LE INSULINE BASALI NELLA TERAPIA DEL DMT2
TIMING E RAZIONALE D'USO

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E GERIATRIA

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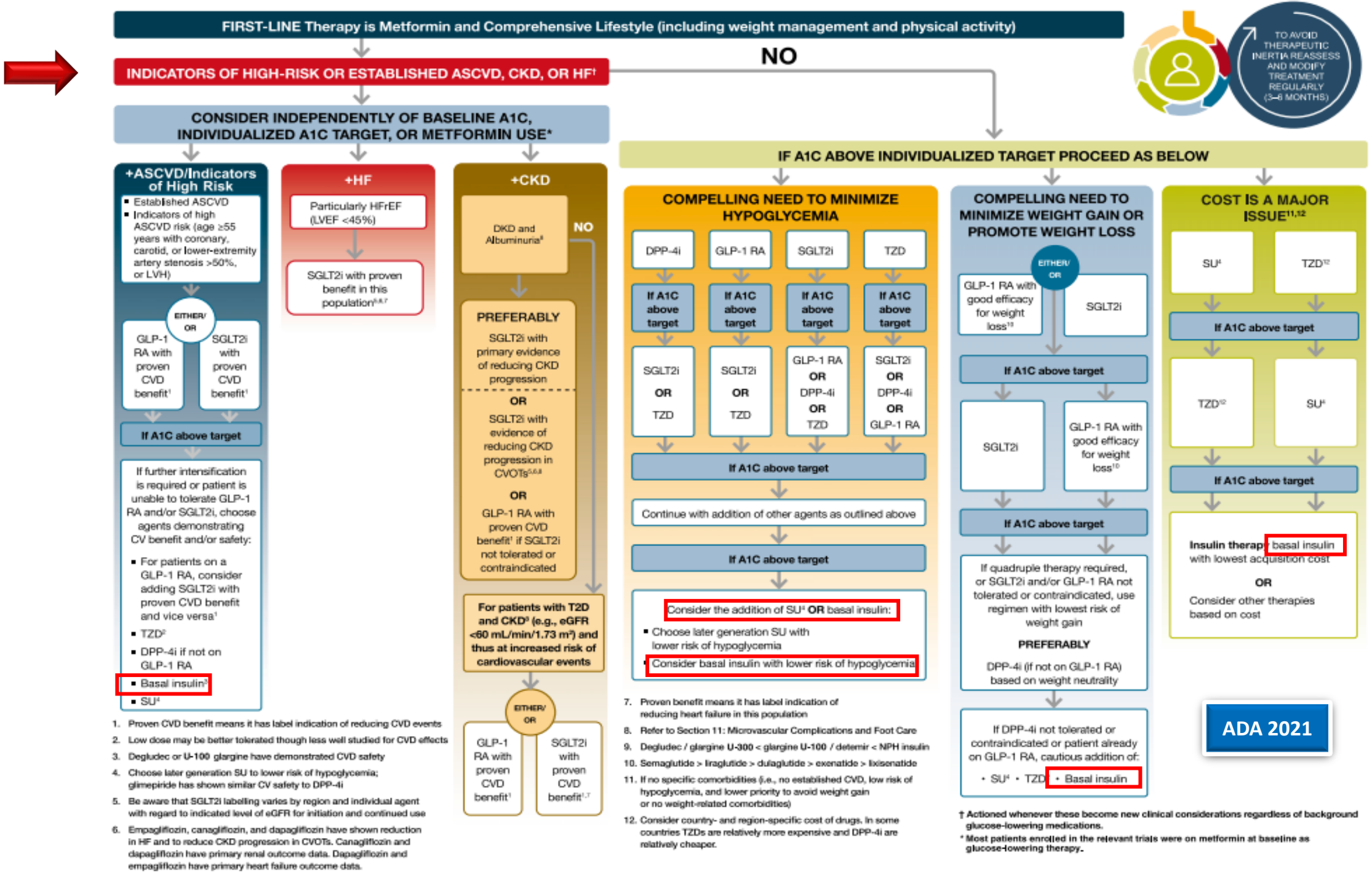
UNIVERSITÀ CATTOLICA DEL SACRO CUORE



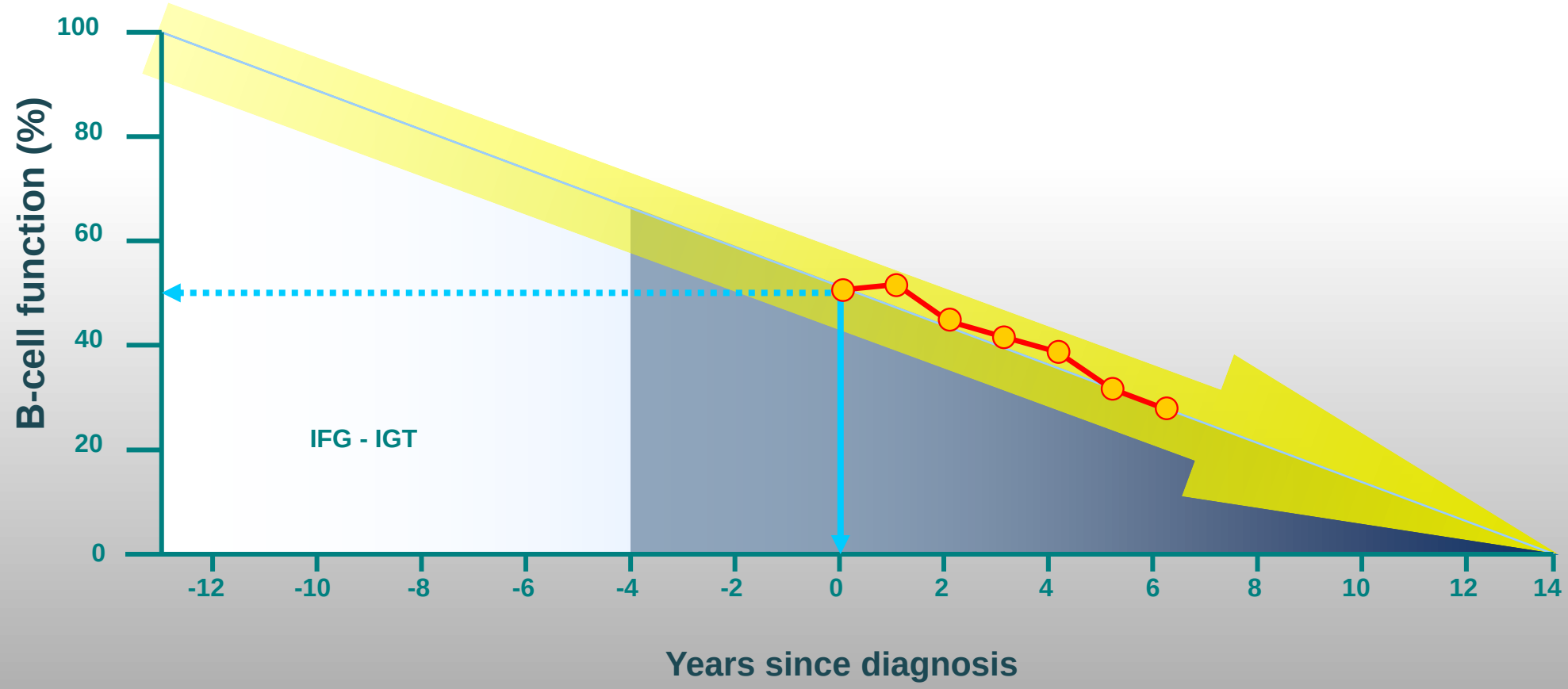
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

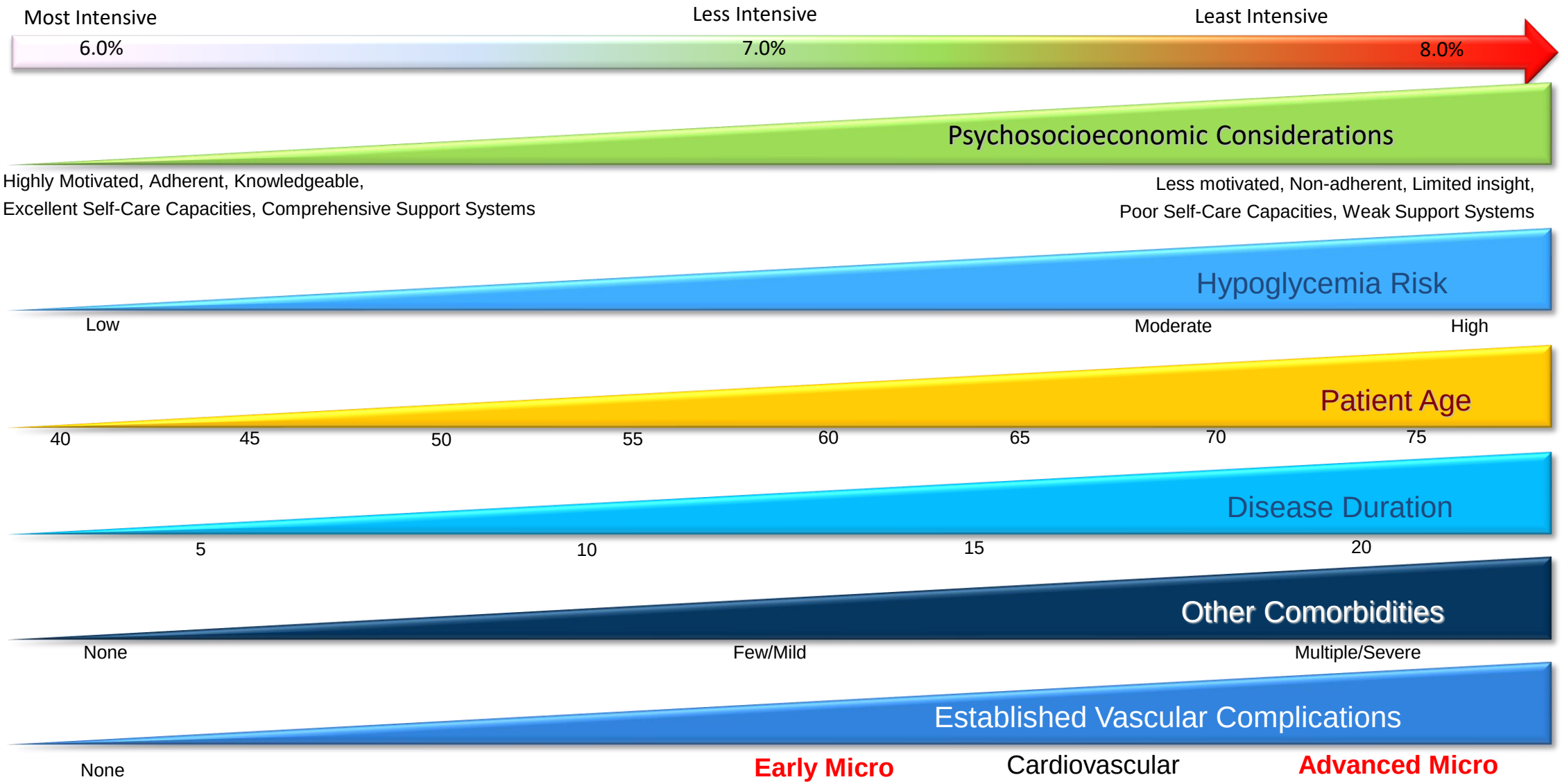
T2DM and β-cell Function

At the time of diagnosis of T2DM some 50% of the β-cell function may be already lost



UKPDS Study Group, UKPDS 16 – Diabetes 1995

Elements of “decision-making” in determining glycaemic treatment target in T2DM



Ismail-Beigi et al. Arch Intern Med 154: 554-559, 2011

Timely* insulin therapy in T2DM has multiple benefits

Benefits
Restores β-cell function[1]
Provides long-term near-normal glycemic control[2]
Reduces microvascular complications, providing long-term end-organ protection[3,4]
May enhance patient QoL[5]
May reduce macrovascular events[4]

Challenges
Weight gain[1,5]
Hypoglycemia[1,5]
Need for injection[1]

Given the benefit / risk ratio of insulin therapy, international best-practice guidelines recommend timely insulin initiation using individualized targets based on patient characteristics[6–9]

*After lifestyle modification and failure of one or more OAD treatments

1. Grunberger G. Diabetes Obes Metab. 2013;15 Suppl 1:1-5; 2. ORIGIN Investigators. N Engl J Med. 2012;367:319-28;
3. UKPDS 33. Lancet 1998;352:837-53; 4. Holman RR et al. N Engl J Med 2008;359:1577-89; 5. Owens DR. Diabetes Technol Ther. 2013;15:776-85
6. Inzucchi SE et al. Diabetes Care. 2012;35:1364-79;7. IDF Global Guidelines for Type 2 Diabetes 2012. http://www.idf.org/global-guideline-type-2-diabetes-2012 Accessed August 2014;8. ADA. Diabetes Care. 2014;37 Suppl 1:S14-80 9. Garber A et al. Endocr Pract. 2013;19:536-57

CHALLENGES IN INSULIN THERAPIES

Patients' concerns

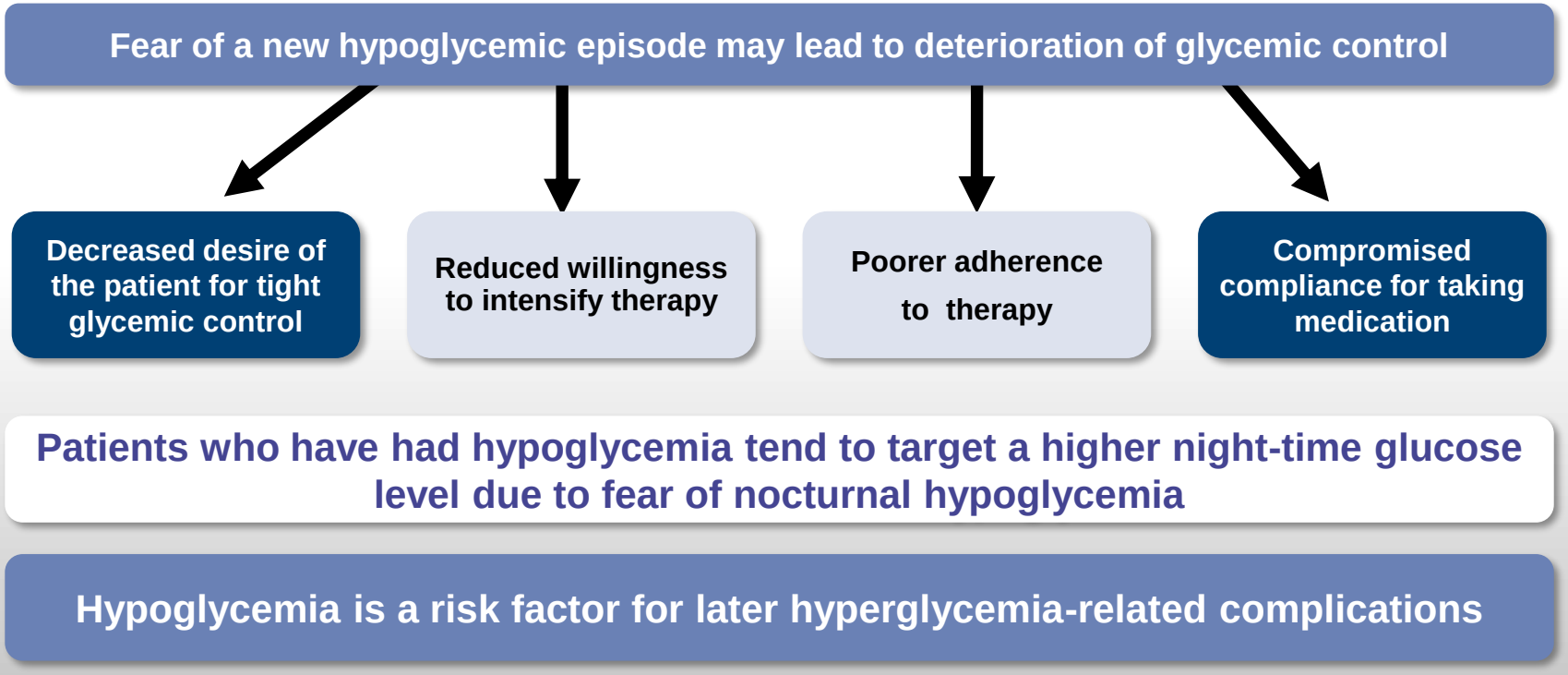
- ✓ Insulin treatment leading to increased body weight
- ✓ Risk of Hypoglicaemia
- ✓ Complex treatment: skills?
- ✓ Misconceptions
  - Lose independency
  - Bothersome/Painful injections
  - Need to finger stick measurement

Doctors' concerns

- ✓ Therapeutic inertia: insulin started too late
- ✓ Which regimen is the best for which patients
- ✓ Compliance with treatment
- ✓ Skill to manage hypoglicaemia and patients' fear

FEAR OF HYPOGLYCEMIA IS A MAJOR BARRIER

In clinical practice, fear of hypoglycemia is a common barrier to optimal titration, adherence and achieving glycemic targets with insulin



Ahrén B. Vasc Health Risk Manag. 2013;9:155-163

Journal of Medical Economics

Fidler C et al, 2011

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: https://www.tandfonline.com/loi/ijme20

Hypoglycemia: An overview of fear of hypoglycemia, quality-of-life, and impact on costs

Nocturnal hypoglycaemia occurs in up to 50% of adult diabetic patients on insulin therapy

Severe nocturnal hypoglycaemia is suspected to contribute to the «dead-in-bed-syndrome», responsible for about 6% of death in diabetic patients

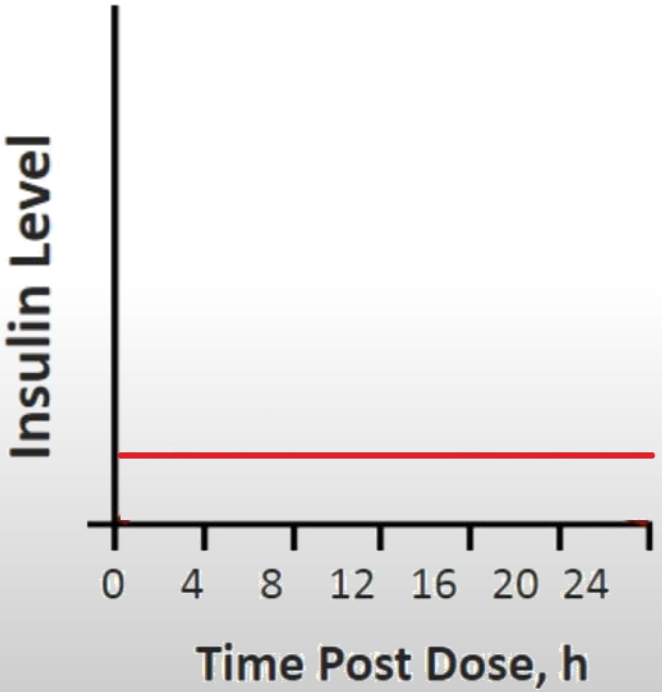
Objectives of developing a new basal insulin

Longer duration of action	Control fasting blood glucose with one injection per day for all individuals
Flat time-action profile	Lower risk of hypoglycaemia
Less day-to-day variability	Potential for titration to lower FPG target without hypoglycaemia

FPG, fasting plasma glucose

Properties of the Ideal Basal Insulin

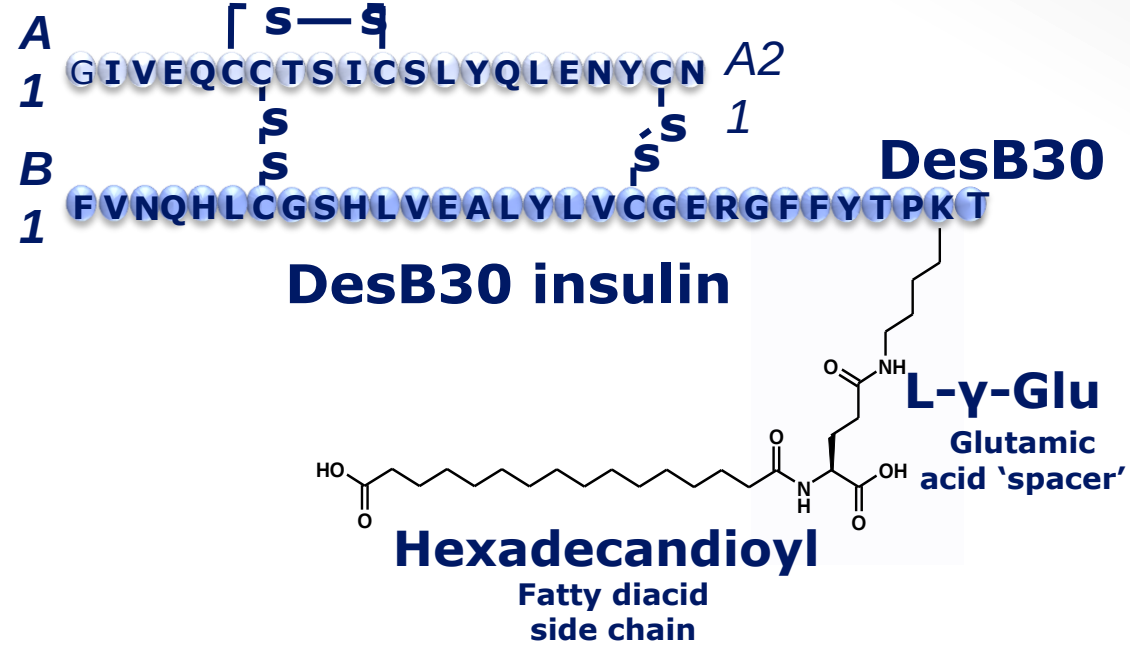
- Mimics normal pancreatic basal insulin secretion
- Long duration of action
- Smooth, peakless profile
- Reproducible and predictable effects
- Flexible dosing
- Reduce risk of nocturnal hypoglycemia



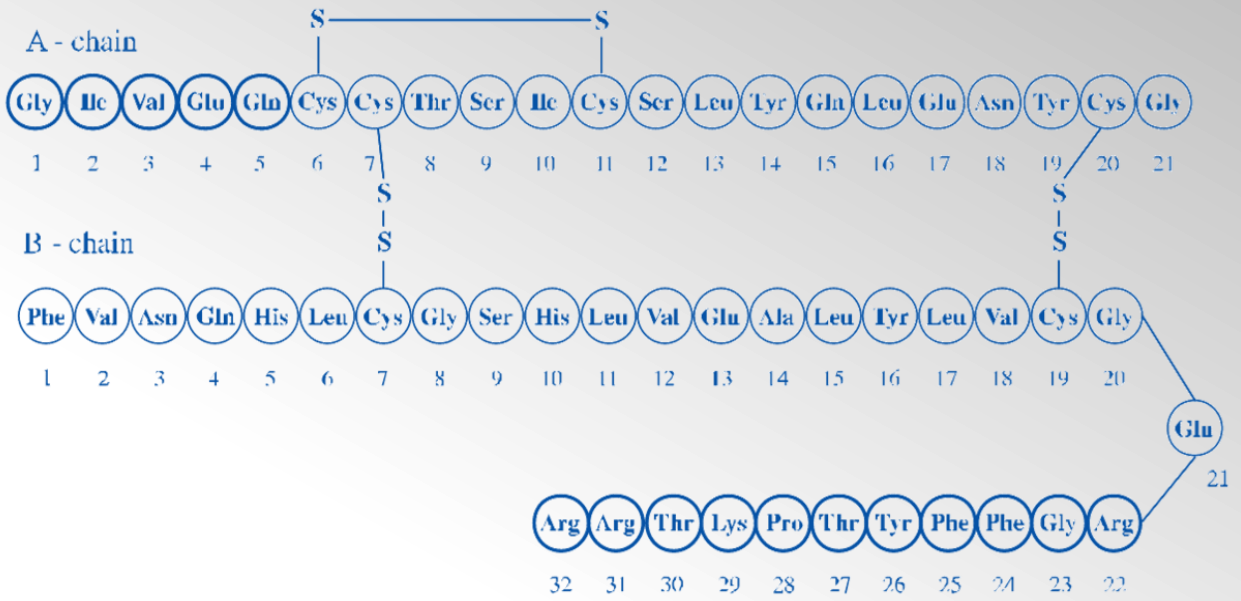
Rosenstock J. *Clin Cornerstone*. 2001;4:50-64.

Insulina DEGLUDEC

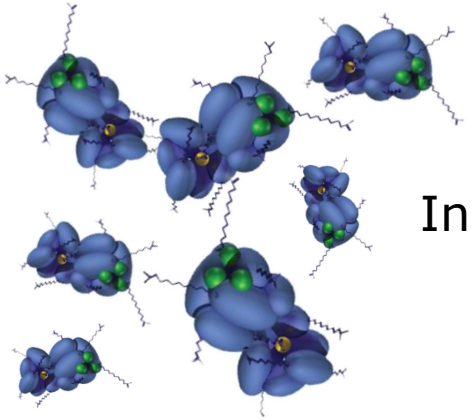
Des(B30) LysB29(γ-Glu Nε-hexadecandioyl) human insulin

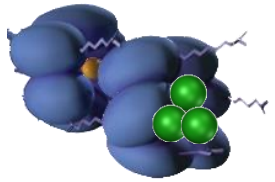


Insulina GLARGINE-300



Insulin degludec from solution to subcutaneous depot

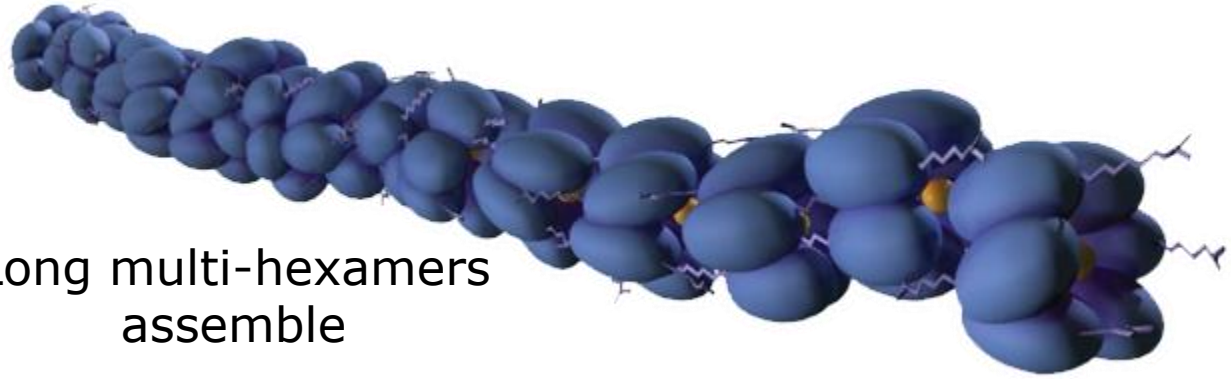




Insulin degludec injected

Phenol Zn^{2+}

As phenol from the vehicle diffuses degludec hexamers link up via single side-chain contacts

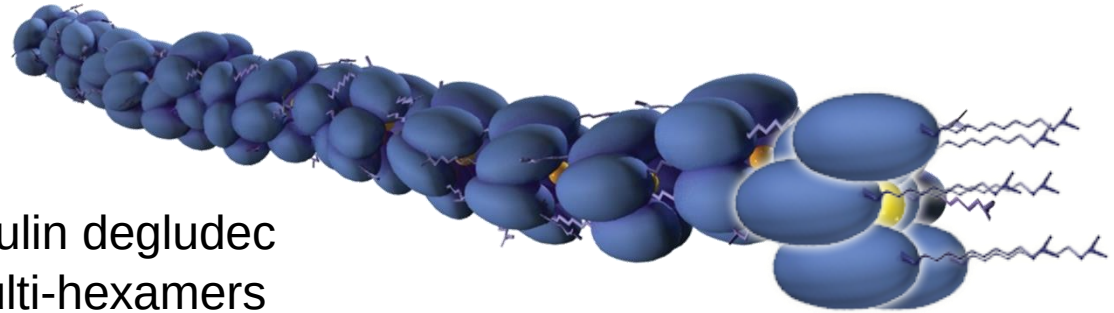


Long multi-hexamers assemble

Insulin degludec: slow release following injection

Subcutaneous depot

Zn^{2+}



Insulin degludec multi-hexamers

Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers

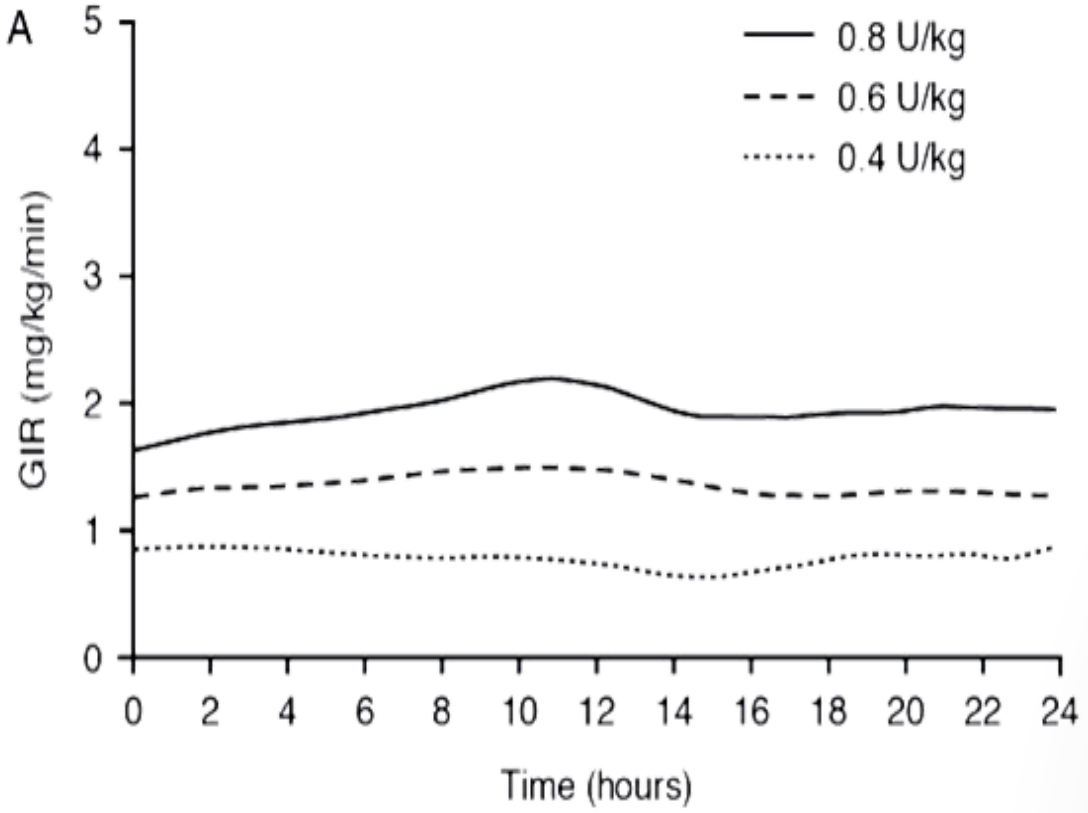
Monomers are absorbed from the depot into the circulation

original article

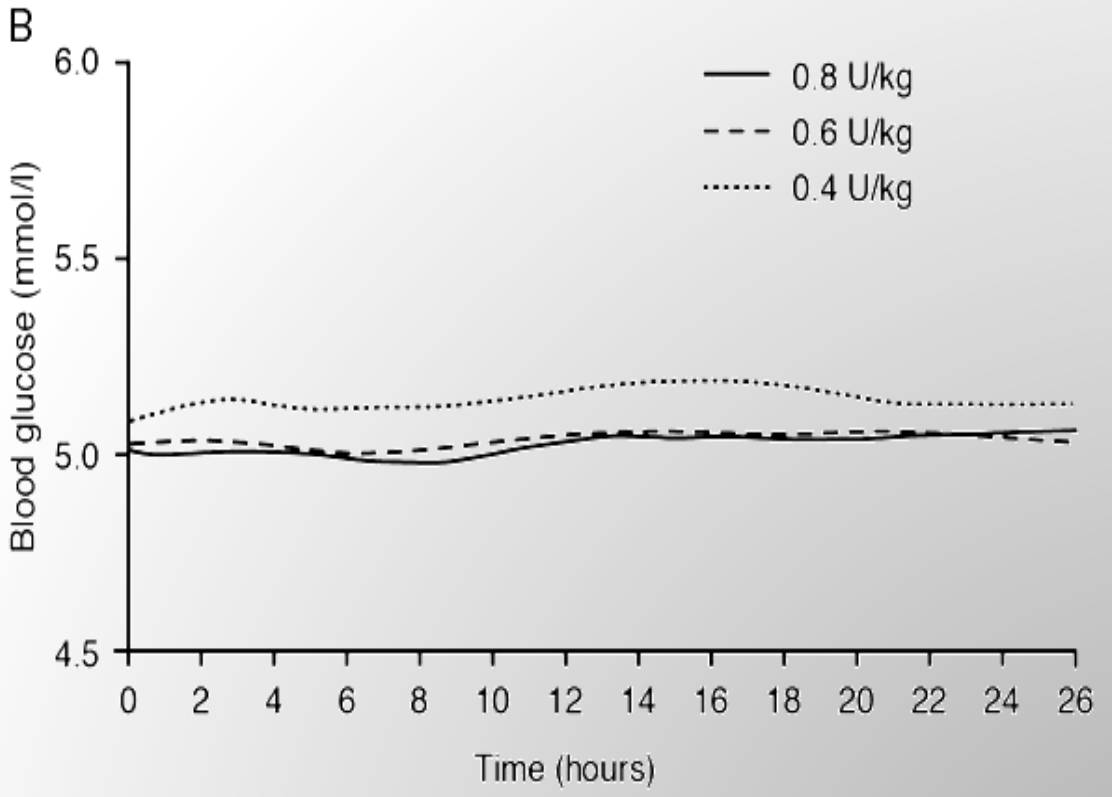
Diabetes, Obesity and Metabolism 14: 944–950, 2012.

Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes

T. Heise[1], L. Nosek[1], S. G. Bøttcher[2], H. Hastrup[2] & H. Haahr[2]



24-h GIR mean profiles-IDEG at steady state

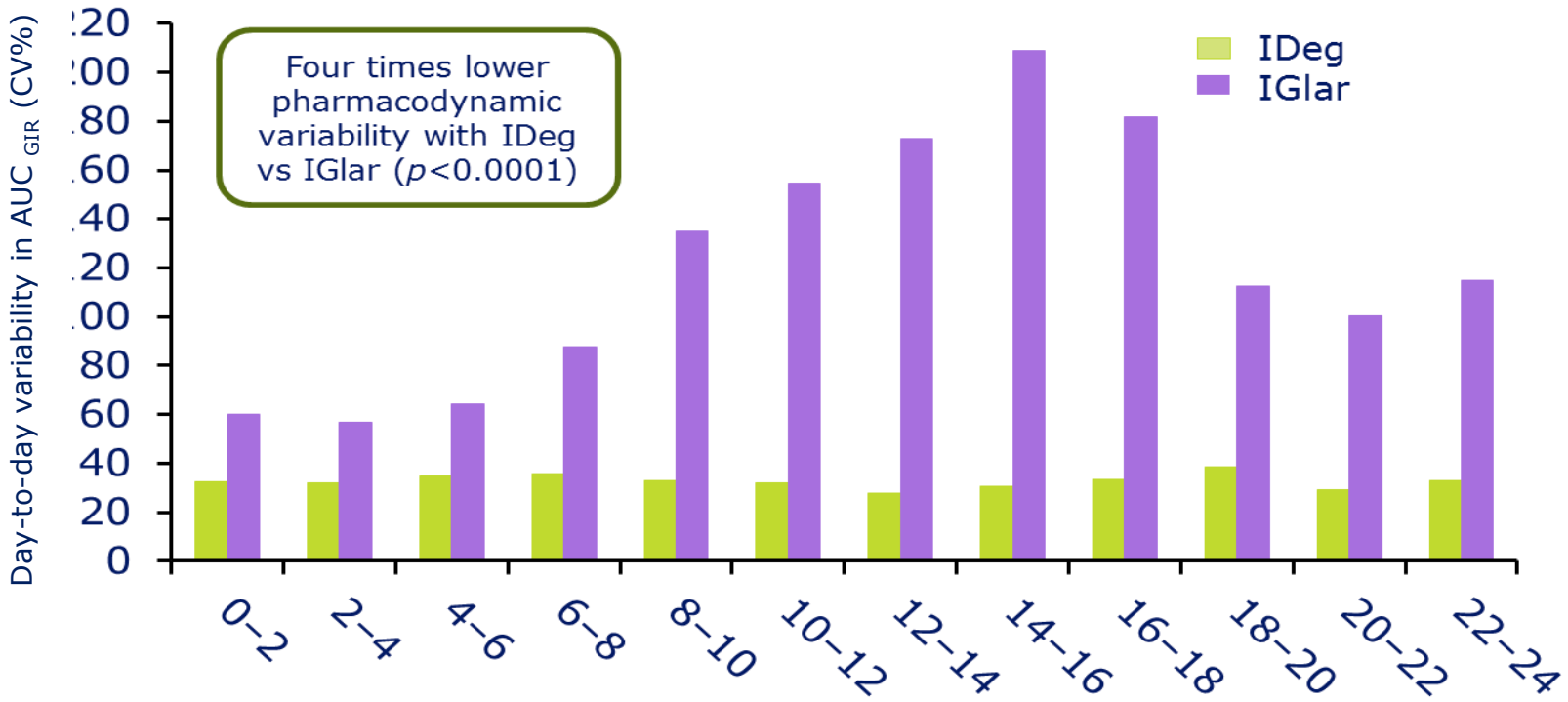


26-h blood glucose mean profiles-IDEG at steady state

REVIEW ARTICLE

A Review of the Pharmacological Properties of Insulin Degludec and Their Clinical Relevance

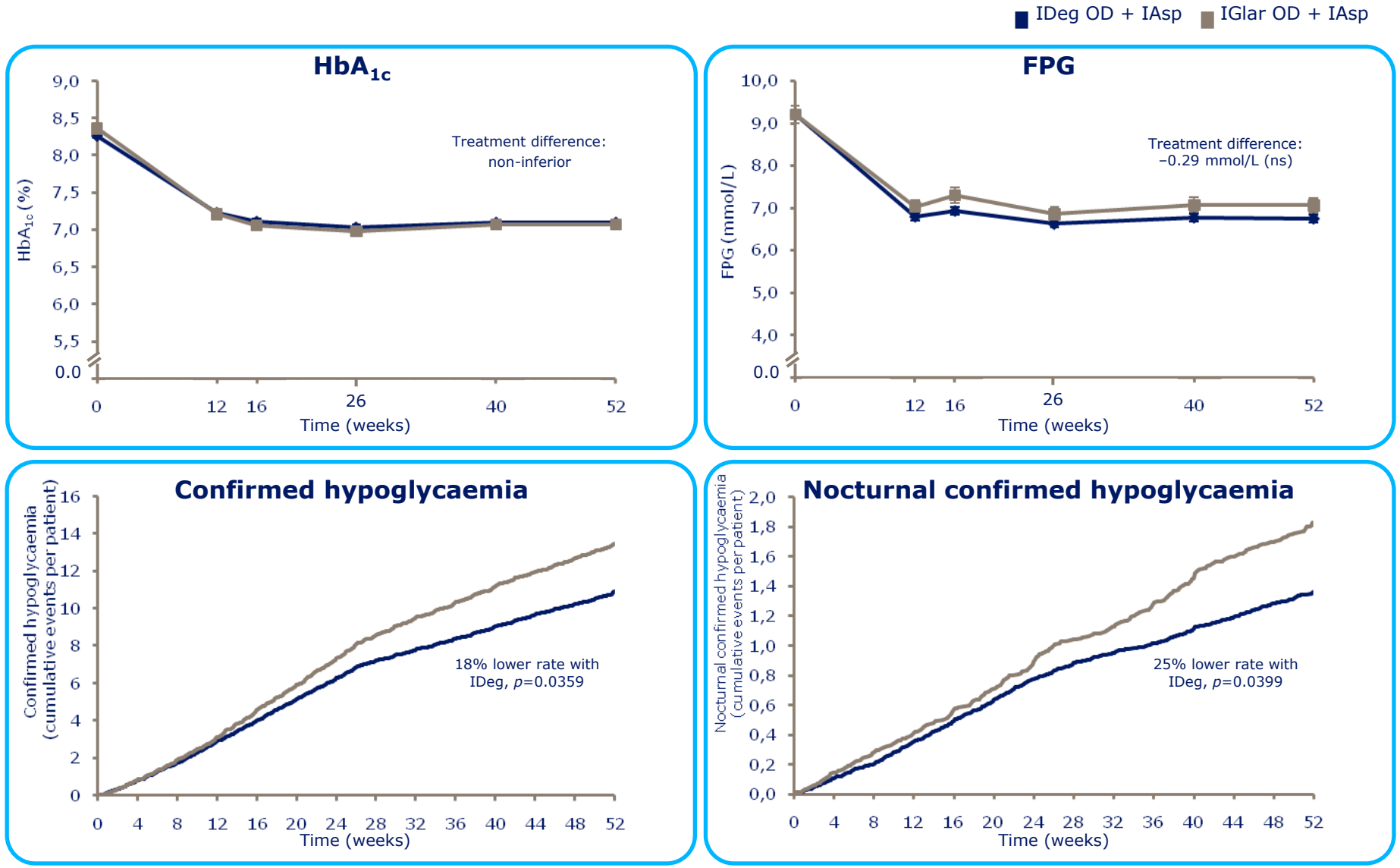
Day-to-day variability in glucose-lowering effect of IDeg and IGlar over 24 h at steady state



Haahr H et al., Clin Pharmacokinet 2014

Basal–bolus in T2D: results

BEGIN BB T2D



Garber *et al. Lancet* 2012

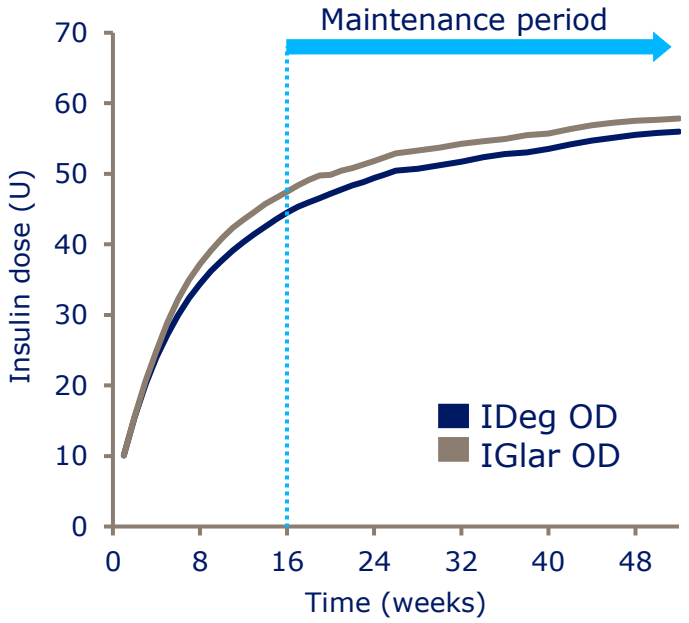
Insulin degludec phase 3a study program:

meta-analysis across seven treat-to-target confirmatory trials in patients with type 1 and type 2 diabetes mellitus

	Full trial	Maintenance
Overall		
Pooled T2D/T1D	**–9%***	**–16%***
Nocturnal		
Pooled T2D/T1D	**–26%***	**–32%***

Hypoglycaemia risk reduction IDeg versus IGlar

*Statistically significant, $p<0.05$

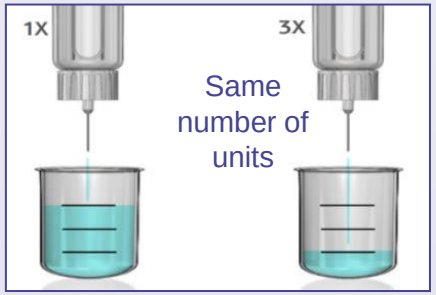


Degludec afforded a lower number of confirmed hypoglycaemic episodes and nocturnal confirmed hypoglycaemic episodes compared to insulin glargine.

Ratner *et al. Diabetes Obes Metab* 2013

Difference between Gla-300 and Gla- 100

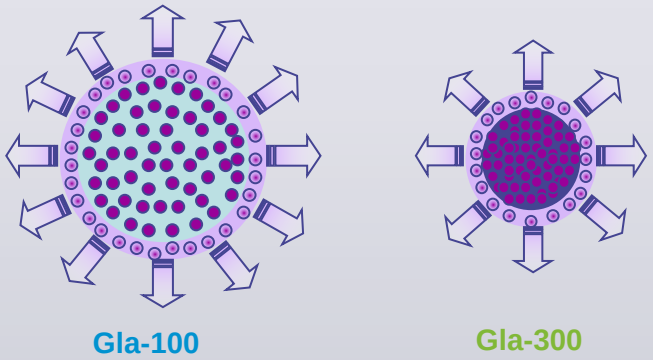
Reduction of volume by 2/3



Glargine 300 (300 U/mL) is a new long-acting basal insulin built on Gla-100 legacy.

Smaller volume of injection for Gla-300 vs. Gla-100

Smaller surface area



Smaller subcutaneous depot for Gla-300 vs. Gla-100

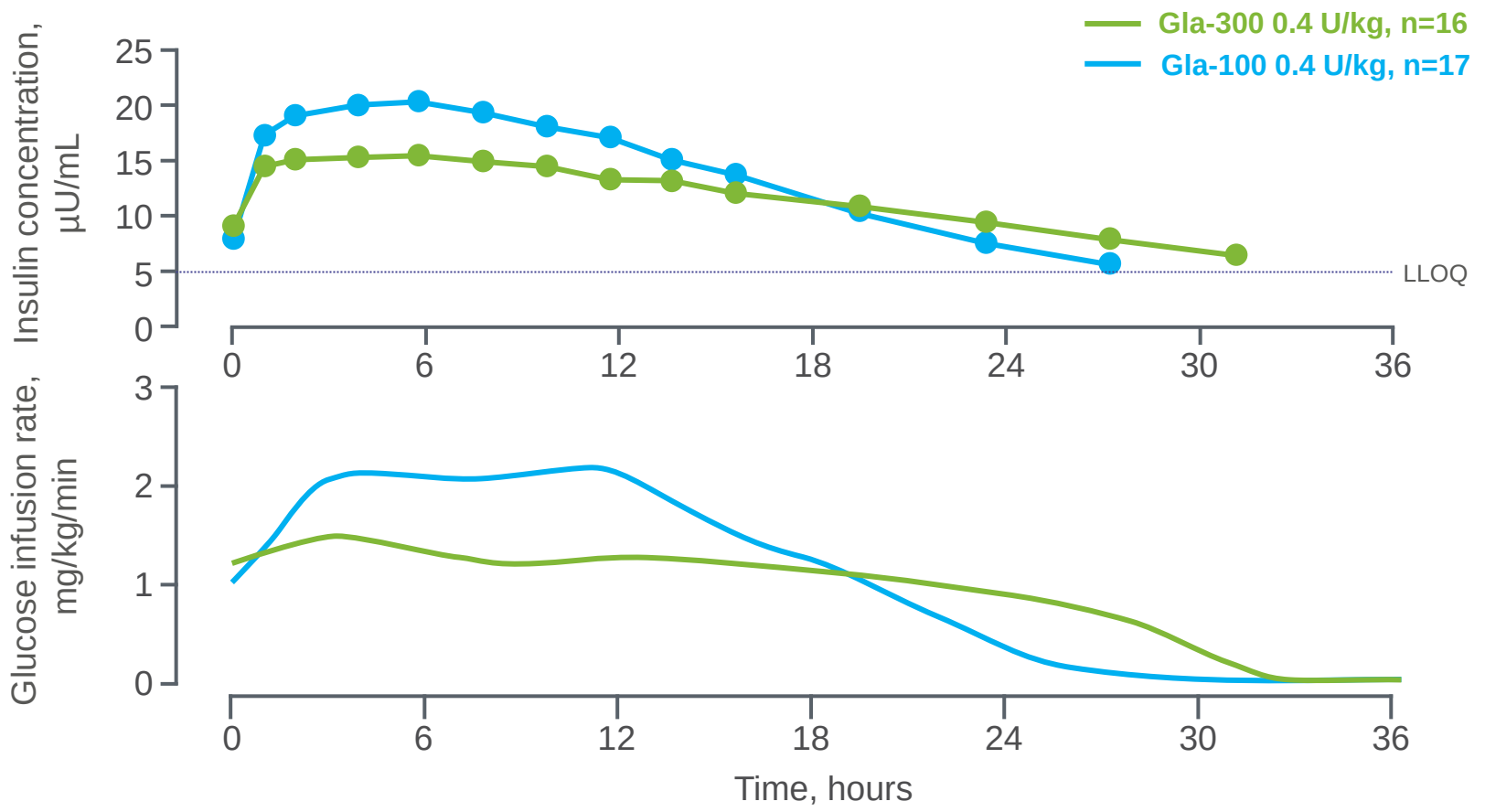
Different absorption kinetics "More gradual release"

Distinct Gla-300 PK/PD profile compared to Gla-100

- Gla-300 has the same mode of protraction (forming precipitates) and metabolism as Gla-100

Adapte d from Dailey G, et al. Diabetes Obes Metab. 2015 ; Steinstraesser A et al. Diabetes Obes Metab. 2014; ; Becker RH et al. Diabetes Care. 2015

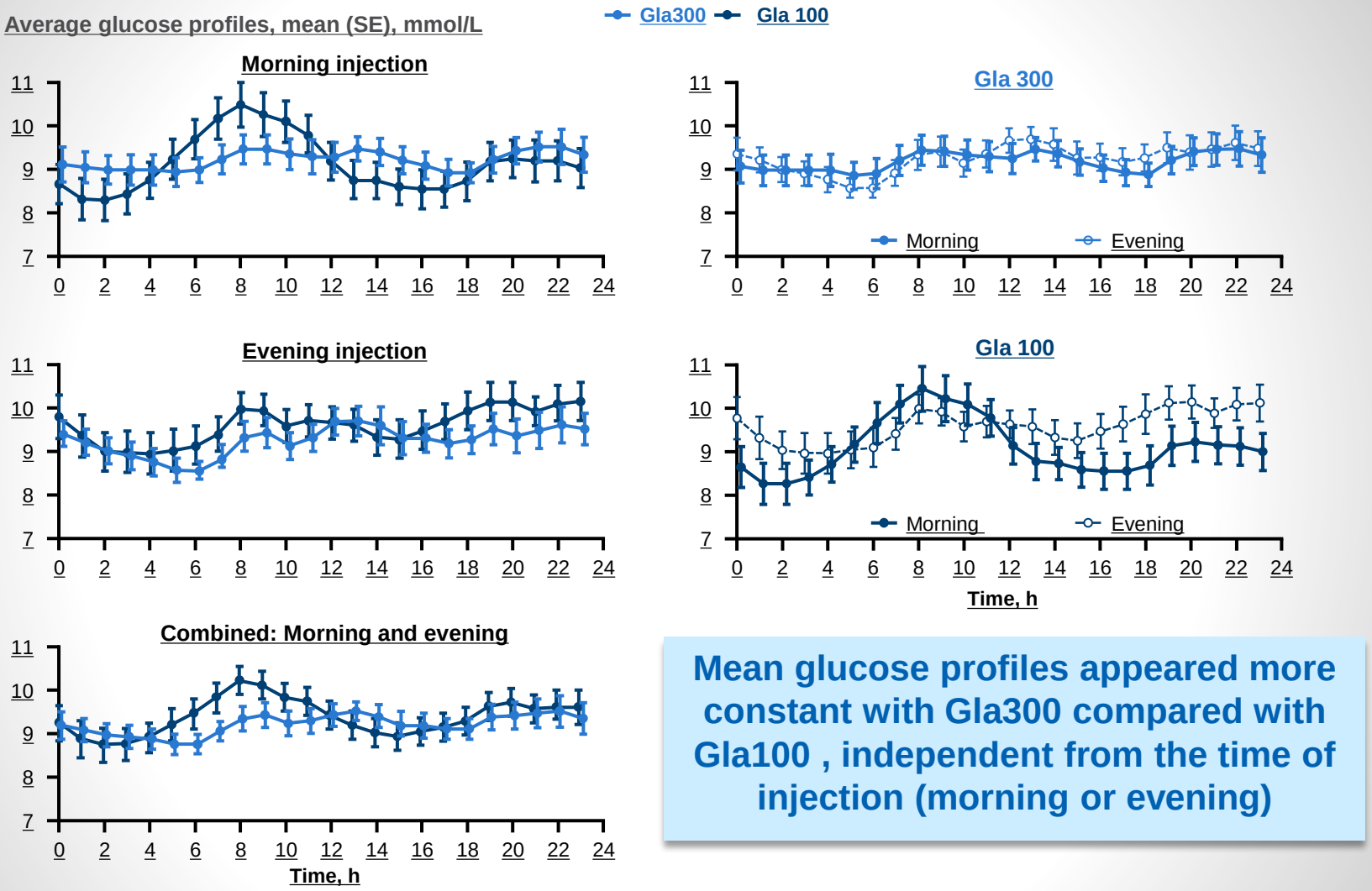
More stable and prolonged (beyond 24 hours) PK/PD profile with Gla-300 vs Gla-100



- **Double-blind, crossover euglycemic clamp study of Gla-300 vs Gla-100 in 30 patients with T1DM**

Becker RH et al. Diabetes Care; 2015

More constant glucose profile with Gla-300 vs Gla-100



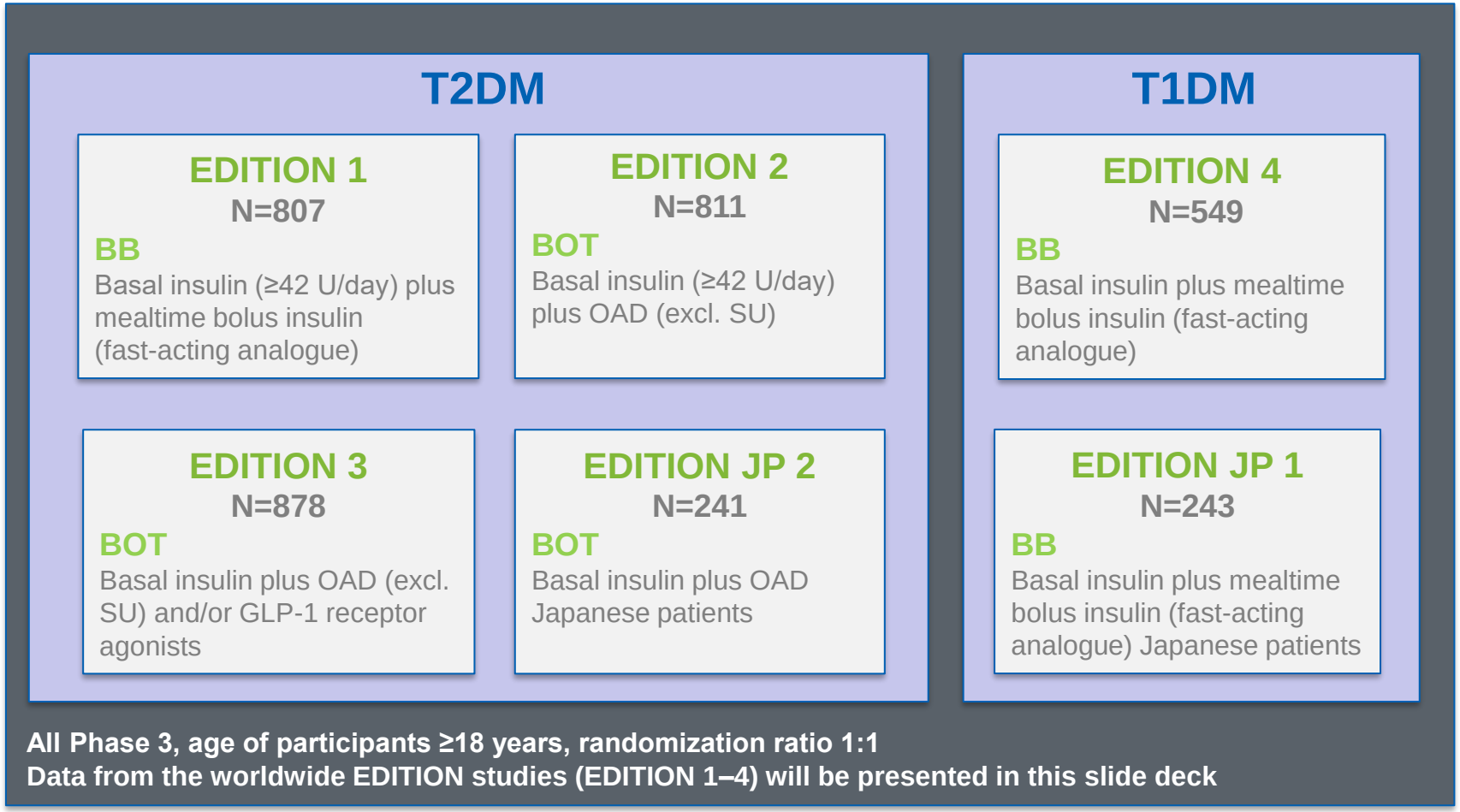
Mean glucose profiles appeared more constant with Gla300 compared with Gla100 , independent from the time of injection (morning or evening)

Average 24-h glucose profiles during the last 2 weeks of each treatment period (CGM population; pooled data period A + B)

Bergenstal RM et al Diabetes Care 2017

EDITION program

Gla-300 vs Gla-100 studies in different populations

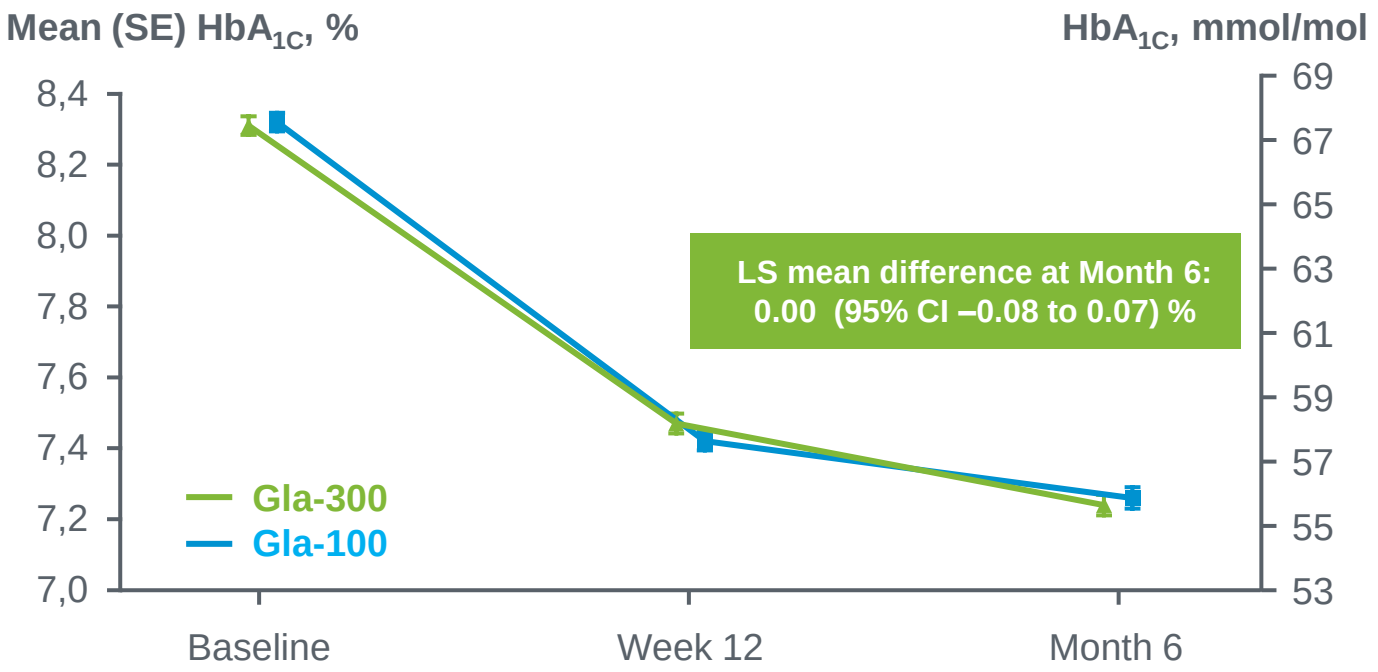


BB, basal-bolus therapy; BOT, basal only therapy; GLP-1, glucagon-like peptide-1; OAD, oral antihyperglycemic drug; SU, sulfonylurea; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Riddle MC et al. Diabetes Care. 2014;
Bolli GB et al. Diabetes Obes Metab. 2015;
Terauchi Y et al. presentation at EASD 2014;
Yki-Järvinen H et al. Diabetes Care. 2014;

EDITION 1-2-3 T2DM Pooled Analysis

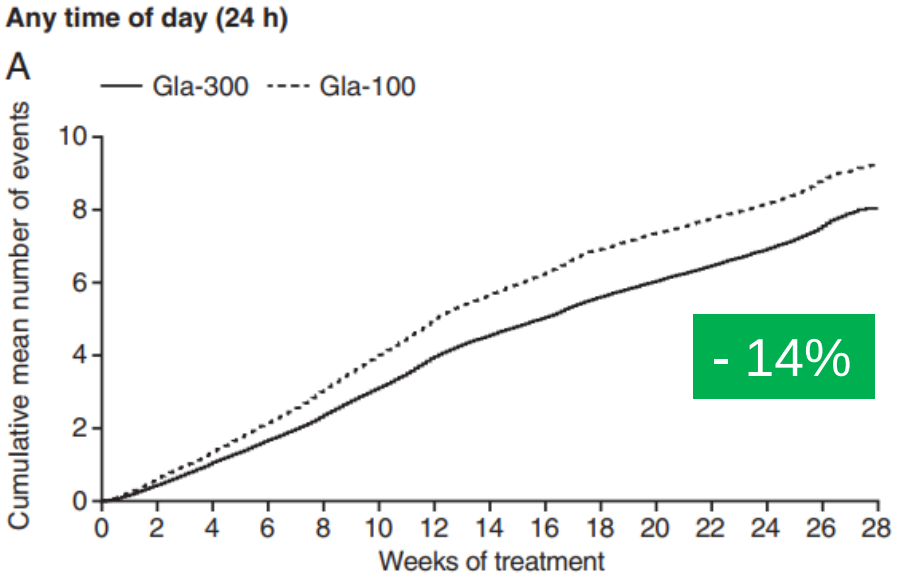
Similar reductions in HbA_{1C}

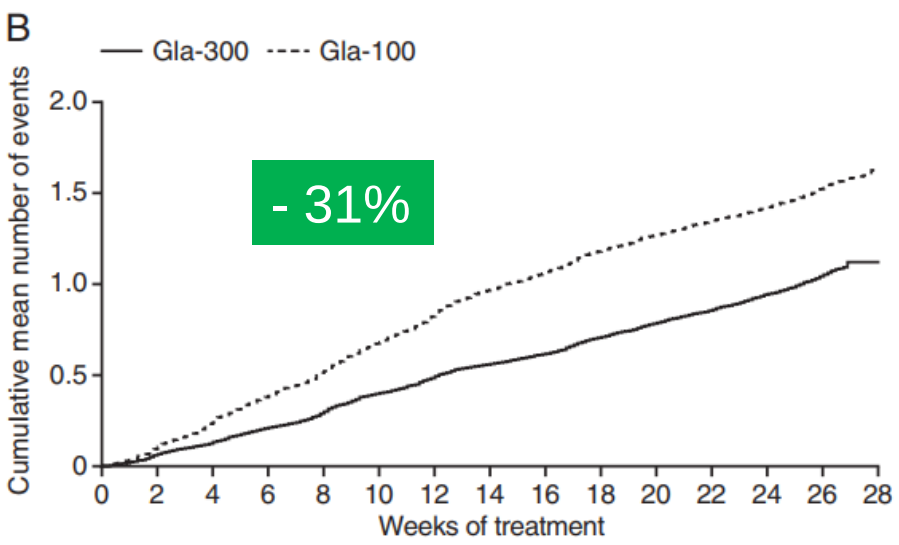


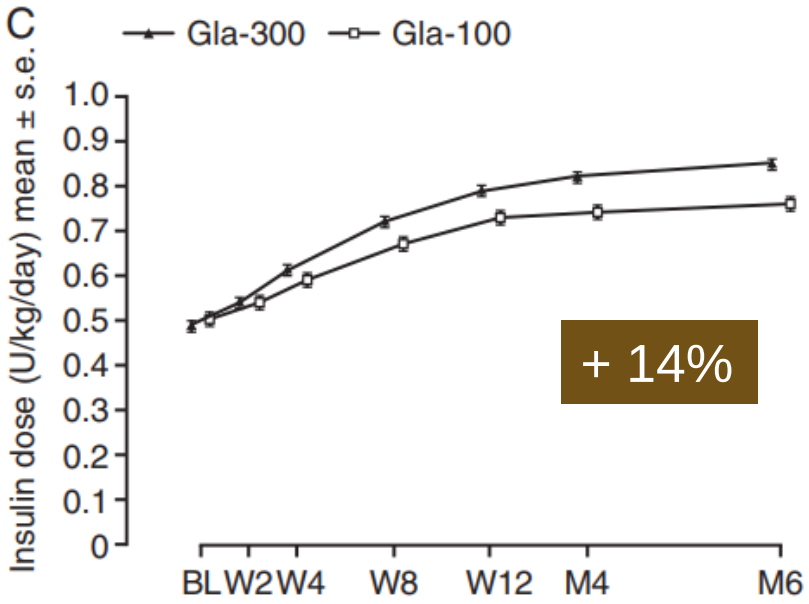
- At Month 6, FPG decreased similarly in both groups
  - LS mean (SE) change was −2.0 (0.1) mmol/L with Gla-300 and −2.3 (0.1) mmol/L with Gla-100
  - LS mean difference 0.2 (0.1) mmol/L

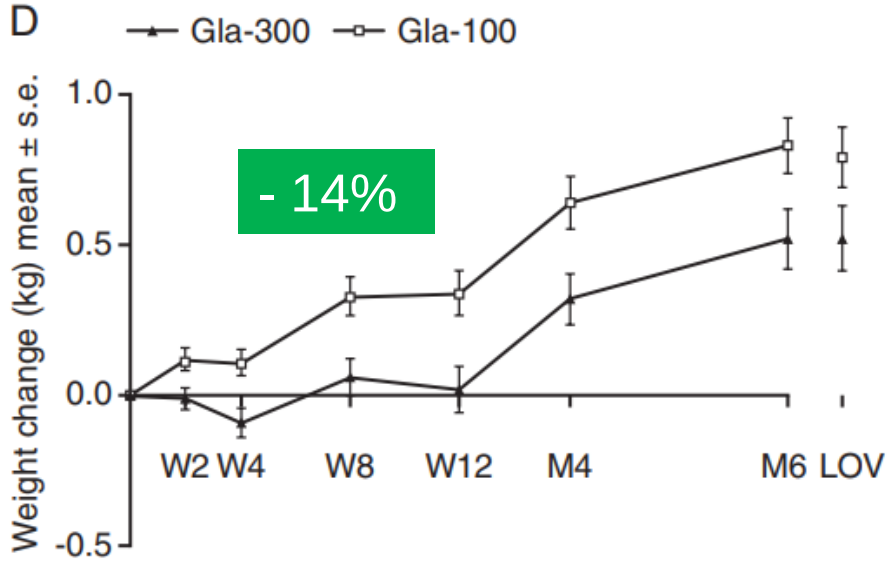
Diabetes, Obesity and Metabolism 2015

Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes





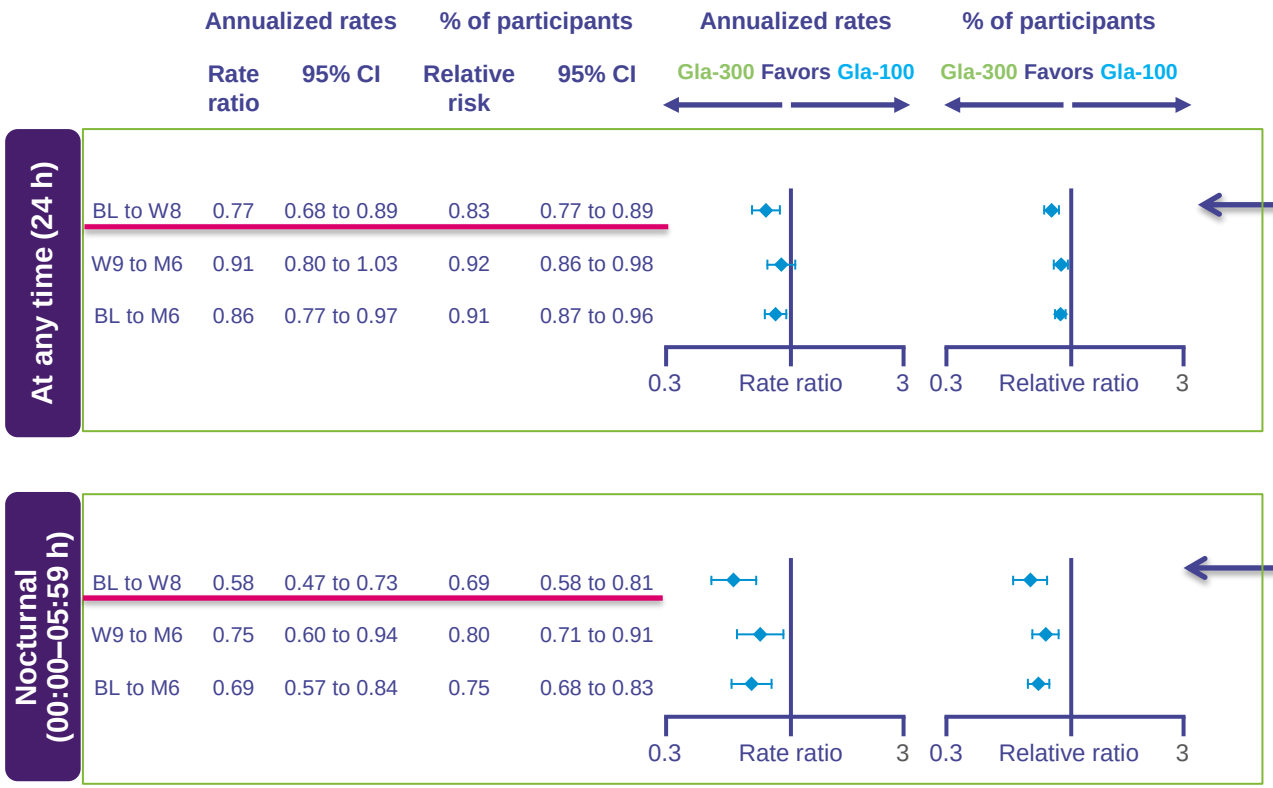




Ritzel R et al, Diabetes Obes Metab, 2015

Gla-300 reduced hypoglycemia even during the titration phase

Incidence/annualized rates of confirmed (≤70 mg/dL [3.9 mmol/L]) or severe hypoglycemia



From baseline to Week 8
Annualized rate
-23% (0.68 to 0.89)
Incidence
-17% (0.77 to 0.89)

From baseline to Week 8
Annualized rate
-42% (0.47 to 0.73)
Incidence
-31% (0.58 to 0.81)

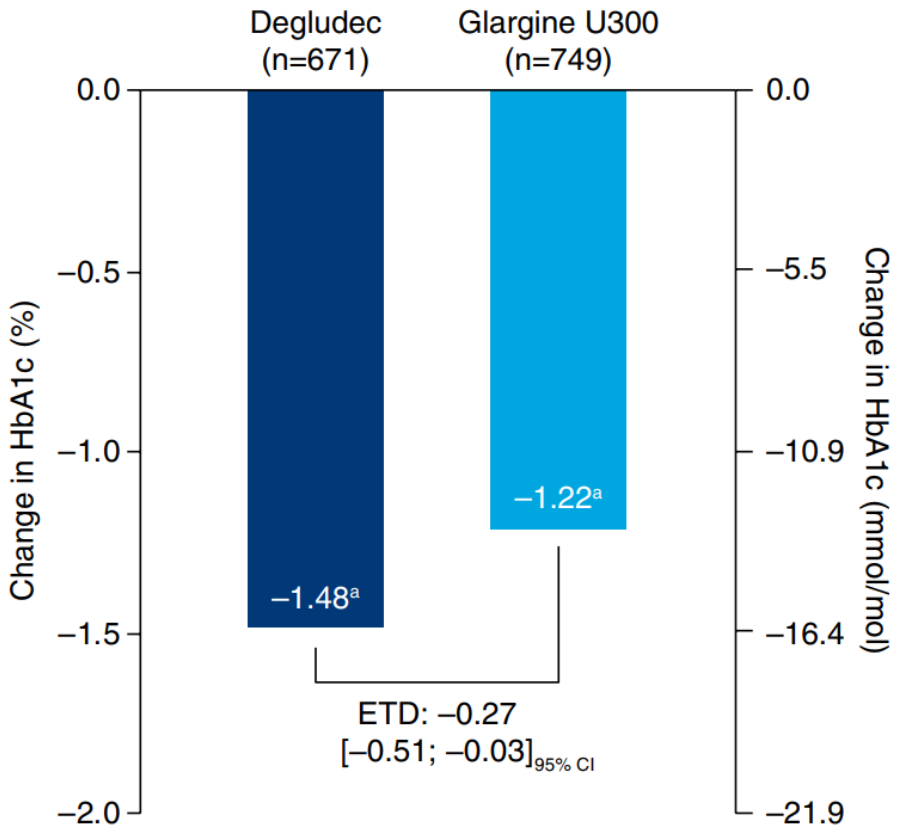
BL, baseline; M6, Month 6; W8, Week 8; W9, Week 9

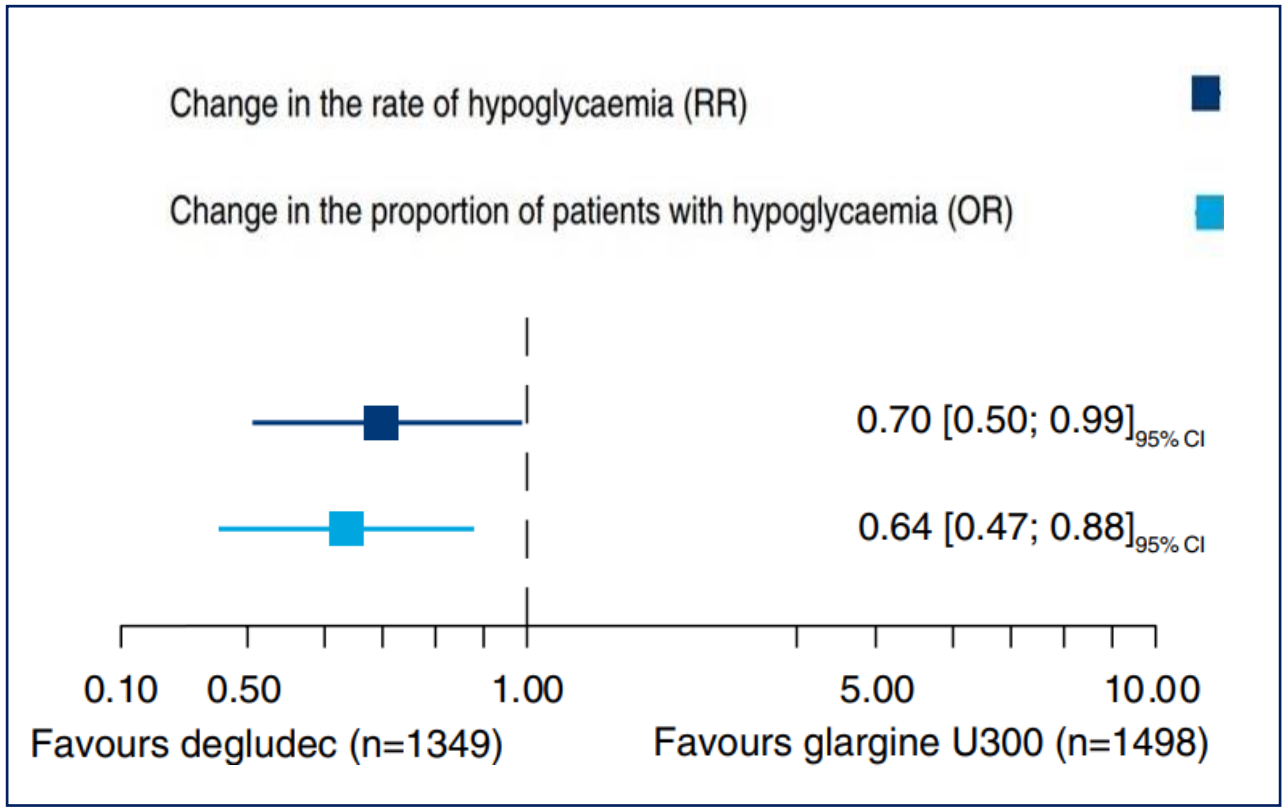
Adapted from Ritzel R et al. Diabetes Obes Metab. 2015

A comparative effectiveness study of degludec and insulin glargine 300 U/mL in insulin-naïve patients with type 2 diabetes

CONFIRM study

Change in HbA1C over 180 days of treatment with degludec or glargine U300

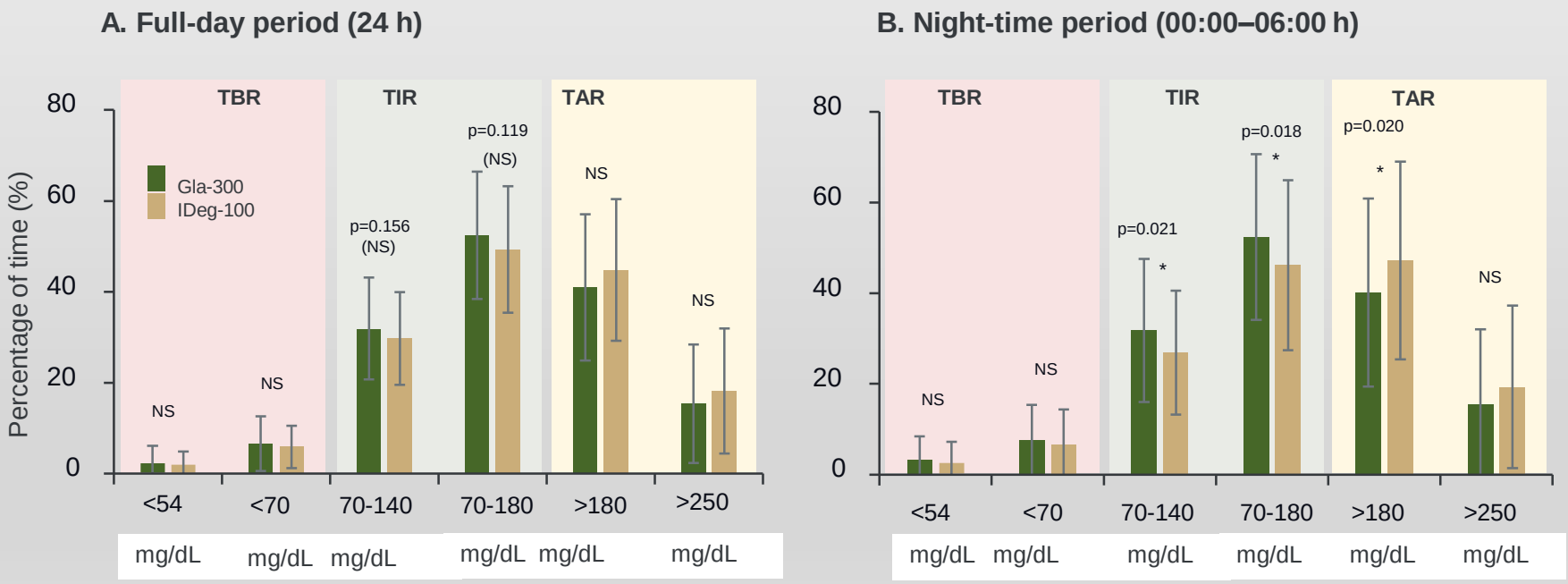




Tibaldi J et al., Diabetes Obes Metab 2019

Effectiveness and safety of Gla-300 vs IDeg-100 evaluated with continuous glucose monitoring profile in 199 adults with type 1 diabetes in routine clinical practice in Spain: OneCARE study

- There were no significant differences in TIR, TAR or TBR between the treatment groups during the full-day period (A)
- Differences favouring Gla-300 were observed during the night for TIR (both 70–140 and 70–180 mg/dL ranges) and TAR (>180 mg/dL) (B)



In a real-world setting the effectiveness and safety of Gla300 was similar to IDeg100. However people on Gla300 spent more time in target glucose range at night

Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; NS, not significant; TAR, time above range; TBR, time below range; TIR, time in range

Conget I et al., Diabetes Ther 2021

More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial

Multicenter, open-label, 1:1 randomized, active-controlled, 2-arm parallel-group, non-inferiority study in adult participants with uncontrolled T2DM

Pre-defined study endpoints

Primary efficacy endpoint:

- Change in HbA_{1c} from baseline to week 24

Secondary efficacy endpoints included:

- Change in FPG, fasting SMPG and 8-point SMPG profiles from baseline to week 24

Safety endpoints included:

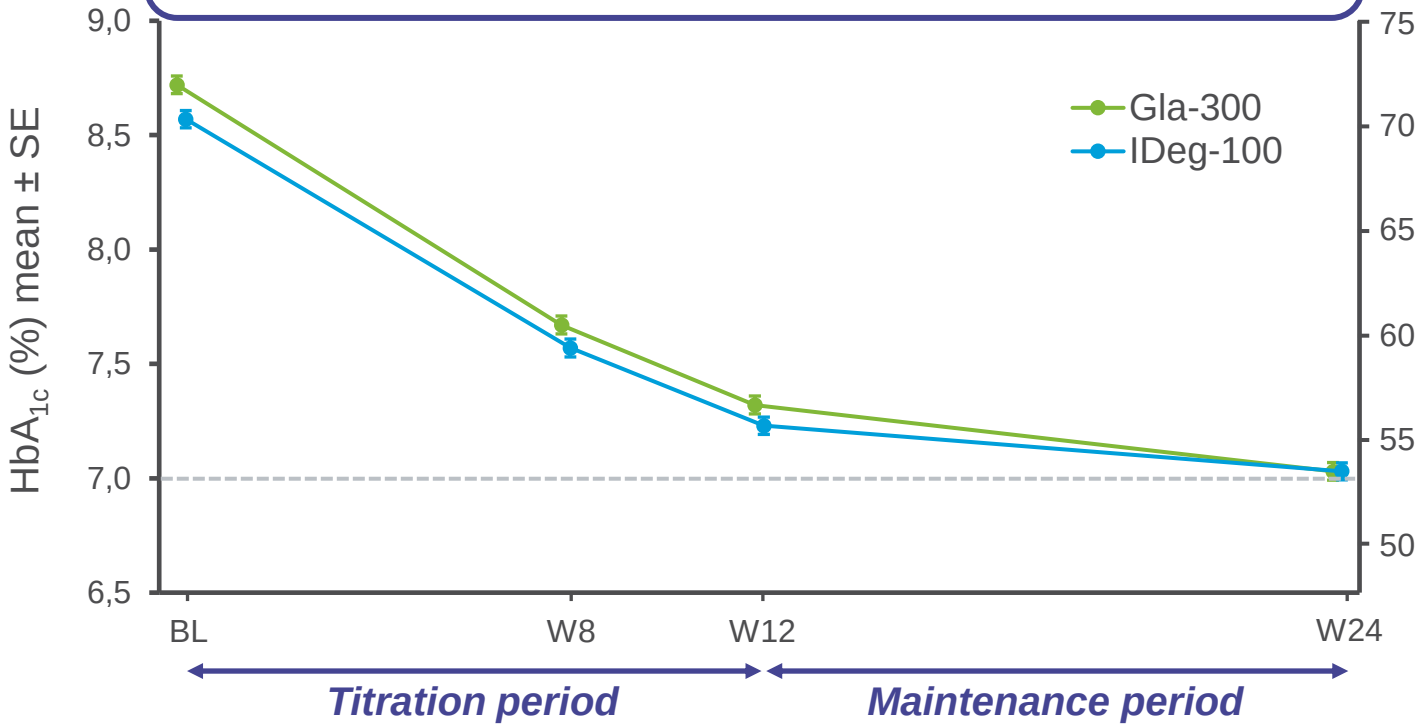
- Incidence and annualized rates of confirmed hypoglycemia (≤70 and <54 mg/dL) over the full 24-week period, and during weeks 0–12 (titration period) and weeks 13–24 (maintenance period)
- TEAEs

FPG, fasting plasma glucose; SMPG, self-monitored plasma glucose; TEAE, treatment-emergent adverse event

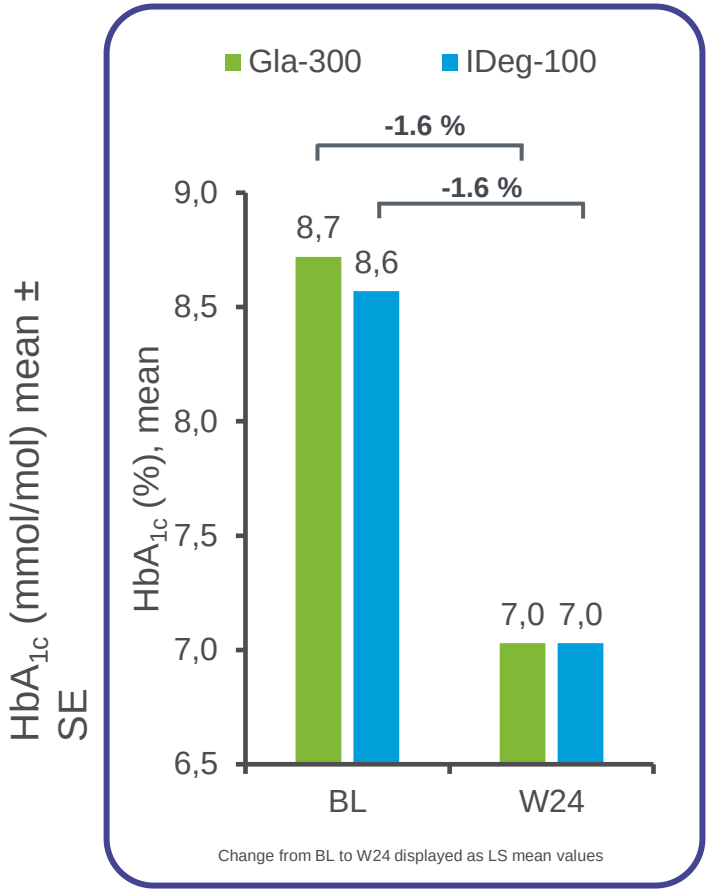
Rosenstock J et al., Diabetes Care 2018

Non-inferiority of Gla-300 vs IDeg-100 in HbA_{1c} reduction at study end

LS mean difference for Gla-300 vs IDeg-100:
-0.05 % (95 % CI -0.15 to 0.05) (−0.6 mmol/mol [−1.7 to 0.6]),
non-inferiority p-value <0.0001



No. of participants:					
	Gla-300	462	448	448	430
	IDeg-100	462	447	445	425



ITT population.
BL, baseline; ITT, intention-to-treat; LS, Least square; SE, standard error; W, week

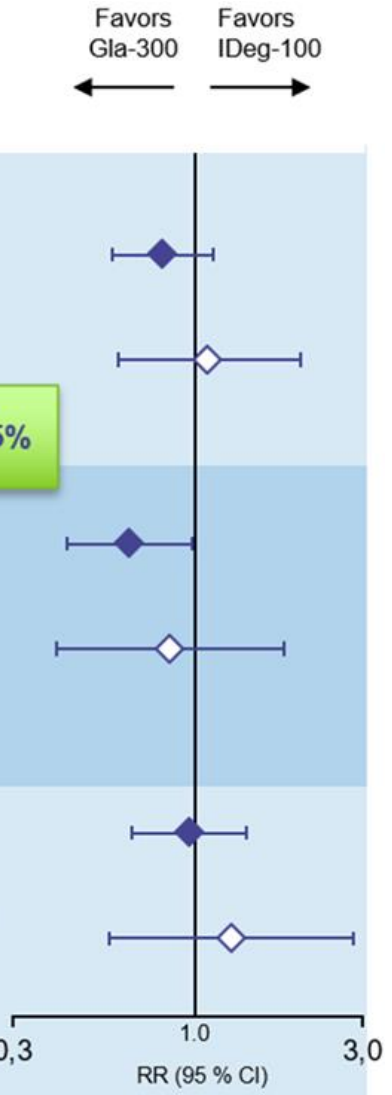
Cheng et al, American Diabetes Association 2018,

Incidence rate of hypoglicaemia

Any time (24h)

Nocturnal (00:00-06:00)

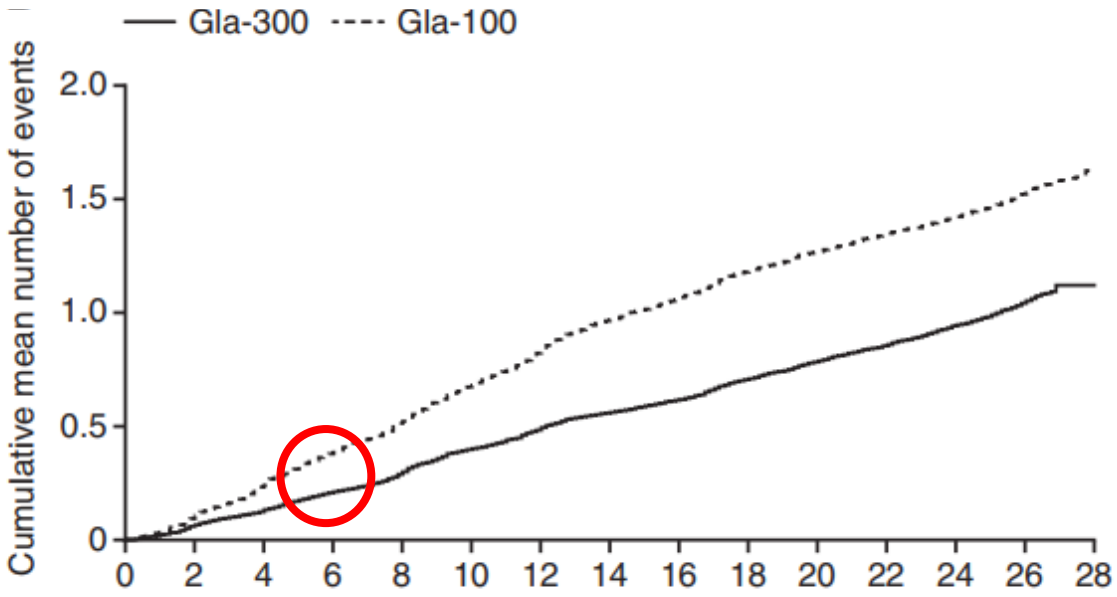
	Any time (24h) Events per patient-year Gla-300	IDeg-100	RR (95 % CI)	p-value	Nocturnal (00:00-06:00) Events per patient-year Gla-300	IDeg-100	RR (95 % CI)	p-value
Full study period (0–24 weeks)								
Confirmed (≤70 mg/dL [≤3.9 mmol/L])	9.34	10.83	0.86 (0.71 to 1.04)	0.130	1.83	2.26	0.81 (0.58 to 1.12)	0.204
Confirmed (<54 mg/dL [<3.0 mmol/L])	0.61	0.88	0.69 (0.45 to 1.08)		0.24	0.22	1.09 (0.60 to 2.00)	0
Titration period (0–12 weeks)								
Confirmed (≤70 mg/dL [≤3.9 mmol/L])	8.08	10.47	0.77 (0.62 to 0.96)		1.42	2.20	0.65 (0.43 to 0.98)	0.040
Confirmed (<54 mg/dL [<3.0 mmol/L])	0.49	0.86	0.57 (0.34 to 0.97)	0.038	0.16	0.19	0.85 (0.40 to 1.79)	0.662
Maintenance period (13–24 weeks)								
Confirmed (≤70 mg/dL [≤3.9 mmol/L])	10.64	11.21	0.95 (0.76 to 1.19)	0.650	2.24	2.33	0.96 (0.66 to 1.40)	0.839
Confirmed (<54 mg/dL [<3.0 mmol/L])	0.73	0.91	0.81 (0.48 to 1.39)	0.448	0.33	0.26	1.27 (0.57 to 2.83)	0.555



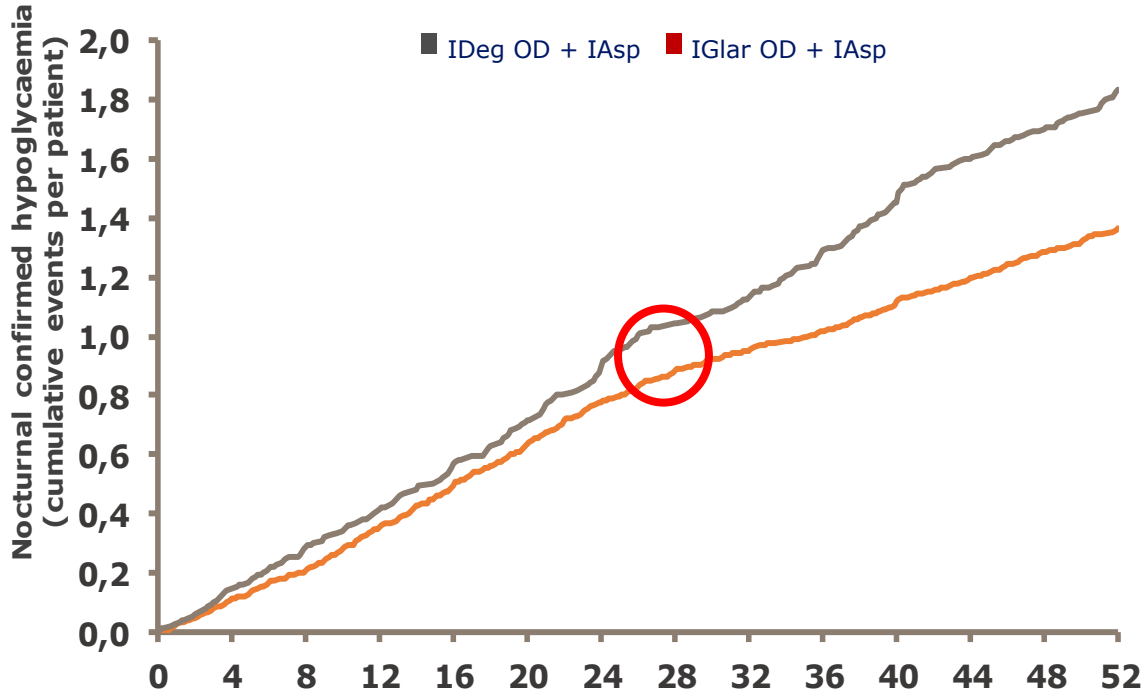
Rosenstock J et al., Diabetes Care 2018

NOCTURNAL HYPOGLICAEMIA

GLA-300 vs GLA-100 in The EDITION PROGRAM



IDEG vs GLA-100 in The BEGIN PROGRAM



WEEKS OF TREATMENT

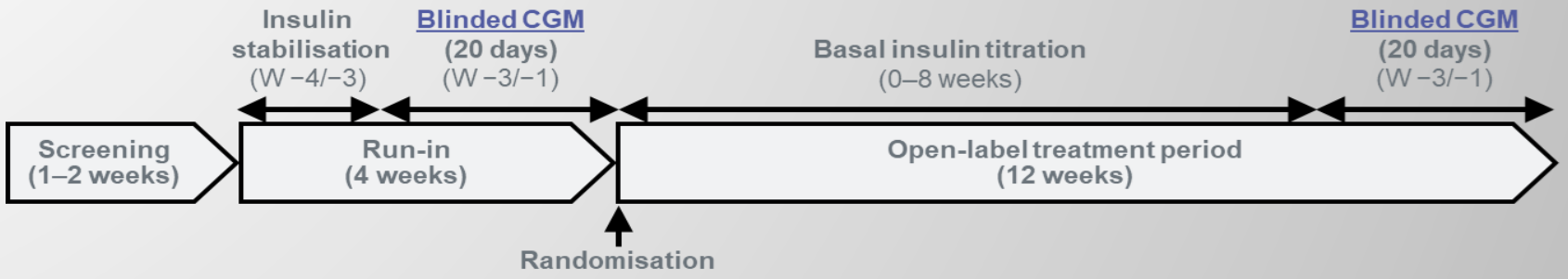
EASD
September 2022

Continuous glucose monitoring-based time-in-range using insulin glargine 300 units/ml versus insulin degludec 100 units/ml in type 1 diabetes: The head-to-head randomized controlled InRange trial

Study population (N=343)
- Adults aged 18–70 years with T1D
- HbA_{1c} ≥7 % to ≤10 %
- No Gla-300 or IDeg-100 in the last 30 days

Gla-300 (N=172)
Once daily (morning)

IDeg-100 (N=171)
Once daily (morning)



- Glycaemic variability was comparable between groups
- At any time of day, TAR, TIR, and TBR were comparable between groups
- TIR and TBR were also comparable during the night

Using clinically relevant CGM-based metrics, the InRange study shows that after 12 weeks of treatment with Gla-300 or IDeg-100, comparable CGM-derived outcomes are observed in people with T1D

Battelino T et al. Diabetes Obes Metab 2022

CONCLUDING REMARKS

- Time to start insulin therapy depends on several individual factors. Evidence suggests that a faster insulin approach may help in preserving endogenous insulin and reducing complications
- Fear of hypoglicaemia is a major barrier against Insulin therapy
- The scenario of insulin treatment has been enriched by new interesting therapeutic options, namely 2nd generation BI
- Both Insulin Degludec and Glargine-300 have been shown to be as effective as Glargine-100 but with less glycemic variability and fewer hypoglycemic episodes, the two moleculs being substantially comparable
- The reduction of hypoglycaemic episodes induced by Glargine-300 appears to be significant already during the titration phase; also, Gla-300 is associated with less weight gain compared to Gla-100

LE INSULINE BASALI NELLA TERAPIA DEL DMT2
TIMING E RAZIONALE D'USO

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SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE