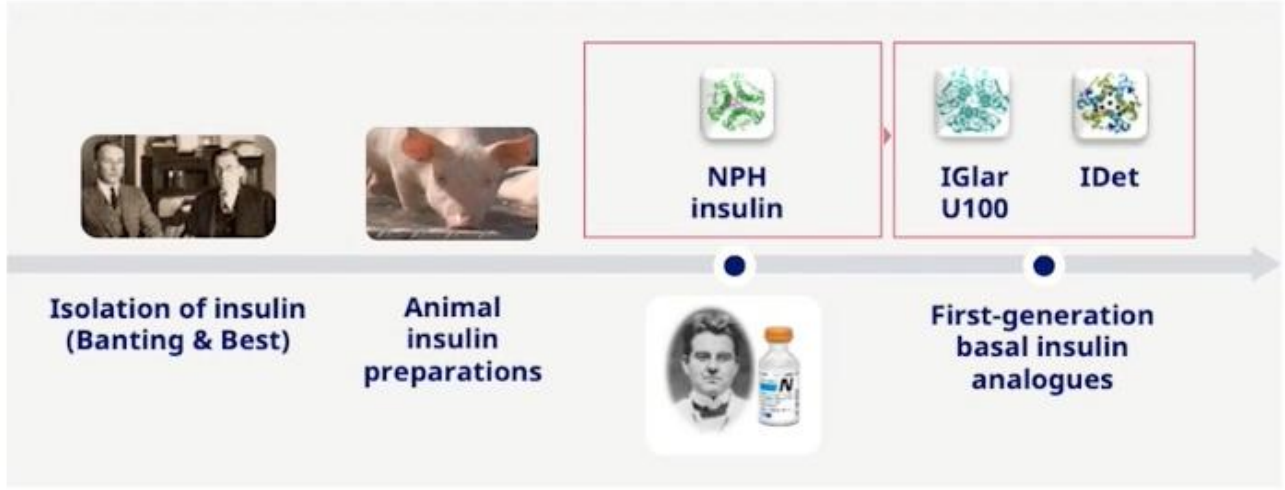
The development of insulin analogues

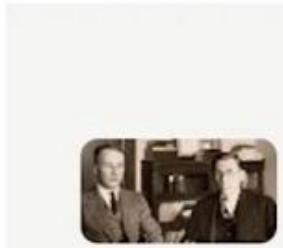


Half life (hours)	5–10	12–19
Variability	High	Medium
Hypoglycaemia	High	Medium

Appearance. IDet insulin detemir; IGlar, insulin glargine; NPH, neutral protamine Hagedorn; IAsp, insulin aspart; ILis, insulin lispro; IGlu, insulin glulisine. 1. NPH SmPC. Available here; 2. IDet SmPC. Available here; 3. IGlar U100 SmPC. Available here; 4. IASp SmPC. Available here; 5. Ilis SmPC. Available here; 6.IGlu SmPC. Available here.

Fachklinik Bad Heilbrunn

The development of insulin analogues



Isolation of insulin (Banting & Best)

Animal insulin preparations

NPH insulin

IGlar U100

IDet

First-generation basal insulin analogues

ILis

IAsp

IGlu

Rapid-acting insulin analogues

Half life (hours)	5–10	12–19
Variability	High	Medium
Hypoglycaemia	High	Medium

Onset*	5-15 mins
Peak	1-2 hours

**Appearance. IDet insulin detemir; IGlar, insulin glargine; NPH, neutral protamine Hagedorn; IAsp, insulin aspart; ILis, insulin lispro; IGlu, insulin glulisine. 1. NPH SmPC. Available here; 2. IDet SmPC. Available here; 3. IGlar U100 SmPC. Available here; 4. IASp SmPC. Available here; 5. Ilis SmPC. Available here; 6.IGlu SmPC. Available here.*

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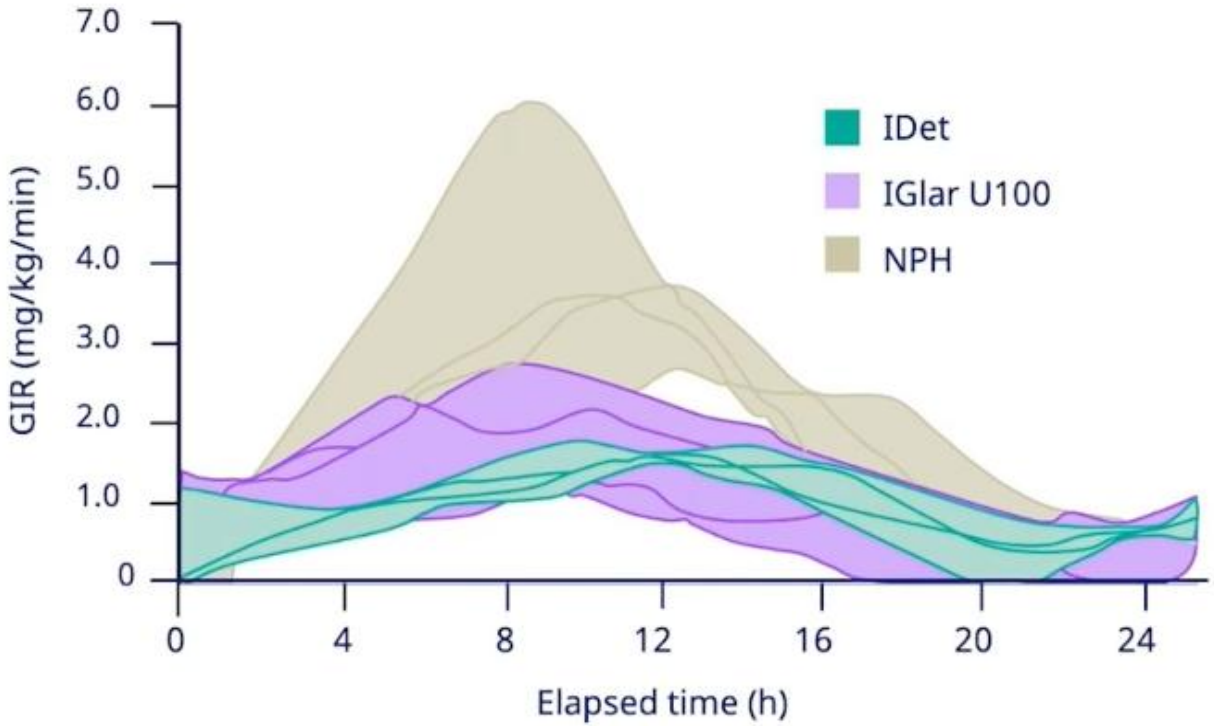
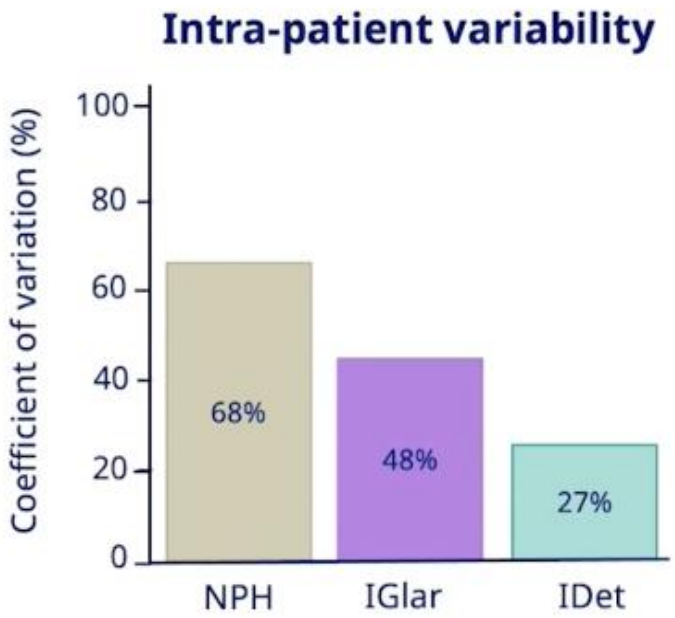
Improving the insulin time-action profile





GIR, glucose infusion rate; IDet, insulin detemir; Iglar U100, insulin glargine; NPH, neutral protamine Hagedorn.
Heise T et al. Diabetes 2004;53:1614–20.

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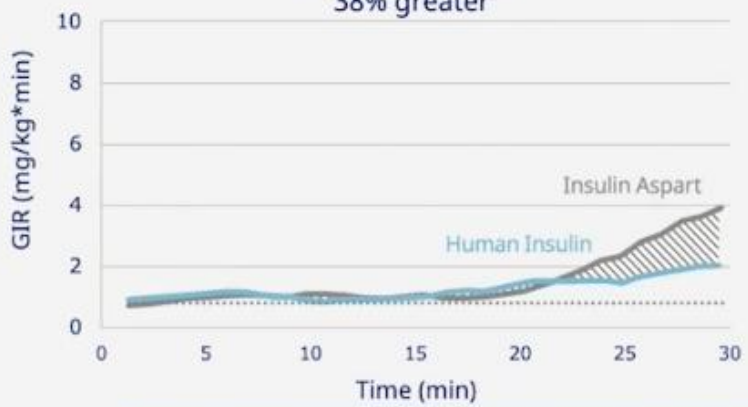
Continuous innovation

From regular human insulin to rapid-acting insulin analogues

Glucose-lowering effect

$AUC_{GIR,\ 0–30\ min}$
38% greater



Treatment difference:
−0.12% (95% CI:−0.03;−0.22) p<0.02

Greater early-glucose lowering effect and improvement in HbA_{1c} with IAsp vs. RHI

AUC, area under the curve; CI, confidence interval; GIR, glucose infusion rate; IAsp, insulin aspart;RHI, regular human insulin.
Heinemann et al. Exp Clin Endocrinol Diabetes. 1997;105:140–4; Home et al. Diabet Med 2000;17.

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Hypoglycemia in diabetes:
The dark side of diabetes treatment

Hypoglycaemia is a major limiting factor for achieving stringent glycaemic control[1]

Common in both T1D and T2D[1]

Non-severe hypoglycaemia[2]		Severe hypoglycaemia[2]	
3.5–7.2	0.8–4.0	68%	19%
T1D	T2D	T1D	T2D
Events per month		Over a 3-month period	

T1D, type 1 diabetes; T2D, type 2 diabetes.

1. Khunti et al. Diabetes Obes Metab. 2016;18:907–15; 2. Malkani et al. J Diabetes Res. 2017;2017:7425925.

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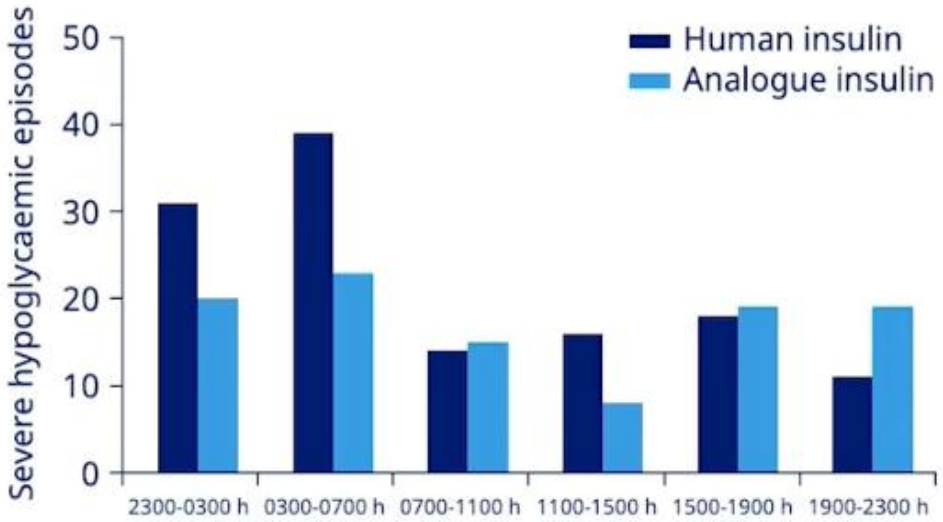
Severe hypoglycaemia rates can be reduced with insulin analogues in T1D – HypoAna study



Relative rate reduction in severe hypoglycaemia

29%

Absolute rate reduction

0.51 episodes

per patient-year

Analogue insulin included insulin detemir and insulin aspart. T1D; type 1 diabetes.

1. Bjergaard et al. Lancet Diabetes Endocrinol. 2014;2:553–61.

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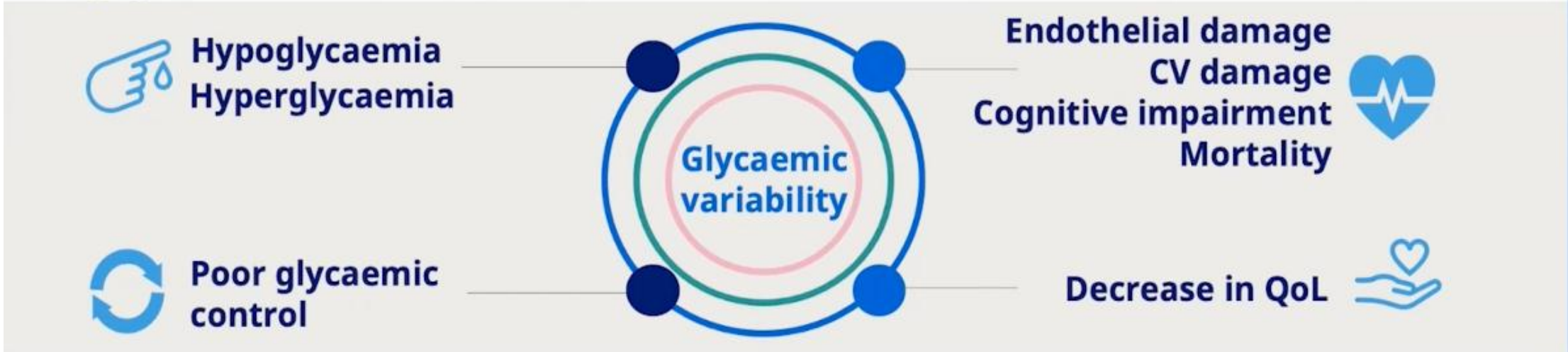
Reducing glycaemic variability is key for glycaemic control



CV, cardiovascular IDet, insulin detemir; IGlar, insulin glargine; IGlu, insulin glulisine; ILis, insulin lispro; NPH, neutral protamine Hagedorn; IAsp, insulin aspart; QoL, quality of life; T2D, type 2 diabetes.
Umpierrez et al. Am J Med Sci. 2018;356:518–27.

Fachklinik Bad Heilbrunn

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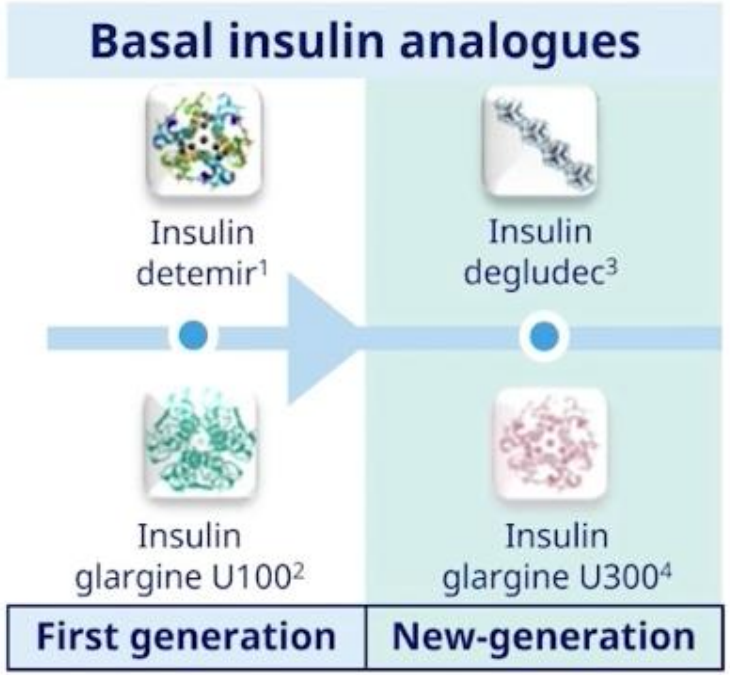
Umpierrez et al. Am J Med Sci. 2018;356:518–27.

Fachklinik Bad Heilbrunn

Insulin innovations – the present: current scenario

Long-acting new-generation basal insulin analogues



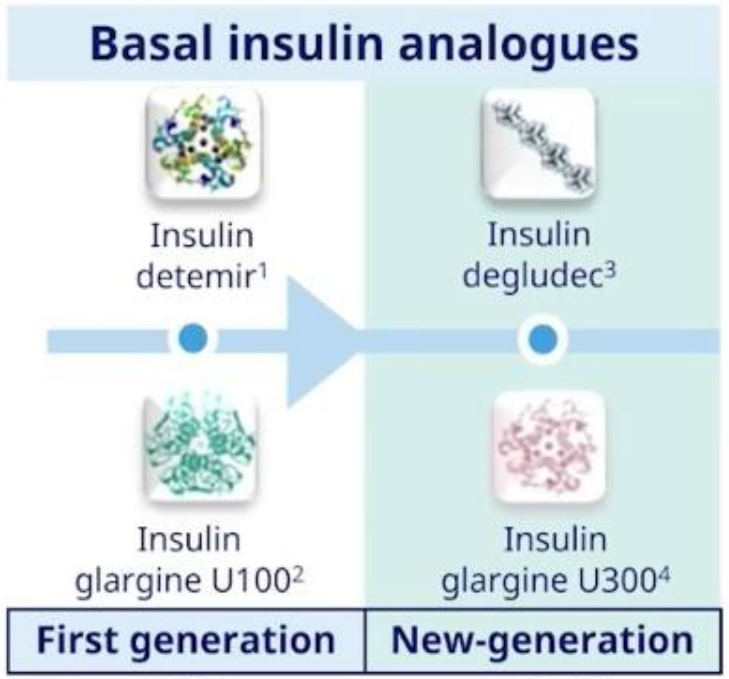
Half-life (hours):	***12***	***19–25***
Glycaemic variability:	***Medium***	***Low***

IDegAsp, insulin degludec/insulin aspart; IDegLira, insulin degludec/liraglutide; MoA, mode of action; SmPC, summary of product characteristics; $t_{½}$, half life; U100, 100 units/mL; U300, 300 units/mL.

1. Insulin detemir SmPC. Available here; 2. Glargine U100 SmPC. Available here; 3. Degludec SmPC. Available here; 4. Glargine U300 SmPC. Available here; 5. FDA Degludec approval. Available here; 6. Jonassen et al. Pharm Res 2012;29:2104–14; 7. Degludec SmPC. Available here; 8. IDegLira SmPC. Available here; 9. IDegAsp SmPC. Available here.

All webpages accessed July 2021.

Long-acting new-generation basal insulin analogues



Half-life (hours):	***12***	***19–25***
Glycaemic variability:	***Medium***	***Low***

Insulin degludec

- Approved in 2015[5]
- Distinct molecule with unique MoA[6]
- $t_{1/2}$ ~ 25 hours[7]

IDegAsp, insulin degludec/insulin aspart; IDegLira, insulin degludec/liraglutide; MoA, mode of action; SmPC, summary of product characteristics; $t_{½}$, half life; U100, 100 units/mL; U300, 300 units/mL.

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All webpages accessed July 2021.

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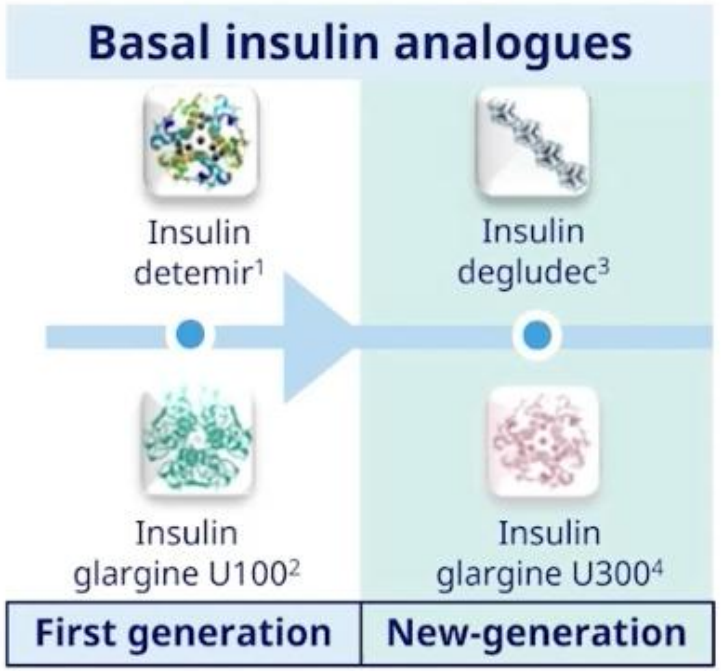

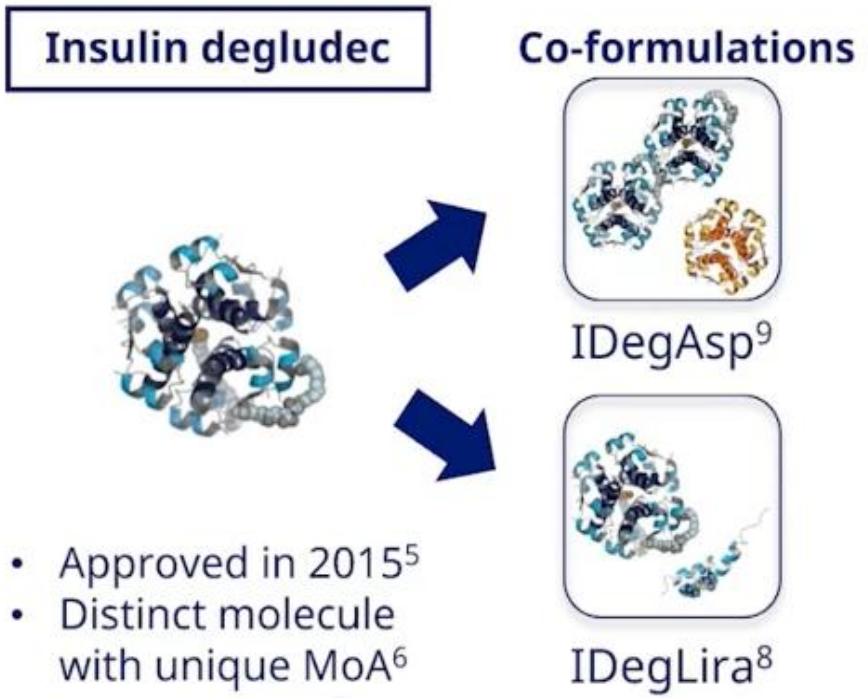

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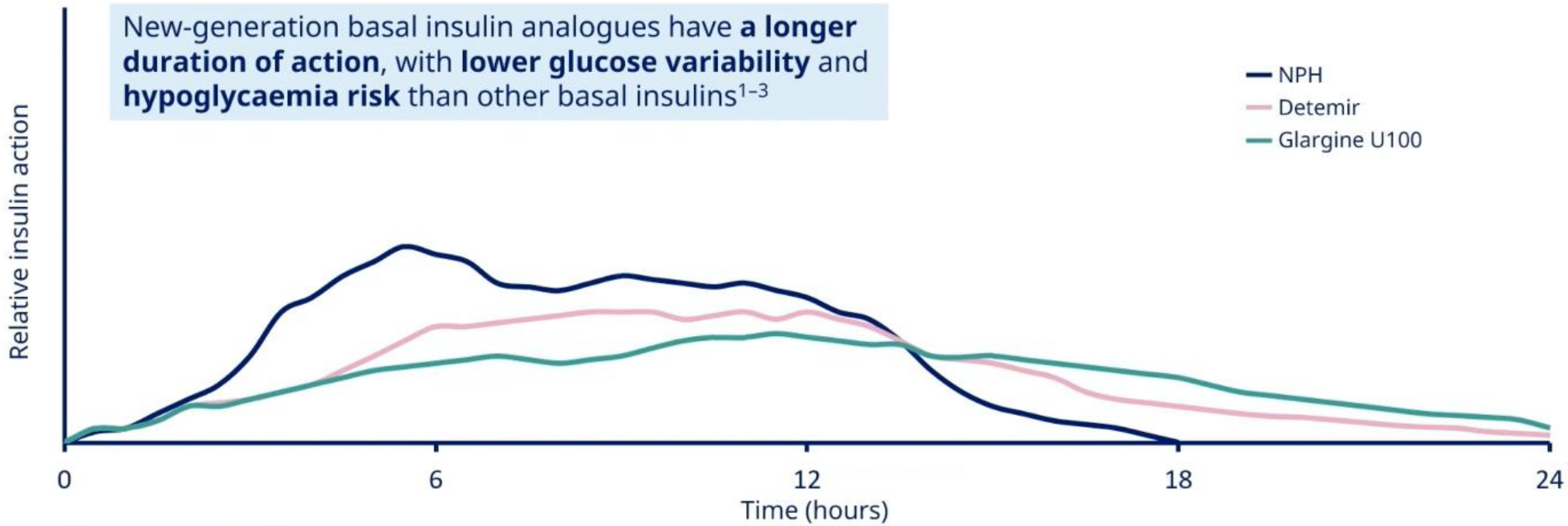
New-generation basal insulin analogues have an improved duration of action vs other basal insulins

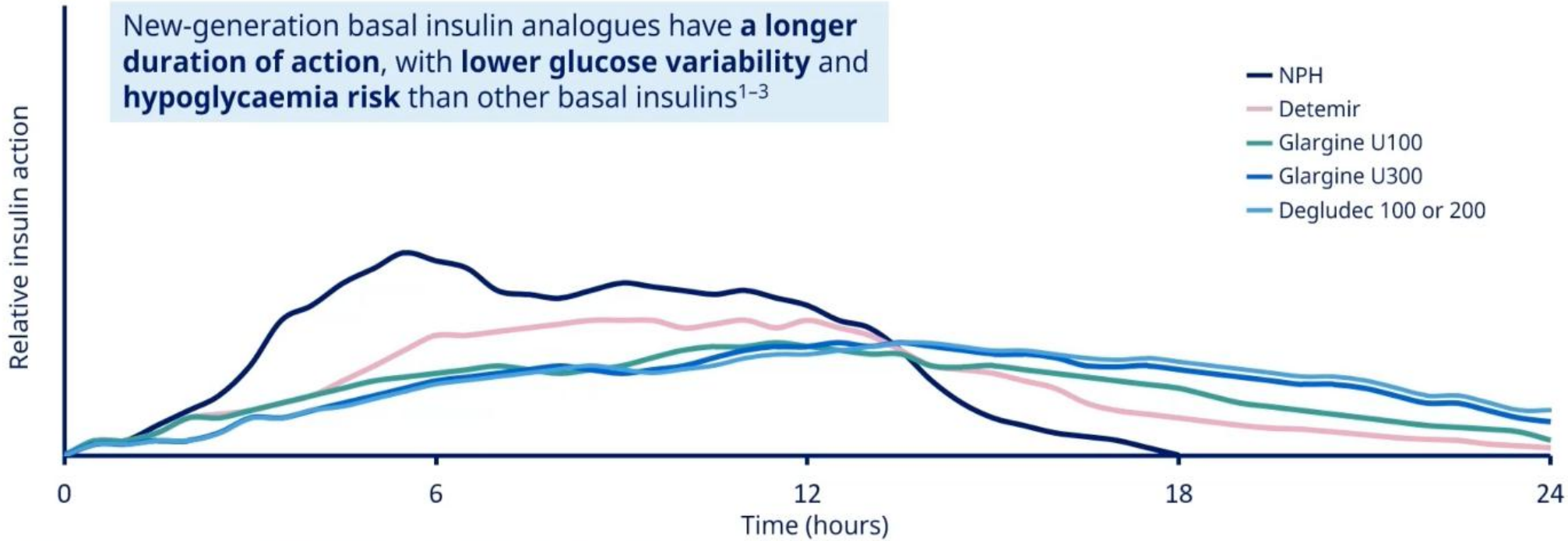


The images of the effects of insulin are theoretical representations and are not taken from clinical study data.
Degludec 100 or 200, insulin degludec 100 or 200 units/mL; detemir, insulin determir; glargine U100, insulin glargine 100 units/mL; glargine U300, insulin glargine 300 units/mL; NPH, Neutral Protamine Hagedorn insulin.

1. Lane et al. JAMA 2017;318:33–44; 2. Wysham et al. JAMA 2017;318:45–56; 3. Marso et al. N Engl J Med 2017;377:723–32.

New-generation basal insulin analogues have an improved duration of action vs other basal insulins

New-generation basal insulin analogues have **a longer duration of action**, with **lower glucose variability** and **hypoglycaemia risk** than other basal insulins[1–3]



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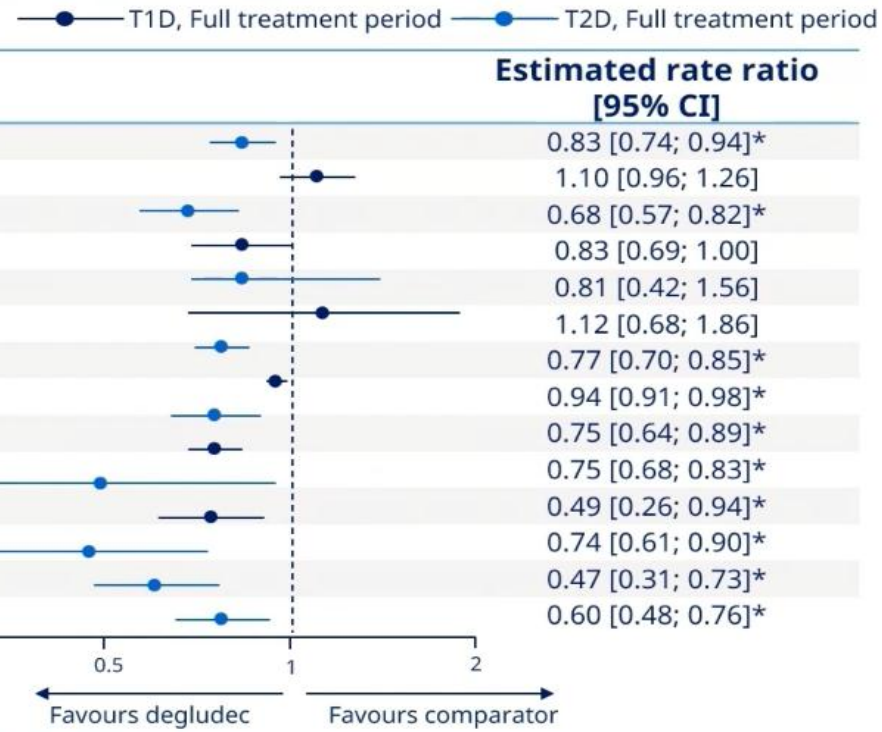
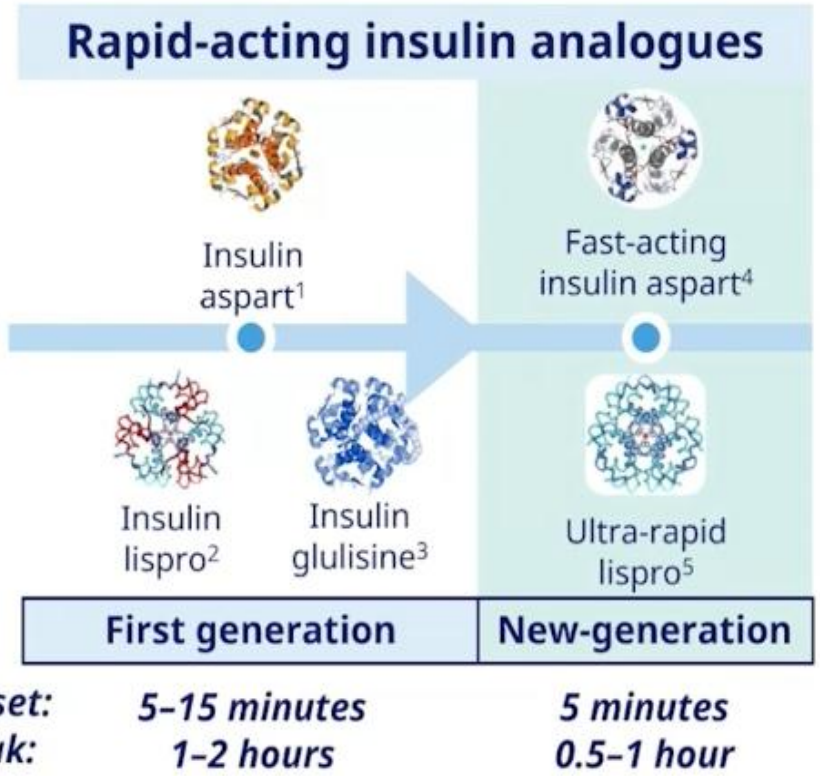
Hypoglycaemia: Consistency across degludec clinical trial programme in T2D and T1D patients



Trial	vs. Glargine	Hypoglycaemia Definition		Estimated rate ratio [95% CI]
BEGIN Meta-analysis[1]	U100	Overall confirmed‡	T2D	0.83 [0.74; 0.94]*
			T1D	1.10 [0.96; 1.26]
		Nocturnal confirmed‡	T2D	0.68 [0.57; 0.82]*
			T1D	0.83 [0.69; 1.00]
		Severe	T2D	0.81 [0.42; 1.56]
			T1D	1.12 [0.68; 1.86]
SWITCH[2]	U100	Overall confirmed‡	T2D	0.77 [0.70; 0.85]*
			T1D	0.94 [0.91; 0.98]*
		Nocturnal confirmed‡	T2D	0.75 [0.64; 0.89]*
			T1D	0.75 [0.68; 0.83]*
		Severe	T2D	0.49 [0.26; 0.94]*
			T1D	0.74 [0.61; 0.90]*
DEVOTE[3]	U100	Nocturnal severe	T2D	0.47 [0.31; 0.73]*
		Severe		0.60 [0.48; 0.76]*

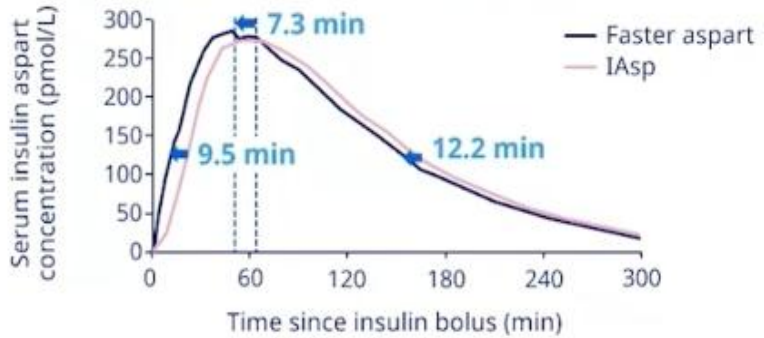
**Significant difference; ‡Severe or BG-confirmed (<3.1 mmol/L); All nocturnal hypoglycaemia reported between 00:01 and 05:59.*
BG, blood glucose; CI, confidence interval; T1D, type 1 diabetes; T2D, type 2 diabetes; U100, 100 units/mL.
1. Ratner et al. Diabetes Obes Metab 2013;15:175–84; 2. Wysham et al. JAMA. 2017;318(1):45-56; 3. Marso et al. N Engl J Med 2017; 377:723–732.

Ultra-rapid insulin analogues: improved time-action profile



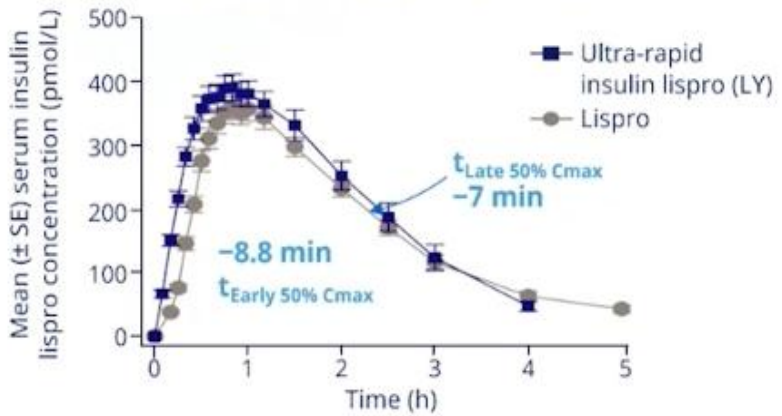
Compared with insulin aspart, faster aspart has:[6]

2x higher exposure in first 30 min



Compared with insulin lispro, ultra-rapid lispro has:[7]

2x higher exposure in first 30 min

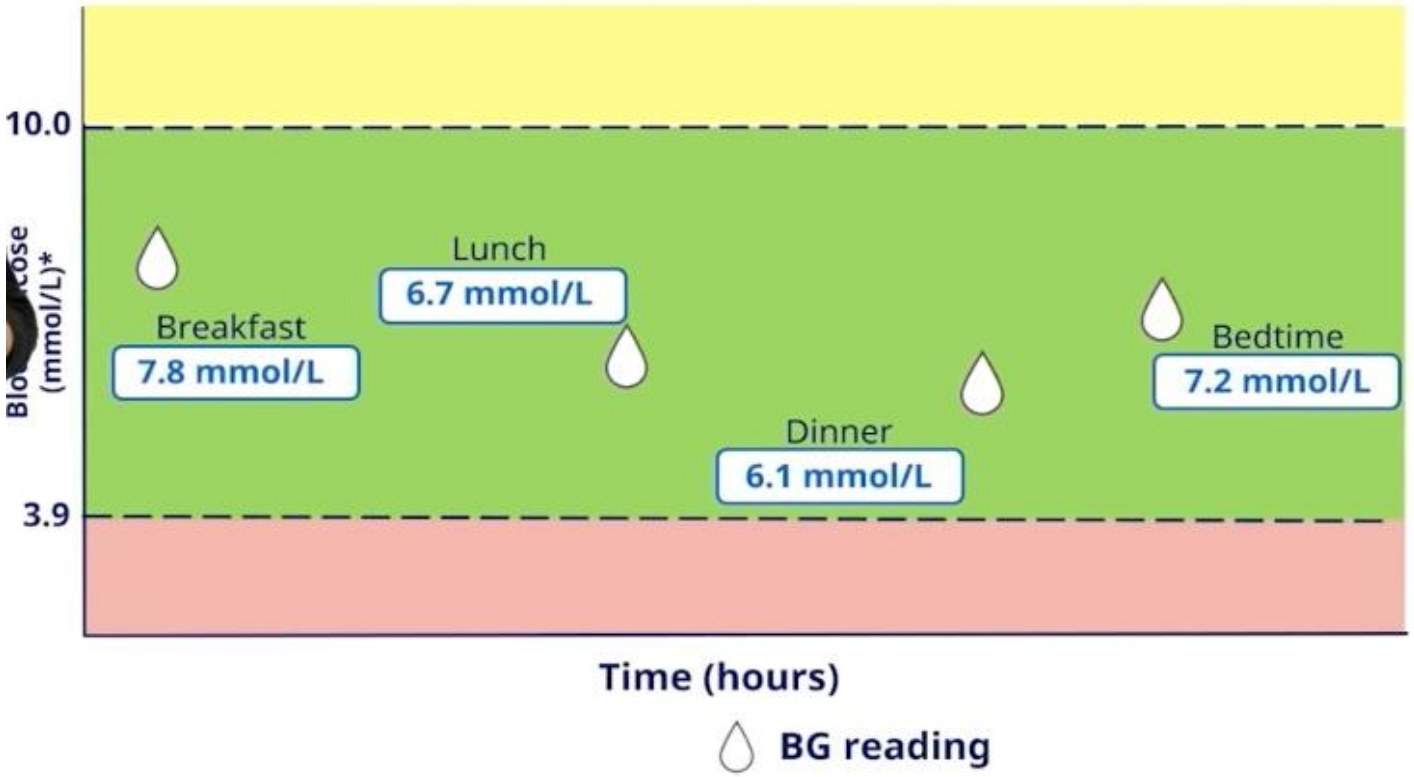


**Plasma concentration plot is for illustrative purposes only.*

Faster aspart, fast-acting insulin aspart; SmPC, summary of product characteristics.

1. Insulin aspart SmPC. Available here. Accessed July 2021; 2. Insulin lispro SmPC. Available here. Accessed July 2021; 3. Insulin glulisine SmPC. Available here. Accessed July 2021; 4. Faster aspart SmPC. Available here. Accessed July 2021; 5. Ultra-rapid lispro. Available here. Accessed July 2021; 6. Heise et al. Clin Pharmacokinet 2017;56:551–9; 7. Kazda et al. Diabetes 2017;66 (Suppl. 1):A247–8.

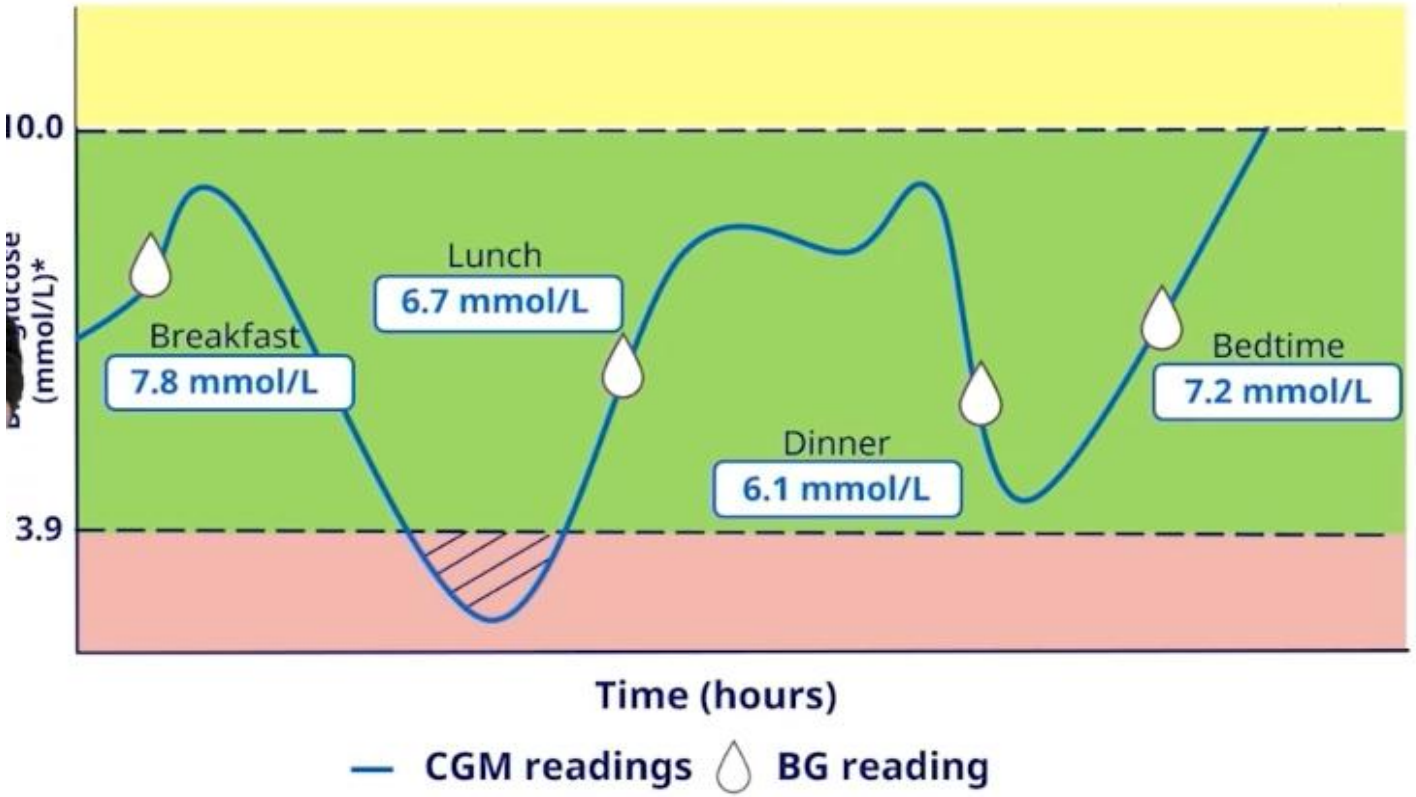
Improving glucose monitoring with continuous glucose monitoring



Finger stick self-measured glucose levels only show a fragmented picture of glucose throughout the day

**Glucose values uncovered with CGM, illustrative example.*
BG, blood glucose; CGM, continuous glucose monitoring.
1. Battelino et al. Diabetes Care 2019;42:1593–603.

Improving glucose monitoring with continuous glucose monitoring



Finger stick self-measured glucose levels only show a fragmented picture of glucose throughout the day

With CGM, the full picture of real-time trends in glucose levels are uncovered

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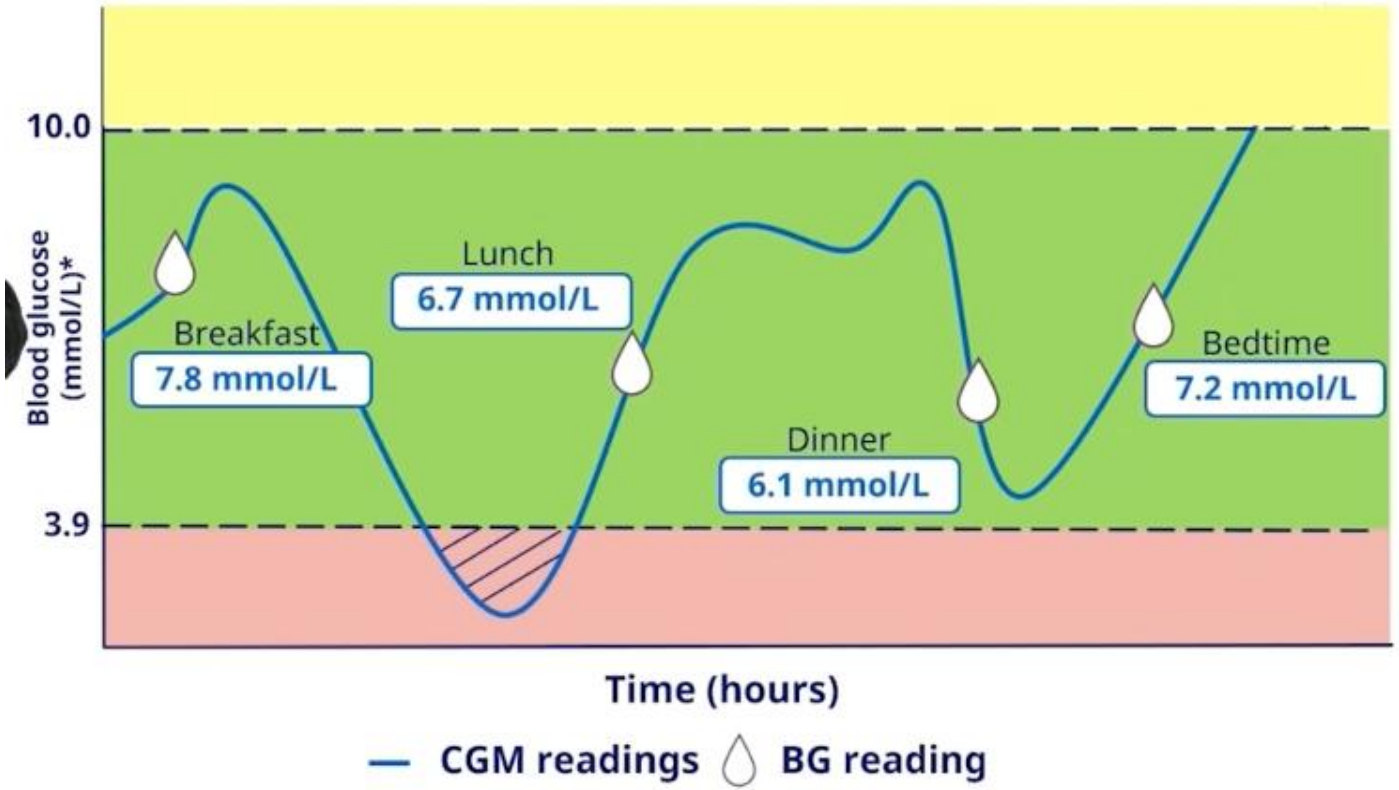

Finger stick self-measured glucose levels only show a fragmented picture of glucose throughout the day

With CGM, the full picture of real-time trends in glucose levels are uncovered

Time in range is a new metric in diabetes management[1]

**Glucose values uncovered with CGM, illustrative example.*
BG, blood glucose; CGM, continuous glucose monitoring.
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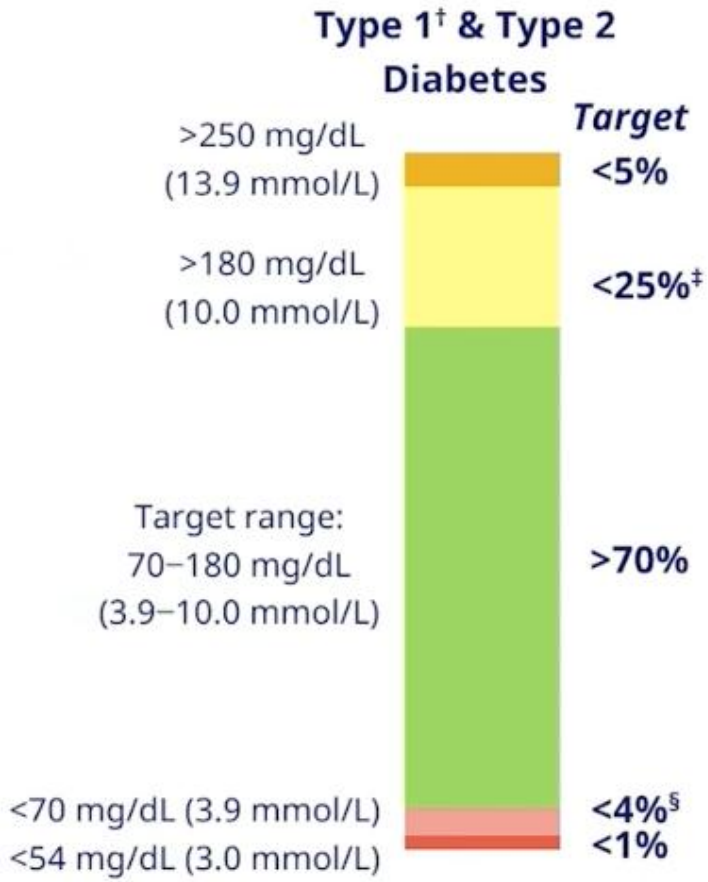
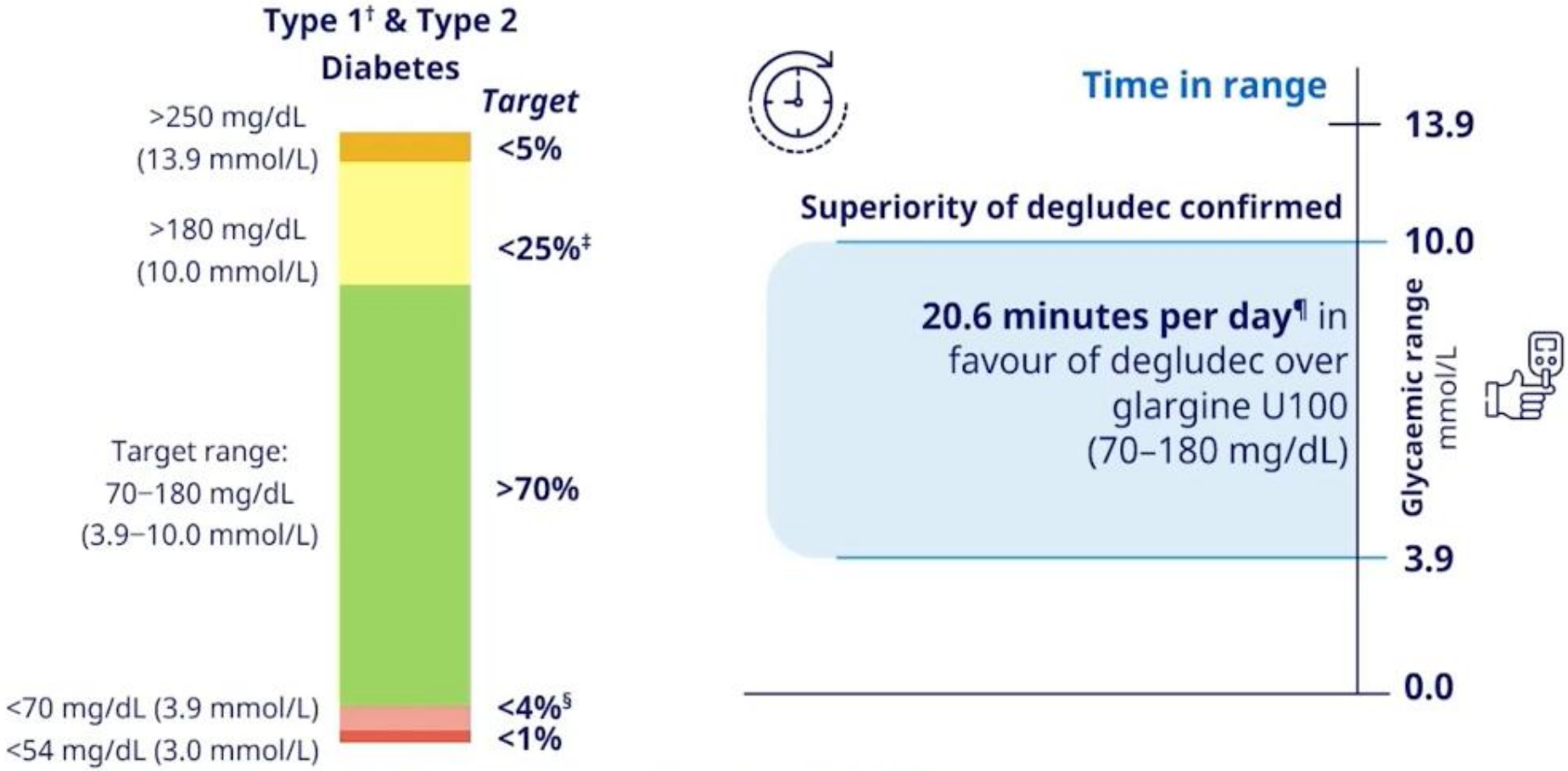


1% difference equals 14.4 minutes a day. Mean time in range (3.9–10.0 mmol/L): 72.11% for IDeg; 70.68% for IGlar U100.
†For age <25 years, if the HbA_{1c} goal is 7.5%, then set TIR target to approximately 60%; ‡Includes percentage of values >250 mg/dL (13.9 mmol/L); §Includes percentage of values <54 mg/dL (3.0 mmol/L); ¶Estimated treatment difference is a significant 1.43%, 95% CI [0.12, 2.74], p=0.032.
CI, confidence interval; degludec, insulin degludec; glargine U100, insulin glargine U100; HbA_{1c}, glycated haemoglobin; TBR, time below range; TIR, time in range.
Battelino et al. Diabetes Care 2019;42:1593–1603; Goldenberg et al. Diabetes Obes Metab 2021;https://doi.org/10.1111/dom.14504.

SWITCH PRO - More TIR with degludec



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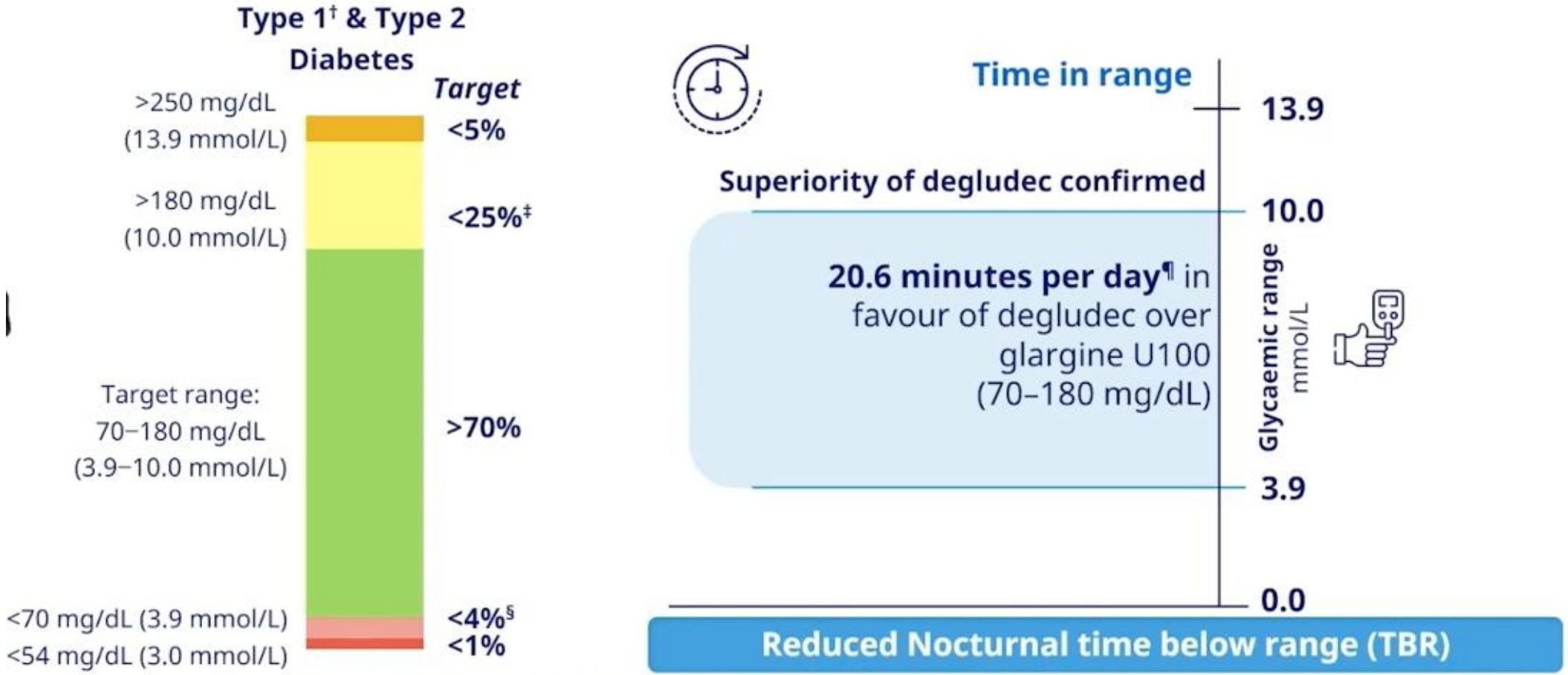
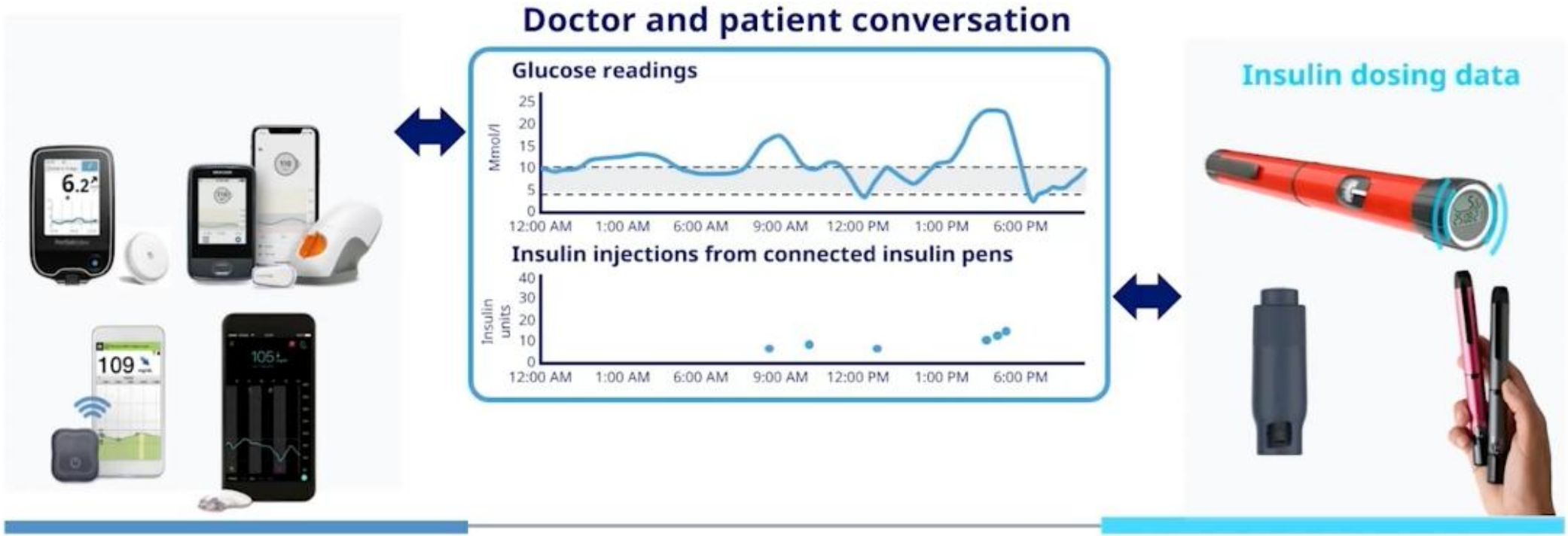
SWITCH PRO - More TIR with degludec



1% difference equals 14.4 minutes a day. Mean time in range (3.9–10.0 mmol/L): 72.11% for IDeg; 70.68% for IGlar U100.
†For age <25 years, if the HbA_{1c} goal is 7.5%, then set TIR target to approximately 60%; ‡Includes percentage of values >250 mg/dL (13.9 mmol/L); §Includes percentage of values <54 mg/dL (3.0 mmol/L); ¶Estimated treatment difference is a significant 1.43%, 95% CI [0.12, 2.74], p=0.032.
CI, confidence interval; degludec, insulin degludec; glargine U100, insulin glargine U100; HbA_{1c}, glycated haemoglobin; TBR, time below range; TIR, time in range.
Battelino et al. Diabetes Care 2019;42:1593–1603; Goldenberg et al. Diabetes Obes Metab 2021;https://doi.org/10.1111/dom.14504.

Combining real-time glucose and insulin data for improved diabetes management



CGM, continuous glucose monitoring.
1. Abbott FreeStyle Libre, Image sourced from here; 2. Dexcom® G6, Image sourced from here; 3. Senseonics Eversense®, Image sourced from here; 4. Medtronic Guardian™ Connect, Image sourced from here; 5. Companion Medical InPen™. Image sourced from here; 6. Common Sensing Gocap™. Image sourced from here; 7. Adolfsson et al. Diabetes 2019;68:1076-P; 8. Jendle et al. Diabetes 2020;69:975-P.
All webpages accessed August 2021.

Insulin innovations: roadmap to the future

Unmet needs in basal insulin therapy

Administration of daily basal insulin can be burdensome and inconvenient[1]

This can result in clinical inertia including delays in insulin initiation, and poor insulin self-management and persistence in T2D[2–5]

Once-weekly medications may offer benefits versus more frequent dosing:[6]

Greater convenience and improved self-management

Improved health-related quality of life

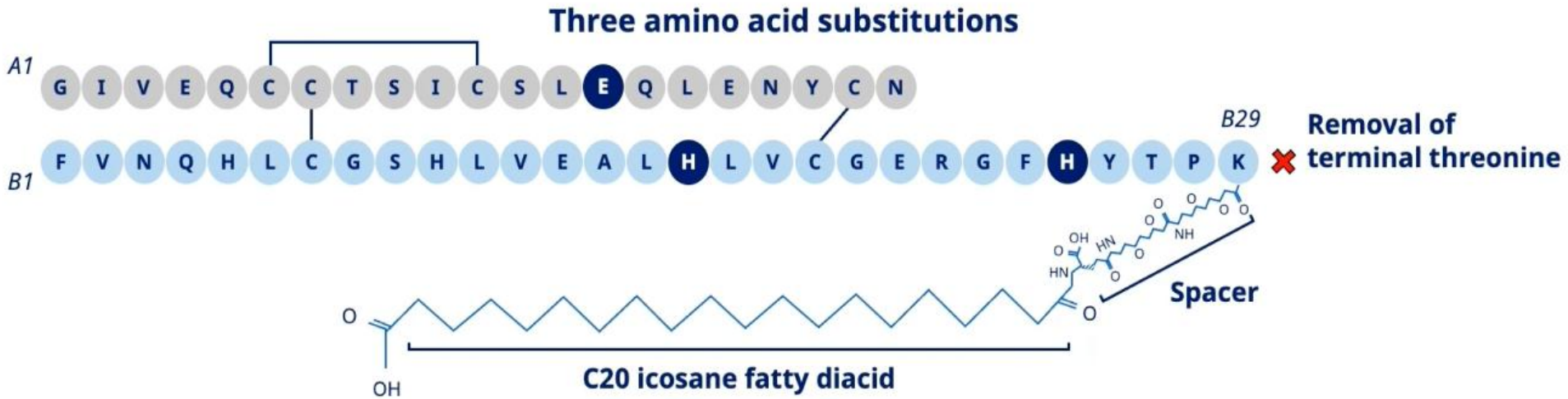
Reduced treatment burden for patients and carers

T2D, type 2 diabetes

1. Peyrot et al. Diabet Med 2012;29:682–9; 2. Sorli et al. J Multidiscip Healthc 2014;7:267–82; 3. Berard et al. Diabetes Obes Metab 2018;20:301–8; 4. Pantalone et al. Diabetes Care 2018;41:e113–4; 5. Khunti et al. Diabetes Obes Metab 2018;20:427–37; 6. Polonsky et al. Diabetes Obes Metab 2011;13:144–9

Molecular structure of insulin icodec

Mechanism of protraction



High and reversible albumin binding

Reduced enzymatic degradation

Reduced insulin receptor-mediated clearance

Nishimura et al. BMJ Open Diab Res Care 2021;9:e002301

Insulin icodec is suitable for once-weekly dosing

Pharmacokinetics

Median $t_{max,\ icodec}$
16 hours

Plasma $t_{½,\ icodec}$
196 hours

Pharmacodynamics

The **half-life of** icodec is approximately **1 week**[1]

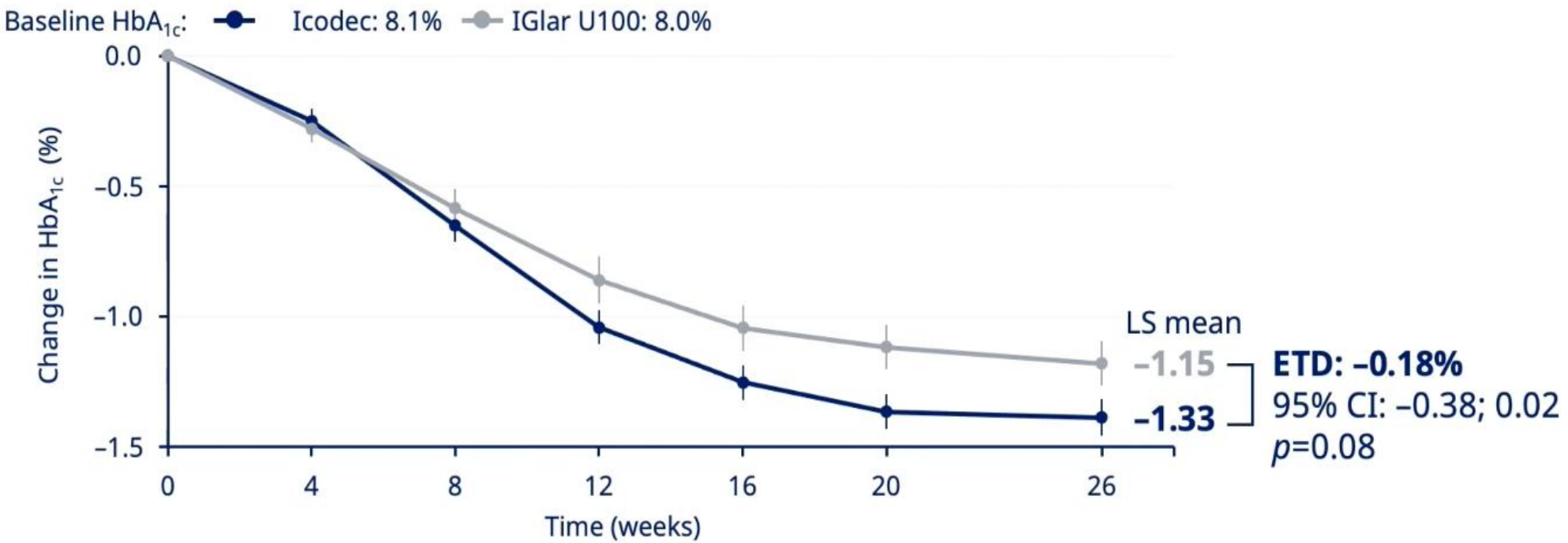
The glucose lowering effect of insulin icodec **was rather consistent** throughout the week[1]

Steady state is achieved after **3–4 once-weekly injections**[2]

Modelled distribution of total glucose-lowering effect (AUC_{GIR}) of insulin icodec within a dosing interval of 1 week at close to steady state. All three dose levels are combined. Participants completing both glucose clamps and with PK data at steady state are included (N=32). Data are arithmetic mean
AUC, area under the curve; degludec, insulin degludec; GIR, glucose infusion rate; icodec, insulin icodec; PK, pharmacokinetic; $t_{½}$, elimination half-life; t_{max}, time of maximum concentration
1. Hövelmann et al. EASD 2020; Poster 656; 2. Nishimura et al. BMJ Open Diab Res Care 2021;9:e002301

Mean change in HbA_{1c}

Icodec vs IGlar U100 in insulin-naïve T2D

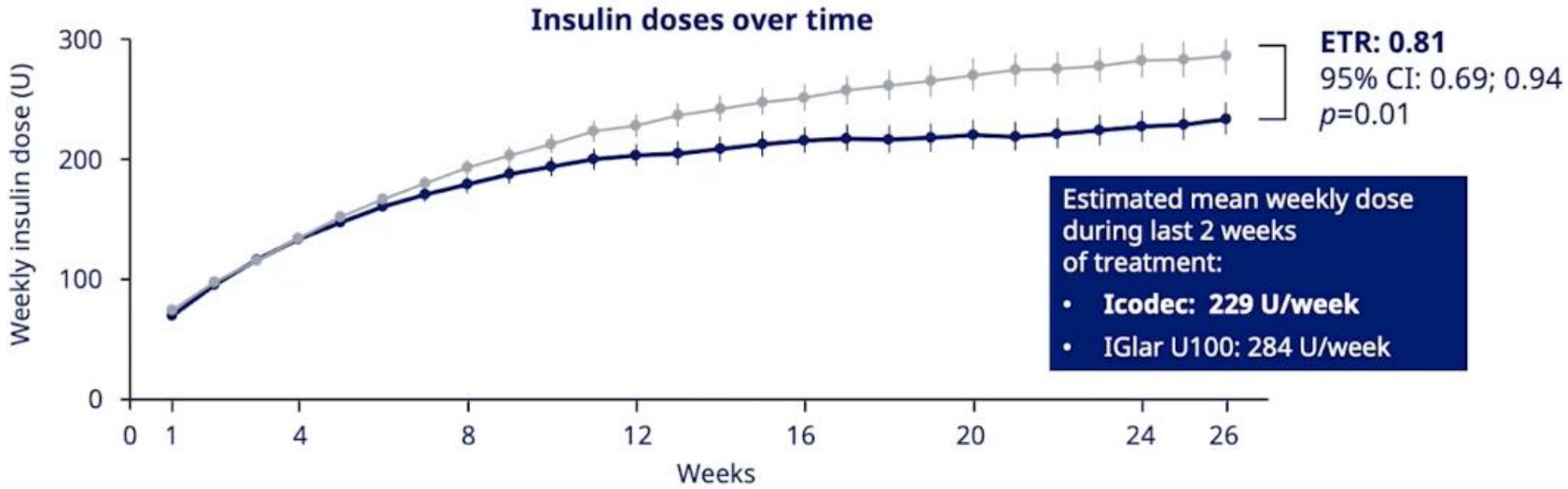


There was a **similar improvement** in **HbA_{1c}** between icodec and IGlar U100

Data are observed mean ± SEM (error bars) on-treatment without ancillary treatment
CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin; icodec, insulin icodec; IGlar U100, insulin glargine 100 units/mL; LS, least squares; SEM, standard error of the mean; T2D, type 2 diabetes
Rosenstock et al. N Engl J Med 2020;383:2107–16

Weekly insulin dose

Icodec vs IGlar U100 in insulin-naïve T2D

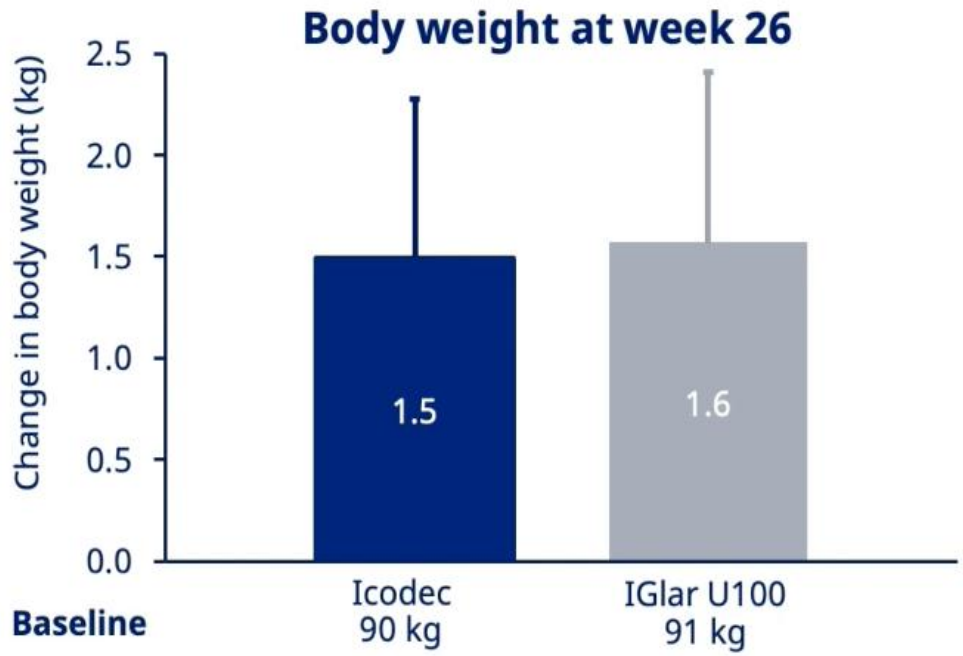


The estimated **mean weekly dose of treatment** was **significantly lower with icodec** vs IGlar U100

The log-transformed response during the last two weeks of treatment was analysed using an ANOVA model (trial product estimand)
ANOVA, analysis of variance; CI, confidence interval; ETR, estimated treatment ratio; icodec, insulin icodec; IGlar U100, insulin glargine 100 units/mL; T2D, type 2 diabetes; U, unit
Rosenstock et al. N Engl J Med 2020;383:2107–16

Change in body weight

Icodec vs IGlar U100 in insulin-naïve T2D



Change in **body weight was similar** between the two treatment arms

Data are mean (symbol) and mean ± SEM (error bars)
Icodec, insulin icodec; IGlar U100, insulin glargine 100 units/mL; SEM, standard error of the mean; T2D, type 2 diabetes
Rosenstock et al. N Engl J Med 2020;383:2107–16

Hypoglycaemic episodes

Icodec vs IGlar U100 in insulin-naïve T2D

Hypoglycaemia Levels	Icodec (N = 125)		IGlar U100 (N = 122)	
	n (%)	E (R)	n (%)	E (R)
Level 1	67 (53.6)	368 (5.09)	46 (37.7)	148 (2.11)
Level 2 or Level 3	20 (16.0)	38 (0.53)	12 (9.8)	32 (0.46)
Level 3	1 (0.8)	1 (0.01)	0	–

- **Level 1** hypoglycaemic episodes were **more common** in patients receiving **icodec** than **IGlar U100**
- **There was no statistically significant difference** between icodec and IGlar U100 for combined clinically significant (**level 2**) or severe (**level 3**) hypoglycaemic episodes

Safety analysis set (table). Full analysis set (supportive statistical analysis). On-treatment: onset date on or after the first dose of trial product and no later than the first date of either the last follow-up visit (FU2), the last date on trial product (+ 5 weeks for once-daily insulin and + 6 weeks for once-weekly insulin), or the end date for the in-trial period. Level 1 defined as <3.9 mmol/L (<70 mg/dL) and ≥3.0 mmol/L (≥54 mg/dL), level 2 as <3.0 mmol/L (<54 mg/dL), and level 3 (severe) hypoglycaemia defined as any episode requiring external assistance for recovery. Number of events was analysed using a negative binomial regression model (log link)

%, percentage of patients with one or more events; E, number of events; icodec, insulin icodec; IGlar U100, insulin glargine 100 units/mL; n, number of patients with one or more events; R, rate (number of events per patient-year of exposure)

Rosenstock et al. N Engl J Med 2020;383:2107–16

Switching from basal insulin to icodec

Icodec ± LD vs IGlar U100 in T2D

Total daily dose depends on pre-trial insulin regimen

Switching from OD basal insulin*	Switching from OD glargine U300 or BID basal insulin	Conversion to OW icodec
1:1	↓ **20%**	**7x total daily dose** *Patients on icodec OW **with loading dose arm** had **first dose doubled***

**Excluding glargine U300. Dose adjustment was based on three pre-breakfast SMBG values, measured two days prior to and on the day of titration. If any of the three pre-breakfast SMBG values were below the lower limit of the target range, titration was based on the lowest recorded value. If all three SMBG values were above the lower limit of the target range, titration was based on the mean of the three measurements*

BID, twice daily; icodec, insulin icodec; IGlar U100, insulin glargine 100 units/mL; LD, loading dose; OD, once daily; OW, once weekly; SMBG, self-measured blood glucose; T2D, type 2 diabetes; U, unit

Bajaj et al. Diabetes Care 2021;doi.org/10.2337/dc20-2877

Insulin icodec phase 3a clinical development: ONWARDS Program

Insulin-naïve T2D

ONWARDS 1[1] — n=970, 78 weeks
- Icodec + non-insulin antidiabetic drugs
- IGlar U100 + non-insulin antidiabetic drugs

ONWARDS 3[2] — n=774, 26 weeks
- Icodec + non-insulin antidiabetic drugs
- Degludec + non-insulin antidiabetic drugs

ONWARDS 5[3] — RCT with real-world elements n=1096, 52 weeks
- Icodec with dose guide
- Once-daily basal insulin analogues

Insulin-treated T2D

ONWARDS 2[4] — Basal switch T2D, n=520, 26 weeks
- Icodec ± non-insulin antidiabetic drugs
- Degludec ± non-insulin antidiabetic drugs

ONWARDS 4[5] — Basal-bolus T2D, n=580, 26 weeks
- Icodec + insulin aspart ± non-insulin antidiabetic drugs
- IGlar U100 + insulin aspart ± non-insulin antidiabetic drugs

T1D

ONWARDS 6[6] — Basal-bolus T1D n=580, 52 weeks
- Icodec + insulin aspart
- Degludec + insulin aspart

Degludec, insulin degludec; icodec, insulin icodec; IGlar U100, insulin glargine 100 units/mL; n, number of participants; RCT, randomised controlled trial; T1D, type 1 diabetes; T2D, type 2 diabetes; U, unit.

1. ONWARDS 1: https://www.clinicaltrials.gov/ct2/show/NCT04460885; 2. ONWARDS 3: https://clinicaltrials.gov/ct2/show/NCT04795531; 3. ONWARDS 5: https://clinicaltrials.gov/ct2/show/NCT04760626; 4. ONWARDS 2: https://clinicaltrials.gov/ct2/show/NCT04770532; 5. ONWARDS 4: https://clinicaltrials.gov/ct2/show/NCT04880850; 6. ONWARDS 6: https://clinicaltrials.gov/ct2/show/NCT04848480

Technologies under development for digital health with insulin icodec

Blood glucose monitors

Glucose readings

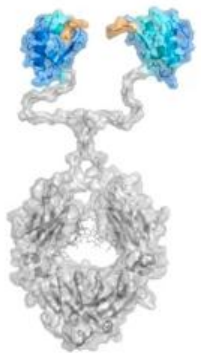
Dosing data

Dose guidance app to support patients with titration

Insulin pen with an add-on connectivity

Other weekly insulin analogues under development

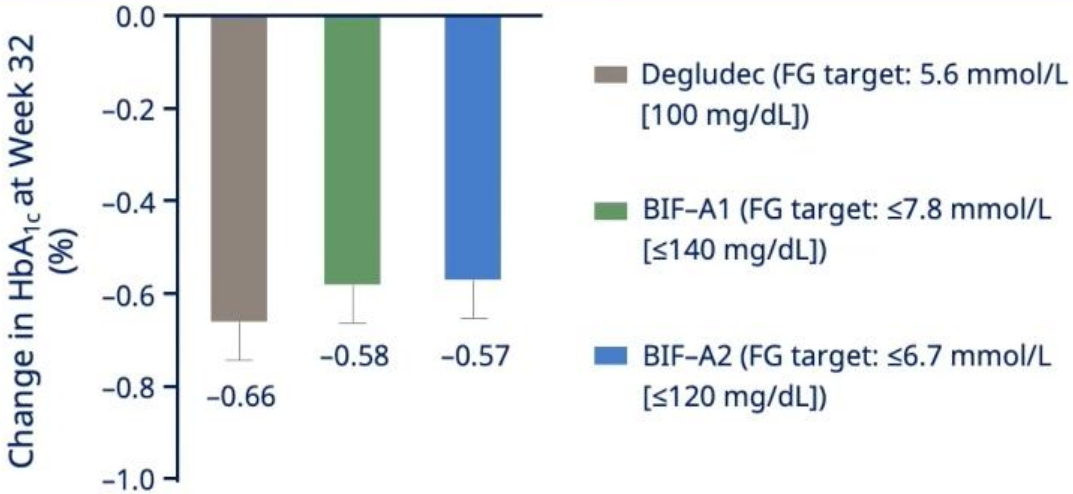
Basal insulin Fc (BIF) – Eli Lilly



A novel single-chain variant of insulin plus the IgG_2 Fc-domain*

An **ongoing phase 2 program** is evaluating the **efficacy and safety of BIF against degludec** with a FG target of 5.6 mmol/L (101 mg/dL) in **patients with T2D and T1D**

Randomised, open-label, phase 2 study of 399 insulin-experienced patients with T2D



BIF achieved non-inferiority for HbA_{1c} change from baseline vs degludec[2]

**Fc, antibody fragment crystallizable domain*
BIF, basal insulin Fc; degludec, insulin degludec; FG, fasting glucose; HbA_{1c}, glycated haemoglobin; IgG_2, immunoglobulin G2; T1D, type 1 diabetes; T2D, type 2 diabetes; TIR, time-in-range.
1. Kazda et al. ADA Scientific Sessions 2021;192–OR; 2. Frias et al. 2021 ENDO Presentation; Session OR09

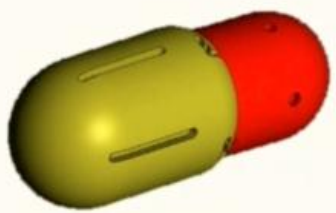
Exploring future diabetes treatments: oral insulins

- The most advanced oral insulins include **insulin tregopil** (Biocon) and **ORMD-0801** (Oramed)[1,2]
  - Phase 2 ORMD-0801 data and early phase 3 tregopil data showed a modest anti-hyperglycaemic effect vs placebo[2,3]
- The challenge of poor bioavailability has resulted in preclinical investigation of other oral insulin technologies:

Self-orienting millimetre-scale applicator (SOMA)[4]

Brigham and Women's Hospital, MIT, Novo Nordisk

High velocity liquid injection[5]

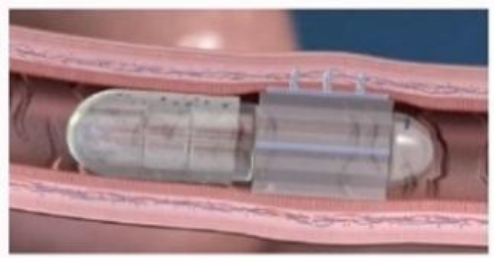


Baywind Bioventures Propel Biologics™ JetCAP™

Passive hooking method[6]

Biograil BIONDD®

Dissolvable microneedle in enteric capsule[7]



Rani Therapeutics RaniPill®

1. Khedkar A et al. Clin Pharmacol Drug Dev 2020;9:74-86; 2. Eldor R et al. Diabetes Obes Metab 2021; 10.1111/dom.14499; 3. Zijlstra E et al. *J Diabetes Sci Technol* 2014;8 (3):458–65;
4. Abramson et al. Science 2019;363(6427):611–5; 5. Baywind Bioventures Propel Biologics™ JetCAP™; baywindbio.com; 6. Biograil™ BIONDD™: https://biograil.com (accessed July 21, 2021);
7. Rani Therapeutics RaniPill™: https://www.ondrugdelivery.com/interview-mir-imran/ (accessed July 21, 2021)

Exploring future diabetes treatments: glucose sensitive insulins or stem cell therapy

Glucose sensitive insulin[1]

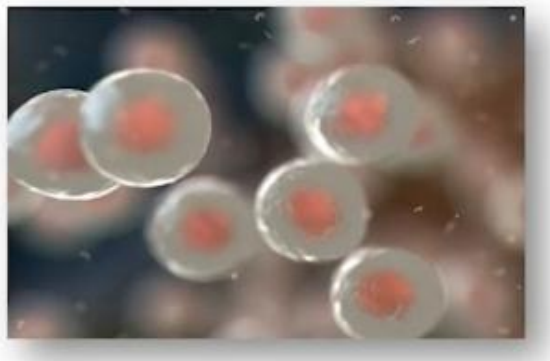
A **'smart' insulin** with built-in glucose sensitivity could minimise **hypoglycaemic episodes**

Low glucose (<5 mM)
Insulin in inactive conformation

High glucose (5–20 mM)
Insulin in active conformation

Stem cell therapy[2,3]

Generating functional **beta cells** eliminating the need for daily self-administration of insulin



1. Jarosinski et al. Diabetologia 2021;64(5):1016–29; 2. Madsen & Serup. Nat Biotech 2006;24:1481–3; 3. Duo et al. PNAS 2018;115(2):E263–72

CellPress

Commentary

Insulin Access and Cost at 100 Years: What Would Dr. Banting Think?

Irl B. Hirsch[1,*]

As we celebrate the 100th anniversary of the discovery of insulin, this is a good time to reflect on how well (or not) our society has succeeded in Sir Frederick Banting's proclamation: "Insulin does not belong to me; it belongs to the world."[1] Dr. Banting and his colleagues, Charles Best and James Collip, sold the patent for $1 each. The desire was straightforward: that everyone who needed this life-saving drug should have it. By 1923, insulin was the highest

aspirations, Dr. Banting's desire for universal access to insulin was wishful thinking. For many years after its discovery, insulin was only available in high-income countries.[2] Perhaps that was inevitable, but it is also true, even today, that we are still a world of "haves" and "have-nots" regarding insulin access.[3] Worldwide, the most common cause of death in a child with diabetes is

the unavailability of insulin.[4] That would surely devastate Dr. Banting and his colleagues, as they believed their medical miracle had reversed the course of this ancient disease. Even more unfathomable is that current subpopulations within high-income countries also struggle to obtain insulin.

Because of my location, the most common reaction to insulin prices I have seen, at least prior to the COVID-19 pandemic, was a quick trip across the Canadian border where insulin could be purchased for 10% of the US retail price. At one point, about 20% of my patients were taking the scenic 2 h drive to stock up on Banting's discovery that at one time "belonged to the world."

In 2019, Herkert and colleagues reported that in a US urban diabetes center, one in four insulin users withheld insulin due to cost, and this was associated with poor glycemic control.[5]

A more recent report from 64 countries noted that both globally and in the US, roughly the same percentage of individuals with type 1 diabetes (about 25% worldwide, 29.8% in the US) were required to ration insulin dosing due to cost.[6] A similar number of patients

Opensecrets.org is a "nonpartisan, independent, and nonprofit premier research group tracking money in US politics and its effects on elections and public policy." In 2018, the pharmaceutical industry spent more on political lobbying ($280 million) than any other industry.[13] In 2020, the three major insulin manufacturers were among the top 11 contributors to "federal candidates, parties, and outside groups."[14]

July 2021, when the Food and Drug Administration, after more than a decade, approved the first biosimilar (a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product) and *interchangeable* insulin. A biosimilar

We have come a long way, for better and worse, since Dr. Banting and his fellow researchers made their miraculous discovery. It is my hope that someday soon, we can celebrate not only the brilliance of their medical breakthrough but also the humanity of their vision: a world with insulin for all.