DO WE NEED NEWER INSULINS FOR OUR PATIENTS?

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Learning Objectives

- Examine the benefits and limitations of newer insulins relative to conventional insulins

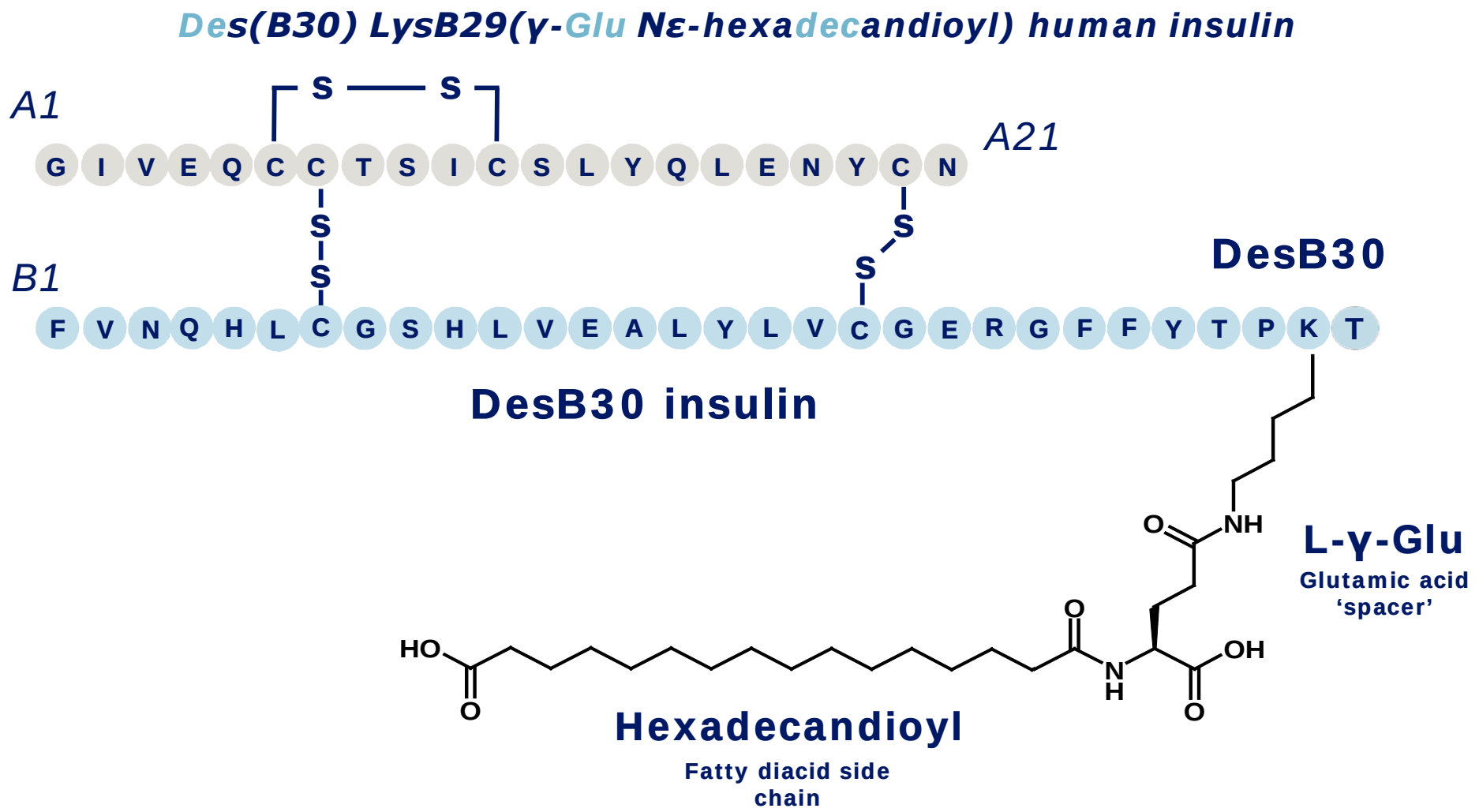
CASE 1

- Mr. J.S. is 52 years old and was diagnosed with diabetes 8 years ago. He is currently on metformin, canagliflozin and semaglutide therapy. Six months ago his HgA1c was 8.5% and he was started on insulin glargine U/100 at 20 units at bedtime with self–titration.
- He returns today; he has increased his dose to 36 units and is seeing a fasting glucose between 6-10 mmol/L most days. His HgA1c is now 7.4% but he has gained 4.8 kg and he has overnight hypoglycemia once every 2 weeks.

Any ideas of what to suggest?

Insulin degludec

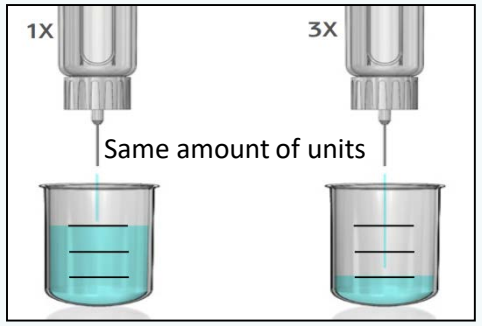
Rationally designed, beyond sequence modification



Jonassen et al. *Pharm Res* 2012;29:2104–2114.

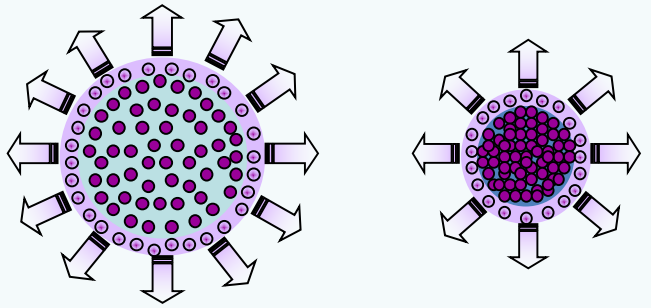
Insulin Glargine 300 U/mL: A New Long-acting Basal Insulin

1/3 of the volume



100 U/mL 300 U/mL

Reduction of depot surface by 1/2

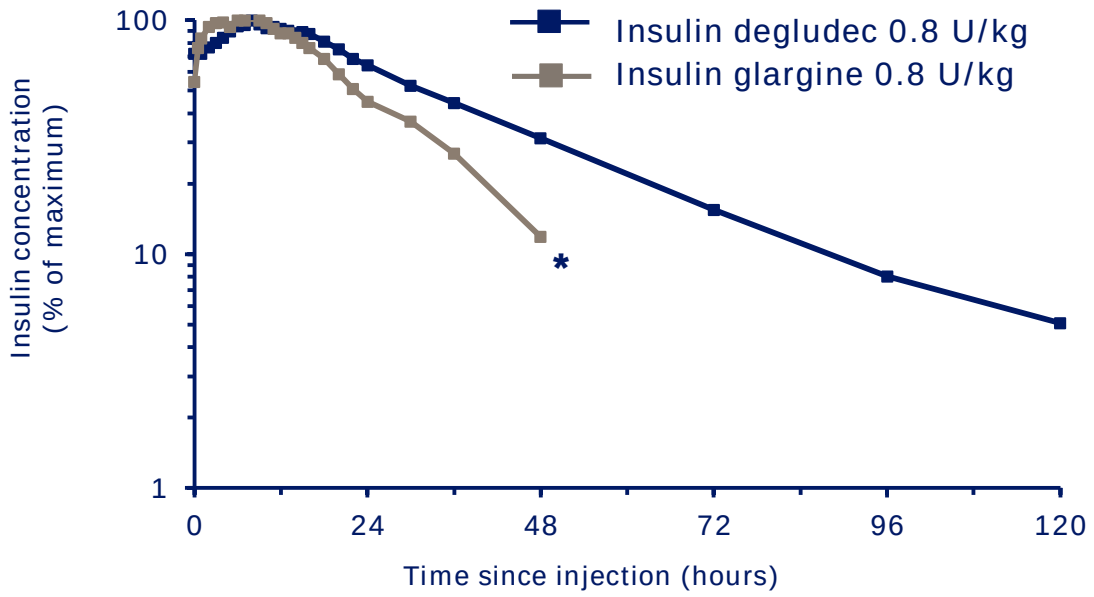


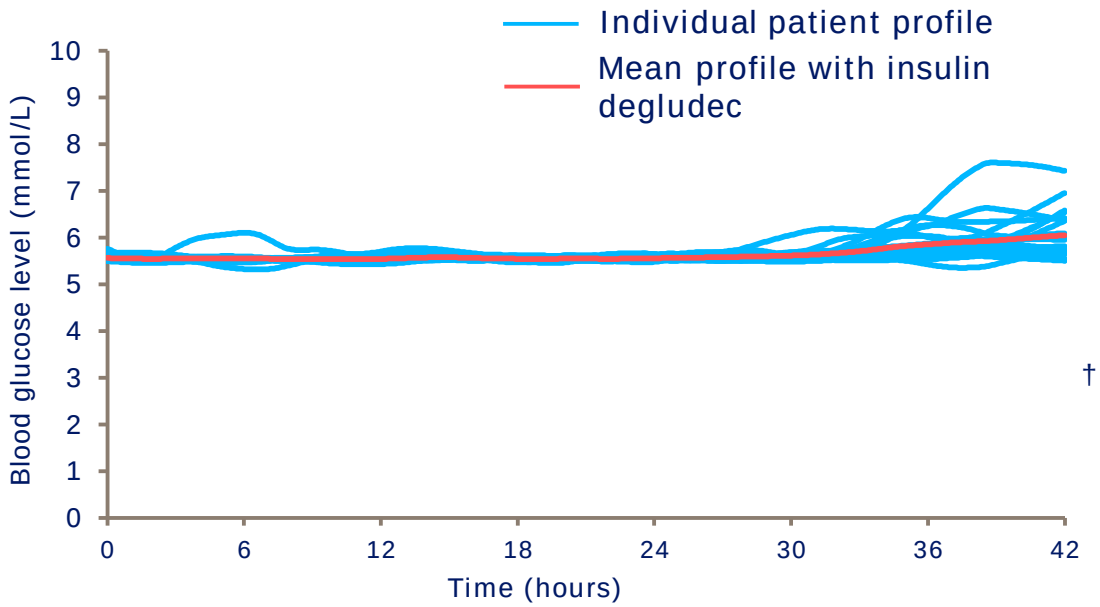
100 U/mL 300 U/mL

- Insulin glargine 300 U/mL contains insulin glargine
- Insulin glargine 300 U/mL is metabolized the same way as insulin glargine 100 U/mL (Lantus®)

Becker RHA *et al. Diabetes Care*. 2015;38:637-643; Steinstraesser A *et al. Diabetes Obes Metab*. 2014;16:873-876

Half-life of insulin degludec is twice as long as that of insulin glargine, with a duration of action extending beyond 42 hours





	Insulin degludec			Insulin glargine		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Half-life (hours)	25.9	27.0	23.6	11.5	12.9	11.9
Mean half-life	**25.4**			**12.1**		

* Insulin glargine was undectable after 48 hours. Results from 66 patients with T1DM. † Mean and individual blood glucose profiles during 42-h clamp.

Heise et al. *Diabetes* 2011;60(Suppl. 1):LB11; Heise et al. *Diabetologia* 2011;54(Suppl. 1):S425; Heise et al. *Expert Opin Drug Metab Toxicol* 2015;11(8):1193–1201; Kurtzhals et al. *Diabetologia* 2011;54(Suppl. 1):S426.

Pre-specified meta-analyses: Overall confirmed hypoglycemia

T2DM

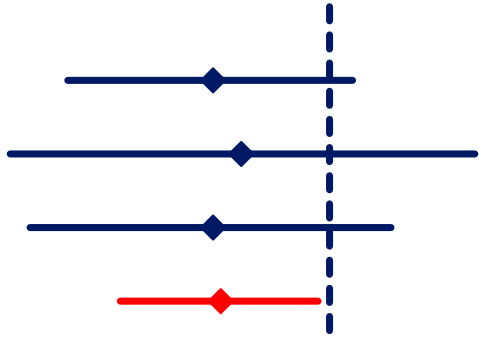
Basal only

ONCE LONG (52 wk)

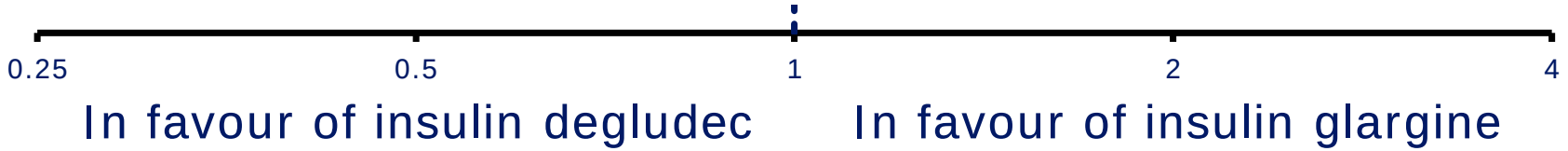
LOW VOLUME (26 wk)

ONCE Asia (26 wk)

Pooled insulin naïve T2DM



0.83 [0.70; 0.98] **Significant***

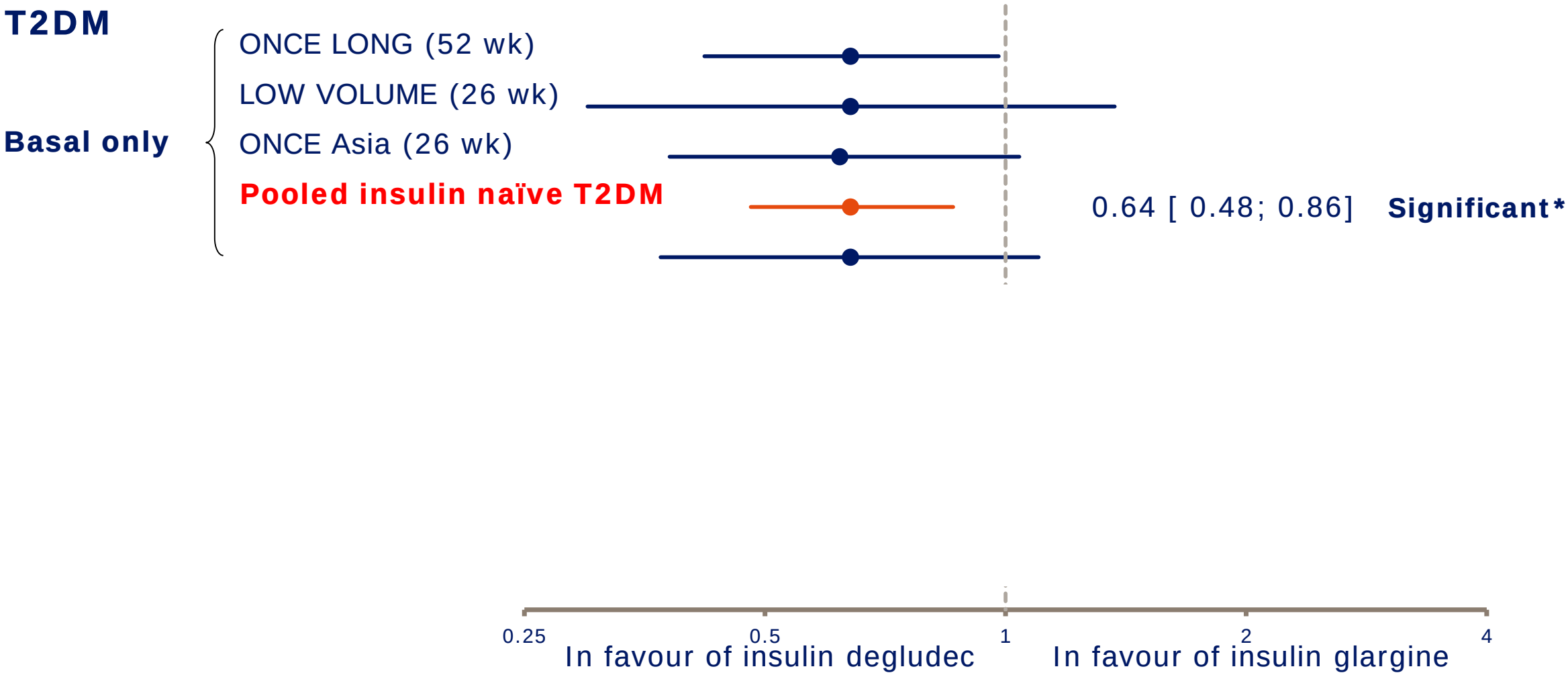


Adjusted for trial, type of diabetes, anti-diabetes therapy at screening, sex, region, age

*Significantly lower risk based on 95% confidence interval

Ratner et al. *Diabetes, Obesity and Metabolism* 15: 175–184, 2013

Pre-specified meta-analyses: Overall confirmed nocturnal hypoglycemia

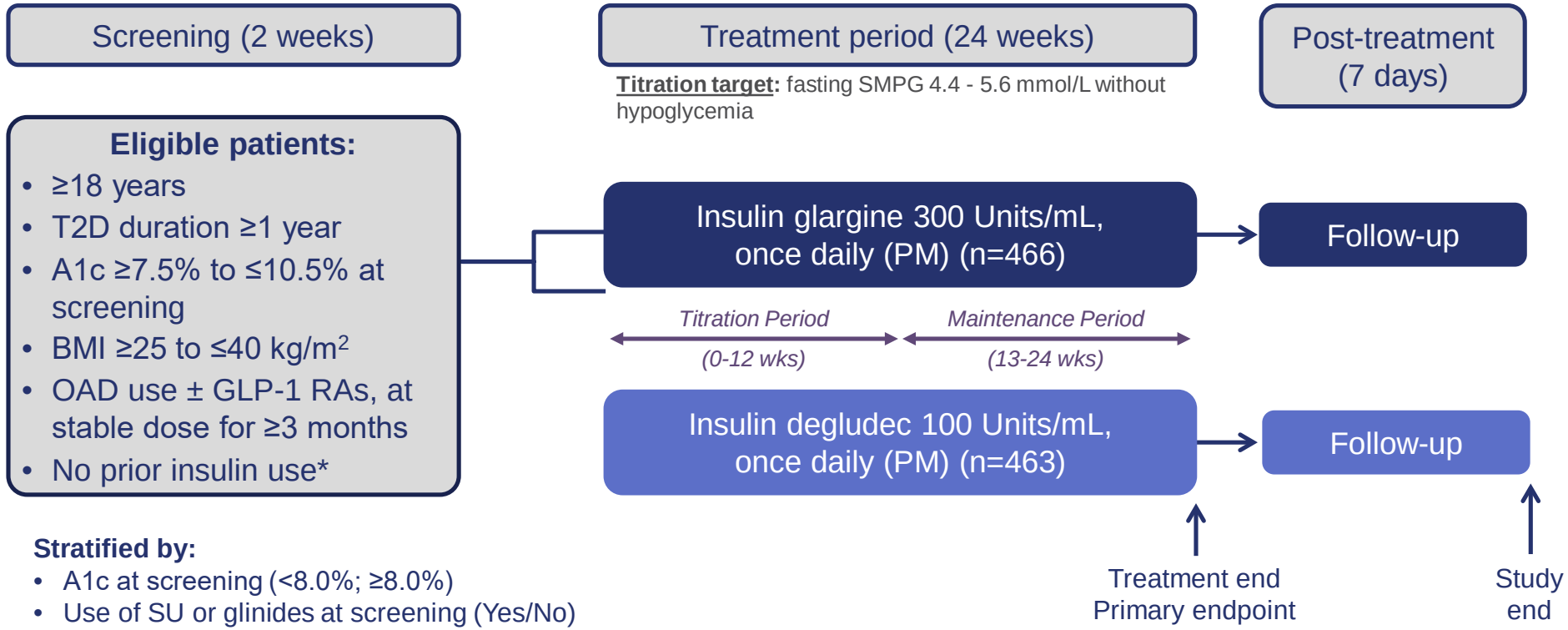


Adjusted for trial, type of diabetes, anti-diabetes therapy at screening, sex, region, age
*Significantly lower risk based on 95% confidence interval

Ratner et al. *Diabetes, Obesity and Metabolism* 15: 175–184, 2013

Study Design

- Multicenter, open-label, 1:1 randomized, active-controlled, 2-arm parallel-group, non-inferiority study in insulin-naive adults with uncontrolled T2D



*With exception of a maximum of 8 consecutive days or 15 days total prior insulin use.
BMI: body mass index; GLP-1 RA: glucagon-like protein-1 receptor agonist; n: number; OAD: oral antidiabetic drug; PM: evening; SMPG: self-monitoring plasma glucose; SU: sulfonylurea; T2D: type 2 diabetes.

Rosenstock J, et al. *Diabetes Care*. 2018;41(10):2147-2154.

Insulin Dose and Titration

Insulin dose:

- Self-administered once daily between 6-8 PM
- Starting daily dose (per label):
  - Insulin glargine 300 Units/mL: **0.2 Units/kg**
  - Insulin degludec 100 Units/mL: **10 Units**
- Titrated weekly* to target fasting SMPG of 4.4 - 5.6 mmol/L without hypoglycemia
  - Aim of target achievement within 8-12 weeks post randomization (titration period)

Titration algorithm

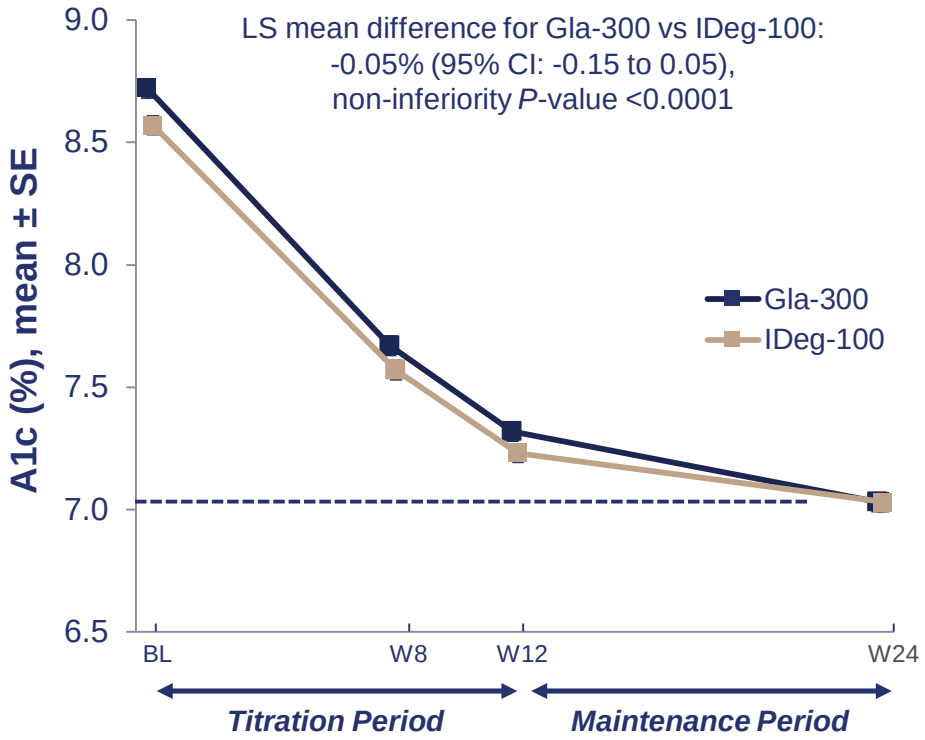
Median† fasting SMPG	Insulin glargine 300 Units/mL and insulin degludec 100 Units/mL dose change
>7.8 mmol/L	+6 Units
>6.7 to ≤7.8 mmol/L	+4 Units
>5.6 to ≤6.7 mmol/L	+2 Units
≥4.4 to ≤5.6 mmol/L	**0**
<4.4 mmol/L *or* 1 episode of symptomatic hypoglycemia in preceding week	-2 Units or at investigator's discretion

*Doses titrated at least weekly, but no more than every 3 days. †From last 3 measurements.
PM: evening; SMPG: self-monitoring plasma glucose.

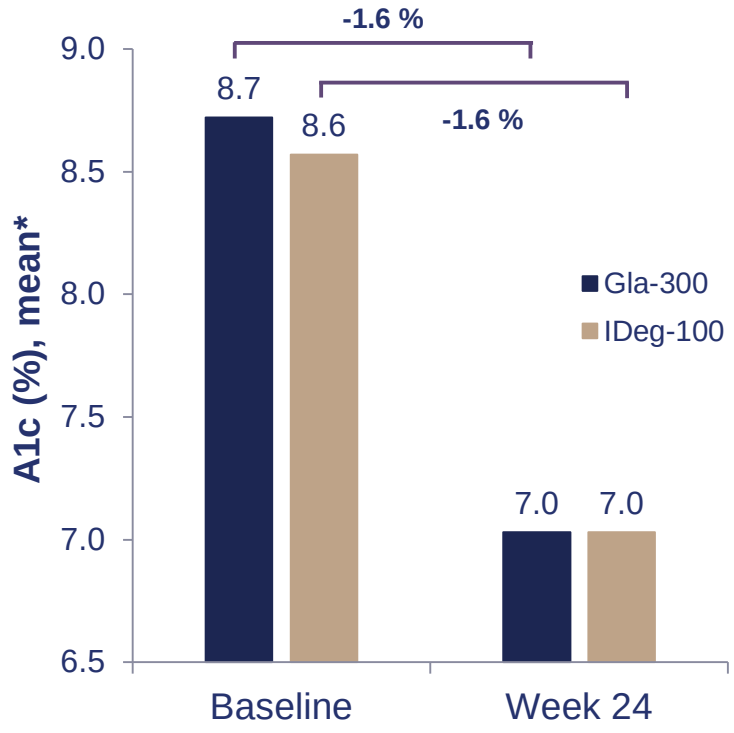
Rosenstock J, et al. *Diabetes Care*. 2018;41(10):2147-2154.

Non-inferiority of Insulin Glargine 300 Units/mL vs Insulin Degludec 100 Units/mL in A1c Reduction at Study End

Mean A1c



Mean A1c at baseline and Week 24

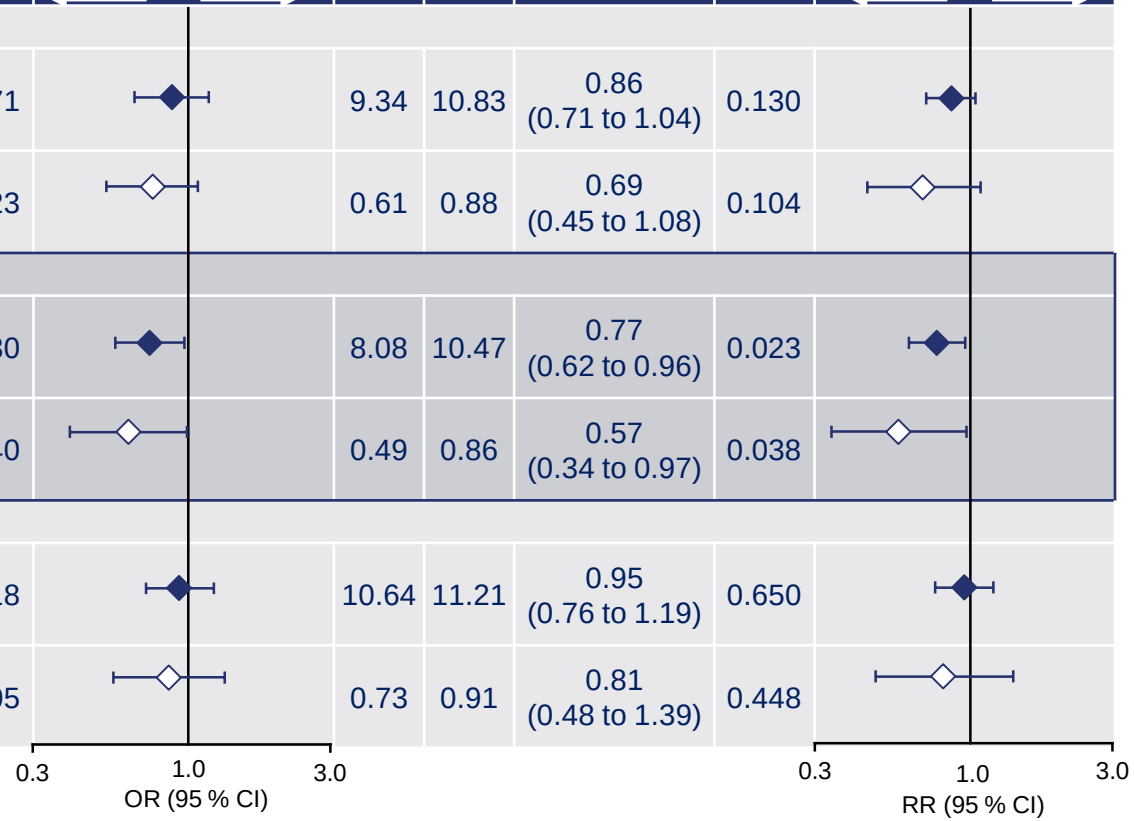


*Change from baseline to Week 24 displayed as LS mean values. Intent-to-treat population. BL: baseline; CI: confidence interval; Gla-300: insulin glargine 300 Units/mL; IDeg-100: insulin degludec 100 Units/mL; LS: least squares; SE: standard error; W: week.

Rosenstock J, et al. *Diabetes Care*. 2018;41(10):2147-2154.

Anytime (24-h) Hypoglycemia

	Incidence, %					Events per patient-year				
	Gla-300	IDeg-100	OR (95% CI)	*P*-value	Favors Gla-300 / Favors IDeg-100	Gla-300	IDeg-100	RR (95% CI)	*P*-value	Favors Gla-300 / Favors IDeg-100
Full study period (0-24 weeks)										
Confirmed (≤3.9 mmol/L)	66.5	69.0	0.88 (0.66 to 1.17)	0.371		9.34	10.83	0.86 (0.71 to 1.04)	0.130	
Confirmed (<3.0 mmol/L)	14.7	18.4	0.76 (0.53 to 1.08)	0.123		0.61	0.88	0.69 (0.45 to 1.08)	0.104	
Titration period (0-12 weeks)										
Confirmed (≤3.9 mmol/L)	47.4	54.3	0.74 (0.57 to 0.97)	0.030		8.08	10.47	0.77 (0.62 to 0.96)	0.023	
Confirmed (<3.0 mmol/L)	7.8	11.7	0.63 (0.40 to 0.99)	0.040		0.49	0.86	0.57 (0.34 to 0.97)	0.038	
Maintenance period (13-24 weeks)										
Confirmed (≤3.9 mmol/L)	54.1	55.8	0.93 (0.72 to 1.22)	0.618		10.64	11.21	0.95 (0.76 to 1.19)	0.650	
Confirmed (<3.0 mmol/L)	9.8	11.2	0.86 (0.56 to 1.33)	0.505		0.73	0.91	0.81 (0.48 to 1.39)	0.448	



P-values are for descriptive purposes only and have not been adjusted for multiplicity.
Confirmed hypoglycemia: documented symptomatic or asymptomatic hypoglycemia (≤3.9 or <3.0 mmol/L), and severe events if any; 1 participant experienced severe hypoglycemia in the Gla-300 group, due to a skipped evening meal and not reducing insulin dose after a non-severe event 2 days earlier. Safety population: insulin glargine 300 Units/mL (Gla-300), n=463; insulin degludec 100 Units/mL (IDeg-100), n=462. OR: odds ratio; RR: rate ratio.

Rosenstock J, et al. *Diabetes Care*. 2018;41(10):2147-2154.

Clinician-reported insights of insulin degludec across five European countries

Robinson A, *et al*. Diabetic Medicine. 2015;32(Suppl 1):168 (P457).

Ratner *et al, Diabetes Obes Metab* 2013;15:175–184

Objectives

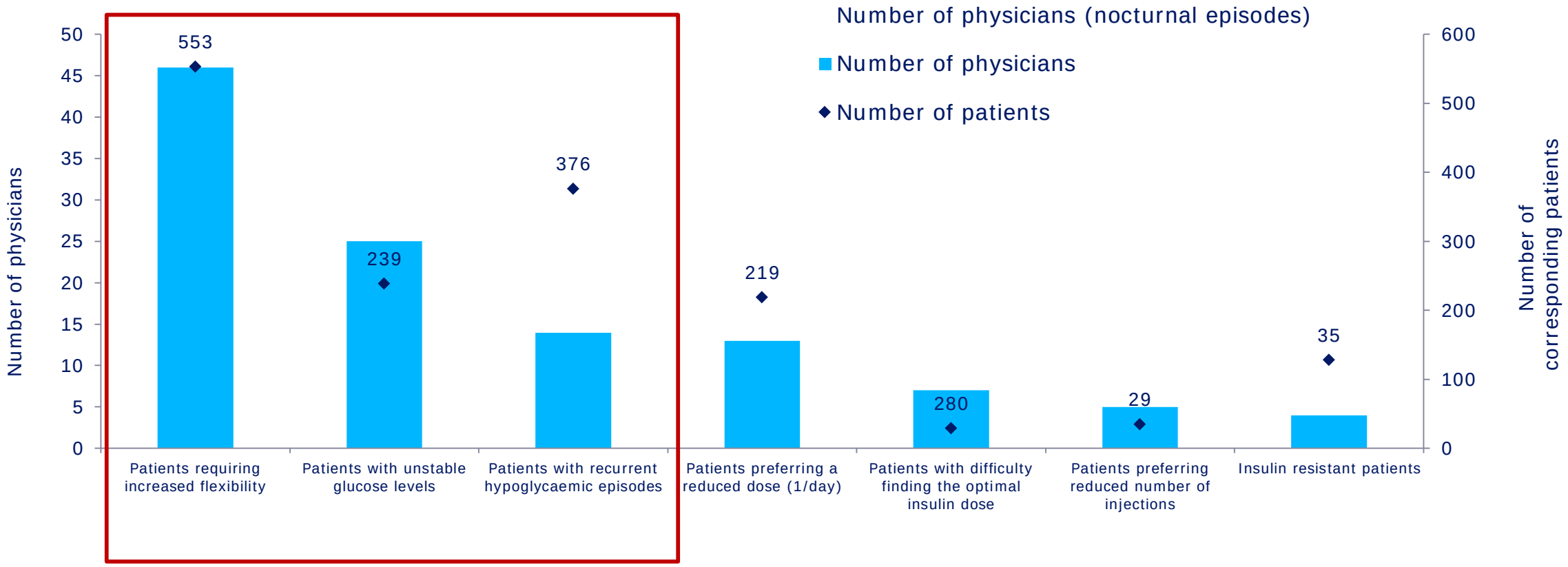
- To garner initial feedback on clinical experience with IDeg from prescribing clinicians across Europe.

- Five European countries: Germany, Luxembourg, Sweden, Switzerland and the UK

Robinson A, *et al*. Diabetic Medicine. 2015;32(Suppl 1):168 (P457).

Ratner *et al, Diabetes Obes Metab* 2013;15:175–184

Type of Pts to get benefits from switching to IDeg



Robinson A, *et al*. Diabetic Medicine. 2015;32(Suppl 1):168 (P457).

Ratner *et al, Diabetes Obes Metab* 2013;15:175–184

What are **your patients'** biggest challenges with the current mealtime insulin options?

What are **your** biggest challenges with the current mealtime insulin options?

What are your current perceptions of Fiasp®?

CASE 2

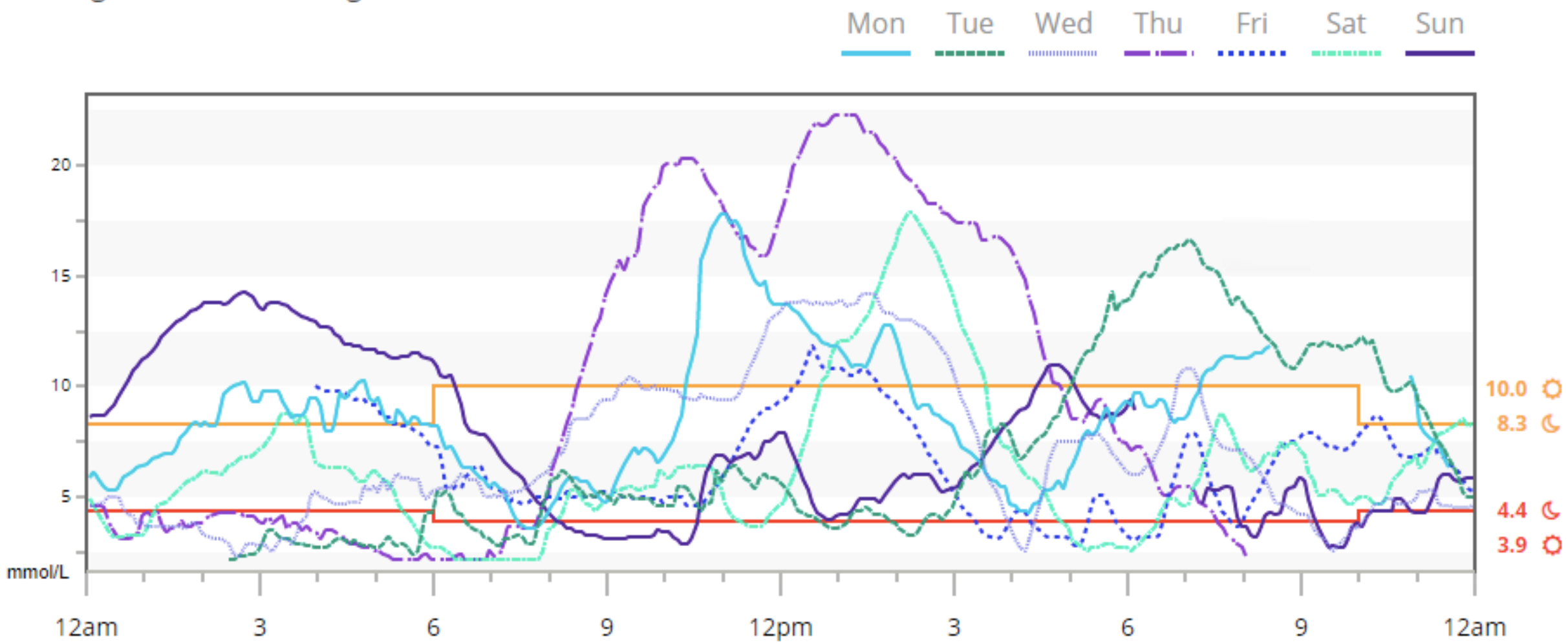
- Ms. D.S. is a 26 year old mother of 2 small children.
- She has been on an insulin pump and CGM for the last 6 years. She works as an engineer at the Bruce nuclear plant. She has good stable control with an HgA1c at 7.4%. She finds that she is persistently hyperglycemic at lunch despite good carb counting. She has tried decreasing her insulin/carb ratio and increasing basal rates with out success. When she corrects at lunch, she is often hypoglycemic before supper, which is a busy time with her family.

Any ideas of what to suggest?

Time in range

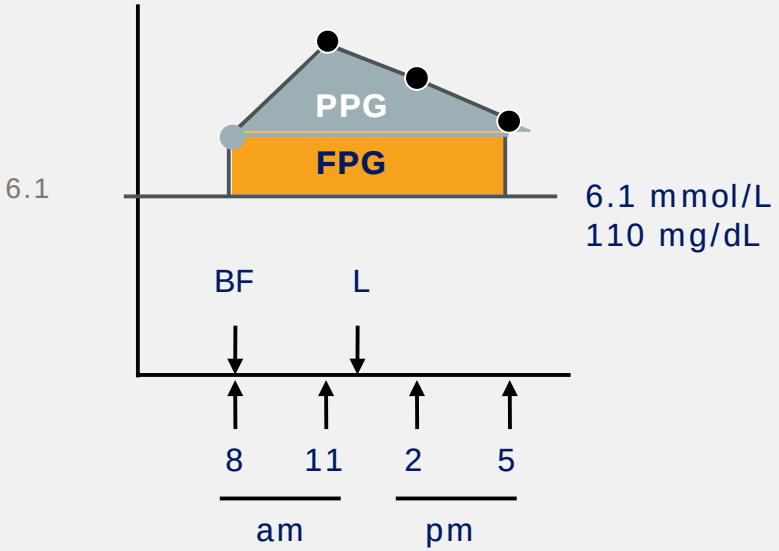
Week 2

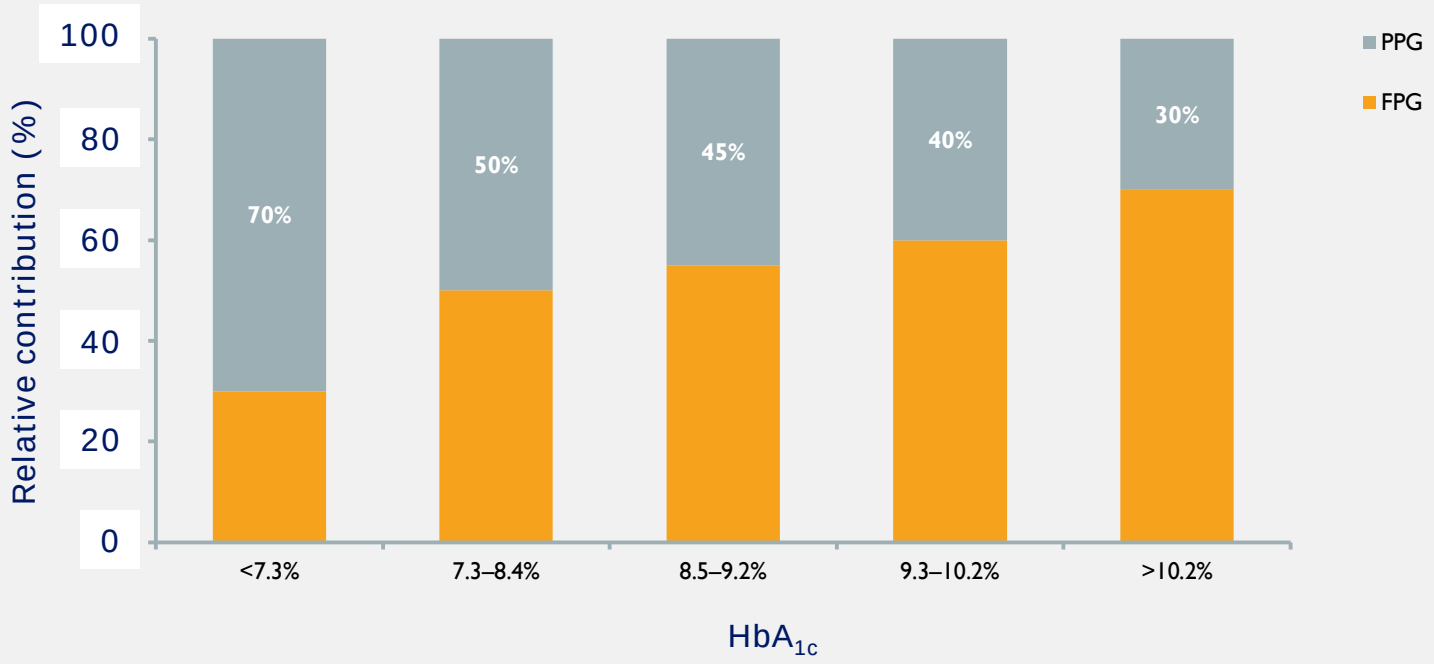
Thu Aug 23, 2018 - Wed Aug 29, 2018



RELATIVE CONTRIBUTION OF PPG TO HBA_{1C}

- 290 non-insulin-treated patients with type 2 diabetes
  - 4-point profile: FPG (8 am) vs. PPG (11 am, 2 pm, 5 pm)
- Relative contribution to the average diurnal hyperglycaemia

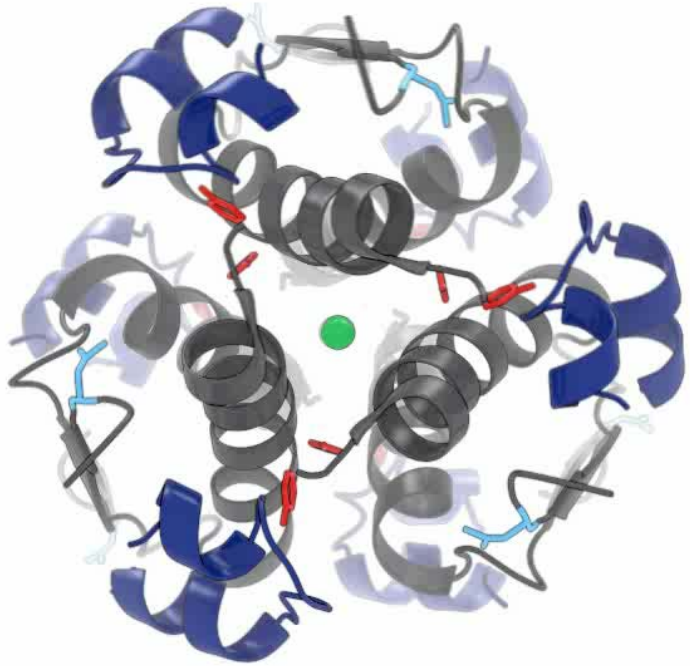




BF, breakfast; FPG, fasting plasma glucose; L, lunch; PPG, postprandial plasma glucose

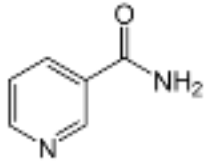
Monnier *et al. Diabetes Care* 2003;26:881–5

Changing the formulation: Faster aspart is insulin aspart in a new formulation



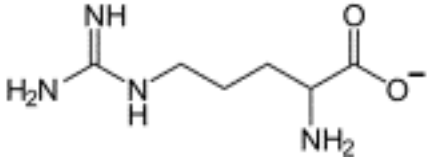
Insulin aspart

Niacinamide: absorption modifier



Vitamin B3

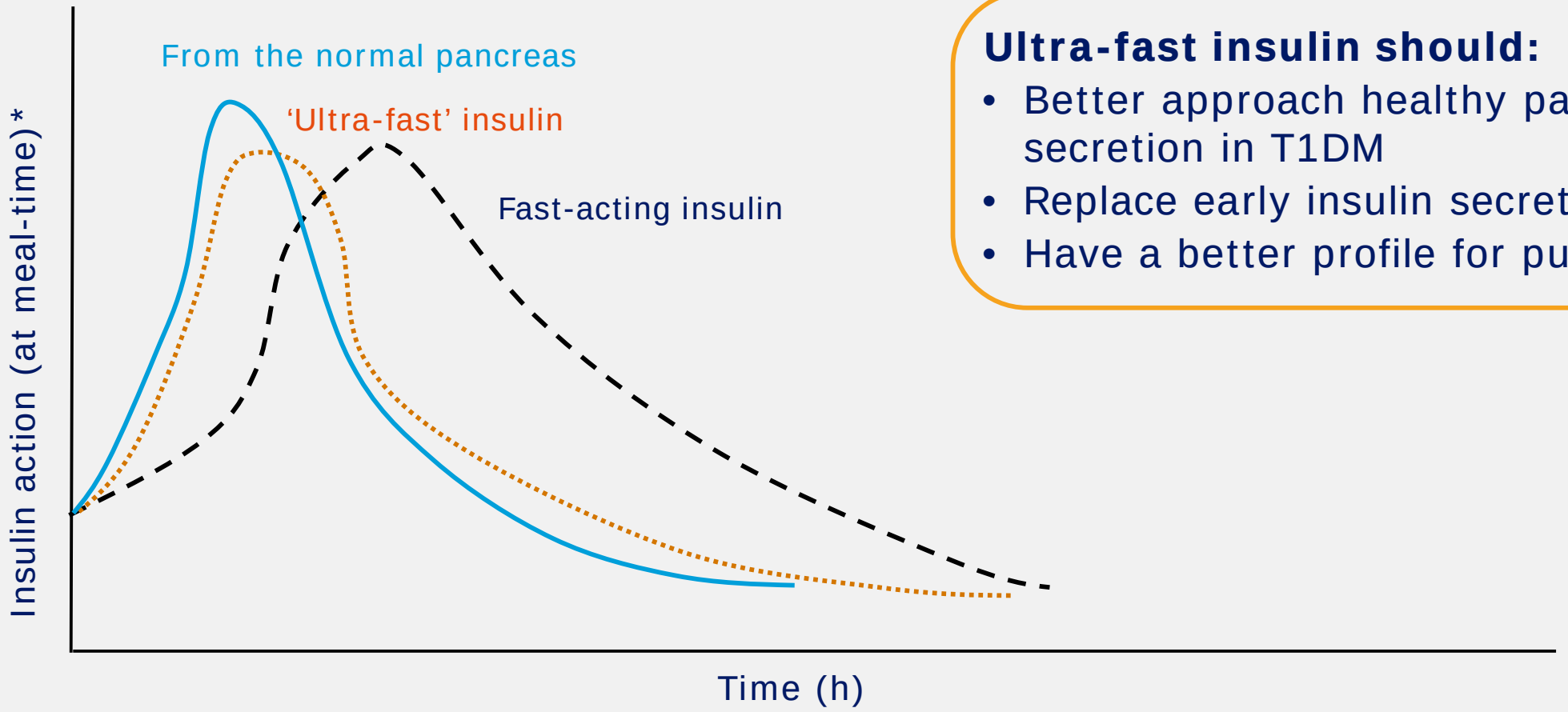
L-Arginine: added for stability



Naturally occurring amino acid

FDA's Inactive Ingredient Search for Approved Drug Products database. Available from: http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Last accessed April 2015

ULTRA-FAST INSULIN: AN EVOLUTION TO BETTER APPROACH THE INSULIN PROFILE OF A HEALTHY PANCREAS



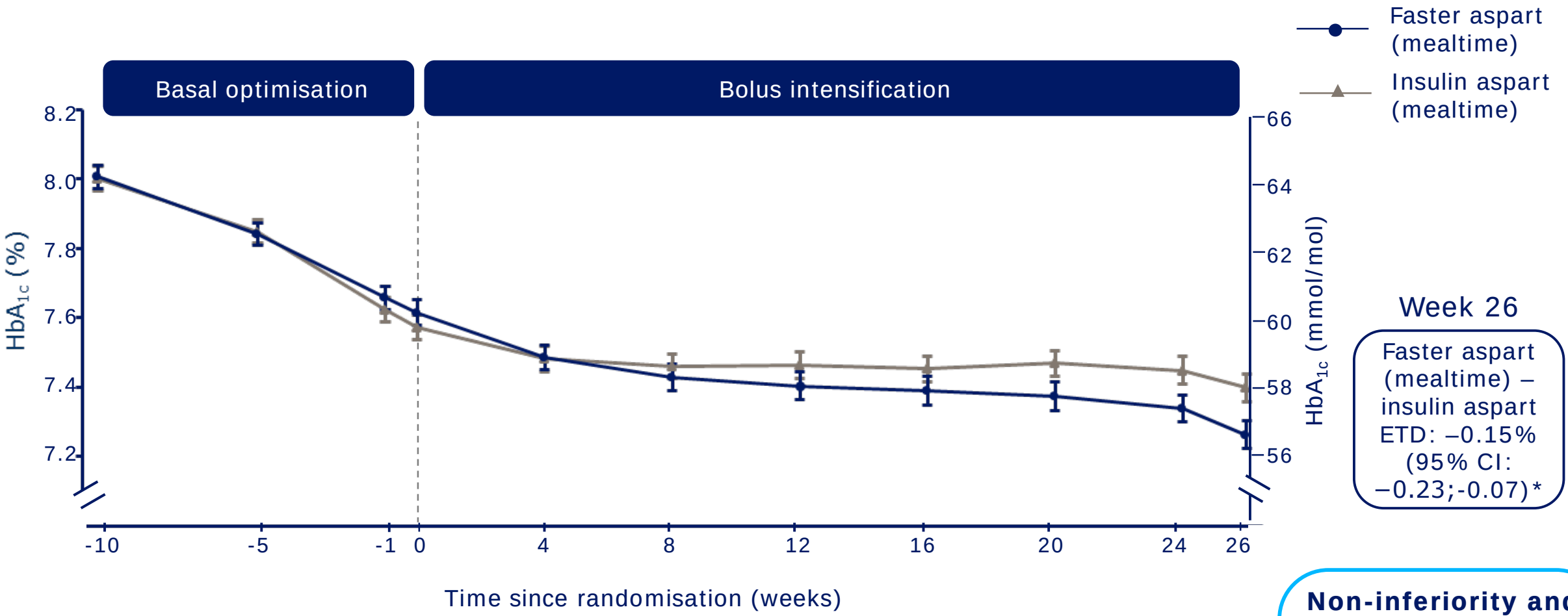
Ultra-fast insulin should:

- Better approach healthy pancreas insulin secretion in T1DM
- Replace early insulin secretion in T2DM
- Have a better profile for pump therapy

*Schematic representation

onset® 1: estimated mean HbA_{1c} change from baseline

Significantly greater reduction with mealtime faster aspart vs. mealtime insulin aspart



Week 26

Faster aspart (mealtime) – insulin aspart ETD: –0.15% (95% CI: –0.23;-0.07)*

Non-inferiority and statistically significant difference was confirmed

*Statistically significant

Change from baseline in HbA_{1c} is analysed using a mixed-effects model for repeated measurements, including changes from baseline in HbA_{1c} at visits 14, 18, 22, 26, 30 and 36. The model includes treatment, region and CGM strata as fixed effects, subject as random effect, HbA_{1c} at baseline as covariate and interaction between all fixed effects and visit, and between the covariate and visit.

Error bars: ± standard error (mean). HbA_{1c}, glycosylated haemoglobin

Data on file, NN1218-3852

Trial design

Patients with T1DM using CSII with a rapid-acting insulin analogue

Trial information
- Double-blinded
- Randomized
- Treat-to-target
- Meal test
- Stratified according to own CGM use

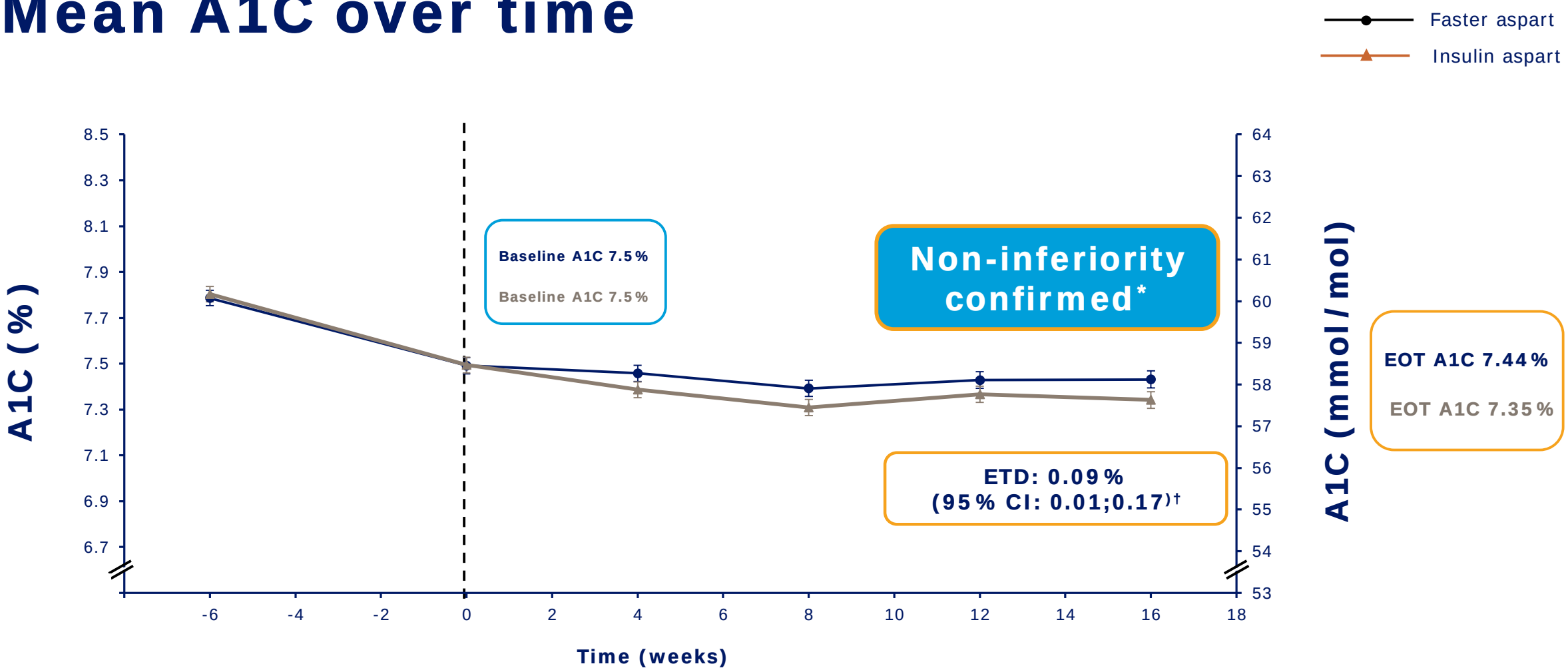
Key inclusion criteria
- T1DM ≥12 months
- Male or female ≥18 years
- CSII with a rapid-acting insulin analog in a basal-bolus regimen for ≥6 months
- Willing to use CSII during the entire trial
- A1C 7.0–9.0% (53–75 mmol/mol)
- BMI ≤35.0 kg/m^2

Primary endpoint
- Change from baseline in A1C

Confirmatory endpoints
- Change from baseline in 1-hour PPG increment (meal test)
- Change from baseline in 1,5-anhydroglucitol
- Change from baseline in time spent in low IG (≤3.9 mmol/L [70 mg/dL]) during CGM

* FU (7 and 30 days).
BMI, body mass index; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; FU, follow-up; IG, interstitial glucose; PPG, postprandial glucose; T1DM, type 1 diabetes mellitus.
Klonoff et al. *Diabetes Obes Metab* 2019;21:961–967.

Mean A1C over time



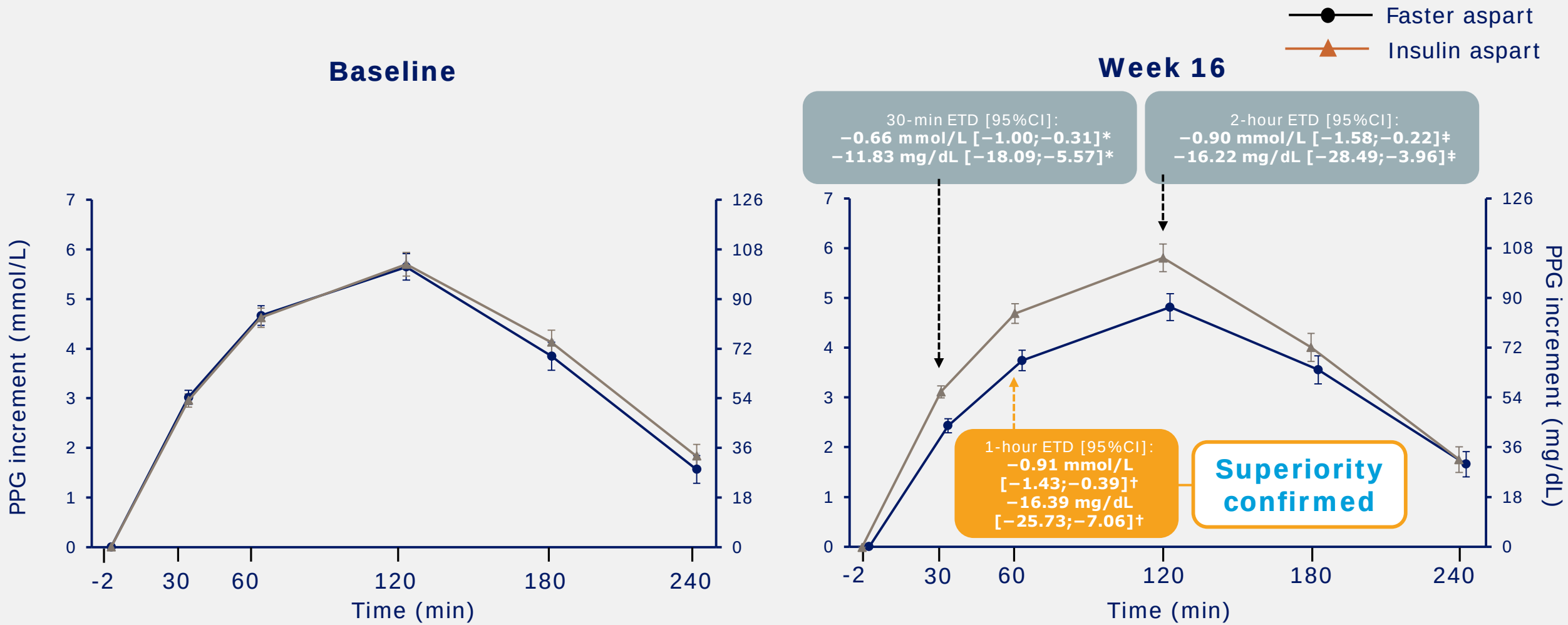
* Non-inferiority confirmed at 0.4% level $p<0.001$, † $p=0.022$.

Error bars: ± standard error (mean). Change from baseline in A1C is analyzed using a Multiple imputation model. ETD represents faster aspart minus insulin aspart values. CI, confidence interval; EOT, end of treatment; ETD, estimated treatment difference.

Klonoff et al. *Diabetes Obes Metab* 2019;21:961–967.

PPG INCREMENT AT BASELINE AND WEEK 16

MEAL TEST



* $p<0.001$, † $p=0.001$, ‡ $p=0.01$.

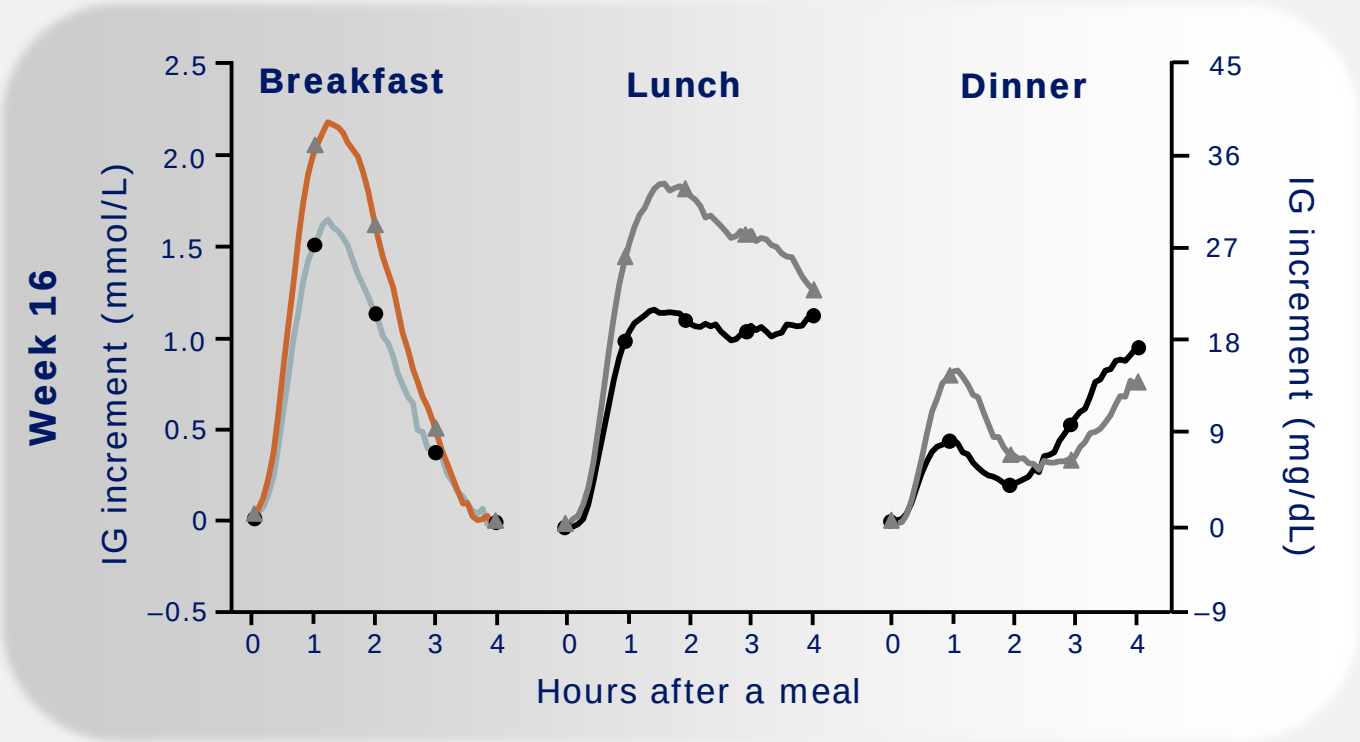
Primary estimand. Error bars: ± standard error (mean). The conversion factor between mmol/L and mg/dL is 0.0555. Change from baseline in PPG and PPG increment are analysed using a Multiple imputation model.

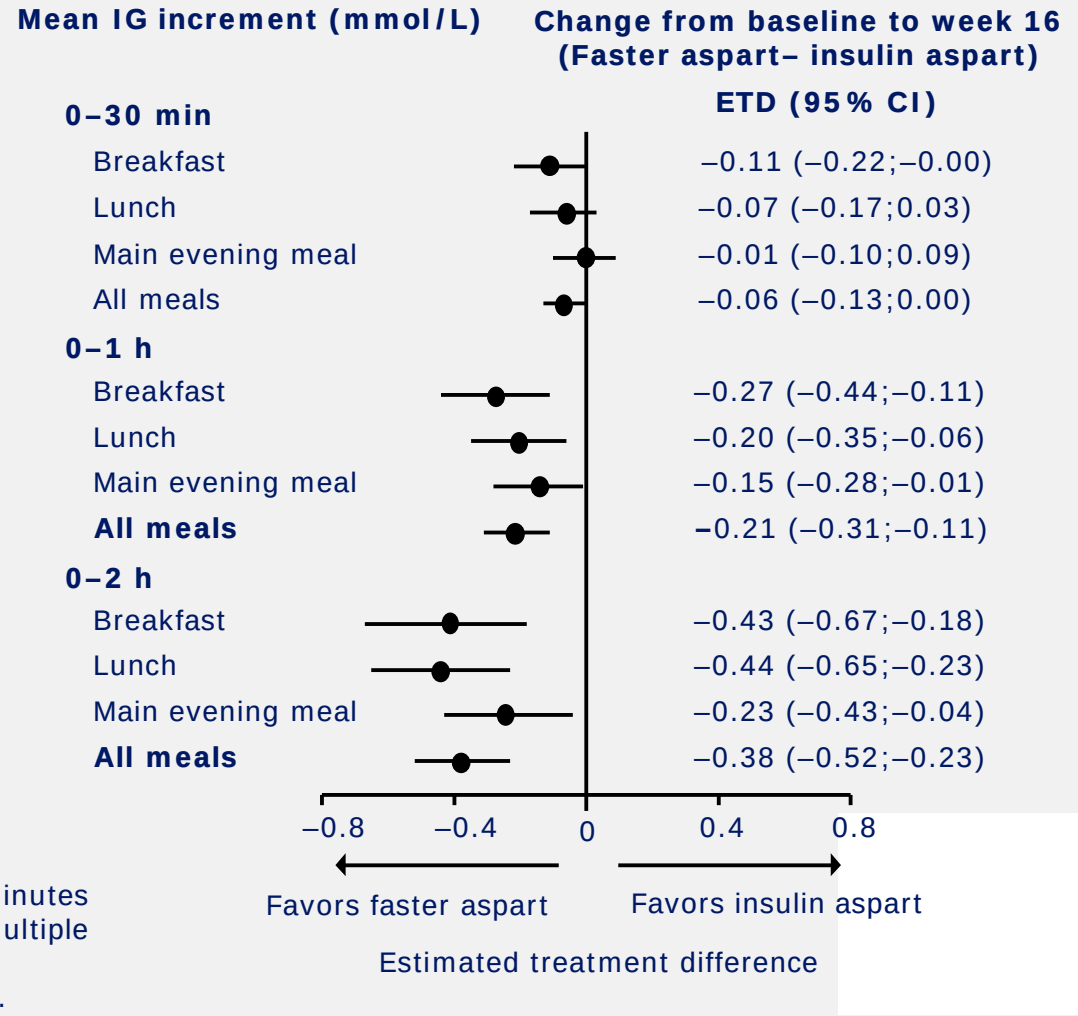
BG, blood glucose; CI, confidence interval; ETD, estimated treatment difference [faster aspart – insulin aspart] for BG changes from baseline; PPG, postprandial plasma glucose.

Klonoff et al. *Diabetes Obes Metab* 2019;21:961–967.

PRANDIAL IG INCREMENTS AT WEEK 16

2-WEEK CGM EXCLUDING MEAL TEST





Primary estimand. All available information regardless of treatment discontinuation was used.

Prandial IG increment was derived as the IG values subtracted by the mean IG values within 15 minutes before the start of the meal. Change from baseline in mean IG increment was analysed using a multiple imputation model.

CGM, continuous glucose monitoring; ETD, estimated treatment difference; IG, interstitial glucose.

Klonoff et al. *Diabetes Obes Metab* 2019;21:961–967.

CASE 3

- Mrs. A.R. is a 44 year old woman who has not been seen by you for several years. She was diagnosed about 6 years ago and is currently taking Janumet. She has had a lot of stress and when she restarted testing, she noticed her blood sugars are now running between 12-20 mmol/L .
- Her family doctor started her on basal insulin and she is currently taking 22 units of insulin degludec .
- Her HgA1c is 10.0% and on closer questioning she has symptoms of recurrent vaginal infections. She has gained 12 kg since you last saw her and she wants to lose weight but is anxious about GI symptoms because she has nausea on occasion .

Any ideas of what to suggest?

RATIONALE FOR INCRETIN–INSULIN COMBINATIONS

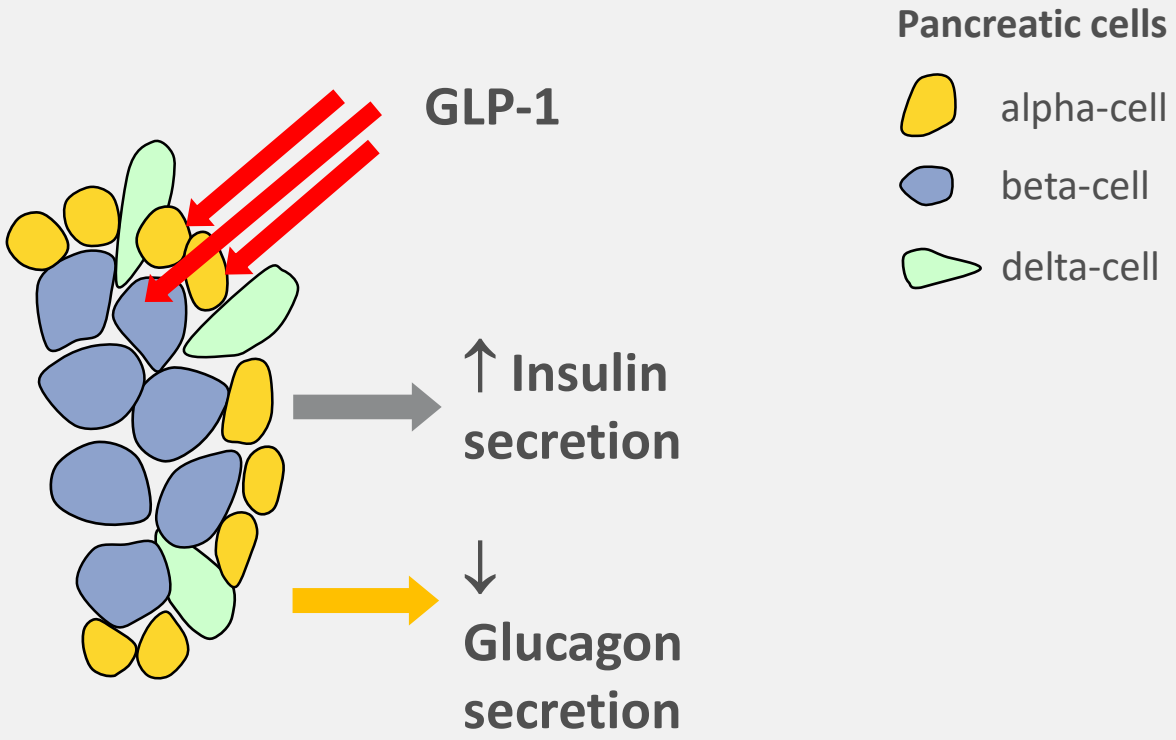
As beta-cell function declines, insulin secretion decreases

Why insulin?

To correct the deficiency

Why incretin-based therapies?

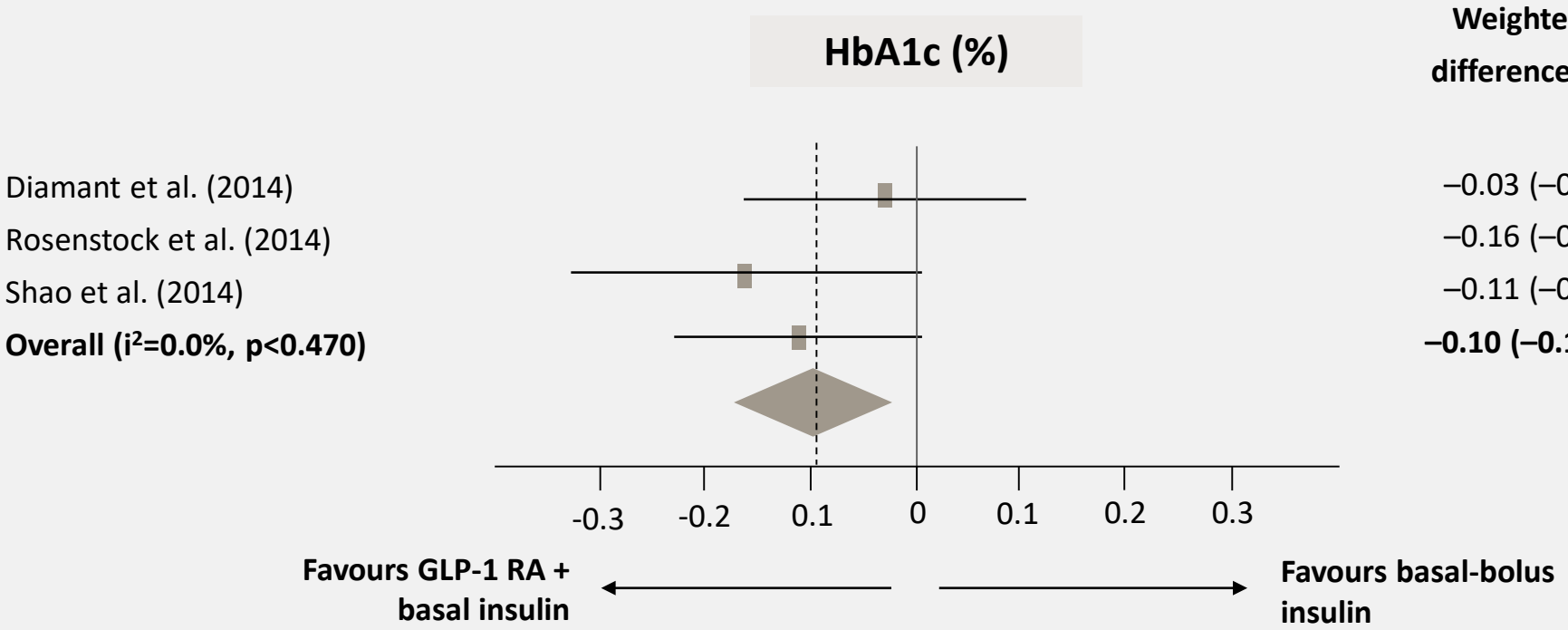
GLP-1 also enhances insulin secretion and modulates glucagon secretion



Drucker DJ, Nauck MA. Lancet 2006;368:1696–705.

GLP-1 RA/basal insulin free combination regimens are associated with greater HbA1c reduction than basal-bolus regimens

Systematic search for RCTs comparing GLP-1 RA/basal insulin combination to other antihyperglycemic treatments; three studies (n=1136) comparing GLP-1 RA/basal insulin regimens vs. basal-bolus insulin regimens were assessed in a sensitivity analysis*

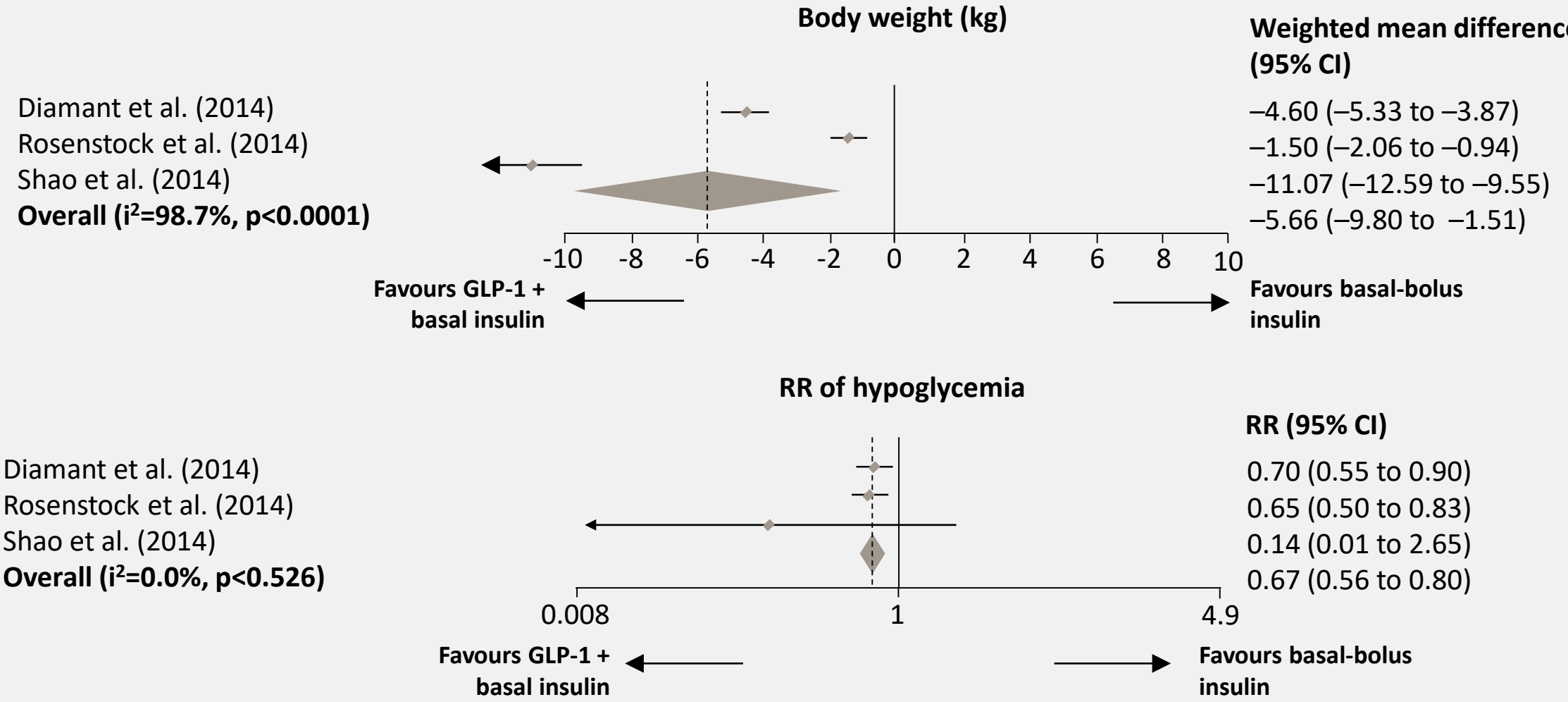


*12 studies not included in sensitivity analysis were either placebo-controlled, ± GLP-1 RA, ± basal insulin or investigating a fixed-dose combination

RA, receptor agonist; RCTs, randomised control trials

Eng C, et al. Lancet 2014;384:2228–28

GLP-1 RA/basal insulin in free combination associated with more favourable changes in body weight and relative risk of hypoglycemia vs. basal-bolus insulin



Eng C, et al. Lancet 2014;384:2228–28

RATIONALE FOR FIXED RATIO COMBINATION

Basal Insulin

- 1 injection
- Predominant FPG lowering
- Significant A1C reduction
- Potential weight gain
- Risk of Hypoglycemia

GLP1-RA

- 1 injection
- PPG and FPG lowering
- Significant A1C reduction
- Potential weight loss
- Low risk of hypoglycemia

Fixed-ratio Combination

- 1 injection, 2 therapies
- FPG + PPG control
- Greater A1C reduction
- Beneficial effects on weight
- No additional risk of hypoglycemia vs. basal insulin
- Minimization of gastrointestinal side effects of GLP-1

FPG: fasting plasma glucose; GLP-1: glucagon-like peptide-1; A1C: glycated hemoglobin; PPG: postprandial plasma glucose

TWO BASAL INSULIN/GLP-1 RA FIXED-RATIO COMBINATIONS AVAILABLE

Insulin glargine 100 U/mL
+
Lixisenatide

iGlarLixi

Insulin degludec
+
Liraglutide

IDegLira

IN WHOM WOULD I CONSIDER FRC?

- First injectable (off-label) if A1c > 8%
- Basal insulin not at target (instead of adding bolus insulin)
- Basal-bolus patient not at target (off-label)

SUMMARY

- GLP1RA + basal insulin = improved control
- Fixed ratio combination provides 1 injection, better A1c, less weight gain, less GI issues
- Remember to start at the recommended starting doses

DO WE NEED NEW INSULIN PRODUCTS ??

In some patients there are advantages.