Insuline basali a confronto

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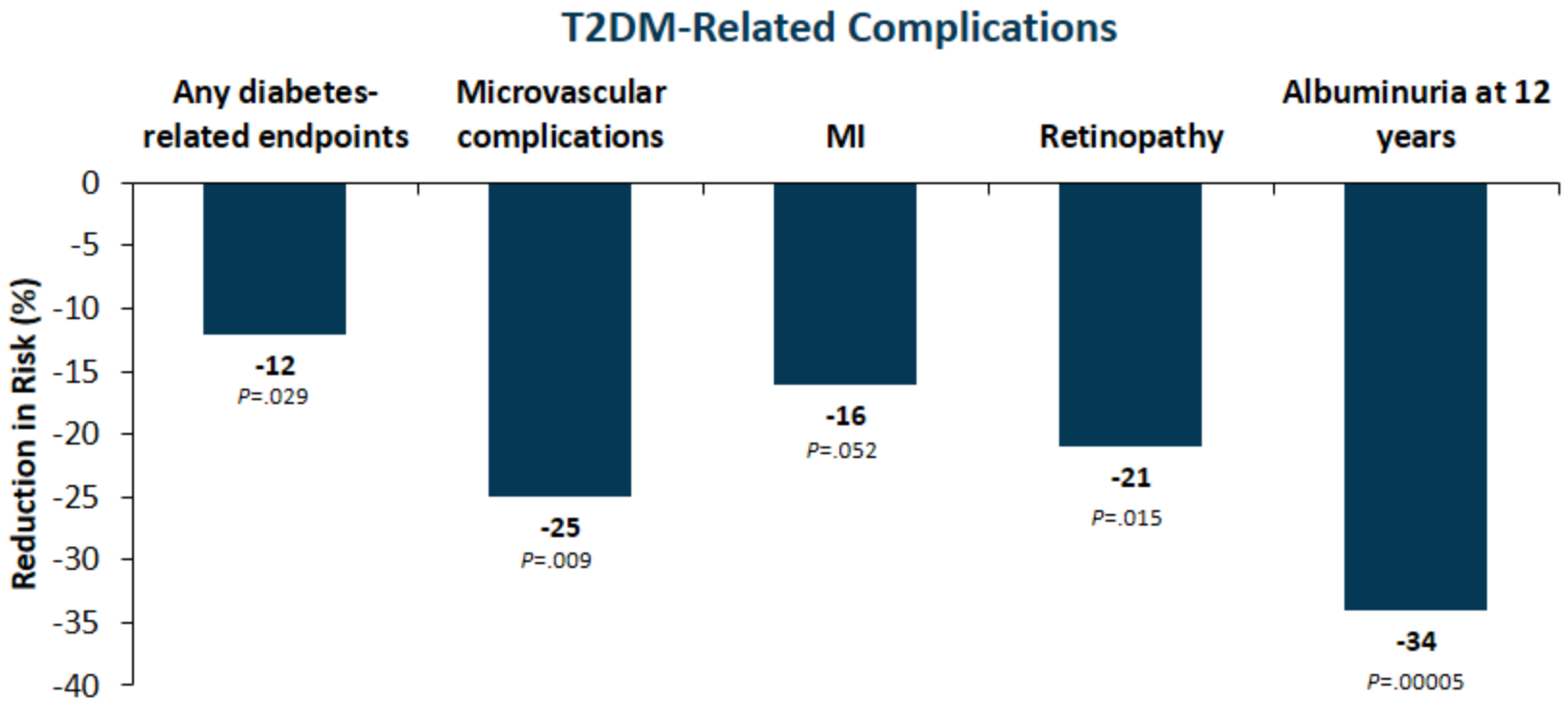
Università degli Studi di Bari "A. Moro"

The Importance of Tight Glycemic Control—UKPDS



Intensive glycemic control was associated with reductions in the risk for T2DM-related complications.*

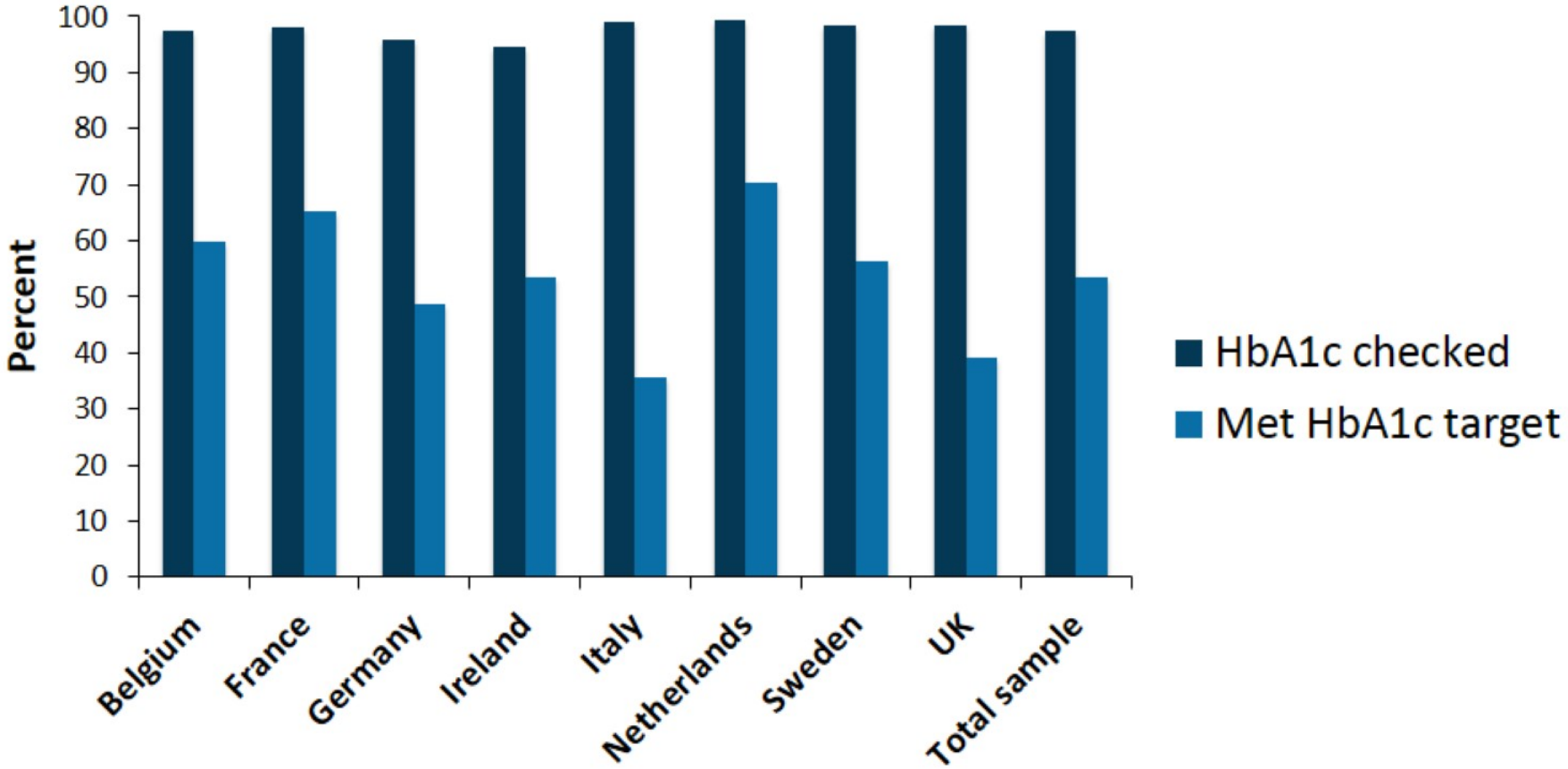
*Risk reduction for 0.9% decrease in HbA1c; HbA1c 7% in intensive control group vs 7.9% in conventional group

UKPDS. *Lancet.* 1998;352:837-853.

Despite Advances in Treatment, a Significant Proportion of Patients With T2DM Still Fail to Reach Target HbA1c Levels

GUIDANCE Study; 7597 T2DM Patients

Gap exists between checking HbA1c and achieving target HbA1c <7%

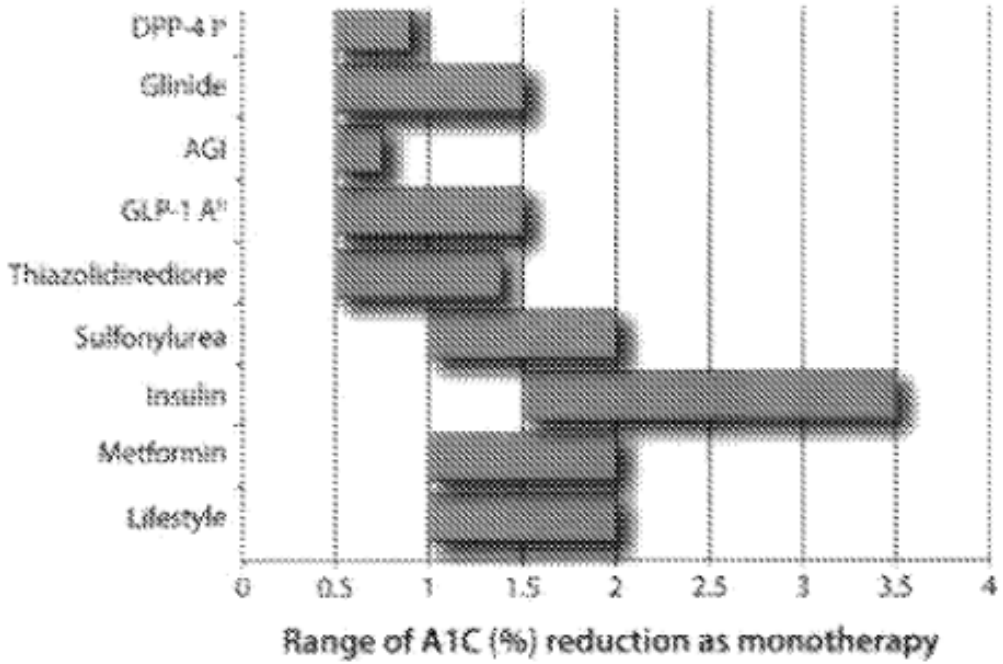


Stone MA, et al. *Diabetes Care*. 2013;36:2628-2638.

Terapie ipoglicemizzanti nel DMT2

L'insulina rappresenta il trattamento più efficace nel ridurre l'HbA1C1

Intervallo di riduzione dell'HbA1C con diversi tipi di terapie ipoglicemizzanti



1. Standard Italiani per la cura del diabete mellito 2009-2010
2. Roman G et al. Horm Metab Res 2009;41:116-122

Effetti positivi dell'insulinizzazione tempestiva

Effetti diretti sulla glicemia

- **Effetti a breve termine**
  - Rapida riduzione della glucotossicità
  - Miglioramento della funzionalità beta-cellulare
  - Protezione beta-cellulare e preservazione della secrezione insulinica
- **Effetti a lungo termine**
  - Prolungato controllo glicemico
  - Remissione

Effetti indiretti sulla glicemia

- Migliora la sensitività all'insulina (riduce la resistenza insulinica)
- Riduce fattori di rischio cardiovascolari
- Riduce i marker dell'infiammazione e il profilo lipidico aterosclerotico

oman G et al. Horm Metab Res 2009;41:116-122

Management of Type 2 Diabetes – Methods for Addition of Prandial to Basal Insulin

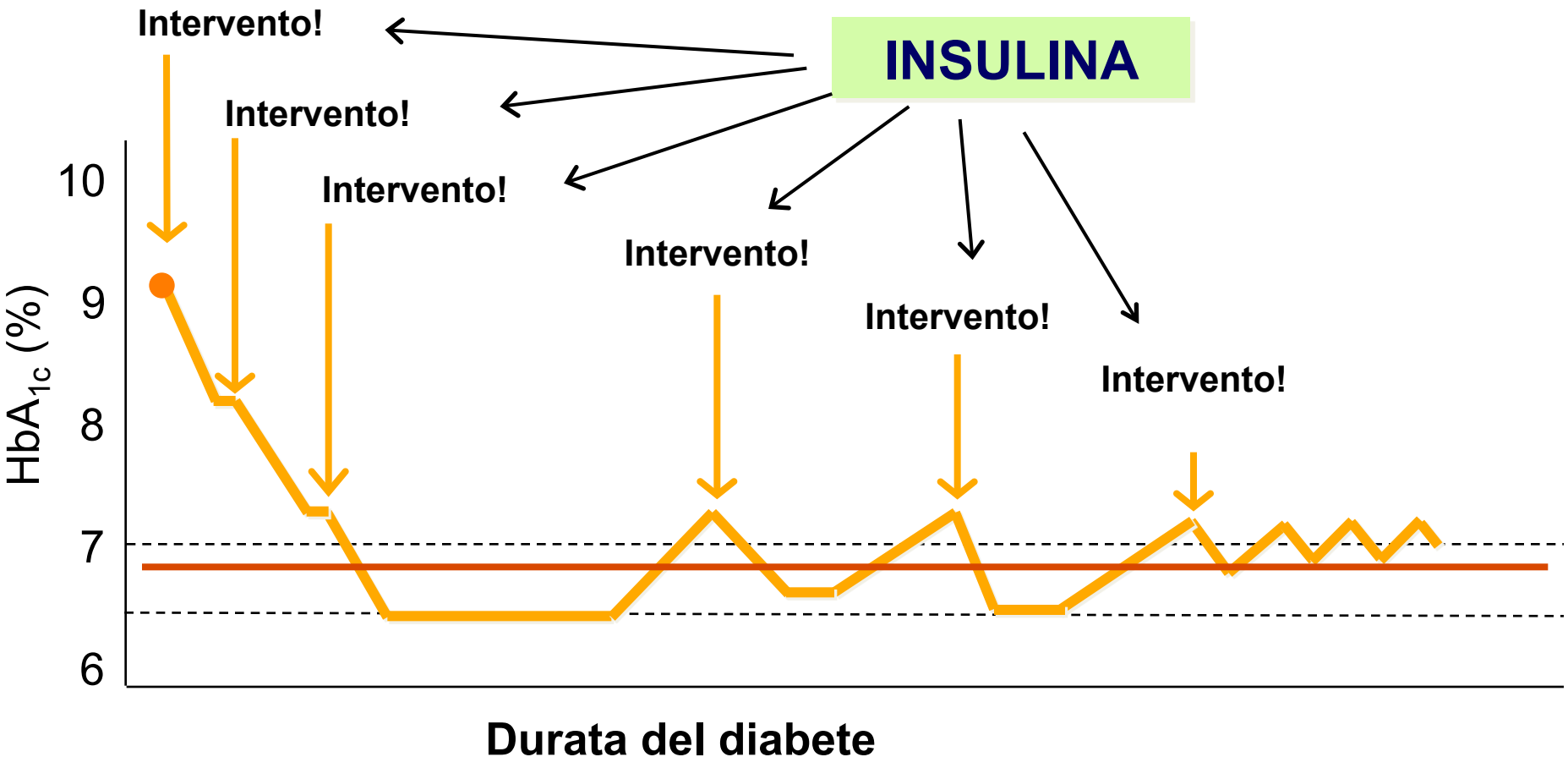
Helena W Rodbard[1] and Boris Karolicki[2]

1. Medical Director, Endocrine and Metabolic Consultants, Rockville, Maryland, US; 2. Medical Director, Novo Nordisk Inc., Princeton, New Jersey, US

Insulin is Underused

Insulin treatment can be initiated at any point in the course of T2D. Early initiation of insulin and improved glycaemic control may help to preserve β-cell function, promote vascular endothelial health and minimise the risk of complications, although long-term clinical data are needed to clarify these potential associations.[35] Nevertheless, rather than occurring early in treatment progression, initiation and intensification of insulin regimens in practice is often delayed in the face of poor or worsening glycaemic control.[11,35]

Citation: *European Endocrinology*, 2014;10(2):124–30


Intervento!
Intervento!
Intervento!
Intervento!
Intervento!
Intervento!
INSULINA
10
9
8
7
6
HbA1c (%)
Durata del diabete

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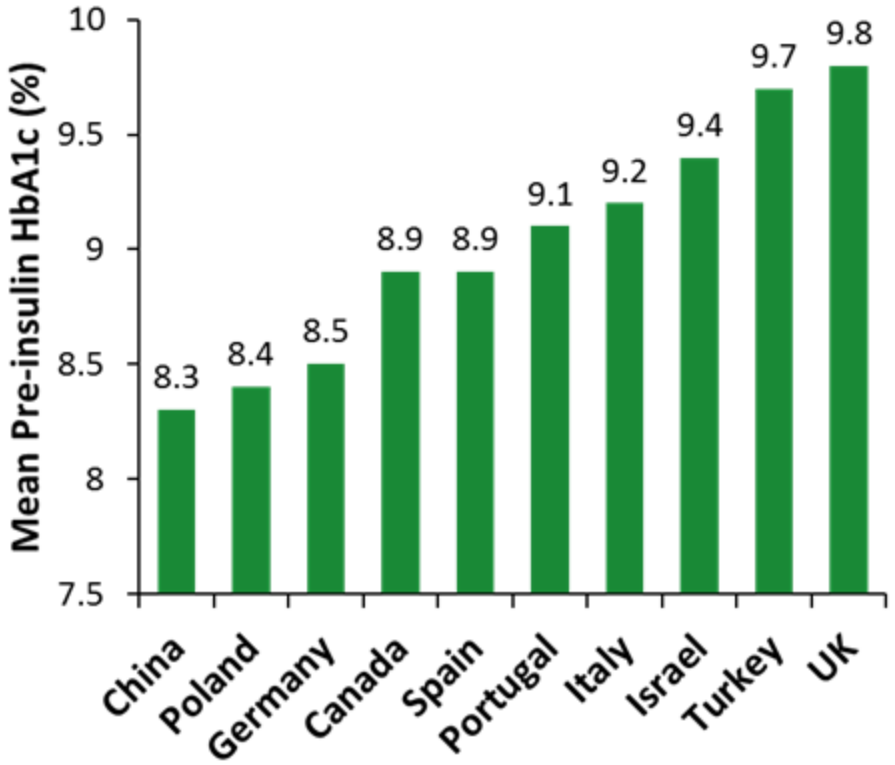
Citation: *European Endocrinology*, 2014;10(2):124–30

Initiation of Insulin Therapy Is Often Delayed



- SOLVE™ study found that pre-insulin mean HbA1c ranged from 8.3% to 9.8%
- Insulin was started later than guidelines recommend in all countries
- Lack of support for patients and physicians is a key problem outside clinical trial settings
- Other reasons for delays include fear of hypoglycemia, weight gain, and needles

Khunti K, et al. *Diabetes Obes Metab.* 2012;14:1129-1136.
Khunti K, et al. *Diabetes Care.* 2013;36:3411-3417.
Petznick AM. *J Am Osteopath Assoc.* 2013;113 (Suppl 2):S6-S16.
Peyrot M, et al. *Diabetes Obes Metab.* 2012;14:1081-1087.

Patient Barriers to Earlier Glycemic Control

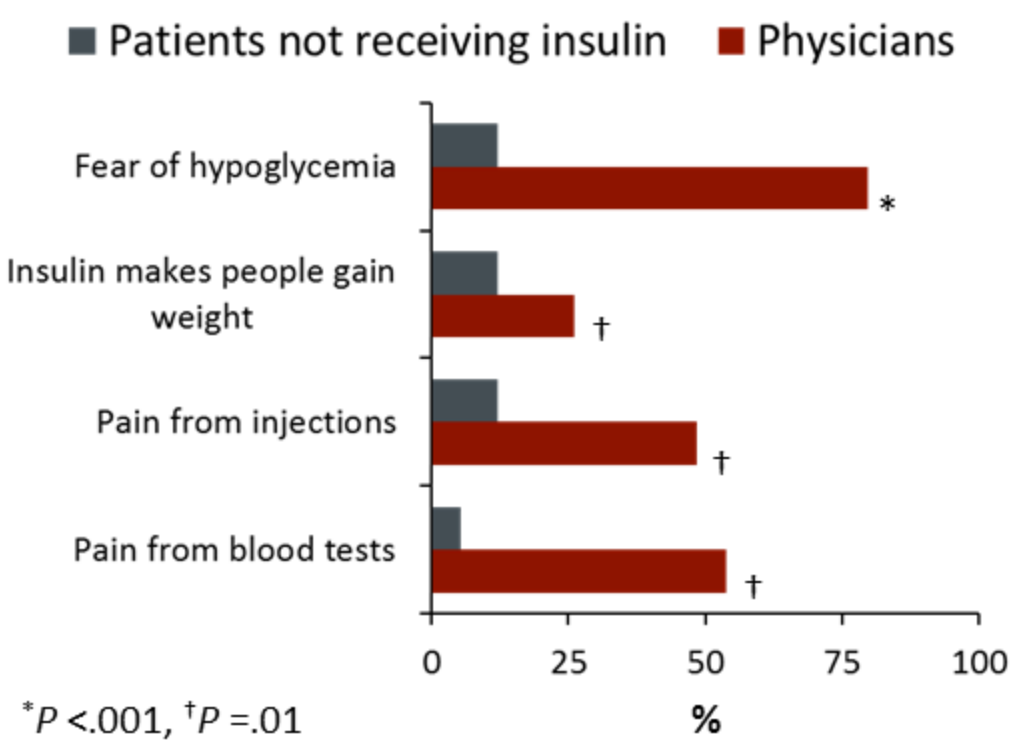
- Fear of hypoglycemia and weight gain
- Sense of personal failure and loss of control
- Perception that insulin is not effective or is actually harmful
- Lack of confidence in ability to manage insulin therapy
- Concerns of family, work, and friends

Patient barriers are often similar to those of physicians

Petznick AM. *J Am Osteopath Assoc.* 2013;113 (Suppl 2):S6-S16.
Polonsky WH, et al. *Diab Care*. 2005;28:2543-2545.

Barriers to Insulin May Be More Prevalent Among Physicians Than Patients

Comparison of barriers cited by physicians and patients not treated with insulin



*P <.001, †P =.01

- Case-control study found that physicians' misconceptions of patient's fears contributed to existing barriers
- Important for physicians to discuss insulin with patients early in the course of T2DM
- Reassure patients that starting insulin does not mean they have failed

Nakar S, et al. *J Diabetes Complications.* 2007;21:220-226.
Petznick AM. *J Am Osteopath Assoc.* 2013;113 (Suppl 2):S6-S16.
Polonsky WH, et al. *Diab Care*. 2005;28:2543-2545.

Tabella 1 *Incidenza delle ipoglicemie sintomatiche nel DM1 e nel DM2: risultati dello studio HYPOS (numero di episodi per persona/anno).*

Ipoglicemie	DM2 OHA non secretagoghi	DM2 OHA secretagoghi	DM2 Basal: oral	DM2 Altri schemi insulina	DM2 Basal: bolus	DM1
Sintomatiche totali	5,57	9,5	10,76	14,55	18,36	53,3
Sintomatiche diurne	3,58	8,05	9,0	10,97	14,41	33,9
Sintomatiche notturne	1,16	1,06	1,9	3,75	4,42	13,5

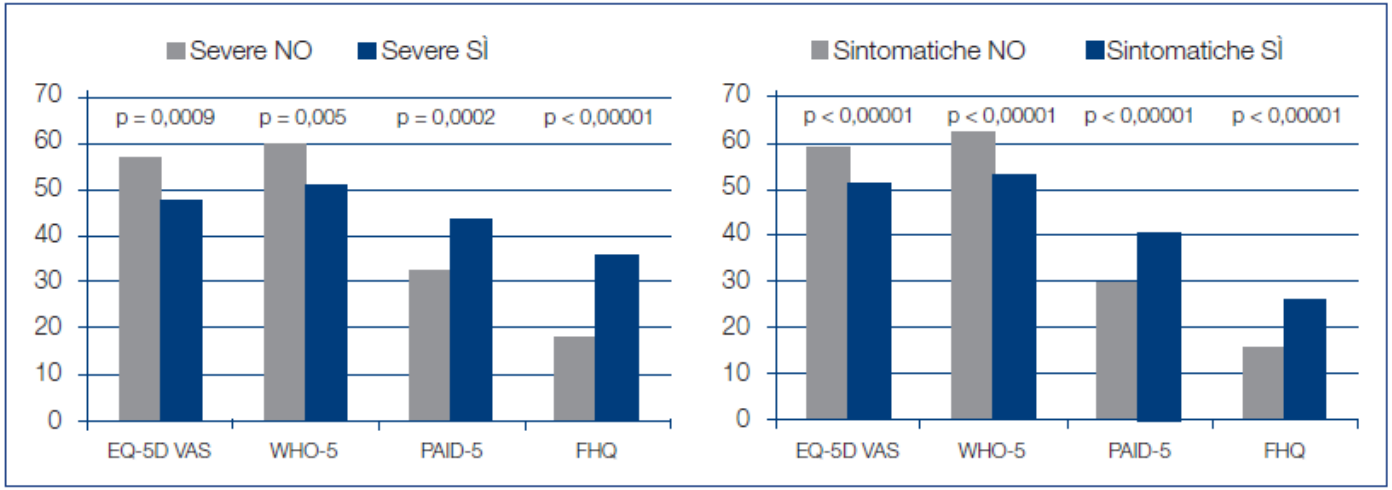
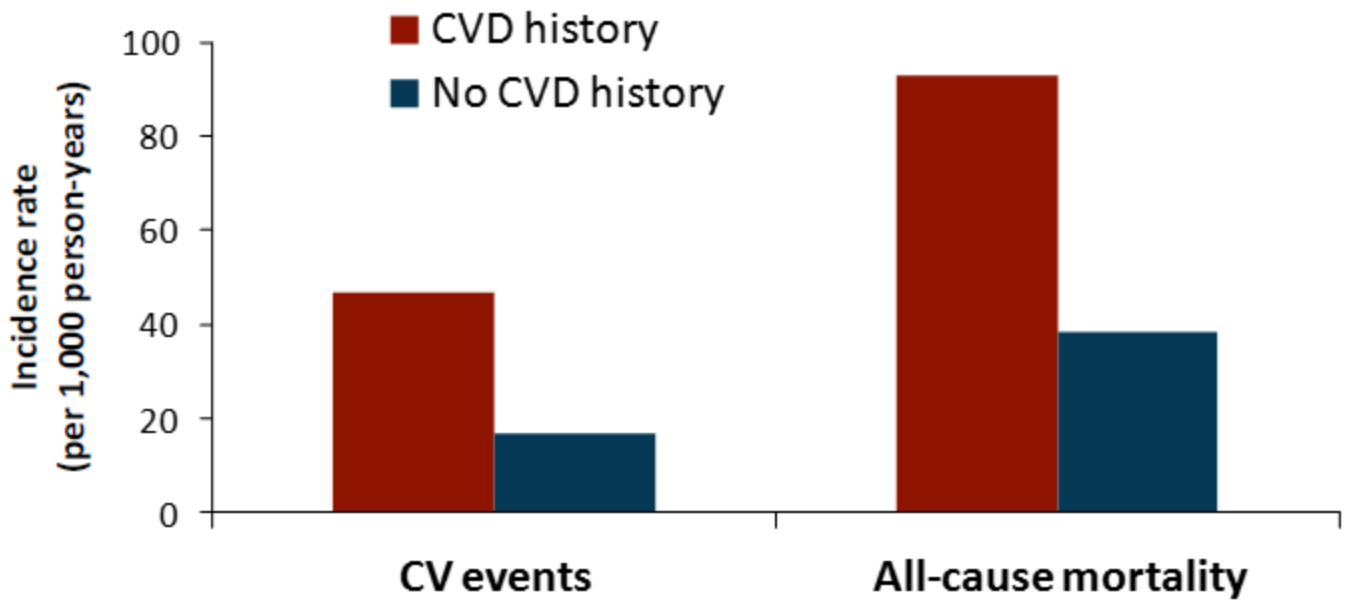


Figura 1. *Studio HYPOS: impatto delle ipoglicemie severe e delle ipoglicemie sintomatiche su diverse dimensioni della qualità di vita nelle persone con DM2. EQ-5D VAS: benessere fisico; WHO-5: benessere psicologico; PAID-5: distress legato al diabete; FHQ: paura delle ipoglicemie.*

Hypoglycemia Increases the Risk for CV Events and All-Cause Mortality

Retrospective cohort study of insulin-treated patients ≥30 years (10,422 with T2DM)



- Hypoglycemia increases the risk for adverse events
- Older patients and those with a long duration of T2DM are at higher risk for hypoglycemia

Khunti K, et al. *Diabetes Care* 2015;38:316-322.
Zoungas S, et al. *N Engl J Med.* 2010;363:1410-1418.

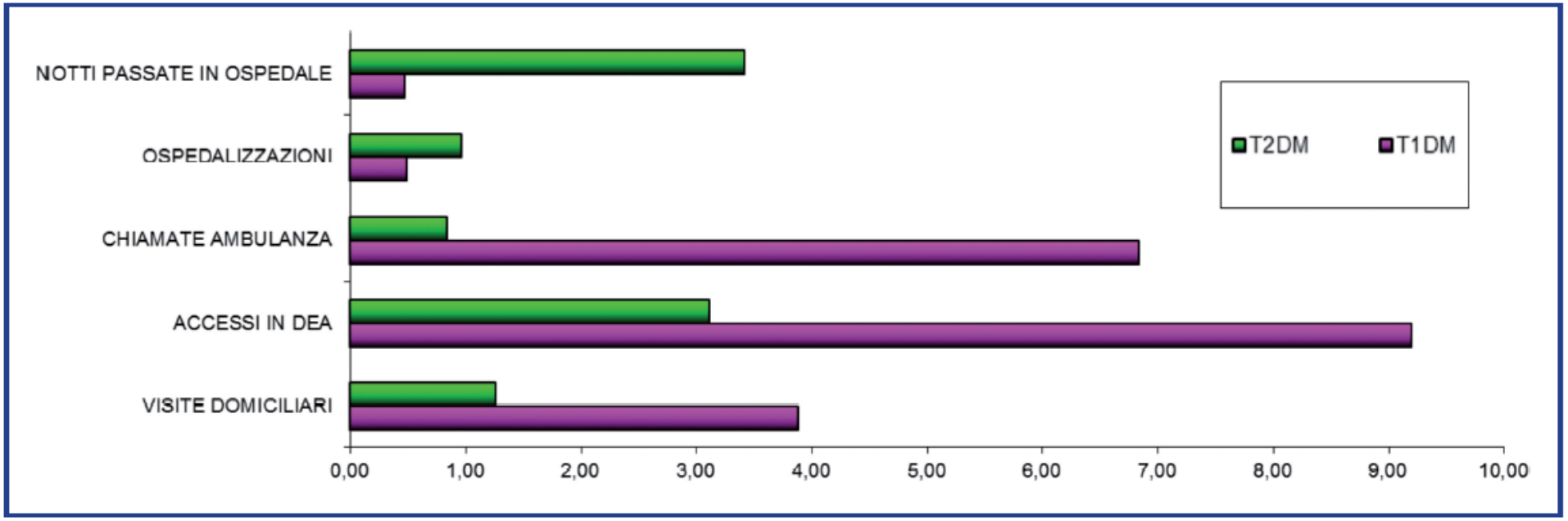


Figura 1. *Studio Hypos-1: impatto delle ipoglicemie sul consumo di risorse sanitarie dirette. Rappresentazione a barra del tasso di incidenza per 100 anni-persona.*

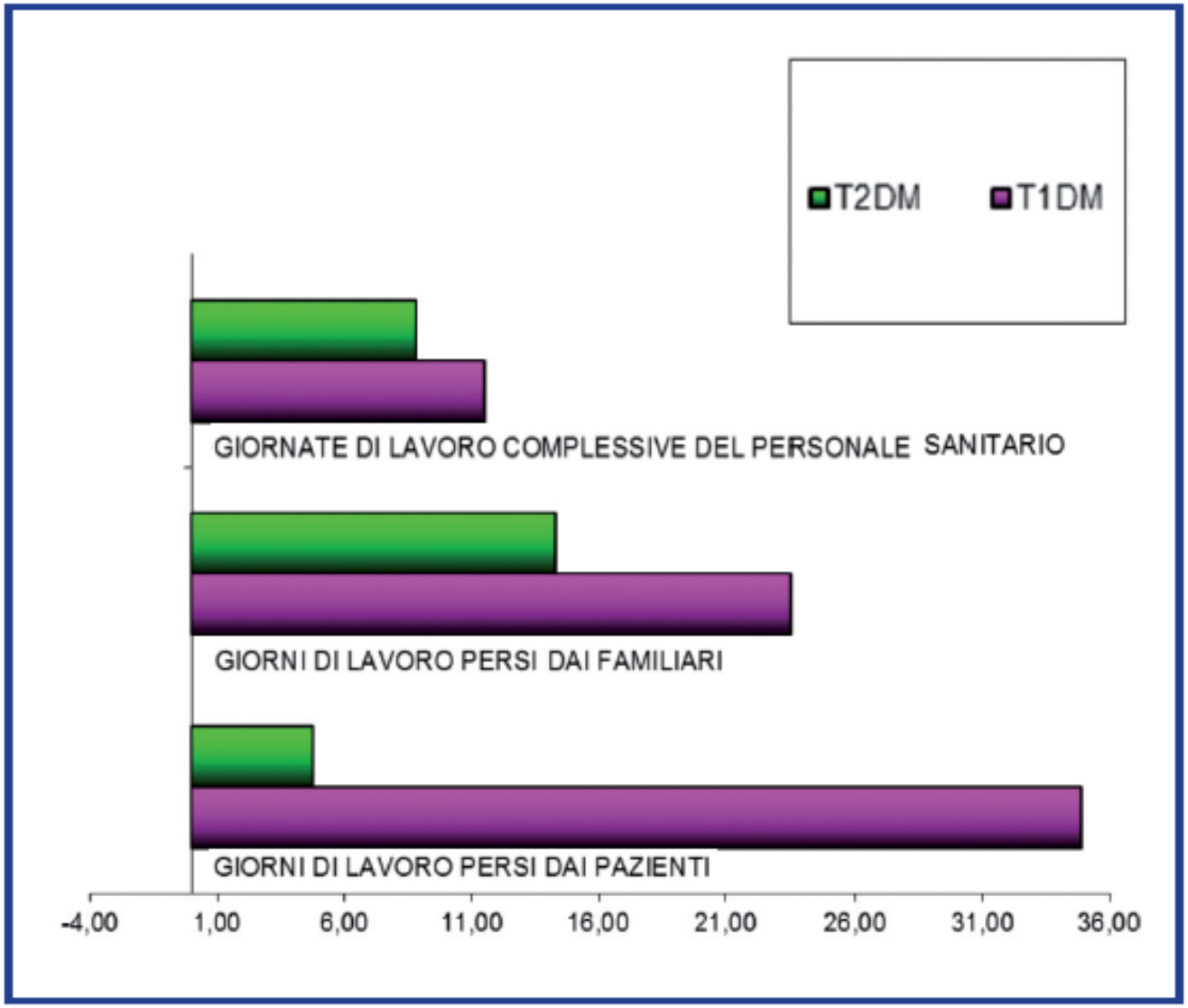


Figura 2. *Studio Hypos-1: impatto delle ipoglicemie sul consumo di risorse sanitarie indirette. Rappresentazione a barra del tasso di incidenza per 100 anni-persona.*

Tabella 2 *Fattori di rischio per l'ipoglicemia nel diabetico.*

- Dosi eccessive di insulina e/o di ipoglicemizzanti orali
- Assunzione concomitante di altri farmaci
- Ridotta assunzione di cibo (carboidrati)
- Per digiuno o pasto saltato
- Interventi chirurgici
- Consumo di alcolici
- Aumentato esercizio fisico
- Diminuzione del peso corporeo
- Insufficienza renale cronica
- Insufficienza renale acuta (uso di diuretici, disidratazione ecc.)
- Precedenti episodi di ipoglicemia grave o di ipoglicemia asintomatica
- Riscontro di basso valore di emoglobina glicata
- Obiettivo di mantenere basse le glicemie
- Presenza di neuropatia vegetativa
- Rifiuto della malattia
- Preparazione alla trasgressione alimentare
- Età avanzata
- Durata del diabete
- Carenze endocrine
- Presenza di altre malattie (per es: insufficienza del rene e del fegato)
- Ospedalizzazione recente

Strategies for Achieving Earlier Introduction of Insulin Therapy

- Educate the patient about T2DM and the benefits of insulin at the initial consultation
- Emphasize the fact that beta-cell dysfunction and insulin deficiency define the disease
- Explain that achieving effective glycemic control will improve outcomes for the patient
- Don't use insulin as a threat

Image courtesy of CDC/ Amanda Mills.

Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149.
Petznick AM. *J Am Osteopath Assoc.* 2013;113 (Suppl 2):S6-S16.
Polonsky W. *Diabetes Educ.* 2007;33 (Suppl 7):241S-244S.

Quando iniziare la terapia insulinica?

Pazienti di nuova diagnosi o già in trattamento che, alla dose massimale di ipoglicemizzanti orali, non raggiungono rapidamente (sei mesi) gli obiettivi

Subito se:

- Glicemia a digiuno > 250 mg/dl
- Glicemia post-prandiale frequentemente > 300 mg/dl
- HbA1c > 10%
- Chetonuria
- Diabete sintomatico (perdita di peso, poliuria, polidipsia)
- Gravidanza
- Patologie acute che richiedono ospedalizzazione
- Precedente cardiopatia ischemica

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

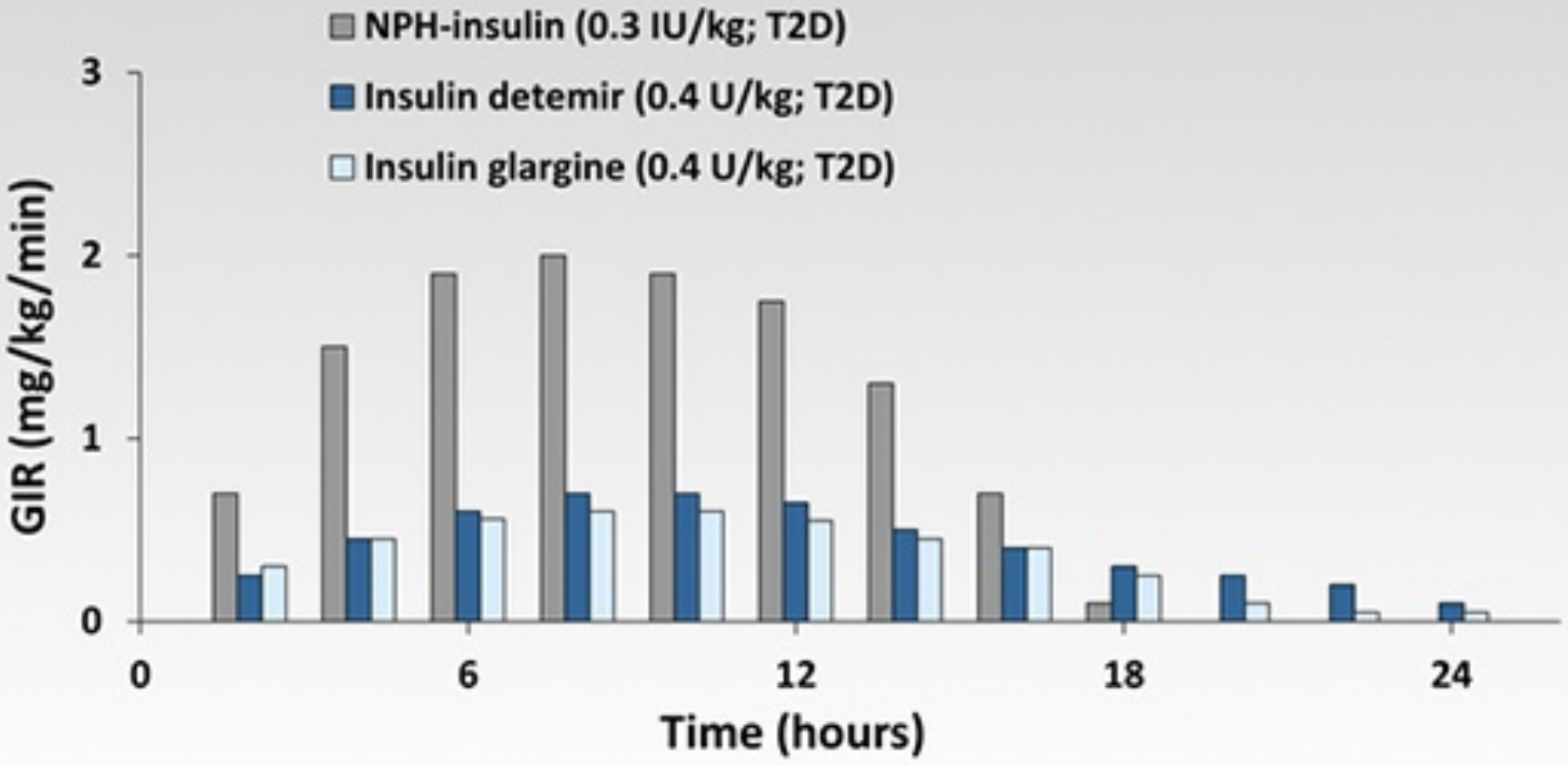
Basal Insulin Analogues

- NPH
- Lente
- Ultralente
- Glargine
- Detemir

Once-daily basal insulin analogues have a flatter time-action profile, with reduced variability

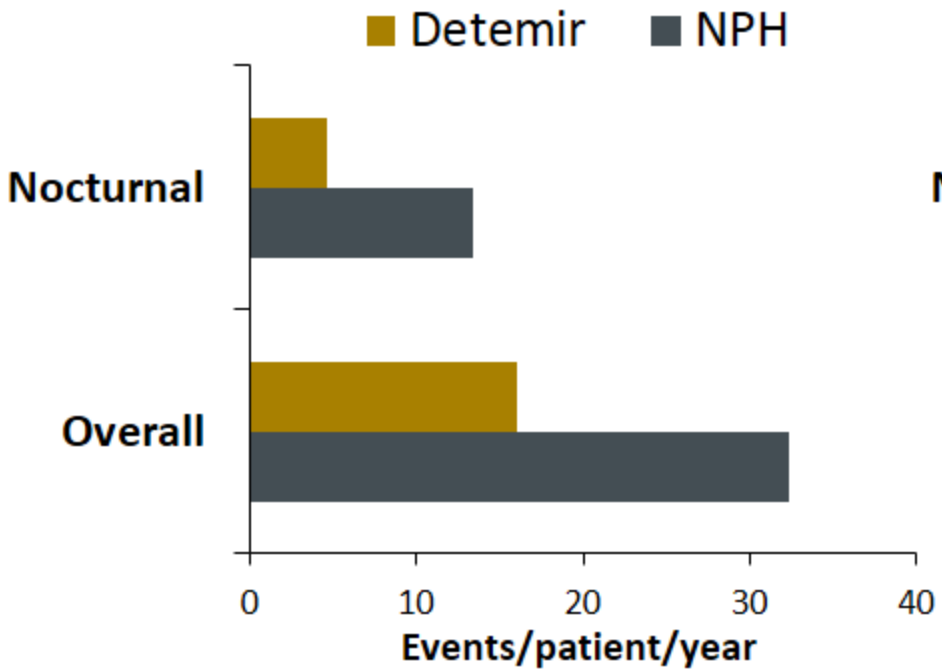
Owens DR, et al. *Diabetes Metab Res Rev*. 2014;30:104-119.[5]

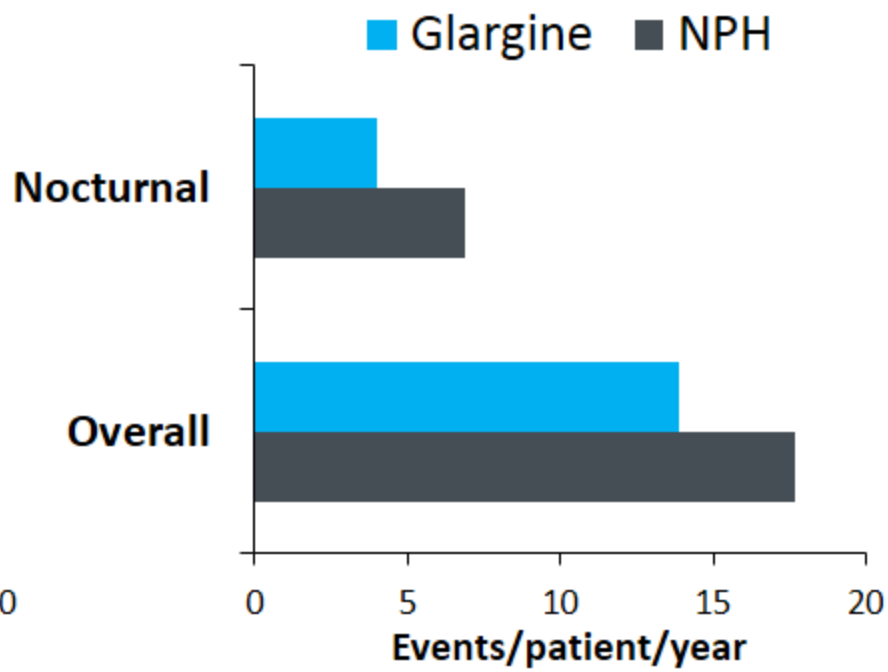
Basal Insulin Analogues: Less Peaked and Longer Duration of Action



Adapted from Hompesch M, et al. *Diabetes Obes Metab.* 2006; 8:568 and Klein O, et al. *Diabetes Obes Metab.* 2007; 9:290.

Less Hypoglycemia With Basal Insulin Analogues





Reduction in nocturnal hypoglycemia is important as most basal insulins are dosed at bedtime.

Riddle MC, et al. *Diabetes Care.* 2002;26:3080-3086.
Philis-Tsimikas A, et al. *Clin Ther.* 2006;28:1569-1581.

Remaining unmet needs and challenges with basal insulin therapy

There is still a compromise between risk of hypoglycemia and target glycemic control[1,2]

Patients compromise between fear of hypoglycemia and glycemic control, which may lead to poor patient adherence[3-6]

- **>70% physicians titrate less aggressively due to hypoglycemia concern[2]**
- **25–~75% patients modify insulin dose following an hypoglycemic event[4-6]**

Less than 50% of insulin-treated patients are at their glycemic target[7-9]

Above HbA_{1C} level of 7%, 38% more macrovascular complications and 40% more microvascular complications per 1% HbA_{1C} increase[10]

HbA_{1c}, glycated hemoglobin A_{1C}

1. Ahrén B. Vasc Health Risk Man. 2013;9:155-63; 2. Peyrot M et al. Diabetes Med. 2012;29:682–89;
3. Brod M et al. Curr Med Res Opin. 2012;28:1947-58; 4. Fidler C et al. J Med Econ. 2011;14:646–55;
5. Leiter LA et al. Can J Diabetes. 2005;29:186-92; 6. Brod M et al. Value Health. 2011;14:665-71;
7. Baser O et al. Clinicoecon Outcomes Res. 2013;5:497-505; 8. Larkin ME et al. Diabet Med. 2010;27:451-8;
9. Casagrande S et al. Diabetes Care. 2013;36:2271-9; 10. Zoungas S et al. Diabetologia. 2012;55:636-43

Desired Properties for A Basal Insulin Product Relative to Existing Therapy

- Clinical needs
  - Easier and safer dose titration without increasing risk of hypoglycemia
  - 1 injection per day
  - Flexibility in timing
- Glycemic control
  - Achieve treatment goals
  - Duration beyond 24 hours
- PK/PD Profile
  - Less variability
  - Consistent delivery of insulin
  - Flat, stable, and prolonged profile

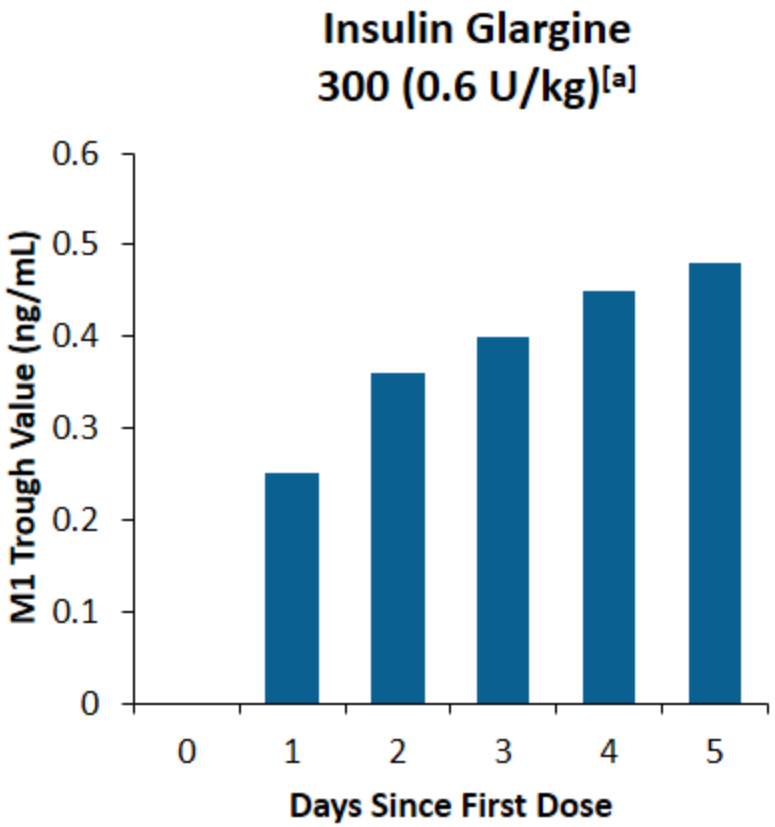
Evans M, et al. *Diabetes Obes Metab.* 2011;13:677-684.[24]

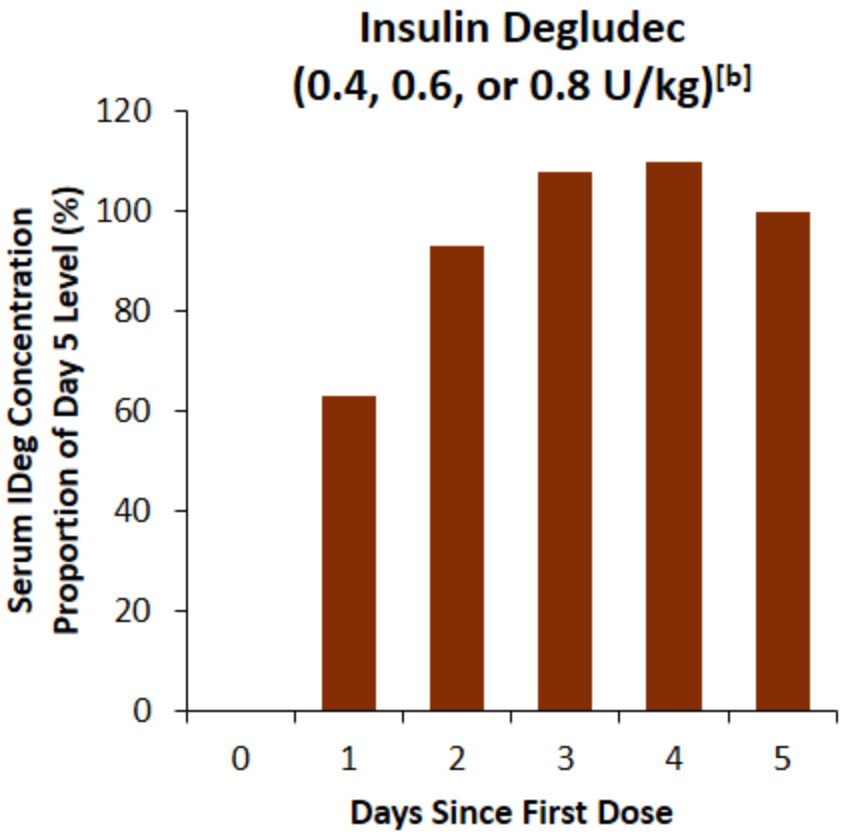
Second-Generation Basal Insulin Analogues

- Introduced to the market or at an advanced stage of clinical testing
- Each has a unique mechanism of protraction:
  - **Degludec**—multihexamer chain (>5000 kDa)[a]
  - **Glargine U300**—3-fold concentrated insulin with a depot surface area half the size of glargine 100[c]
  - **LY2963016 (Insulin Glargine Biosimilar)**

a. Wang F, et al. *Diabetes Metab Syndr Obes.* 2012;5:191-204.
b. Sinha VP, et al. ADA 2012. Poster 1063-P.
c. Maorino MI, et al. *Expert Opin Biol Ther.* 2014;14:799-808.

Novel Basal Insulins Reach Steady State After 3-4 Days

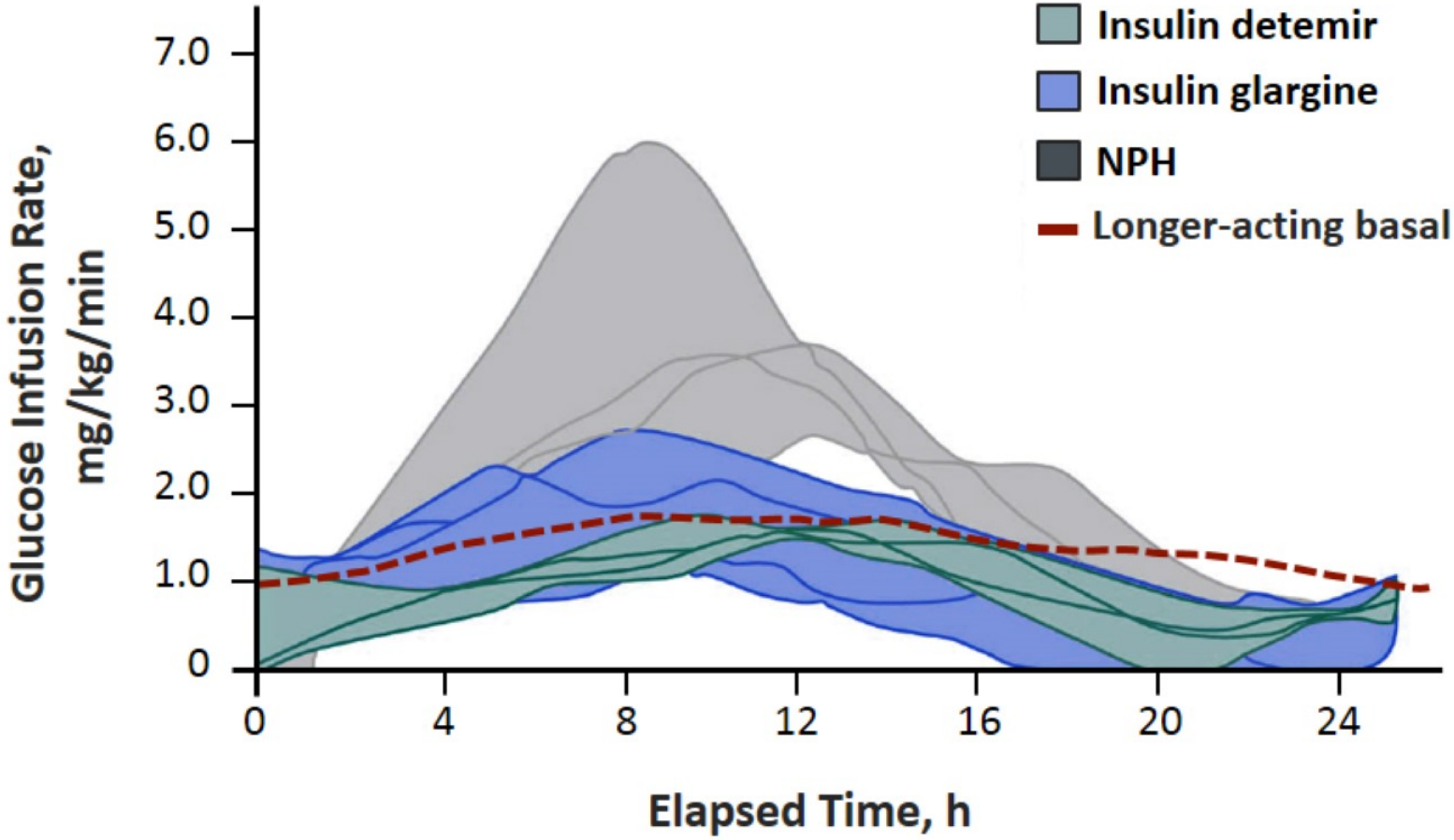




Dosage should not be adjusted more than every 3-4 days after initiation.

a. Steinstraesser A, et al. *Diabetes Obes Metab.* 2014;16:873-876.
b. Heise T, et al. *Diabetes.* 2012;61(Suppl 1):A259. Abstract 1013-P.

PK/PD Evolution of Basal Insulin Preparations

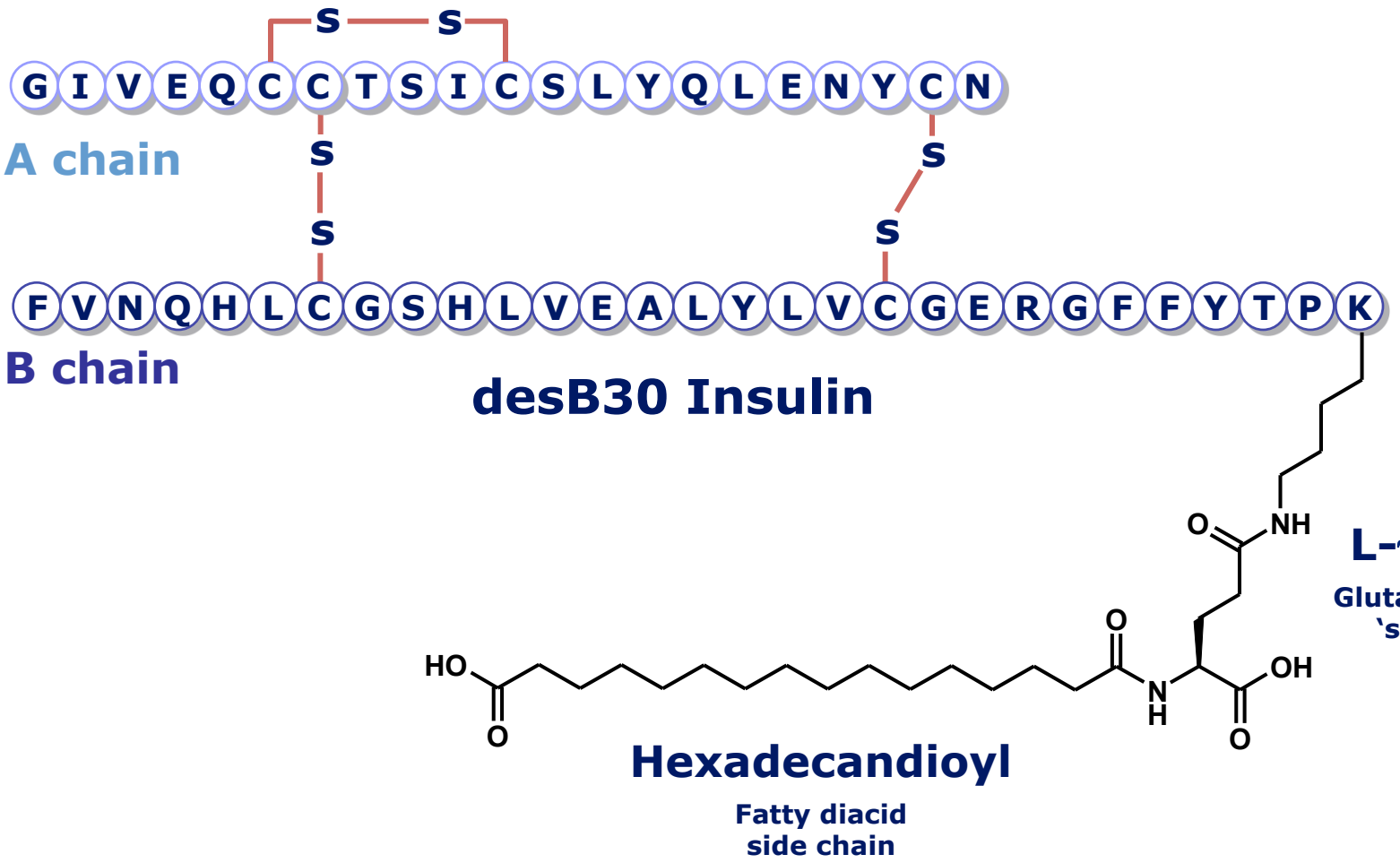


PD = pharmacodynamic; PK = pharmacokinetic.

Heise T, et al. *Diabetes*. 2004;53:1614-1620.[10]

Insulin degludec structure

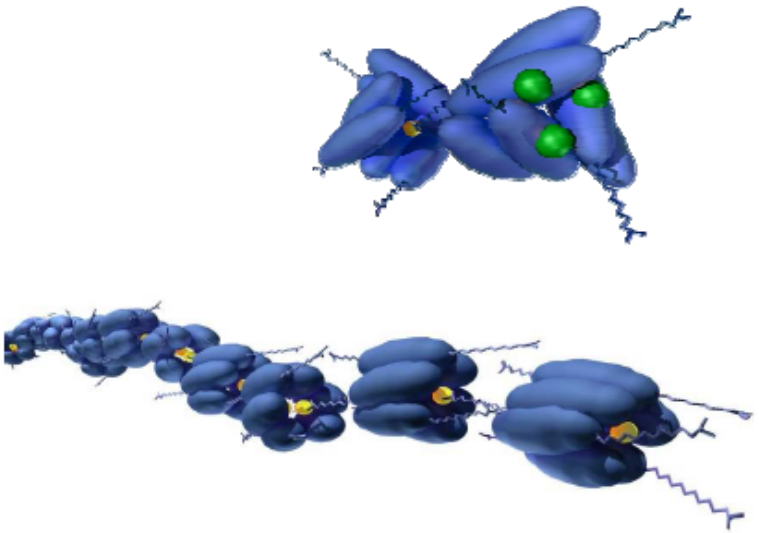
LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin



I Jonassen et al. Diabetes 59 (Suppl. 1): A11, 2010

I Jonassen et al. Diabetologia 2010;53(Suppl.1):S388 972-P

Insulin Degludec from injection to absorption: multi-hexamer formation key to protraction mechanism



Phenol; Zn^{2+}

Insulin degludec di-hexamers

Injected formulation

-Phenol

Insulin degludec multi-hexamers

S.c. depot formation

$-Zn^{2+}$

Insulin degludec monomers

Absorption

Jonassen et al. Diabetes 59 (Suppl. 1): A11, 2010 Jonassen et al. Diabetologia 2010;53 (Suppl.1):S388 972-P

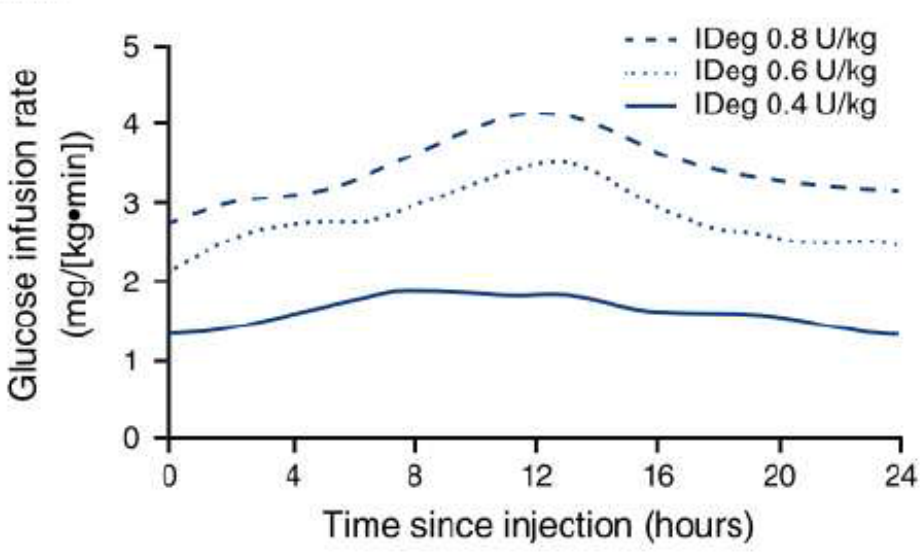
Insulin degludec multi-hexamer formation at the injection site


Insulin degludec di-hexamer formation

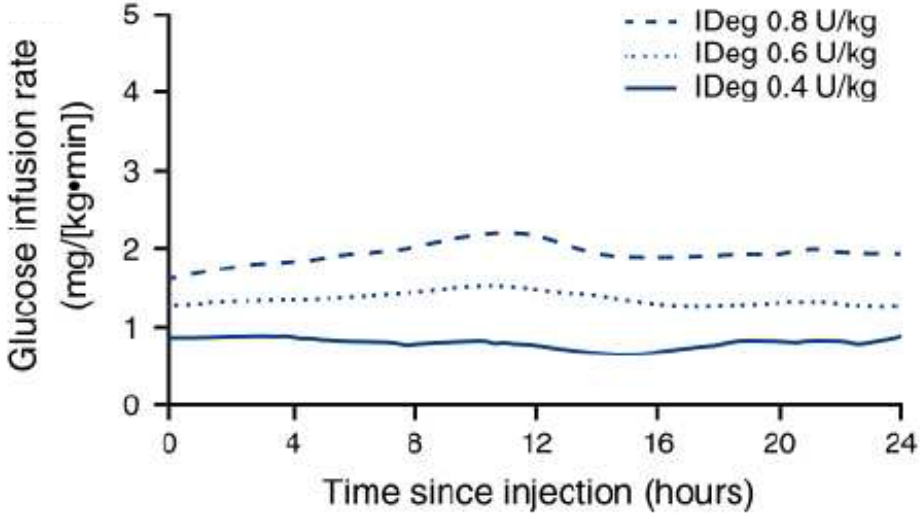
As the zinc concentration decreases, insulin degludec multi-hexamers release monomers from the ends

Jonassen *et al*. *Pharm Res* 2012;29:2104–14

Insulin Degludec PD Profile at Steady State



T1DM [1]

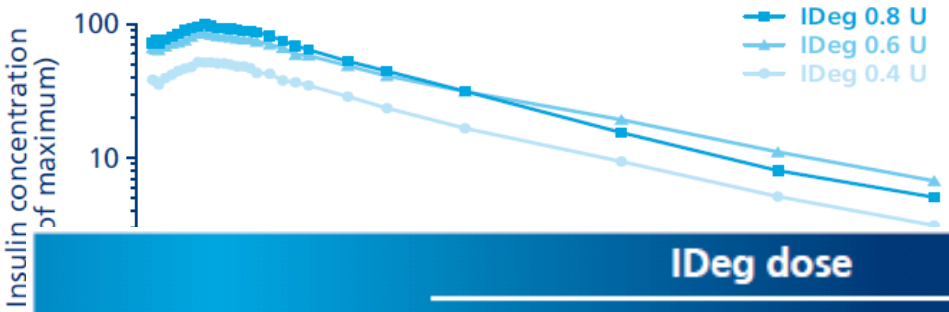


T2DM [2]

PD, pharmacodynamic

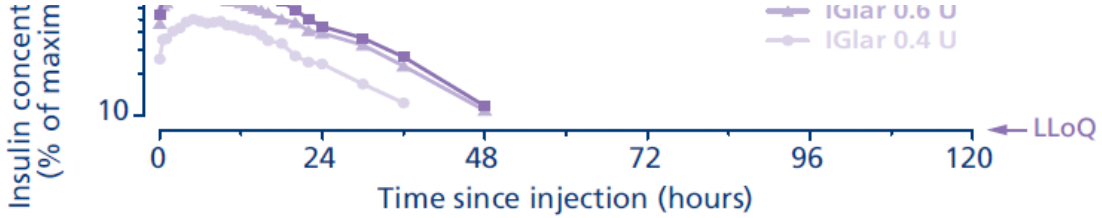
[1] Heise et al. Diabetologia 2011;54(Suppl. 1):S425; [2] Heise T et al., Diabetes Obesity and Metabolism 2012

Insulin Degludec Has a Two-fold Longer Half-life than Insulin Glargine



Estimate	IDeg dose 0.4 U/kg	IDeg dose 0.6 U/kg	IDeg dose 0.8 U/kg	IGlar dose 0.4 U/kg	IGlar dose 0.6 U/kg	IGlar dose 0.8 U/kg
$t_{1/2}$ (h)	25.9	27.0	23.9	11.8	14.0	11.9
Mean $t_{1/2}$ (h)		25.4			12.5	

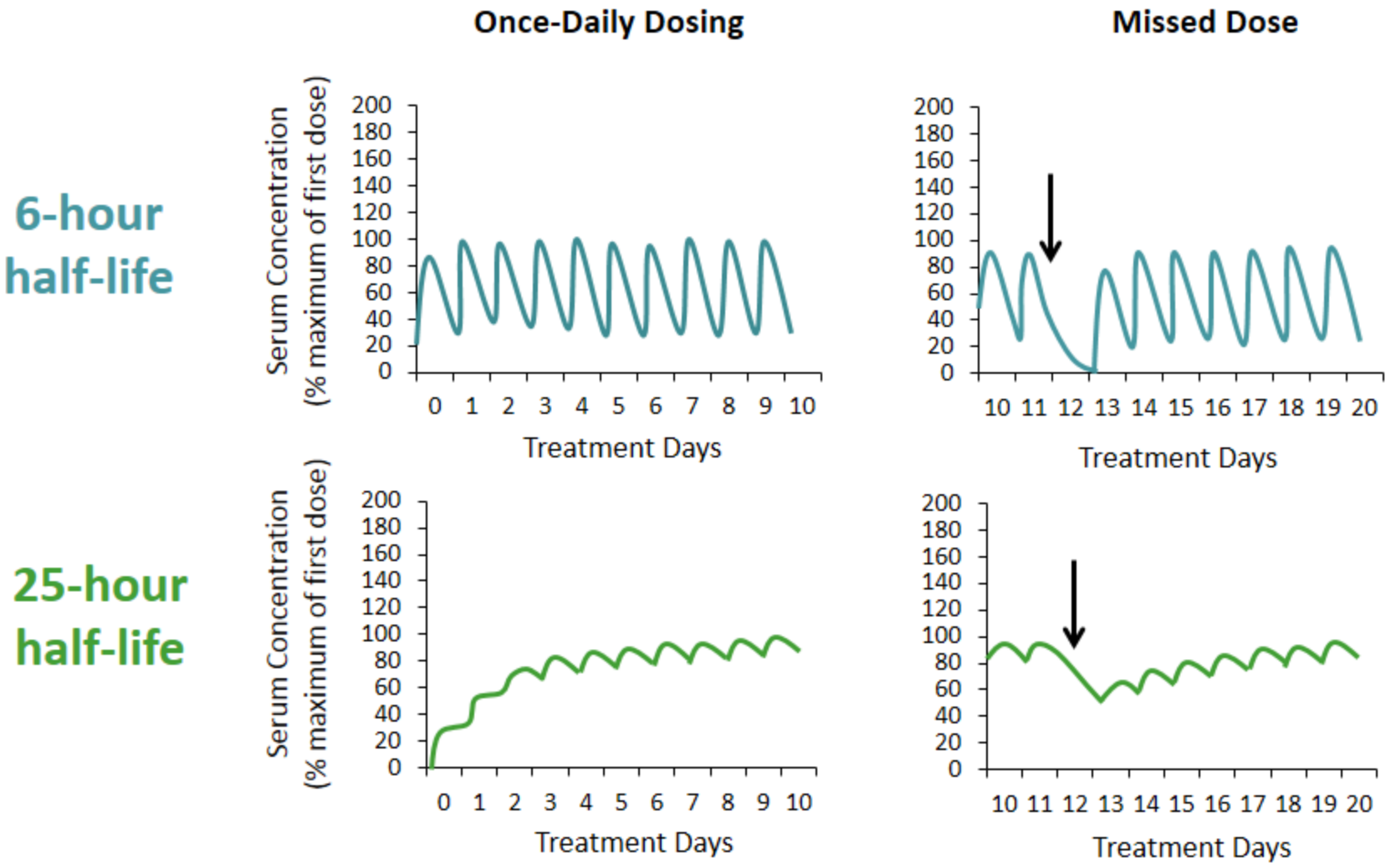
Data are harmonic means.



LLoQ: lower limit of quantification was ~0.3% of maximum IDeg concentration and ~8% of maximum for IGlar.

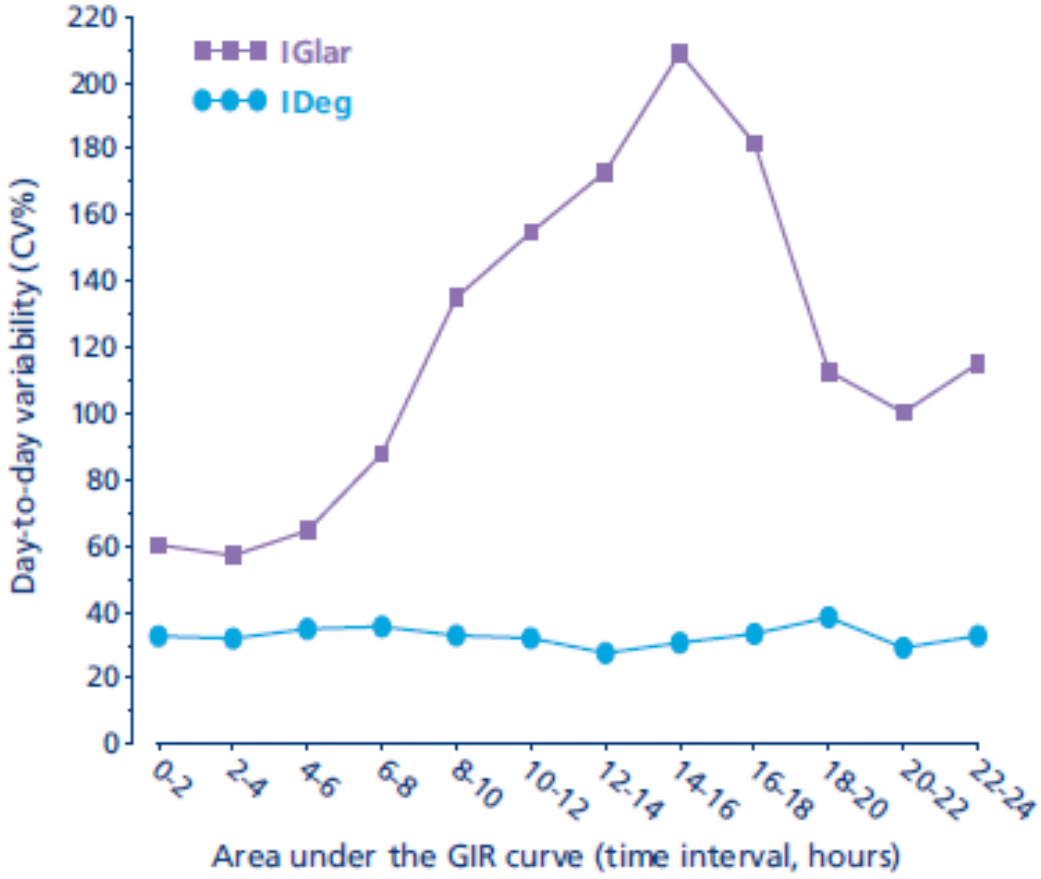
Heise T, Diabetes July 2011; vol 60 (Supplement 1): 37-LB

Lower Impact of Missed Dose With Basal Insulins



Adapted from Heise T, et al. *Endocr Pract.* 2014;20:75-83.

Day-to-day variability in glucose-lowering effect over24 hours at steady state



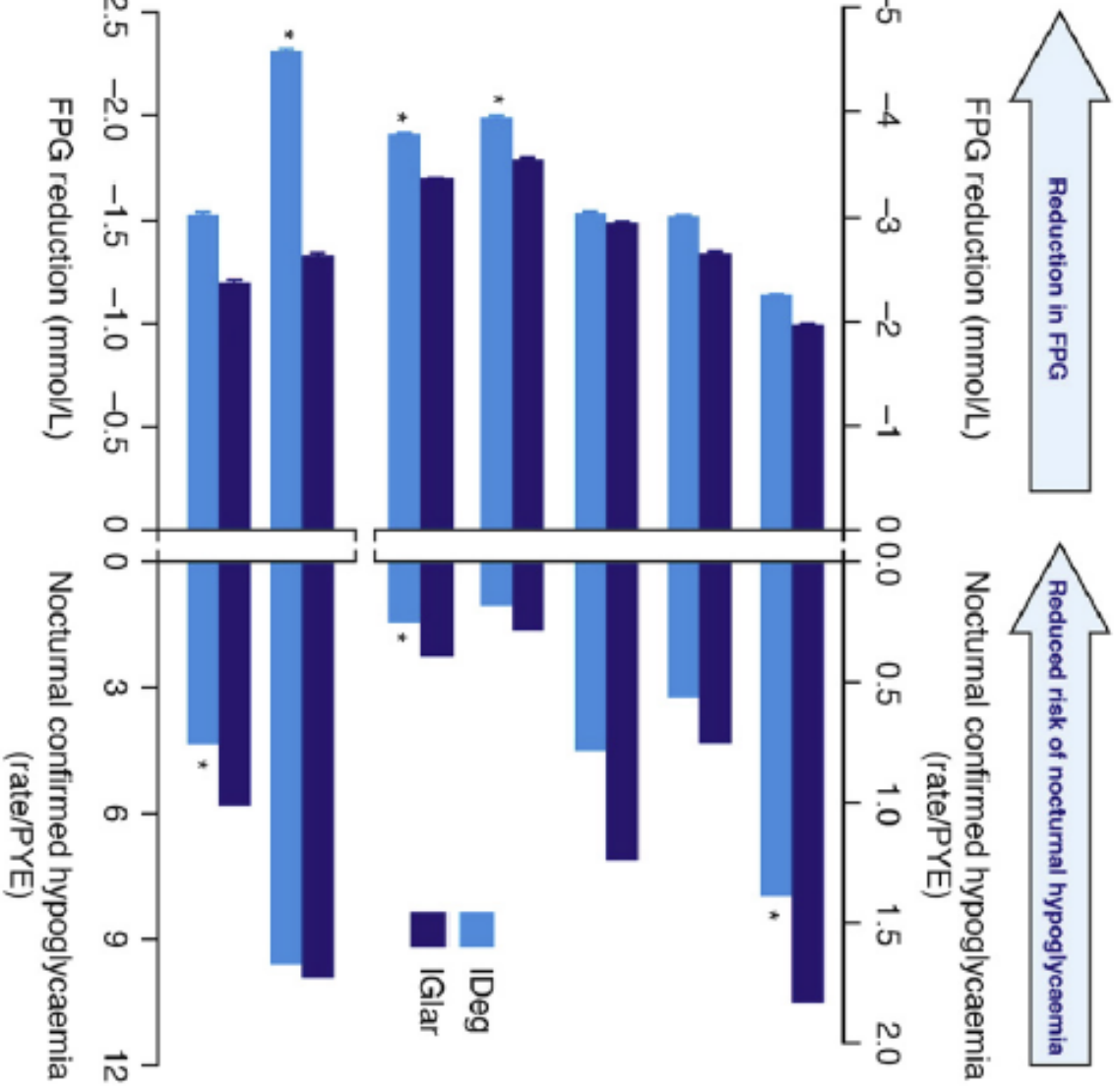
Test for difference between IDeg and IGlar: $AUC_{GIR\ 0\text{-}2h}$ and $AUC_{GIR\ 2\text{-}4h}$: p=0.004, $AUC_{GIR\ 4\text{-}6h}$: p=0.005, $AUC_{GIR\ 6\text{-}8h}$: p<0.001, all other time points p<0.0001.

Heise T, Diabetes July 2011; vol 60 (Supplement 1): 960-P

Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials☆

D. Russell-Jones [a,*], M.-A. Gall [b], M. Niemeyer [c], M. Diamant [d], S. Del Prato [e]

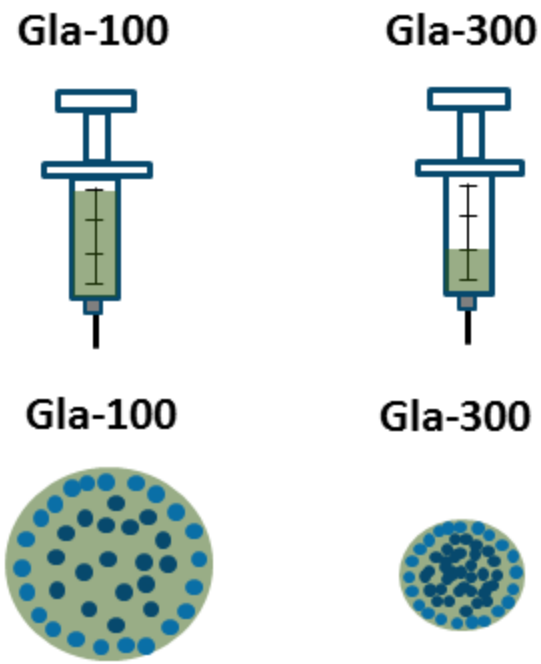
Nutrition, Metabolism & Cardiovascular Diseases (2015) **25**, 898–905



FPG, fasting plasma glucose; IDeg, insulin degludec; IGlar, insulin glargine; PYE, patient years of exposure
*$p<0.05$ for IDeg versus IGlar. Error bars are SEM.

Figure 2 Change from baseline in FPG and rate of nocturnal confirmed hypoglycaemia at the end of the trials.

Benefits for Patients Who Need Higher Insulin Doses



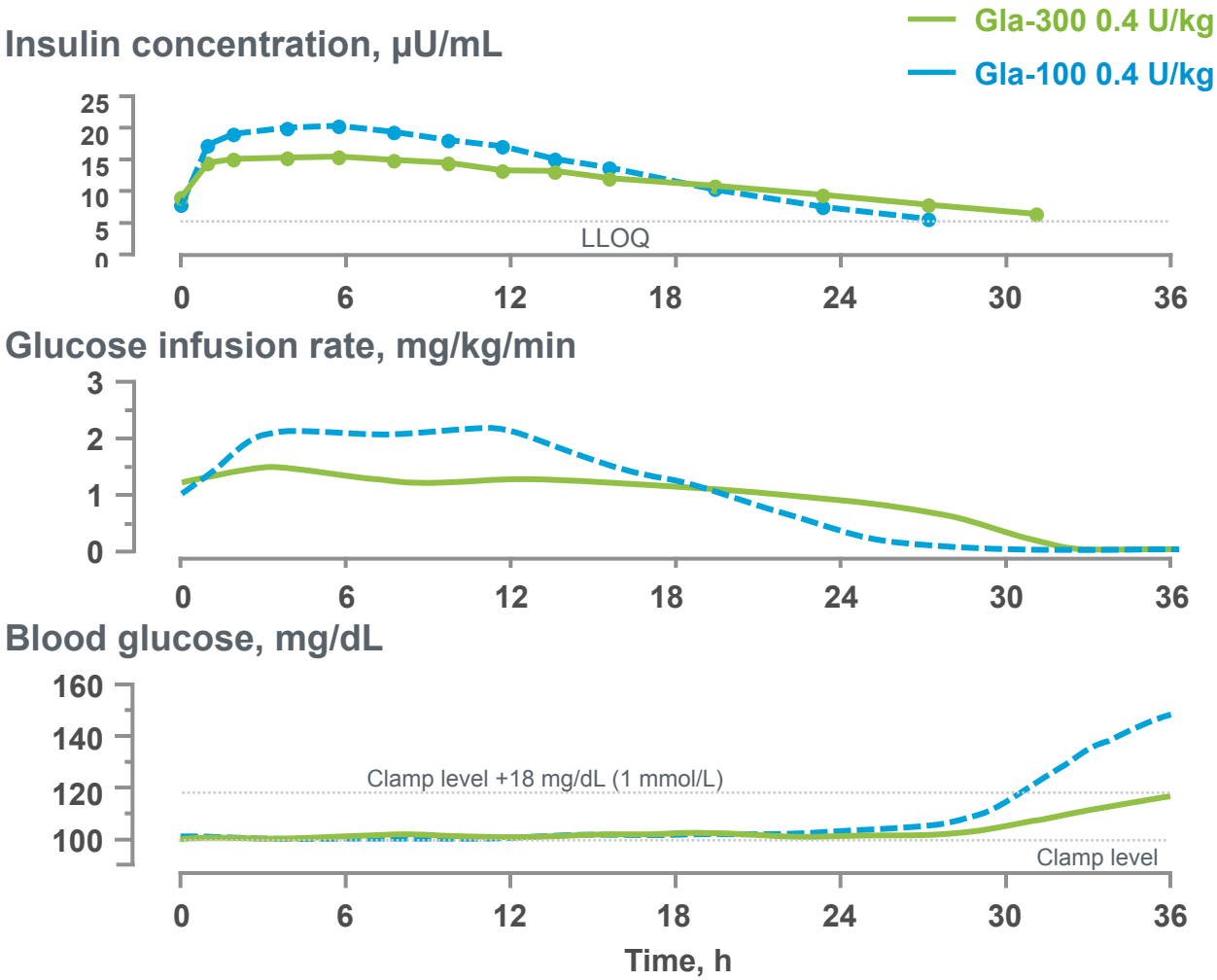
Gla-300 has the same number of units of insulin as Gla-100 in 2/3 less volume[a,b]

Depot surface area reduced by 1/2 leading to slower release and prolonged action profile[a,b]

- Lower injection volume is beneficial to patients who need higher doses of insulin
- A concentrated form of degludec (U200) also available for patients who need higher doses[c]

a. Jax T, et al. EASD, 2014; ePoster 1029.
b. Maiorino MI, et al. *Expert Opin Biol Ther.* 2014;14:799-808.
c. Korsatko S, et al. EASD, 2011; Abstract 2349-PO.

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

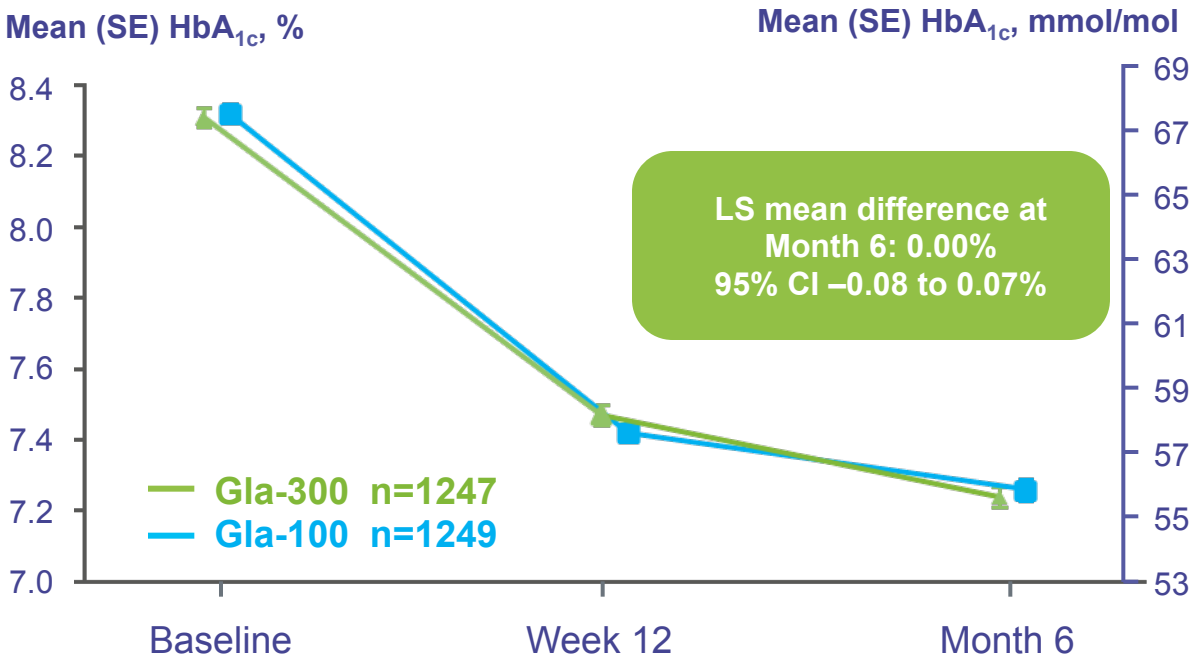


- Double-blind, crossover euglycemic clamp study of Gla-300 vs Gla-100 in 30 patients with T1DM

Becker RHA et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

Similar reductions in HbA_{1c} vs Gla-100 in all T2DM trials

EDITION 1-2-3 T2DM Pooled Analysis



Individual EDITION study data:

EDITION 1
Difference: 0.00%
95% CI –0.11 to 0.11%

EDITION 2
Difference: –0.01%
95% CI –0.14 to 0.12%

EDITION 3
Difference: 0.04%
95% CI –0.09 to 0.17%

Improvement in HbA_{1c} was not affected by gender, age, diabetes duration (<10 years and ≥10 years), HbA_{1c} value at baseline (<8% or ≥8%) or baseline BMI

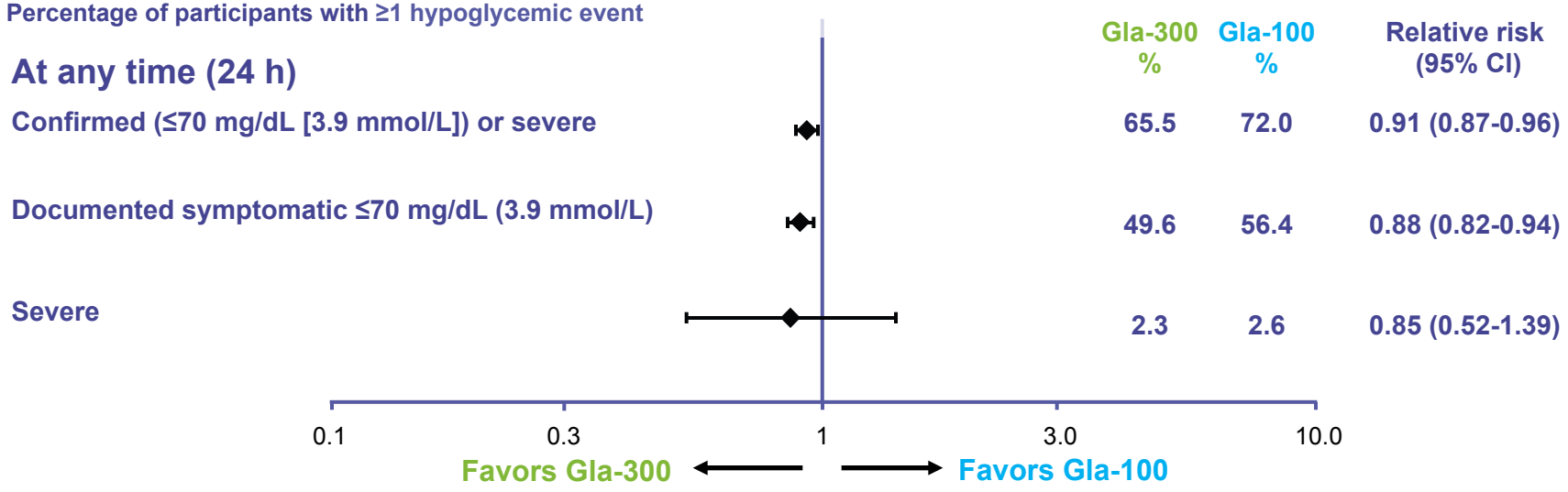
Modified intention-to-treat (mITT) population; LS, least squares

Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print]; Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; Toujeo SmPC. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000309/WC500047935.pdf. Accessed June 2015

Gla-300: Reductions in confirmed or severe hypoglycemia and documented symptomatic hypoglycemia at any time (24 h) in T2DM

EDITION 1-2-3 T2DM Pooled Analysis from Baseline to Month 6

Percentage of participants with ≥1 hypoglycemic event



Consistent results across the program

Relative risk (95% CI) for confirmed (≤70 mg/dL) or severe hypoglycemia at any time (24 h) from baseline to Month 6

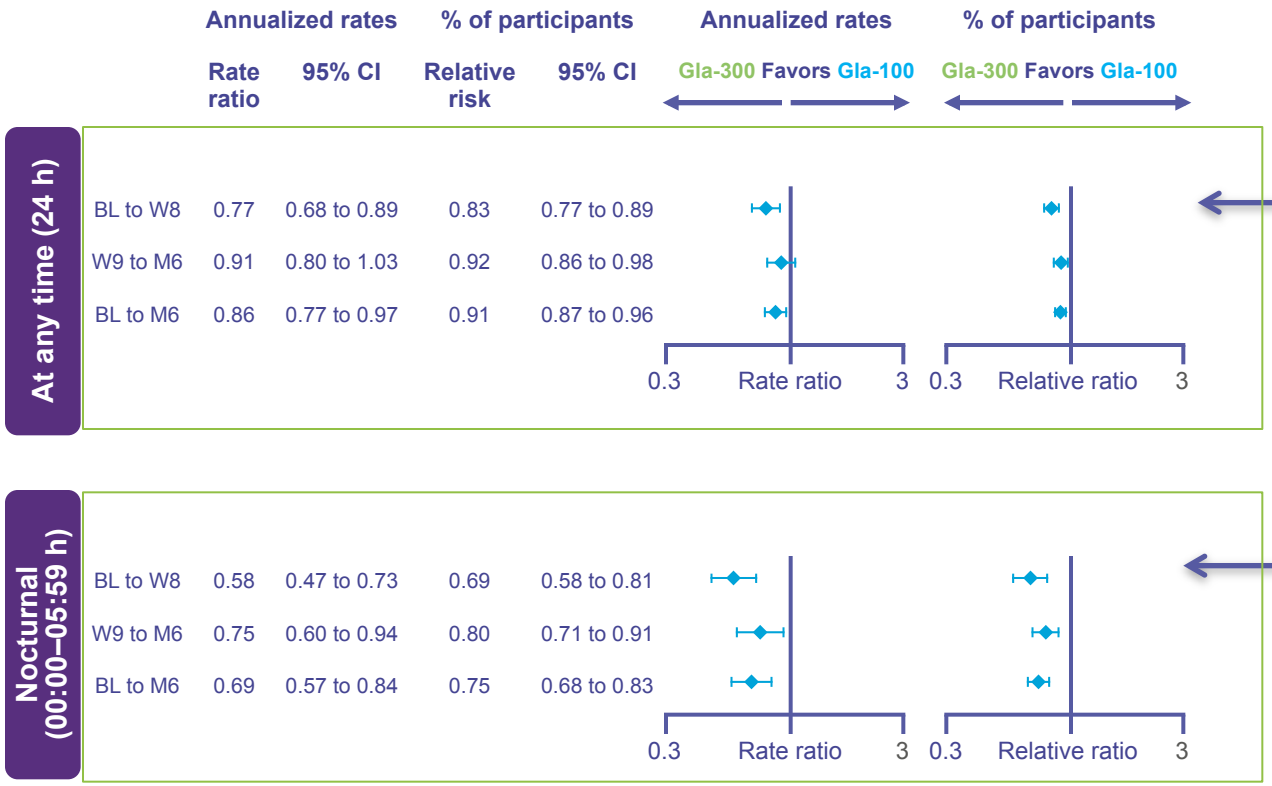
EDITION 1	0.93 (0.88 to 0.99)
EDITION 2	0.90 (0.83 to 0.98)
EDITION 3	0.88 (0.77 to 1.01)

Safety population

Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43;
Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print]

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)

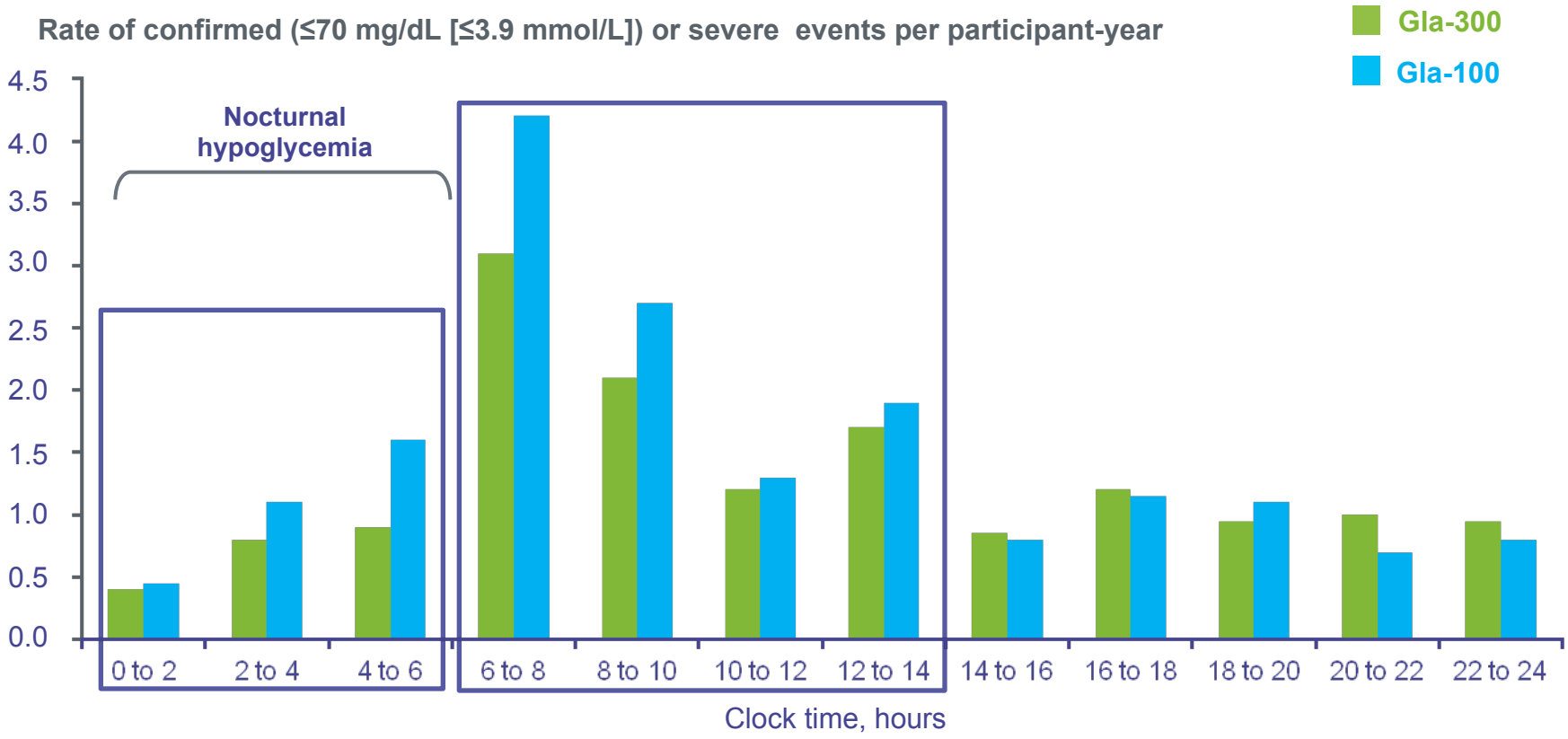
From baseline to Week 8
Annualized rate
-42% (0.47 to 0.73)
Incidence
-31% (0.58 to 0.81)

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

Adapted from Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print]

Gla-300: Reduction of confirmed or severe hypoglycemia beyond the predefined nocturnal period (00:00-05:59)

EDITION 1-2-3 T2DM Pooled Analysis



Safety population

Adapted from Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print]

Glargine U-300 vs Glargine U-100 in Type 2 Diabetes

Meta-Analysis

	Baseline to Month 6		
	Glargine U-300 (n=1247)	Glargine U-100 (n=1249)	RR (95% CI)
HbA_{1c} (%), LS mean	-1.02	-1.02	Not specified
Weight (kg), LS mean	0.49	0.75	*P* =.058
Any hypoglycemia in 24 hr*	67.8	73.8	0.92 (0.87-0.96)
Any nocturnal hypoglycemia*	31.7	41.3	0.77 (0.69-0.85)

- **Titrate dose every 3 days**
- **Higher daily dose may be needed**

*Percent people with 1 or more events.

Ritzel R, et al. *Diabetes Obes Metab*. 2015;17:859-867.

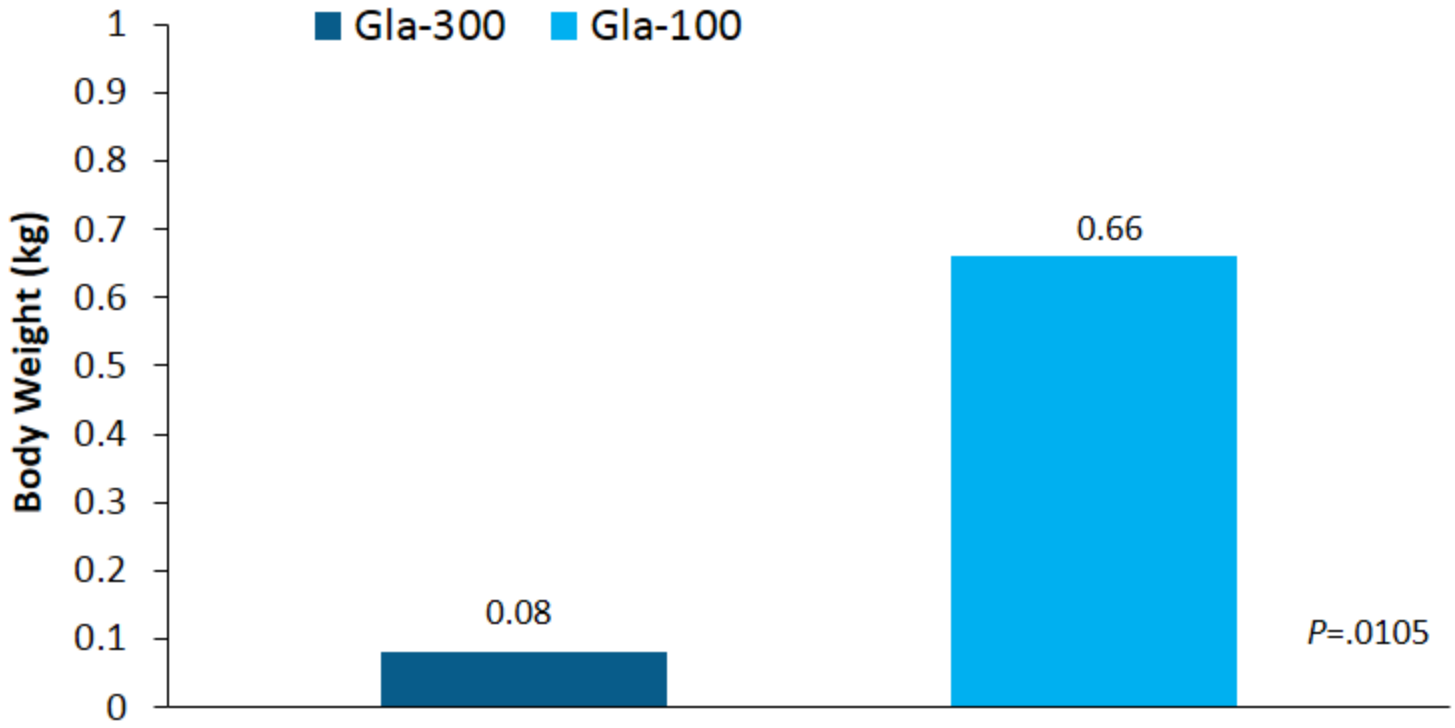
Basal insulin dose at Month 6 in the overall EDITION program

Mean basal daily insulin dose, U/kg	EDITION 1		EDITION 2		EDITION 3		EDITION 4	
	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100
At baseline	0.67	0.67	0.64	0.66	0.19	0.19	0.32	0.32
At Month 6	0.98	0.88	0.93	0.85	0.62	0.53	0.47	0.40
Relative difference for Gla-300 vs Gla-100, %	+11.55		+10.44		+16.58		+15.98	

- The higher final dose with Gla-300 compared to Gla-100 is consistent with the lower 24-h exposure of Gla-300 vs Gla-100 observed under steady-state conditions in PK and PD studies
  - This observation suggests a somewhat lower bioavailability of Gla-300 due to increased residence time in the subcutaneous depot, resulting in additional exposure to tissue peptidases
- This did not impact body weight as similar or less weight gain was observed with Gla-300 vs Gla-100
- Similarly, the higher Gla-300 dose was not associated with increased risk of adverse events (e.g. hypoglycemia) vs Gla-100

Data on file, E19_Insulin dose_Absolute and Relative differences_M12_2014-09-03.doc, pg 6, 12, 14, 22; Becker RH et al. Diabetes Care. 2015;38:637-43; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; Riddle MC et al. Diabetes Care. 2014;37:2755-62; Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; Home PD et al. Diabetes Care. 2015 Jun 17. pii: dc150249. [Epub ahead of print]

EDITION 2—Less Weight Gain With Gla-300



Gla-300 achieves glycemic control with a lower risk for nocturnal hypoglycemia and significantly less weight gain than Gla-100

Yki-Järvinen H, et al. *Diabetes Care.* 2014;37:3235-3243.

Safety profile overview of Gla-300 at Month 6 in the EDITION program

Proportion of patients, %	T2DM						T1DM	
	EDITION 1 BB		EDITION 2 BOT switch		EDITION 3 BOT start		EDITION 4	
	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100
TEAEs	56.4	54.2	58.8	50.7	56.8	55.9	60.9	58.2
Serious TEAEs	6.4	5.2	3.7	3.7	5.5	5.9	6.2	8.0
TEAEs leading to discontinuation	1.5	1.7	1.5	1.0	1.1	1.1	1.1	1.1

- The safety profiles of Gla-300 and Gla-100 at Month 6 were similar

TEAEs, treatment-emergent adverse events
Safety population

Data on file, EDITION 1 CSR, pg 125; EDITION 2 CSR, pg 124; EDITION 3 CSR pg 139;
Home PD et al. Diabetes Care. 2015 Jun 17. pii: dc150249. [Epub ahead of print]

Generic vs. Biosimilar: Manufacturing Differences

Generic

- Not affected by slight changes in production process and environment[1]
- Easy to purify and characterize using analytical methods[1]
- Easy to detect and eliminate contamination[1]
- Easy to establish reproducibility[1]

Biosimilar

- Highly susceptible to slight changes in production process and environment; each step of the process can be a source of variation within the final product[1,2]
- Complex purification process and difficult to characterize[1]
- Difficult to detect or remove contamination[1]
- Difficult to establish reproducibility[1]

1. Sekhon BS and Saluja V. *Biosimilars* 2011;1:1-11
2. Mellstedt H et al. *Ann Oncol* 2008;19:411-9

Regulatory Summary: Requirements for Biosimilarity[1,2]

Similarity demonstrated in preclinical in vitro and in vivo PD and toxicology studies	✓
Similarity demonstrated in clinical trials designed to assess PK and PD against standard acceptance limits	✓
No clinically meaningful differences in immunogenicity	✓
Head-to-head clinical trial(s) to detect relevant differences in efficacy or drug-related safety[a]	✓

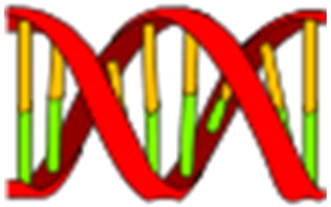
[a]Efficacy/safety trial needed unless biosimilarity convincingly demonstrated by nonclinical, pharmacology, and immunogenicity studies

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf

PD=Pharmacodynamic; PK=Pharmacokinetic

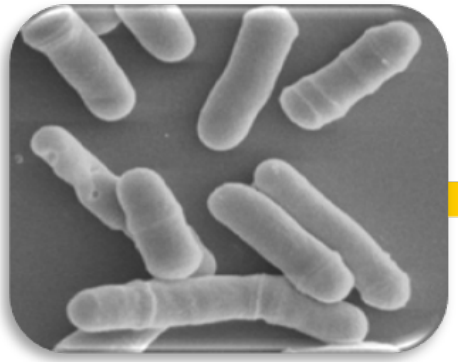
Typical Production Process of Insulin

Gene sequence



Expression vector

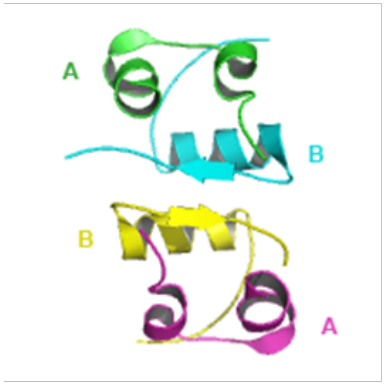
Host cell
(E. coli or yeast)



Fermentation/Culture
(upstream process)

Purification
(downstream process)

Final product
(*insulin*)

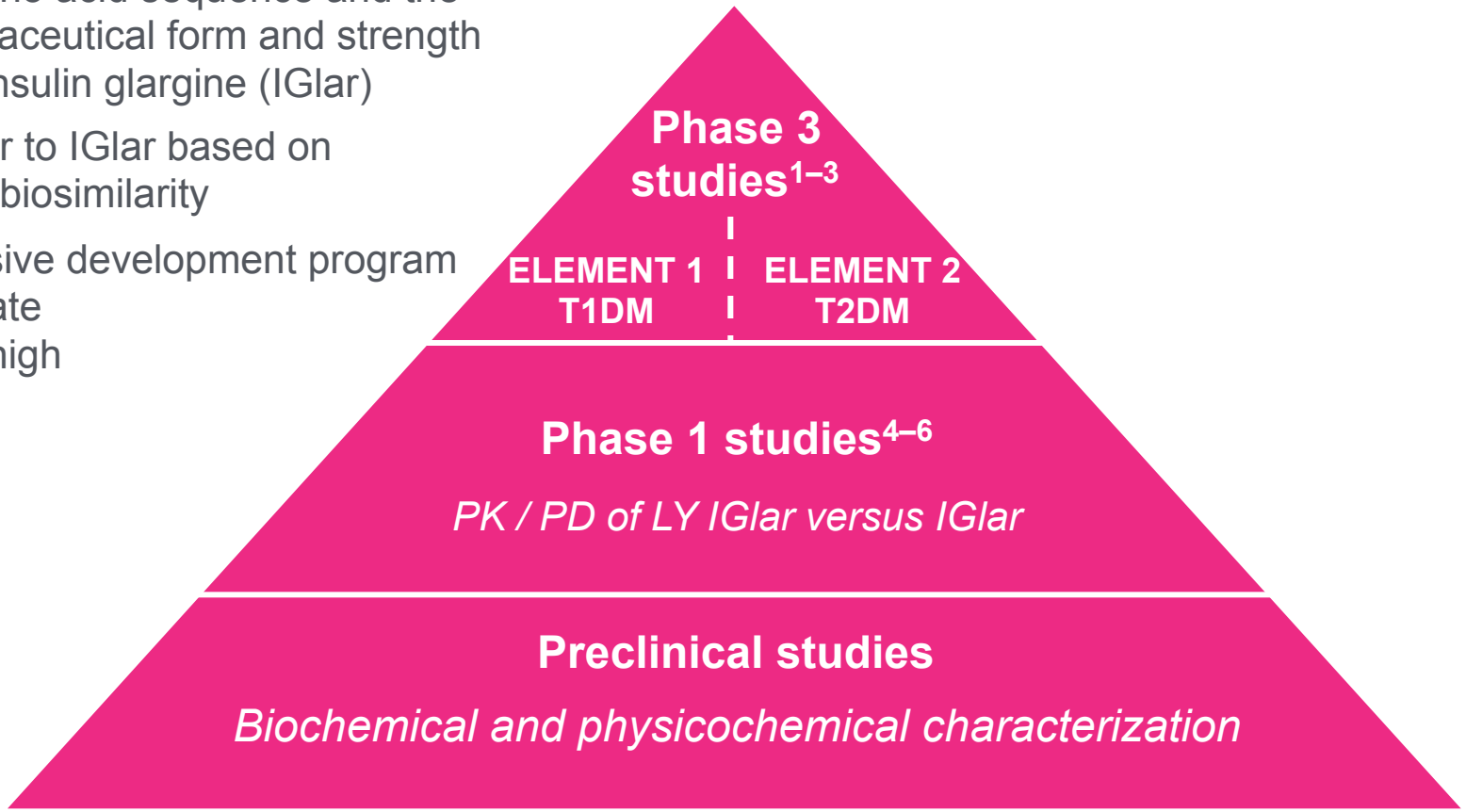


Crommelin DJA et al. Pharmaceutical Biotechnology: Fundamentals and Applications, 3rd Edition, 2008

LY IGlar Development Program

- Identical amino acid sequence and the same pharmaceutical form and strength as Lantus® insulin glargine (IGlar)
- Highly similar to IGlar based on principles of biosimilarity
- Comprehensive development program to demonstrate similarity at high standards

"The Totality of Evidence"



1. Blevins et al., Diabetes Obes Metab. 2015 Aug;17(8):726-33; 2. Rosenstock et al., Diabetes Obes Metab. 2015 Aug;17(8):734-41;
3. Ilag et al, Diabetes Obes Metab. 2015 Oct 5, [Epub ahead of print]; 4. Linnebjerg et al., Diabetes Care. 2015 Dec;38(12):2226-33
5. Zhang et al. *ADA 2014*: 890-P; 6. Heise et al. *ADA 2014*: 891-P

PD=pharmacodynamic; PK=pharmacokinetic;
T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus

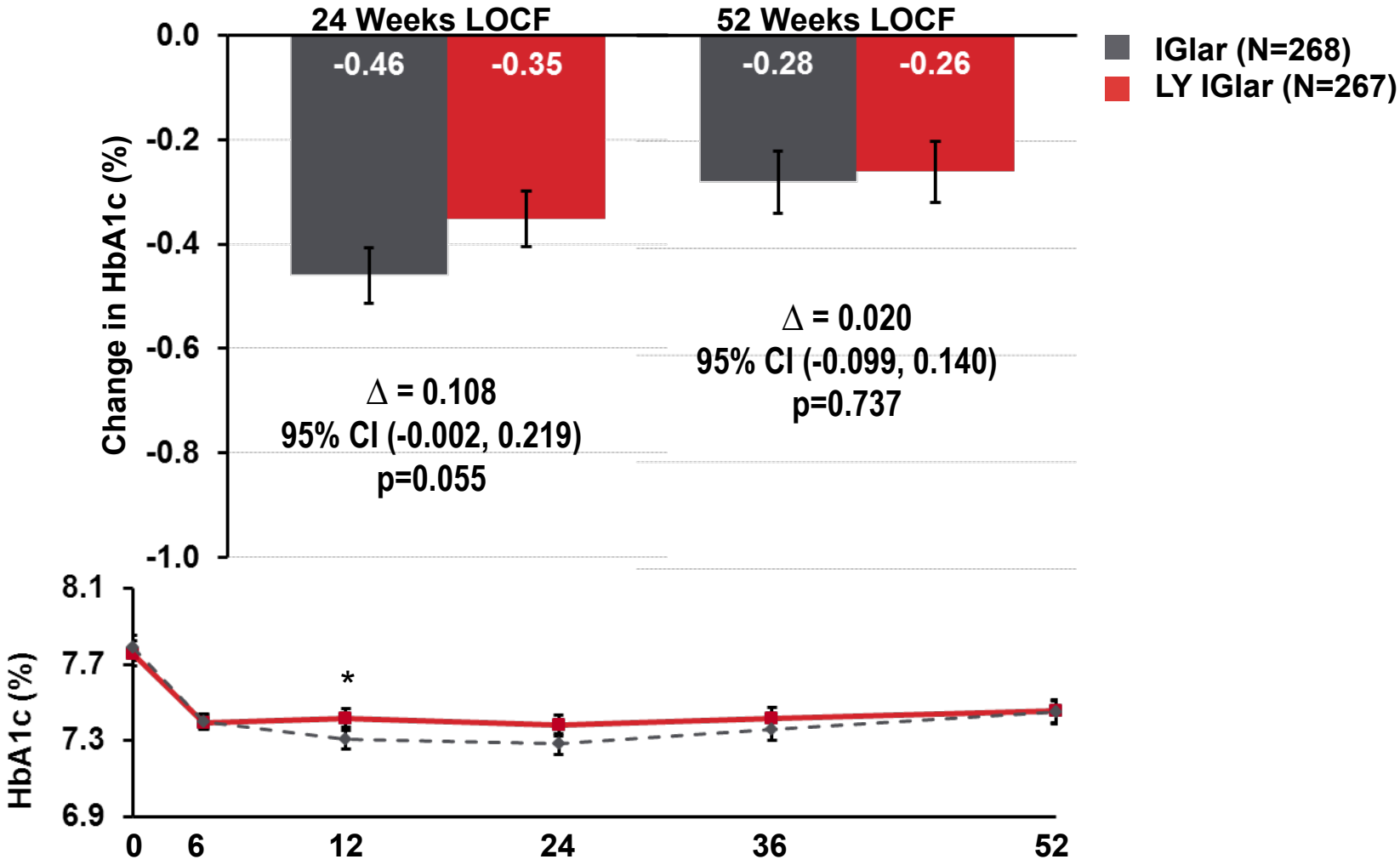
On the Horizon: Biosimilar Insulins

First Biosimilar Insulin Glargine

- Biosimilar insulins are derived from living cells or organisms, most often using recombinant DNA technology
- Development, manufacturing, and approval of biosimilar products more complex than for generic versions of small molecules
- Biosimilar insulin MK-1293 demonstrated pharmacokinetic and pharmacodynamic equivalence vs glargine in single-dose euglycemic clamp study[a]
- Biosimilar glargine approved for use by the EMA; US FDA has given this product tentative approval

a. Crutchlow M. ADA 2015. Abstract 1026-P.[7]

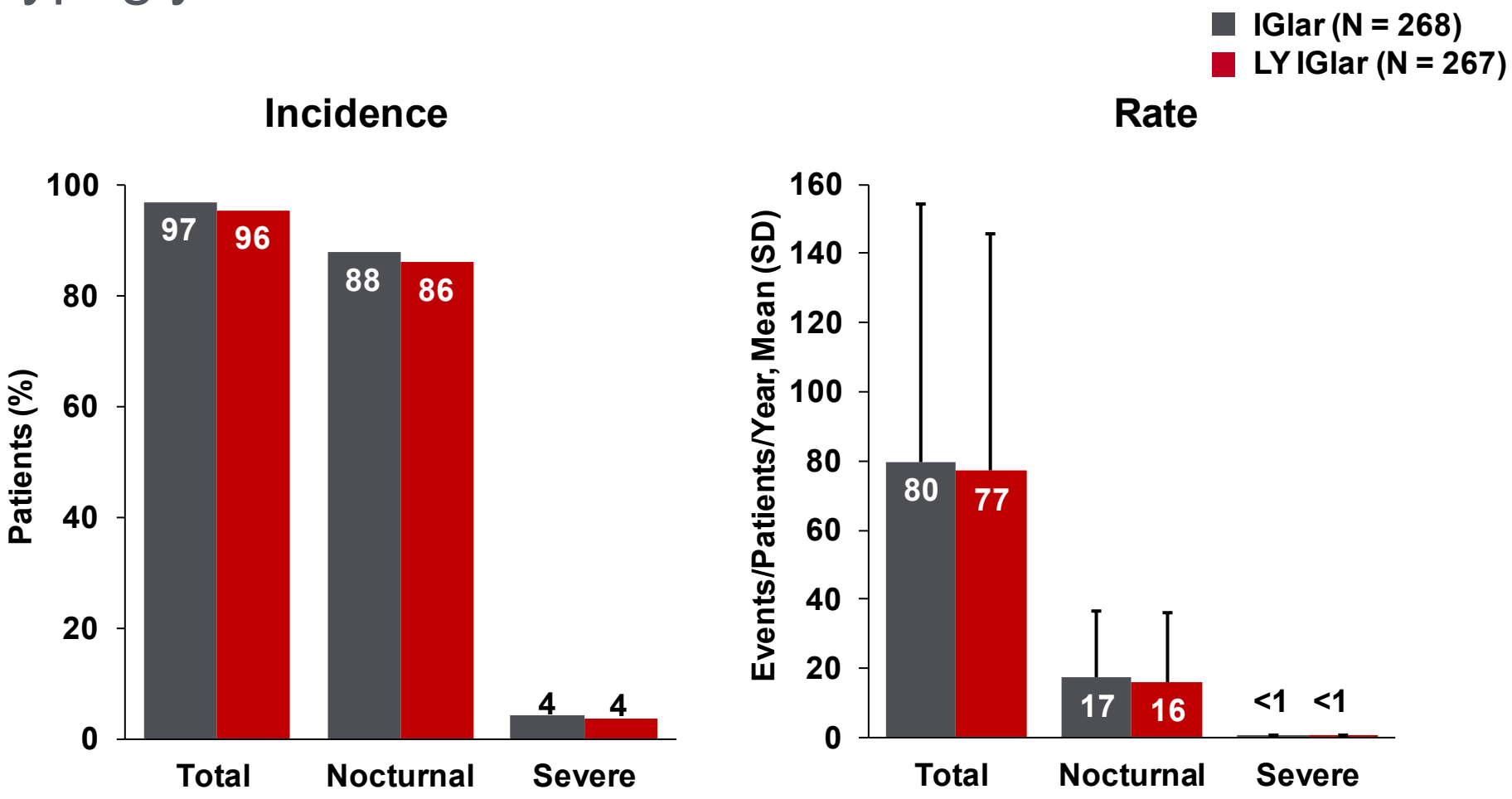
ELEMENT 1: HbA_{1c} Change from Baseline and over Time with LY IGlar and IGlar



Data are least squares mean ± standard error
*p = 0.03; no significant differences between treatment at any other time point
CI=confidence interval; HbA_{1c}=glycosylated hemoglobin; LOCF=last observation carried forward

Blevins et al., Diabetes Obes Metab. 2015 Aug;17(8):726-33

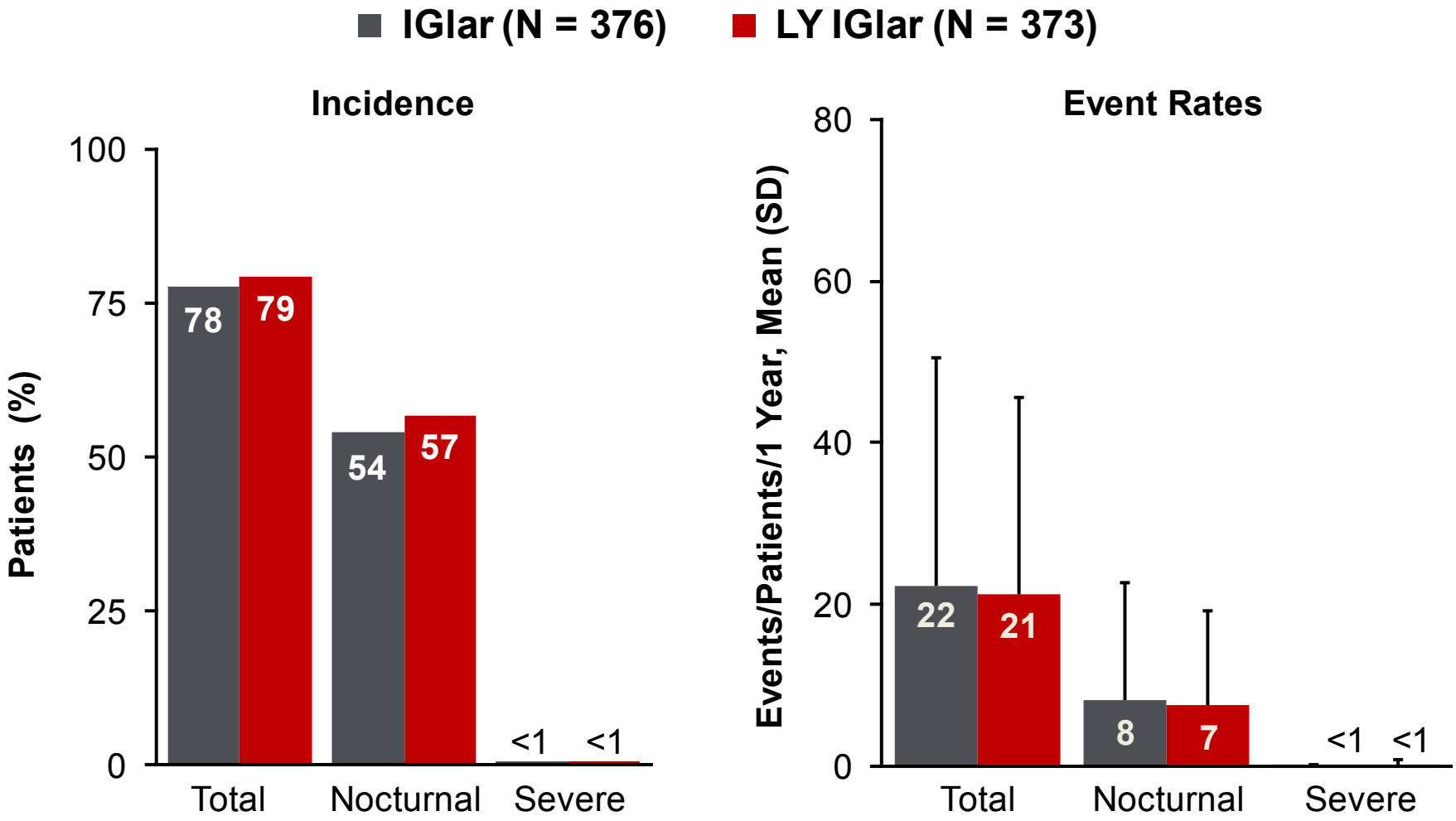
ELEMENT 1: Total, Nocturnal, and Severe Hypoglycemia



All p values >0.05

Blevins et al., Diabetes Obes Metab. 2015 Aug;17(8):726-33

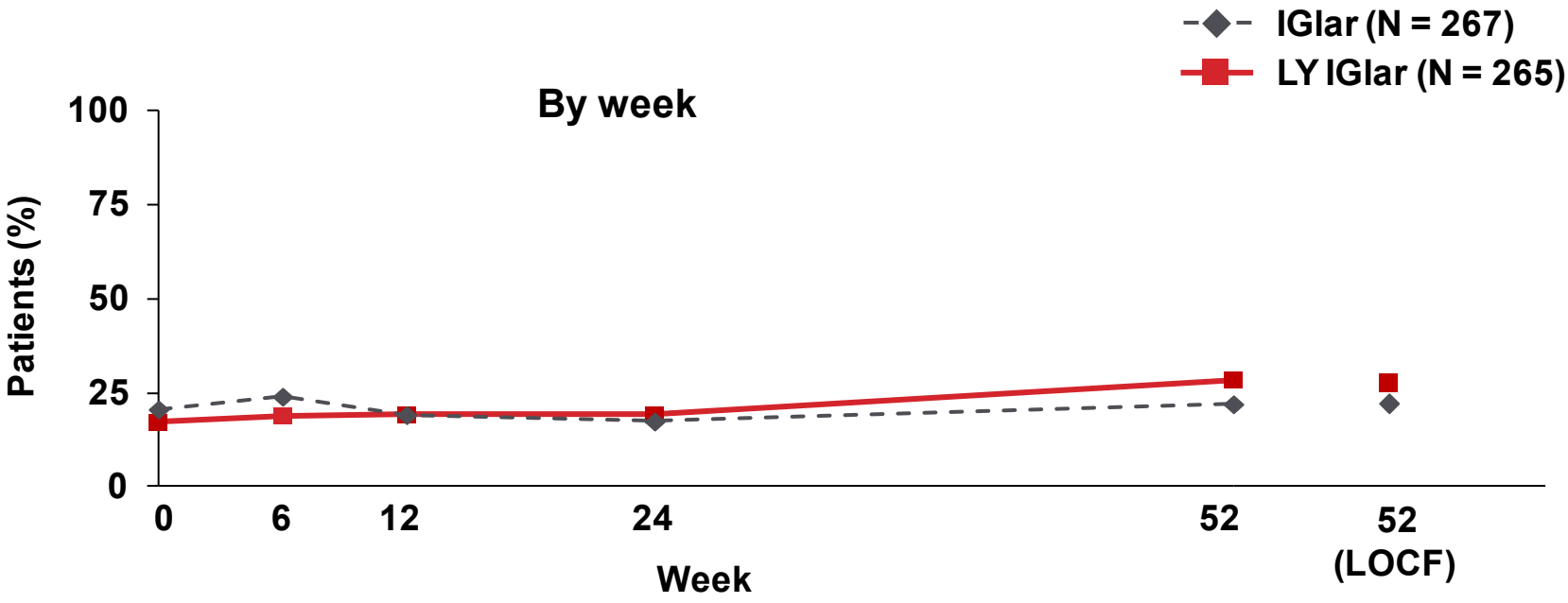
ELEMENT 2: Total, Nocturnal, and Severe Hypoglycemia



All p values >0.05
SD=standard deviation

Rosenstock et al., Diabetes Obes Metab. 2015 Aug;17(8):734-41

Proportion of Patients with Detectable Antibodies: ELEMENT 1

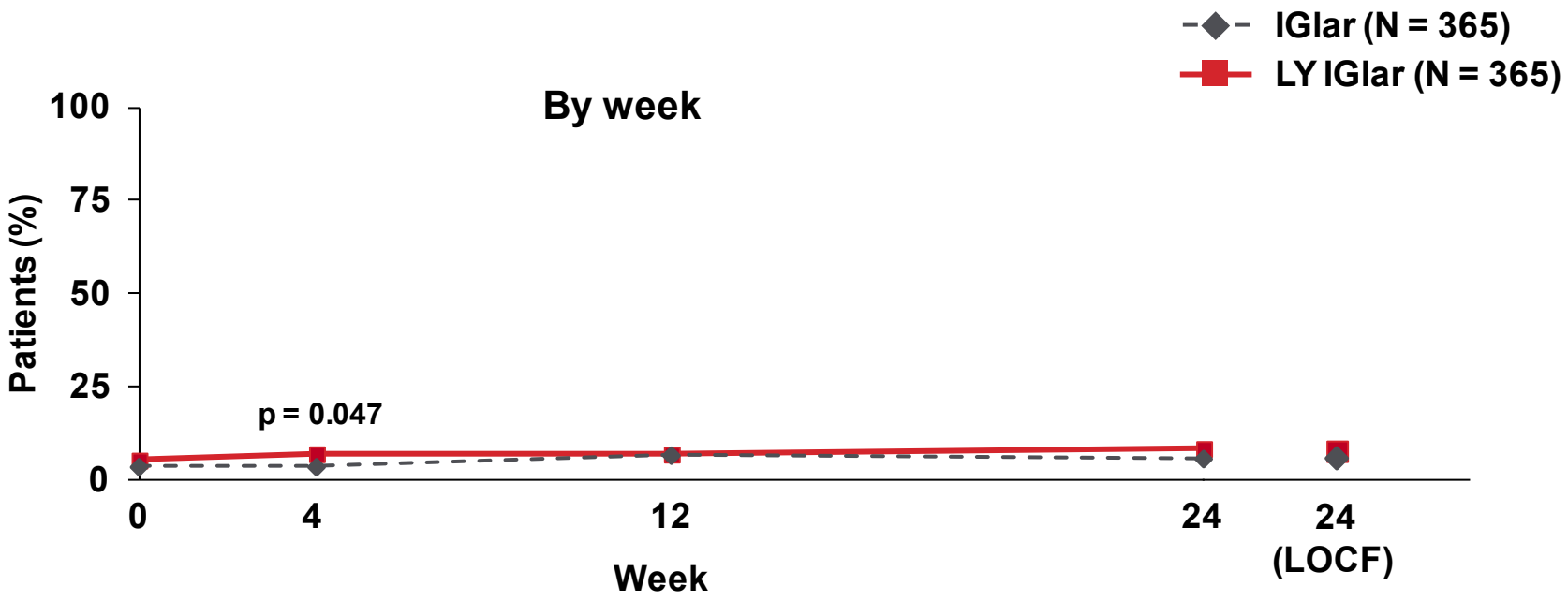


		IGlar	LY IGlar	p value
Patients with detectable antibodies, n (%)	Overall 24 weeks	90 (34)	80 (30)	0.40
	Overall 52 weeks	105 (39)	107 (40)	0.86

LOCF=last observation carried forward

Ilag et a.l, Diabetes Obes Metab. 2015 Oct 5, doi: 10.1111/dom.12584

Proportion of Patients with Detectable Antibodies: ELEMENT 2



		IGlar	LY IGlar	p value
Patients with detectable antibodies, n (%)	Overall 24 weeks	40 (11)	56 (15)	0.10

LOCF=last observation carried forward

Ilag et a.l, Diabetes Obes Metab. 2015 Oct 5, doi: 10.1111/dom.12584

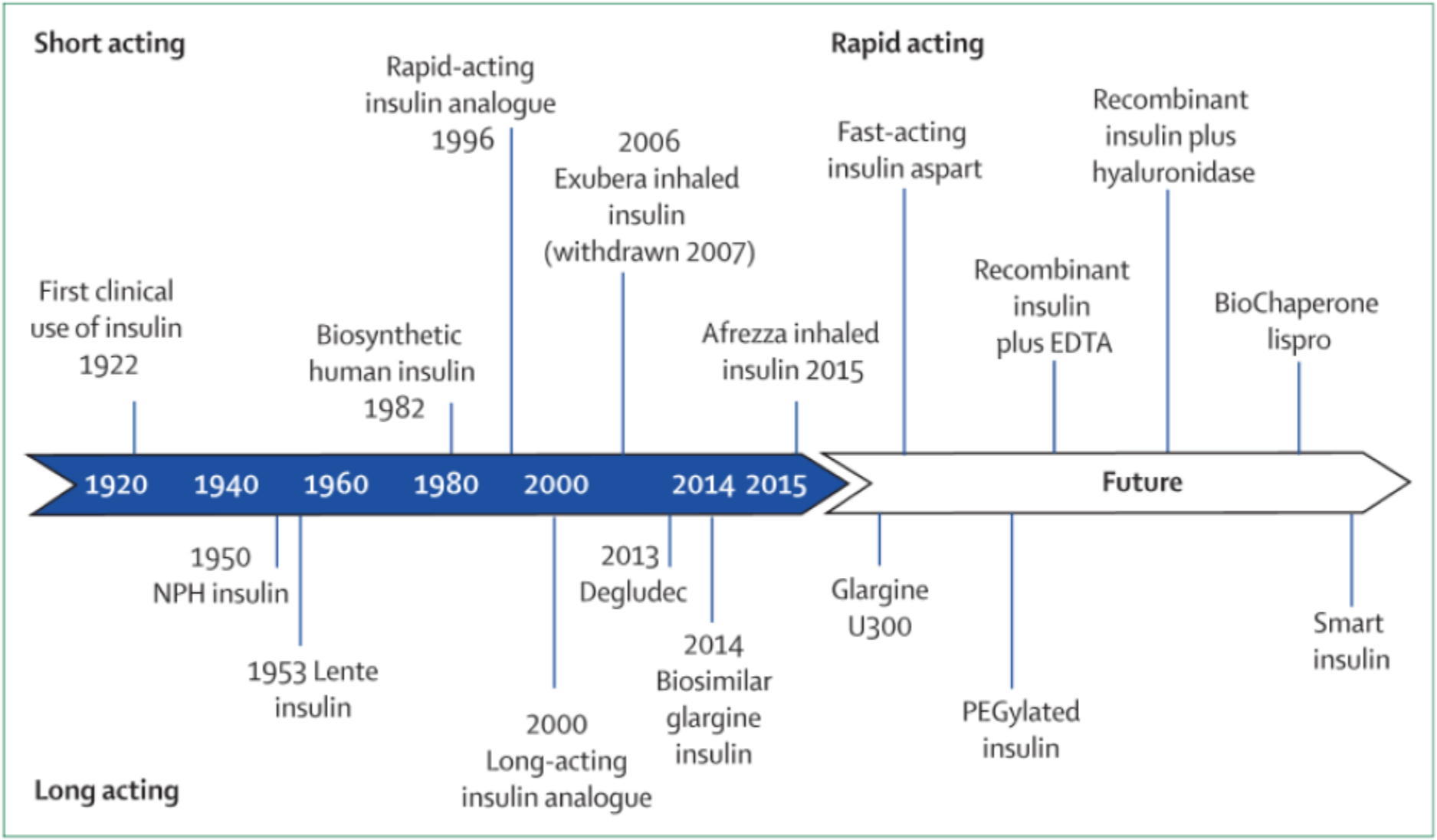


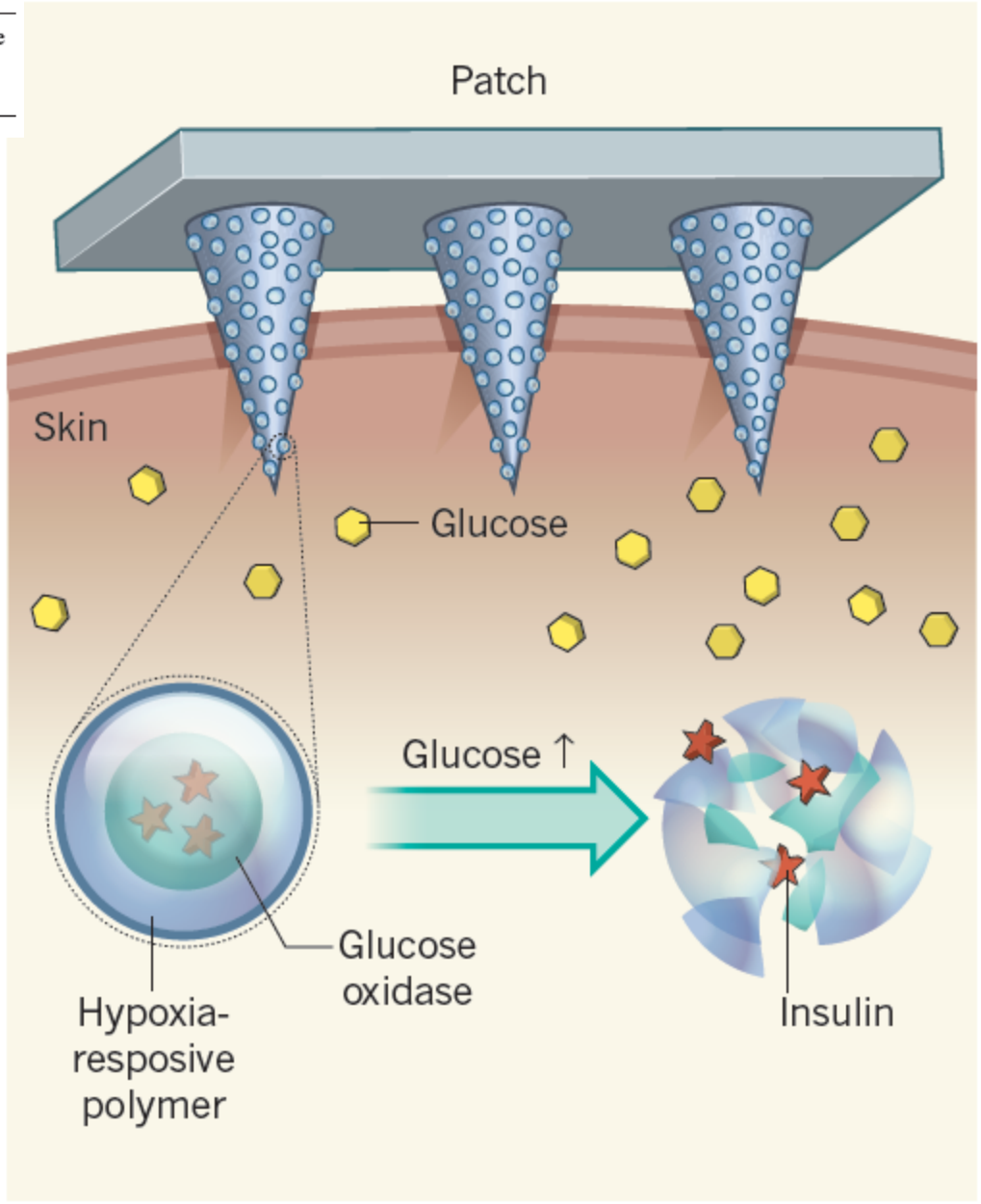
Figure 2: **Timeline for the development of short-acting, long-acting, and future rapid-acting analogues of insulin**
NPH=neutral protamine hagedorn. PEG=polyethylene glycol. EDTA=edetic acid.

The First Recombinant, Fully Human, Monomeric Super-long-acting Basal Insulin

PE0139

A smart insulin patch

A microneedle-containing patch that is designed to sense elevated blood glucose levels and to respond by releasing insulin could offer people with diabetes a less-painful and more-reliable way to manage their condition.



OMID VEISEH & ROBERT LANGER

Benefits of Newer Basal Insulins

- Ultra-long-acting insulin analogs
  - Duration up to 42 hours
- Flat, stable glucose-lowering profile
- Lower within patient day-to-day variability in glucose-lowering effect
- Similar glycemic control compared with available basal insulins
- Flexible timing of injection time, without compromising efficacy or safety
- Less nocturnal hypoglycemia
- Reduced weight gain
- Smaller doses with concentrated insulin
- More “forgiveness” if timing of injection changes or missed dose

Garber AJ. *Diabetes Obes Metab*. 2014;16:483-491.[15]

C O N C L U S I O N I

Nuove formulazioni insuliniche potranno portare ulteriori benefici in termini di efficacia e sicurezza, migliorando il controllo glicemico e la qualità di vita delle persone con diabete.

Tuttavia *le attese* della *novità terapeutica* non devono mai portare in secondo piano l' importanza dell' intervento educativo che rimane la vera chiave di successo del trattamento insulinico nella terapia del diabete

Grazie...