Le nuove insuline: cosa cambia per il medico e per il paziente?

Quali insuline all'orizzonte ?

Dr. Eugenio D'Amico

Agenda

PASSATO

- terapia insulinica

PRESENTE

- Analoghi dell'insulina

FUTURO

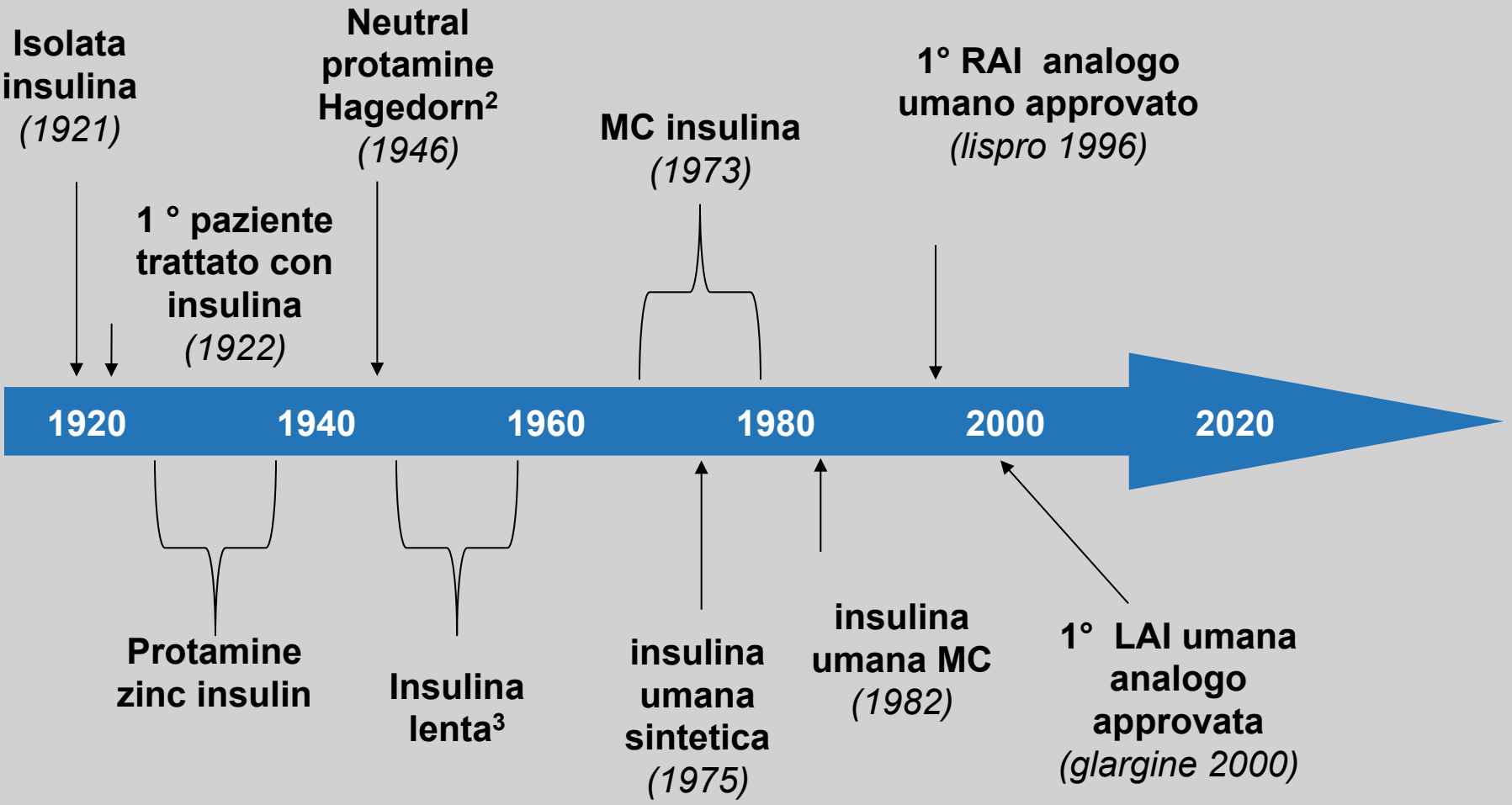
- La prossima generazione
  - Efficacia
  - Sicurezza
- Opportunità
- Conclusioni

- La rotta che ha portato agli analoghi dell'insulina

PASSATO

Evoluzione farmacologica dell'insulina

Roma,
9-11 novembre 2012



1. Banting FG et al. *Can Med Assoc J* 1922;12:141–146;
2. Krayenbuhl C, Rosenberg T. *Rep Steno Mem Hosp Nord Insulinlab* 1946;1:60–73;
3. Whitehouse FW et al. *Ann Intern Med* 1961;55:894–902

MC=monocomponent; RAI=rapid-acting insulin; LAI=long-acting insulin

1° step verso l'insulina umana

Roma,
9-11 novembre 2012

Preparazione insulina impura

- Altri peptidi pancreatici presenti

Novo Nordisk Sviluppa

Insulina Monocomponente

- 1973 – insulina monocomponente
- Preparazione commerciale
- Insulina porcina–zinco sospensione
- Altamente purificata mediante cromatografia

Nuovi standard Purezza

- Riduce la formazione di anticorpi [1,2]

1. Bruni B et al. *Diabetologia* 1978;14:165–169; 2. Kawazu S et al. *Acta Diabetol Lat* 1979;16:339–351.

Insulina Umana

- 1970 – aumento del fabbisogno della domanda di insulina [1]
- 1973 –sviluppata la tecnica del DNA Ricombinante [2]
- 1976 – work congress che ha discusso della possibilità di sviluppare insulina umana con la tecnica del DNA ricombinante
- 1980 – primi test su soggetti sani volontari testati con insulina sintetizzata mediante la terapia del DNA ricombinante

ELI LILLY – US	NOVO NORDISK – EUROPE
Genentech • Synthesized a laboratory strain of *Escherichia coli* bacteria, genetically altered to produce human insulin – 'fully human' • Signed a production agreement with Eli Lilly in 1978	• Initially, enzymatic conversion reaction to substitute the B30 alanine of porcine insulin with threonine to manufacture human insulin • 1975: changed manufacturing process to direct biosynthesis using genetically engineered yeast cells
1982: Humulin R (rapid) and Humulin N (NPH) launched	**1982: Actrapid and Monotard launched**

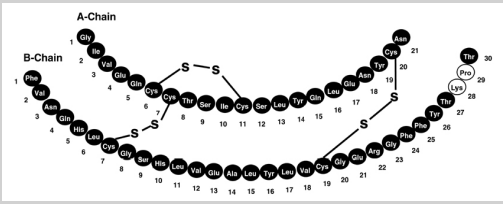
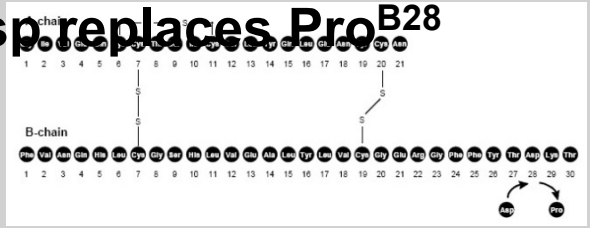
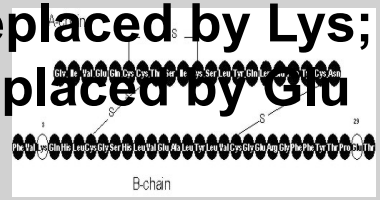
1. Brandenburger A, et al. *Harvard Business Review*1992, Available at http://hbr.org/product/race-to-develop-human-insulin/an/191121-PDF-ENG; 2. Cohen SN et al. *Proc Natl Acad Sci USA* 1973;70:3240–3244; 3. Keen H, et al. *Lancet* 1980;2(8191):398–401

- Attualmente abbiamo a disposizione analoghi dell'insulina a rapida e a lenta durata d'azione

PRESENTE

Analoghi dell'Insulina

- 3 analoghi dell'insulina sono ad oggi approvati per la cura del diabete

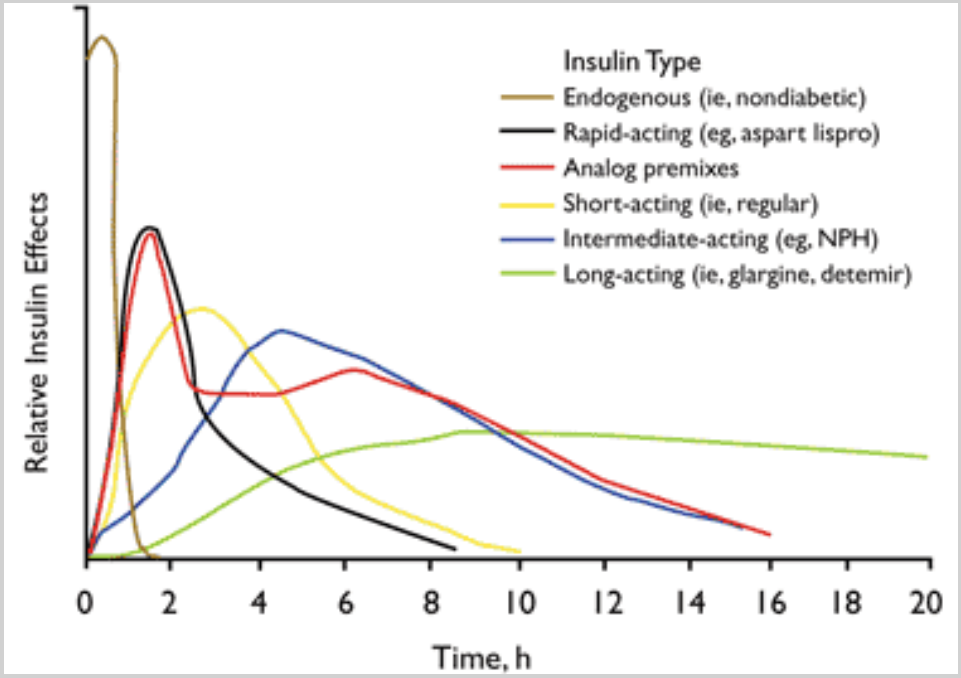
ANALOGO	INDUSTRIA FARM.	ZINC-FREE	STRUTTURA
Insulina lispro	**Eli Lilly & Co**	✗	**Pro^{B28}/Lys^{B29} switched** 
Insulina aspart	**Novo Nordisk**	✗	**Asp replaces Pro^{B28}** 
Insulina glulisina	**sanofi-aventis**	✓	**Asp^{B3} replaced by Lys; Lys^{B29} replaced by Glu** 

Insulina – farmacodinamica, flessibilità di trattamento

– Differenze nell'inizio, nel picco, durata d'azione

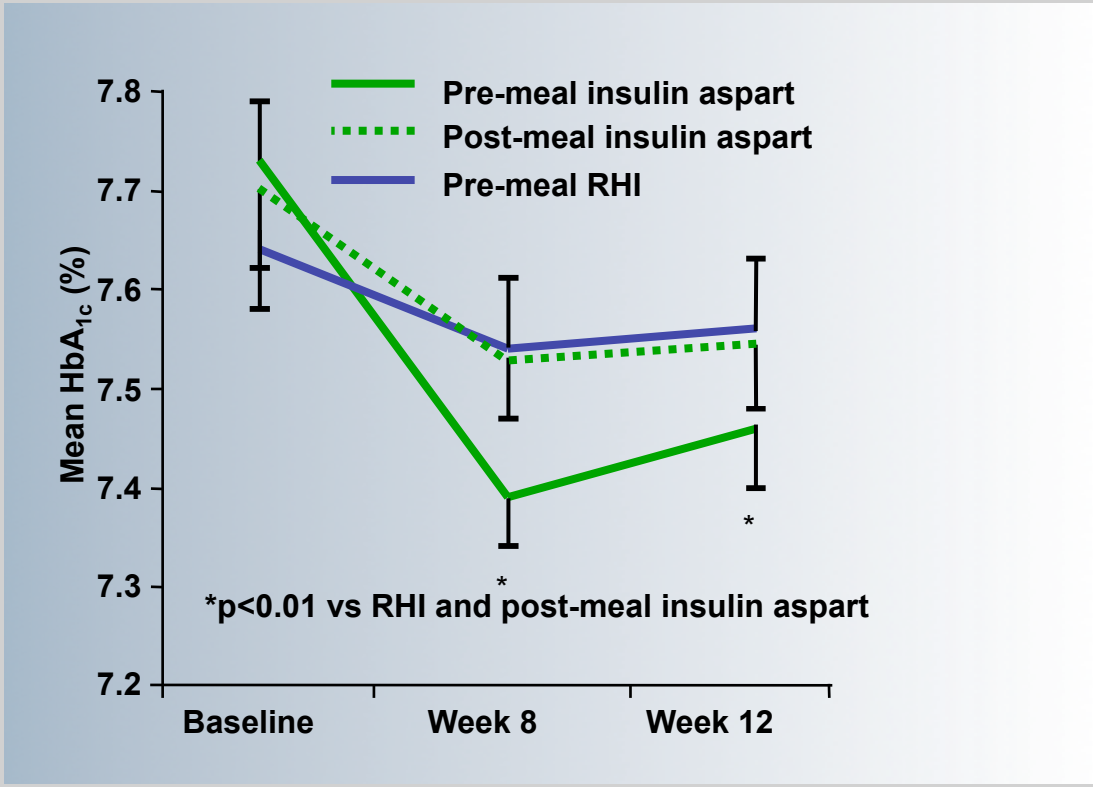
Profilo farmadocinamico - insulina umana e analoghi rapidi

	inizio (h)	Picco (h)	Durata (h)
Rapida			
RHI	0.5–1	2.5–5	8–12
Lispro	0.25–0.5	0.5–1.5	2–5
Aspart		1–3	3–5
Glulisine	0.17–0.33	0.5–1.5	1–2.5
	0.25		
Intermedia			
NPH	1–1.5	6–14	16–24
Lenta			
Glargine	1.1	–	24
Detemir	0.8–2	–	up to 24



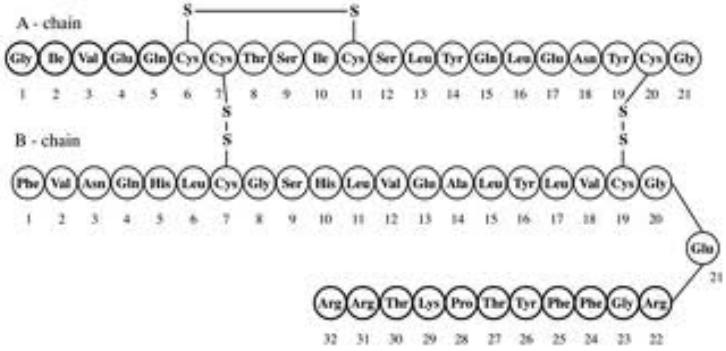
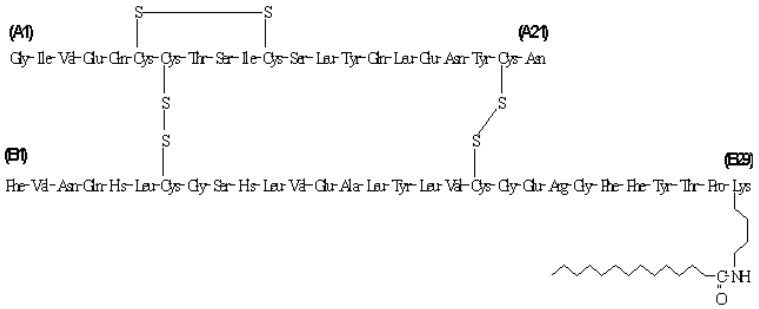
Un Sicuro Analogo Rapido

- Una breve durata d'azione
- Basso rischio di ipoglicemie
- Dose flessibile
- Bassa immunogenicità



1. Becker RH, et al. *Exp Clin Endocrinol Diabetes* 2005;**113**:435–443; 2. Dailey G, et al. *Diabetes Care* 2004;**27**:2363–2368; 3. Garg SK, et al. *Endocr Pract* 2005;**11**:11–17; 4. Mianowska B, et al. *Pediatr Diabetes* 2011;**12**:78–84

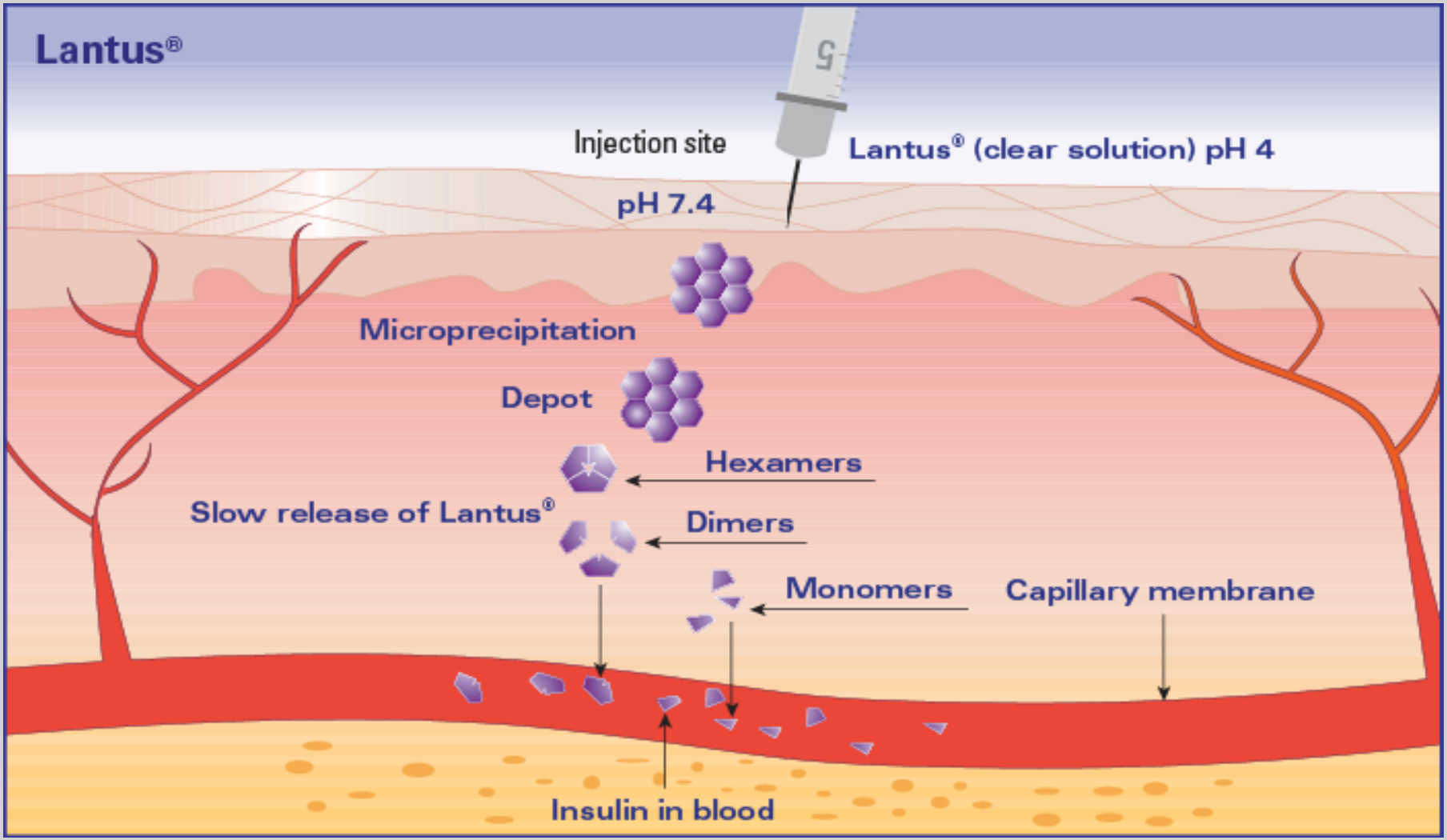
2 Analoghi dell'insulina a lenta durata d'azione

INSULINA GLARGINE	INSULINA DETEMIR
• Precipita nel tessuto sottocutaneo, forma un deposito locale con lenta dissoluzine, una volta al giorno	• Si lega all'albumina sierica umana che ne riduce la biodisponibilità • Una o due volte al giorno
• Asp^{A21} replaced by Gly; two Arg added to C-terminus of B-chain 	• Thr^{B30} omitted; C14 fatty acid chain added at B29 

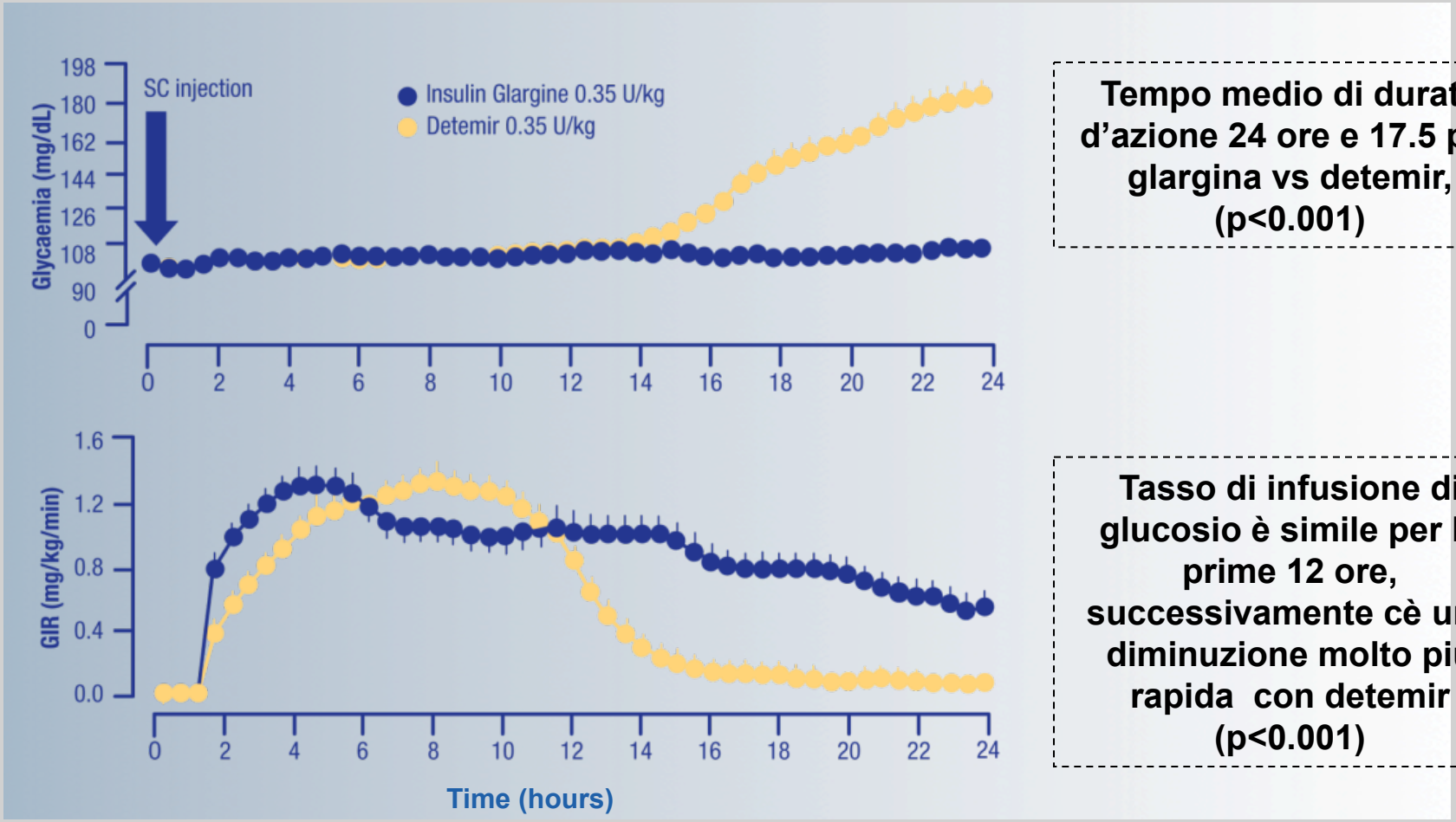
- **La differenza strutturale degli analoghi basali dell'insulina conferisce unicità d'azione**

HSA=human serum albumin

Meccanismo d' azione



FARMACODINAMICA – CONFRONTO
insulina glargina and detemir



Tempo medio di durata d'azione 24 ore e 17.5 per glargina vs detemir, (p<0.001)

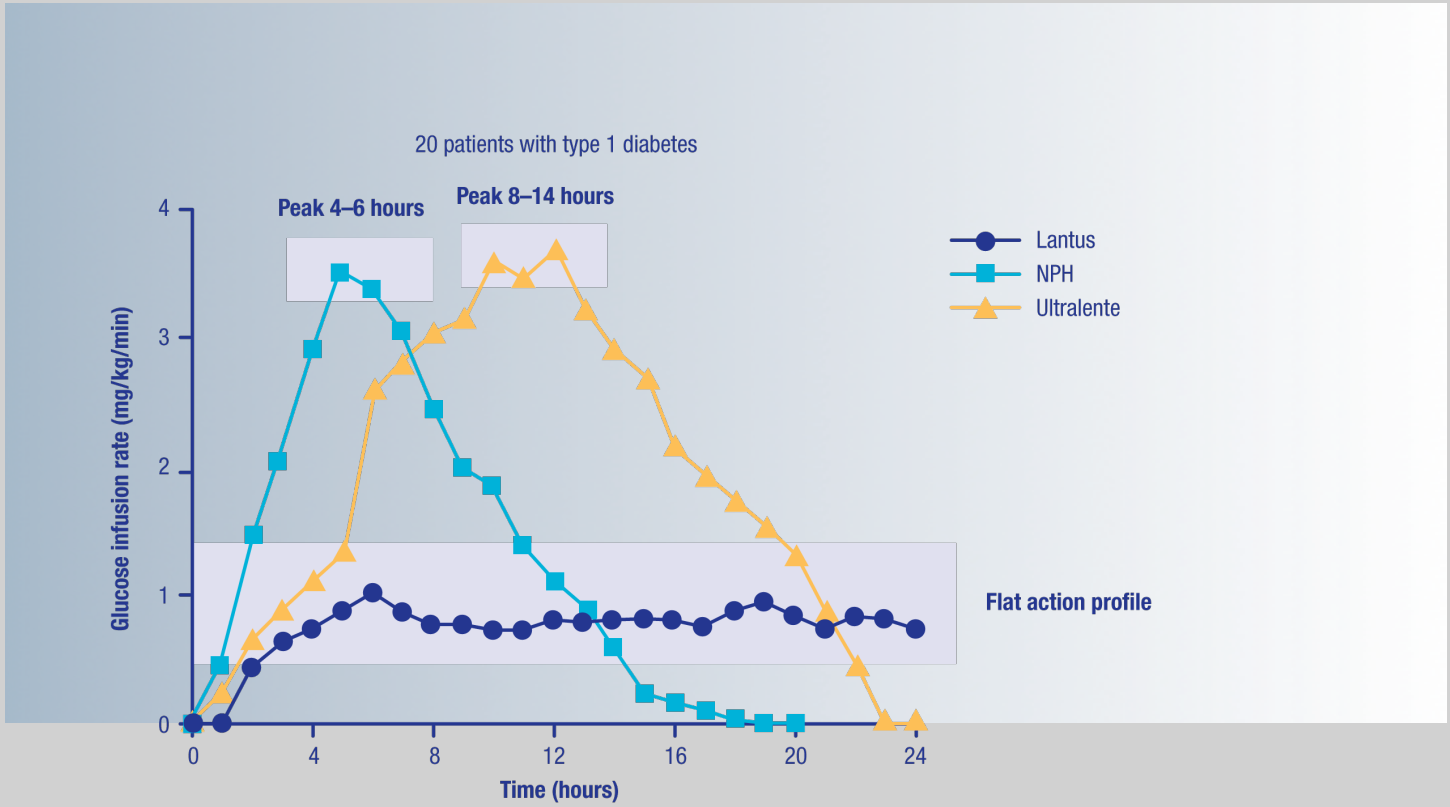
Tasso di infusione di glucosio è simile per le prime 12 ore, successivamente cè una diminuzione molto piu rapida con detemir (p<0.001)

Porcellati F et al. *Diabetes Care* 2007;30:2447–2452

SC=subcutaneous injection; GIR=glucose infusion rate

Insulina glargine
profilo piatto e lunga durata d'azione

– Glargine ha un profilo senza picchi e una durata d'azione di 24 ore ed una bassa inter variabilità

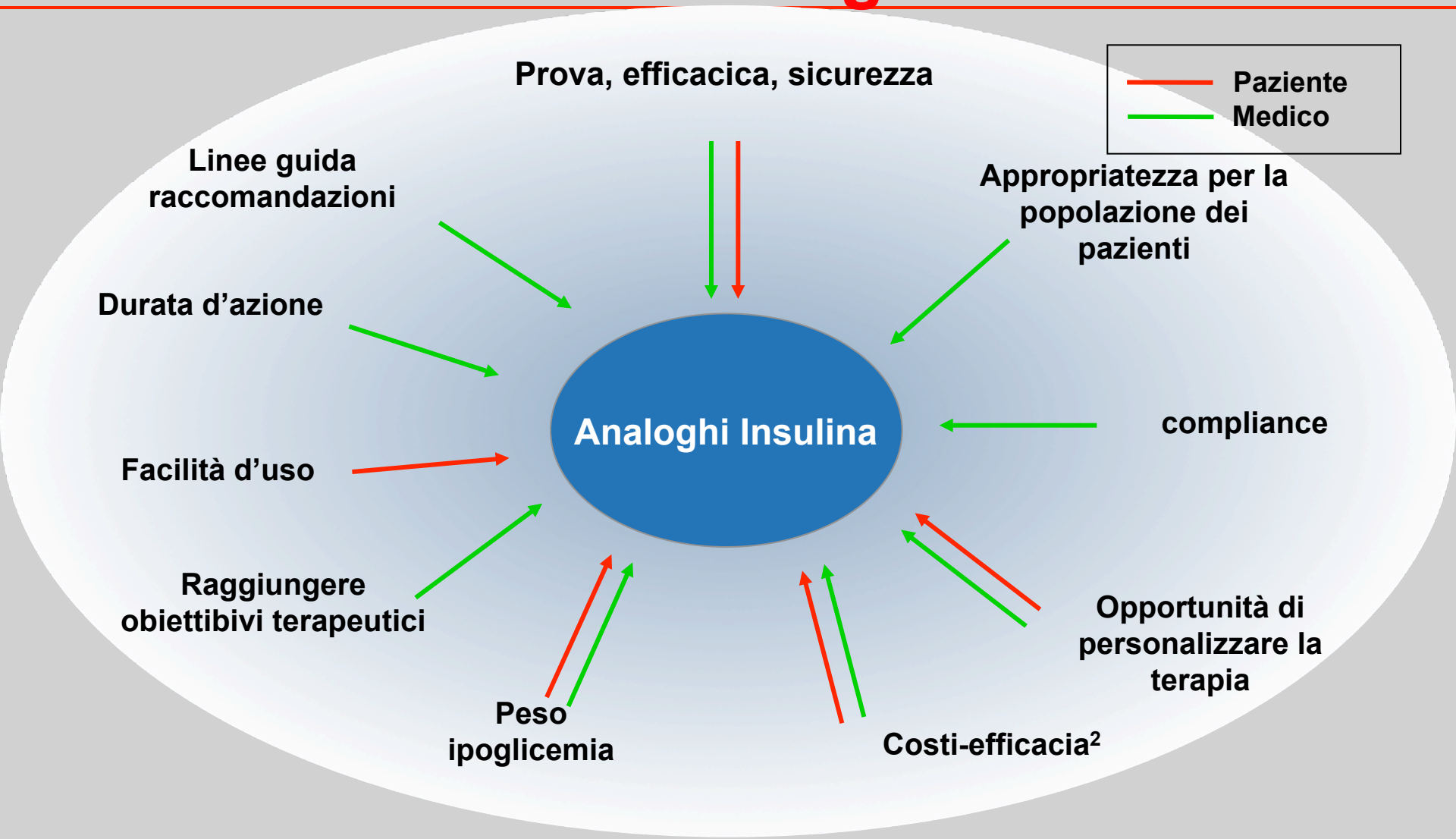


Lepore M et al. *Diabetes* 2000;49:2142–2148

La prossima generazione di analoghi dell'insulina

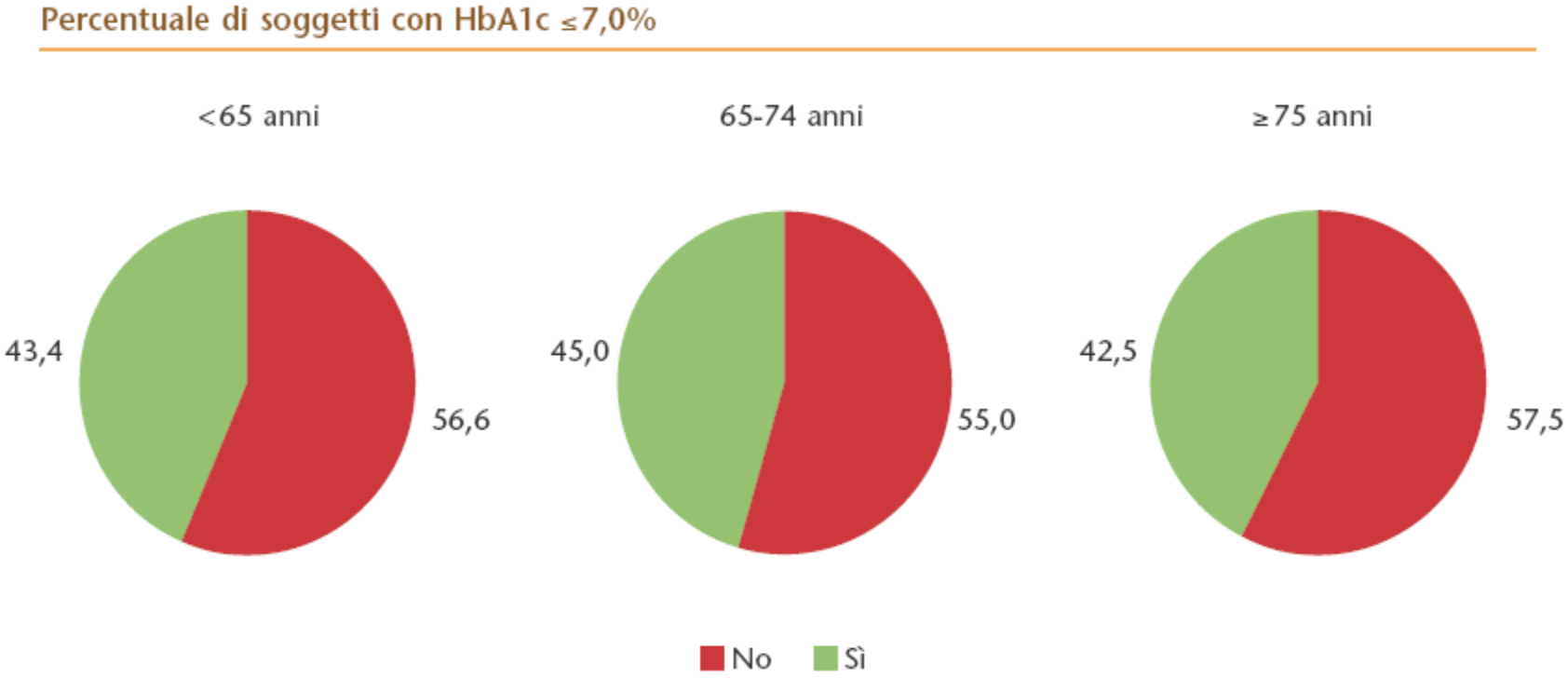
FUTURO

Cosa guida la scelta dell'analogo



1. Nathan DM, et al. *Diabetologia* 2009;52:17–30; 2. Clement FM, et al. *JAMA* 2009;302:1437–1443;
3. Peyrot M. *Diabetes Care* 2005;28:2673–2679; 4. Gong WC. *Pharmacotherapy* 2008;28:1299–1308

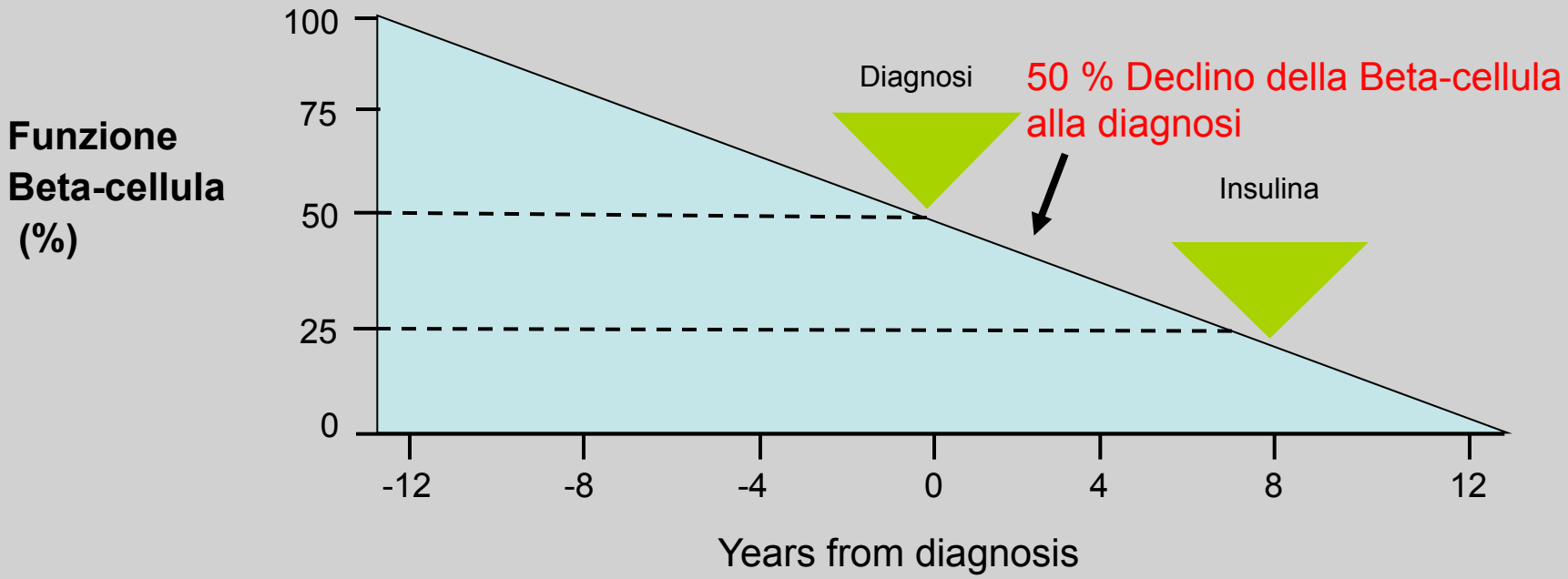
Un controllo metabolico adeguato è raggiunto in poco più del 40% dei pazienti con DMT2, a prescindere dalla fascia di età considerata.



Monografia Annali AMD 2011- Anziani con Diabete

Terapia intensiva

Declino della funzione della Beta-cellula
Nella progressione di malattia DMT2



Lebovitz H. Diabetes Rev 1999;7:139-153.

Tutti I pazienti con DMT2 richiedono insulina:
-7 - 10 anni dopo la diagnosi
-HbA1c >9%

Colpa Del Farmaco?

- Concentrazione costante
- Priva di picchi
- Continua per 24 ore
- Bassa variabilità
- No aumento di peso
- No ipoglicemia
- No induzione mitogenica con i recettori non insulinici

Limiti Glargina:

- Aumento di peso
- Aumento di incidenza di neoplasia (?)
  - Aumento di affinità per il recettore IGF-I
  - Variabilità inter individuale

Colpa Del Diabetologo?

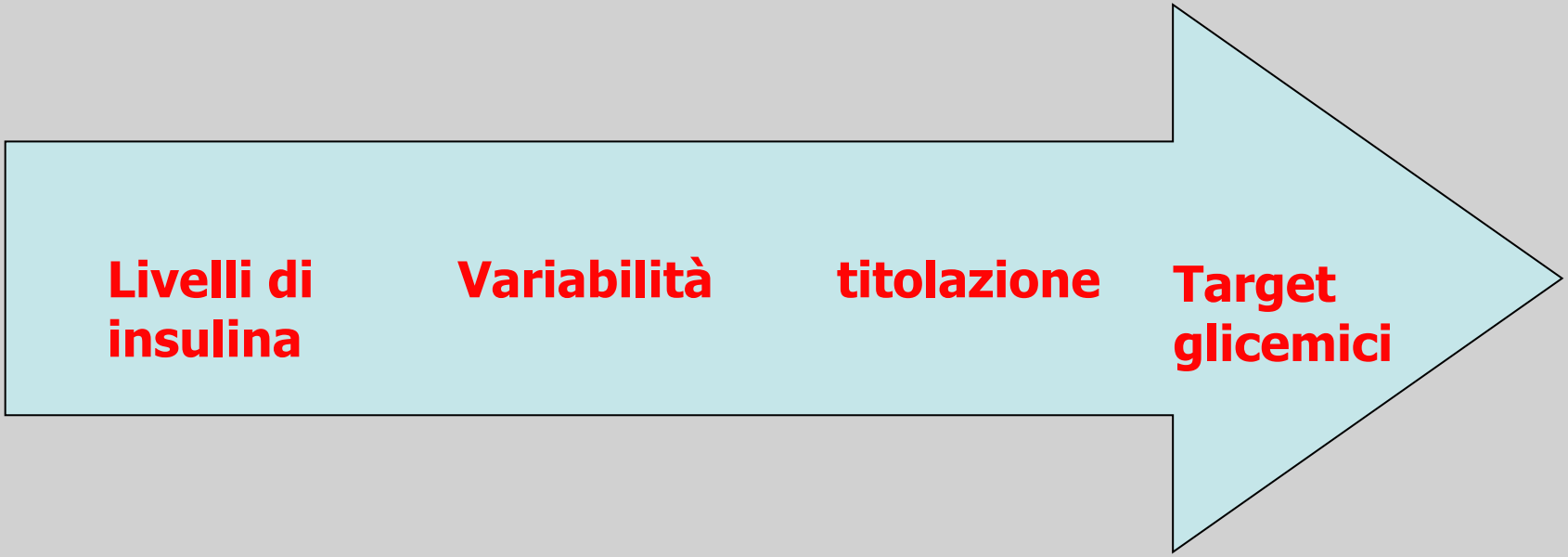
- L'Esperienza
- L'Abitudine
- L'Inerzia Clinica

perché?

- In combinazione con ipo orali
- Analoghe caratteristiche

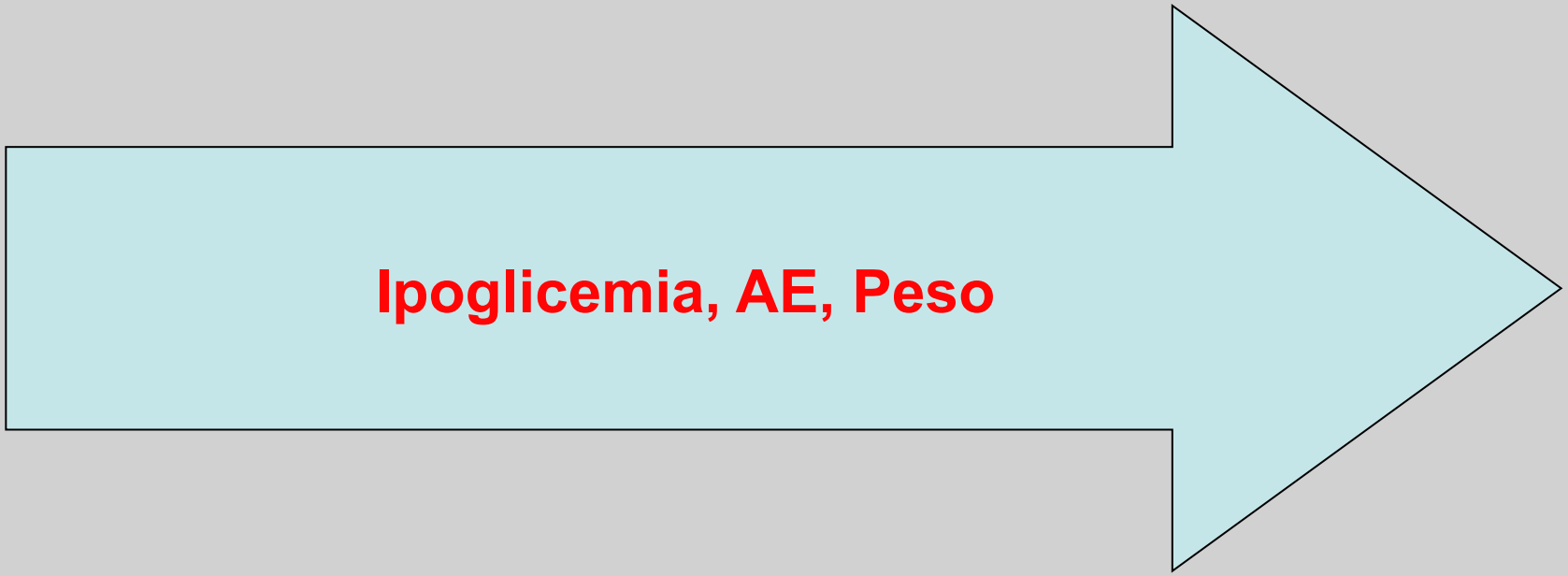
  - **Efficacia**
  - **Sicurezza**
  - **Tollerabilità**
    -- **DMT1, DMT2**

La chiave di lettura dell'efficacia long-acting insulin analogue



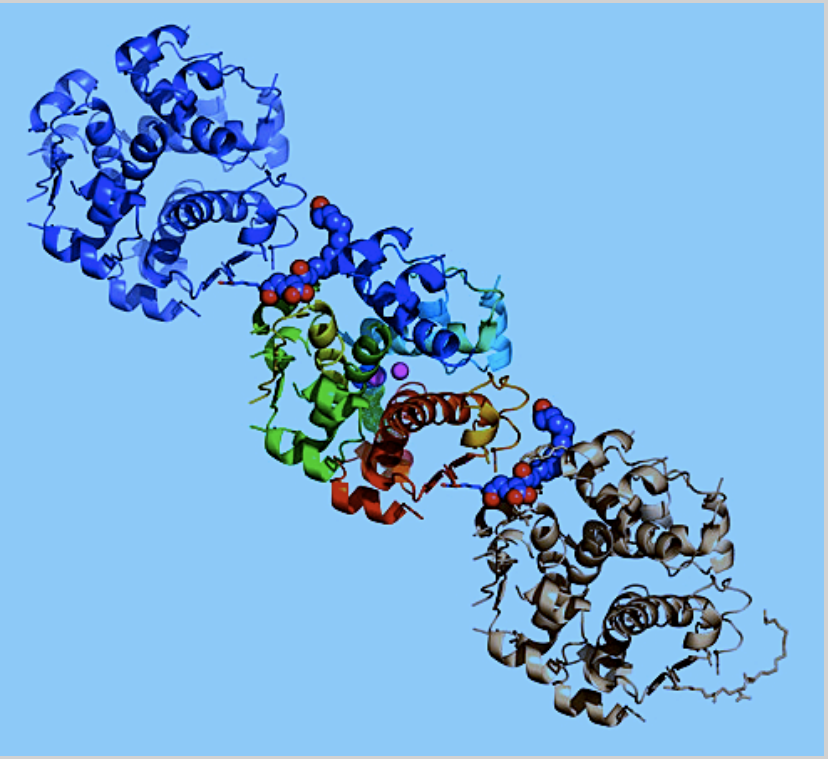
1. Russell-Jones D. *Int J Obese Relat Metab Disord* 2004;**28**(Suppl 2):S29–34

Sicurezza
long-acting insulina analoghi



AE=adverse events

Tresiba® (insulin degludec)

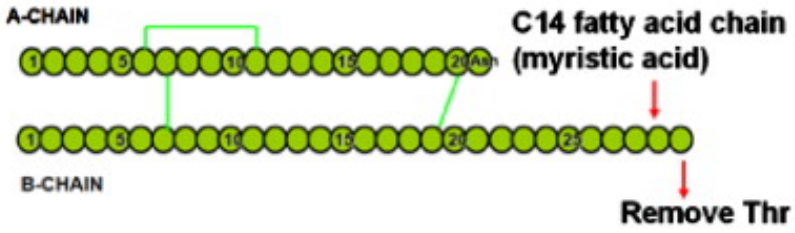


Schema Riassuntivo Insuline Basali

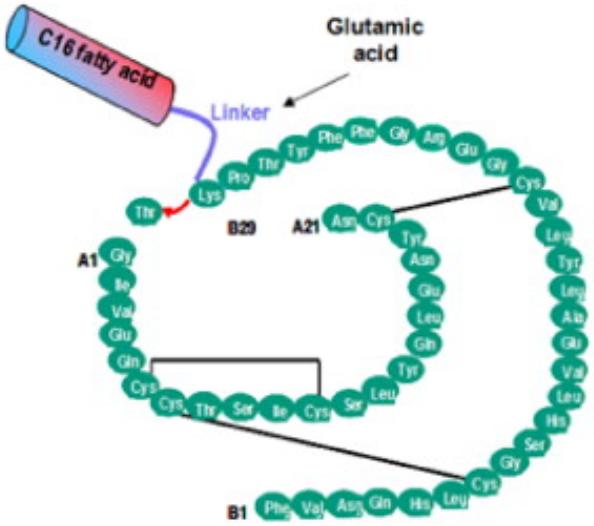
(a)

(a) Insulin Glargine

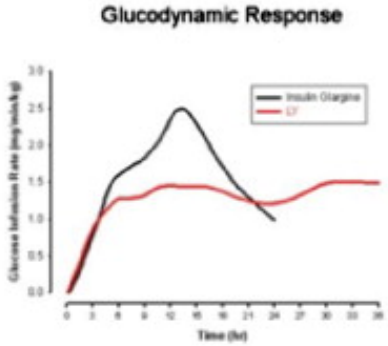
(b) Insulin Detemir



(c) Insulin Degludec



(d) Lilly's Basal Insulin: LY2605541



Derived From Phase 1 Data

Novel engineered insulin goals:

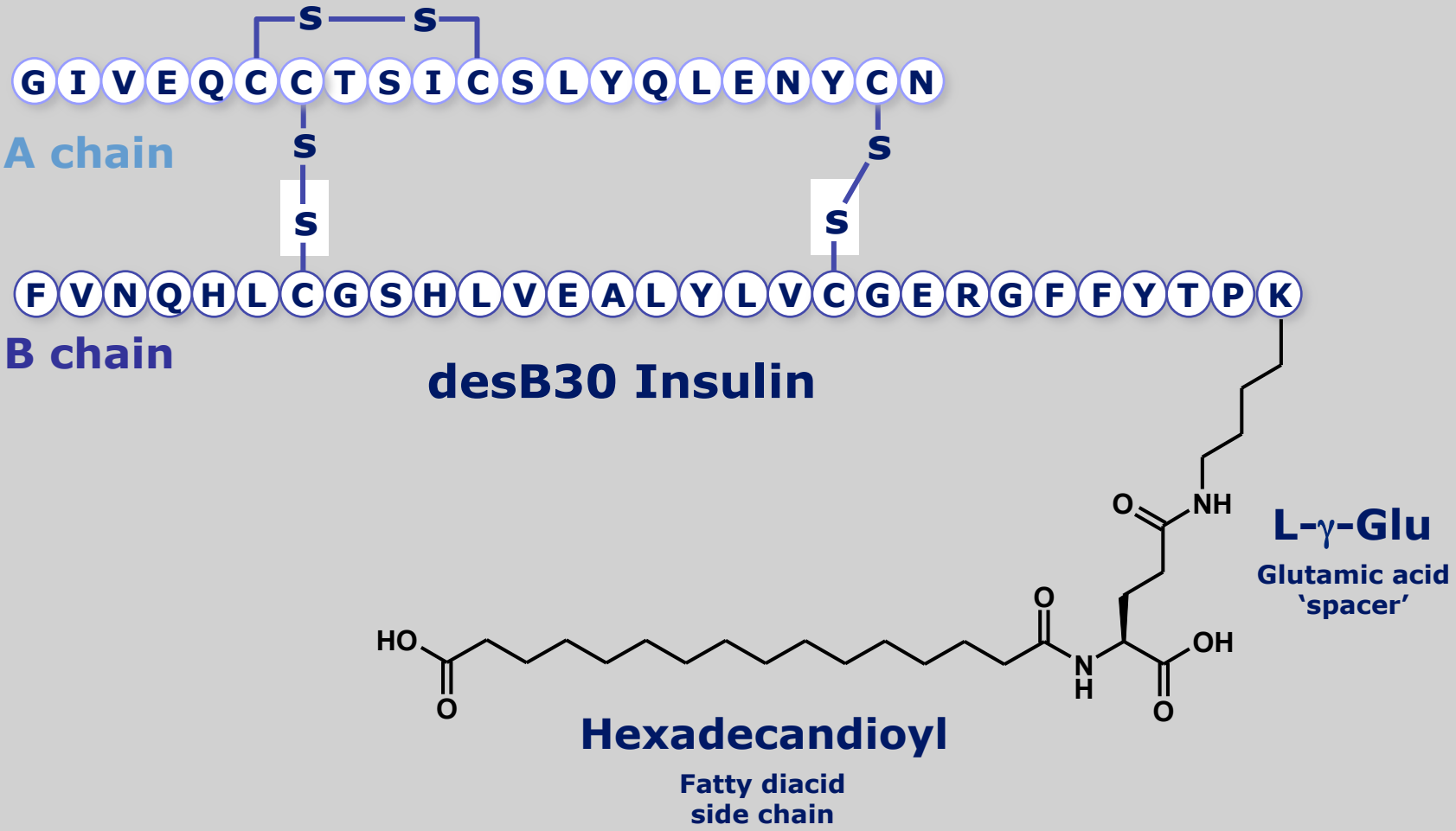
- Less patient variability
- Less hypoglycemia risk
- Better patient control

Status: Phase 1 studies

(b)

Struttura molecolare dell'insulina Degludec

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



Jonassen et al., Pharm Res 2012

Insulin Degludec, The New Generation Basal Insulin or Just another Basal Insulin?

Sami N. Nasrallah and L. Raymond Reynolds

University of Kentucky. Corresponding author email: sami.nasrallah@uky.edu

Table 1. Comparison of insulin degludec and other insulin analogs.

Basal insulin	Onset	Peak	Duration	Comments
NPH	1–2 hours	4–8 hours	8–12 hours	Greatest risk for hypoglycemia
Glargine	30–60 minutes	No peak	16–24 hours	– Greatest potential for weight gain. – Possible mitogenicity
Detemir	30–60 minutes	No peak	16–24 hours	May need twice daily injections.
Degludec	30–90 minutes	No peak	Over 24 hours	– Least risk of hypoglycemia – No mitogenicity
Degludec plus	5–15 minutes	30–60 minutes	Over 24 hours	Same as degludec with advantage of added prandial coverage.

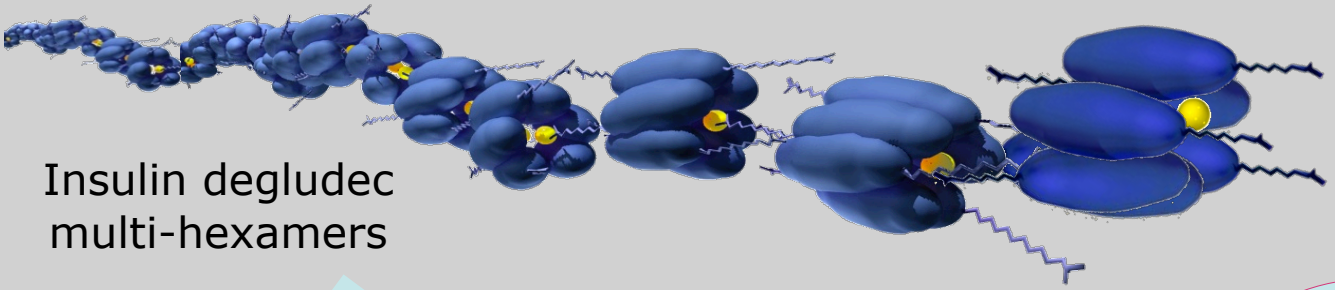
Abbreviation: NPH, neutral protamine hagedorn.

Clin Med Insights Endocrinol Diabetes. 2012;5:31-7. Epub 2012 Apr 11.

Meccanismo di protrazione

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

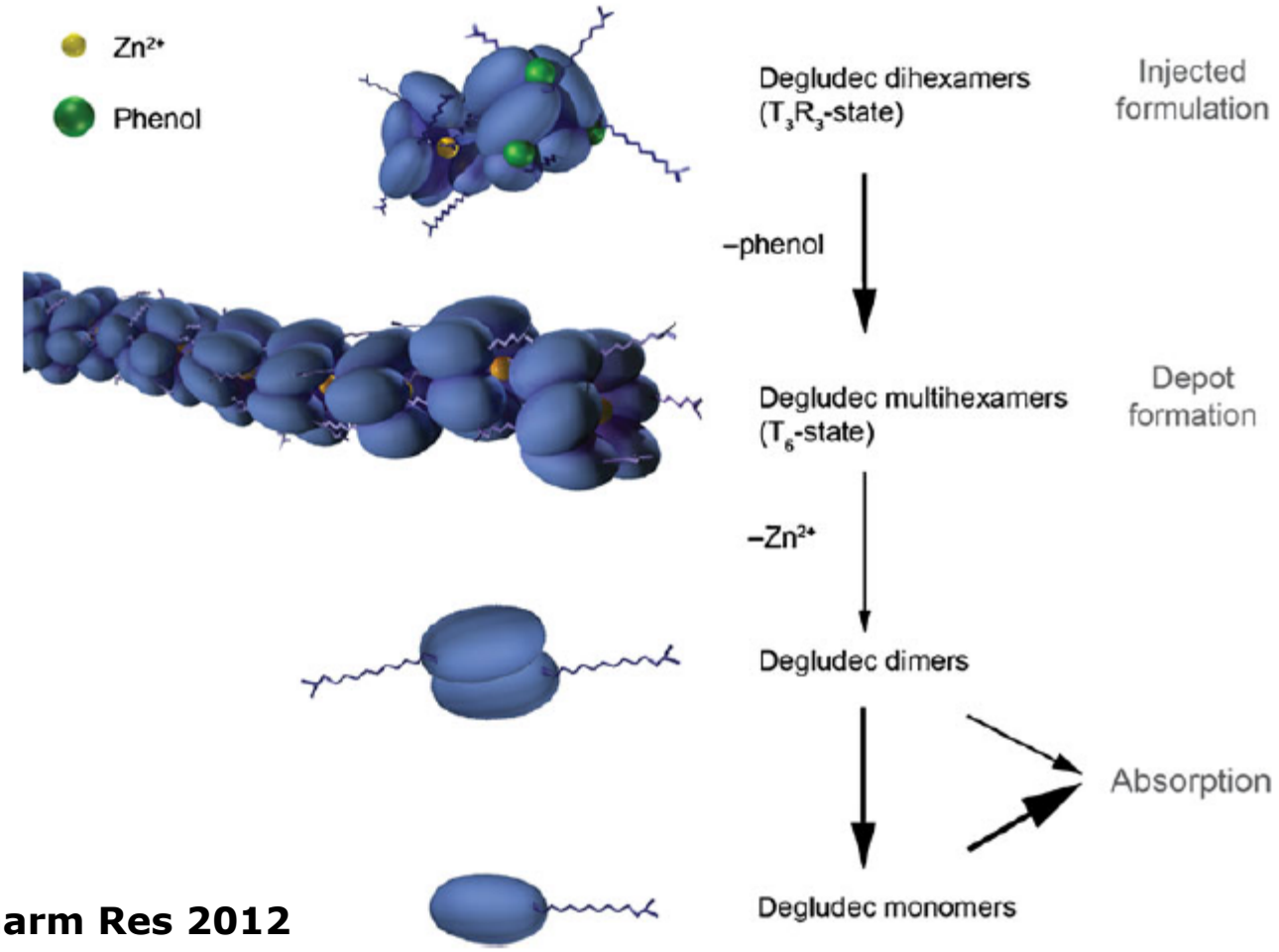
hours

Jonassen et al., Pharm Res 2012

Design of the Novel Protraction Mechanism of Insulin Degludec, an Ultra-long-Acting Basal Insulin

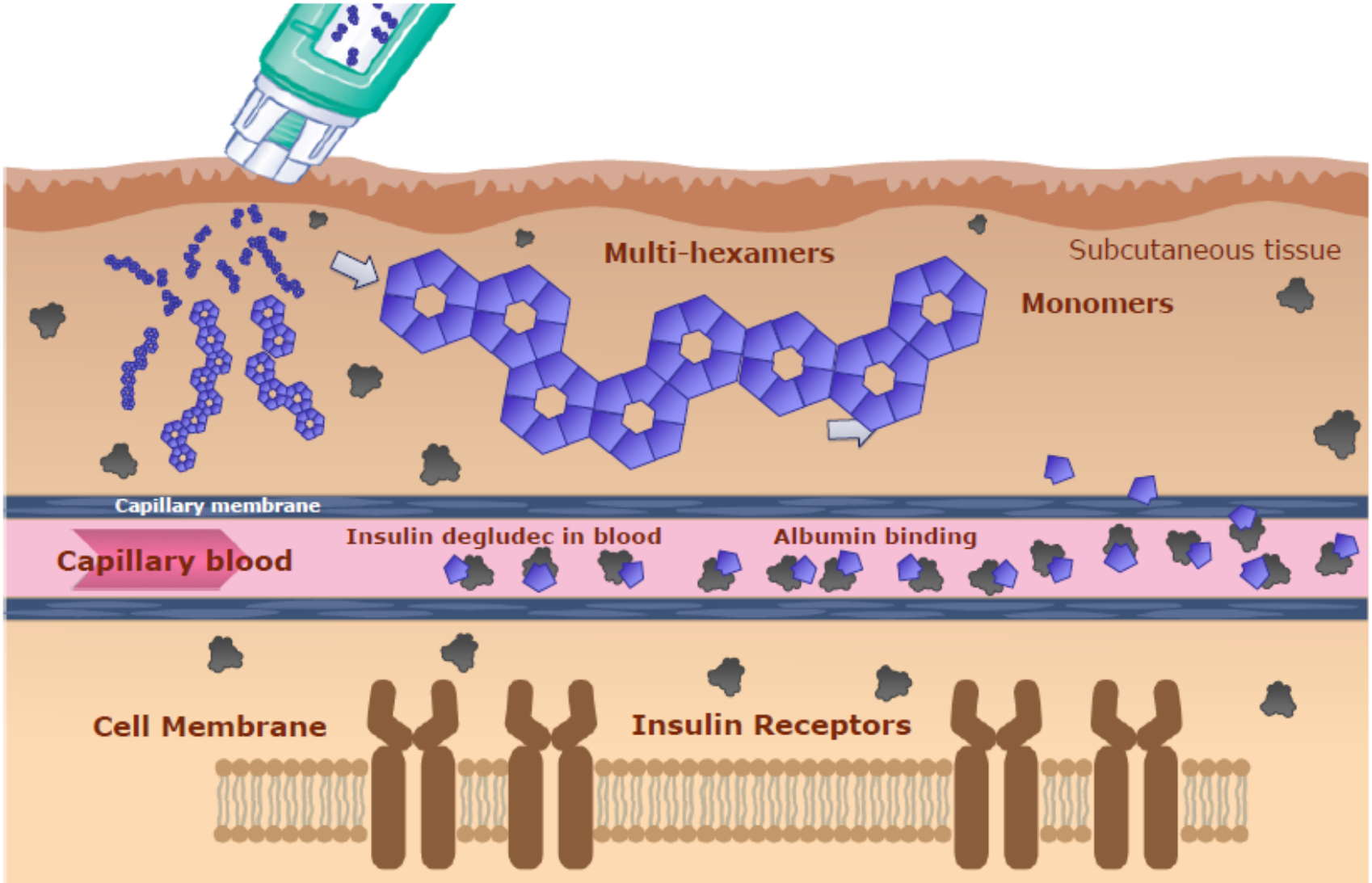
Ib Jonassen • Svend Havelund • Thomas Hoeg-Jensen • Dorte Bjerre Steensgaard • Per-Olof Wahlund • Ulla Ribel

Fig. 5 Schematic representation of the hypothesis for the mode of retarded absorption of insulin degludec: Insulin degludec is injected subcutaneously as a zinc phenol formulation containing insulin degludec dihexamer in the T_3R_3 conformation. Rapid loss of phenol changes the degludec hexamers to T_6 configuration and multi-hexamer chains form. With slow diffusion of zinc, these chains break down into dimers, which quickly dissociate into readily-absorbed monomers.



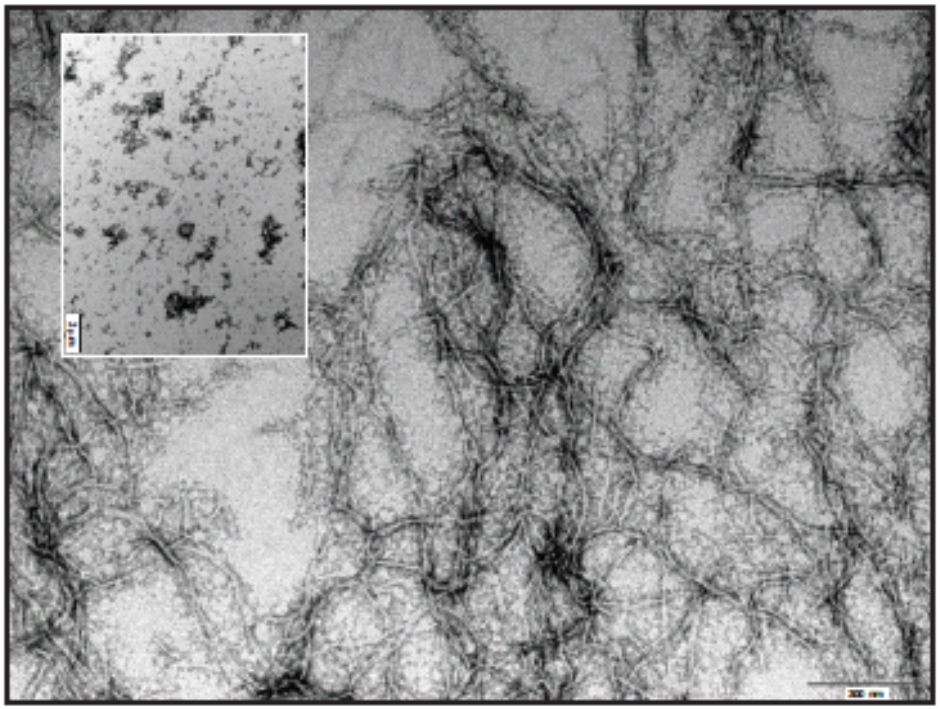
Jonassen et al., Pharm Res 2012

Protraction mechanism for Degludec



Visualizzazione TEM* dei multiesameri di degludec

Roma,
9-11 novembre 2012

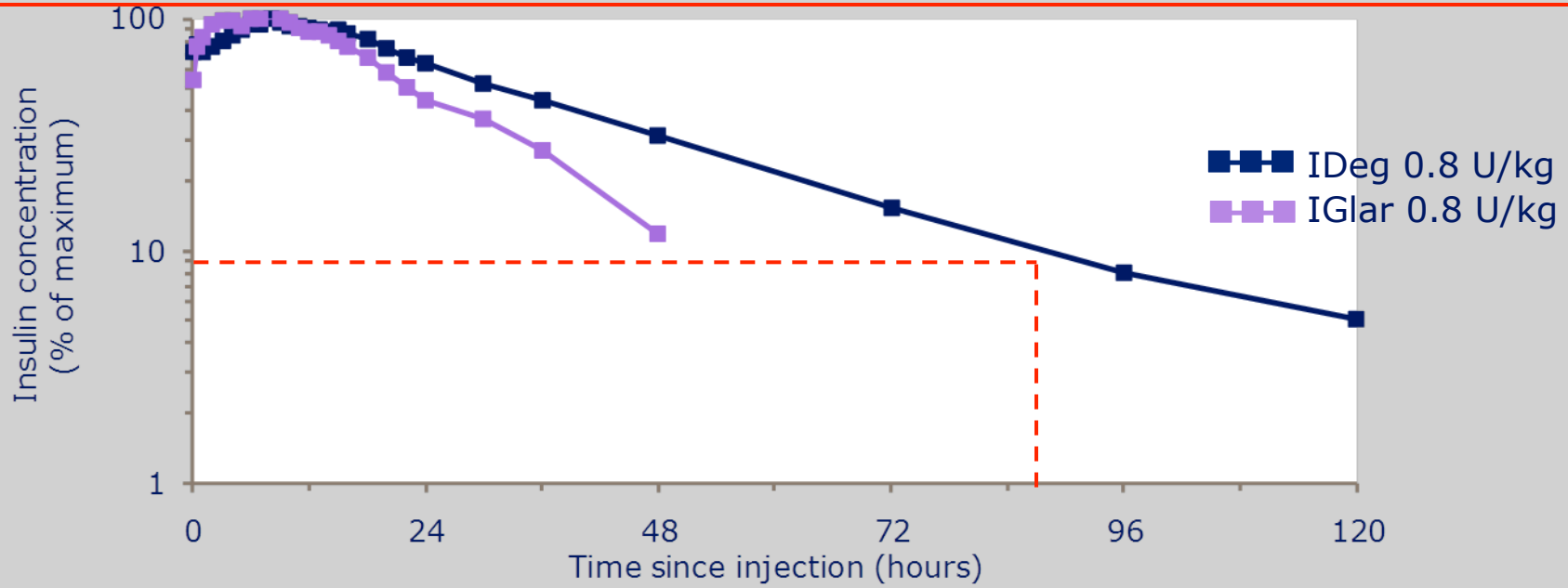


Main picture shows elongated IDeg structures in absence of phenol; inset (white box) shows absence of elongated IDeg structures in presence of phenol.

***TEM: Transmission Electron Microscope**

Kurtzhals P, Diabetes July 2011; vol 60 (Supplement 1): 42-LB. ADA 2011

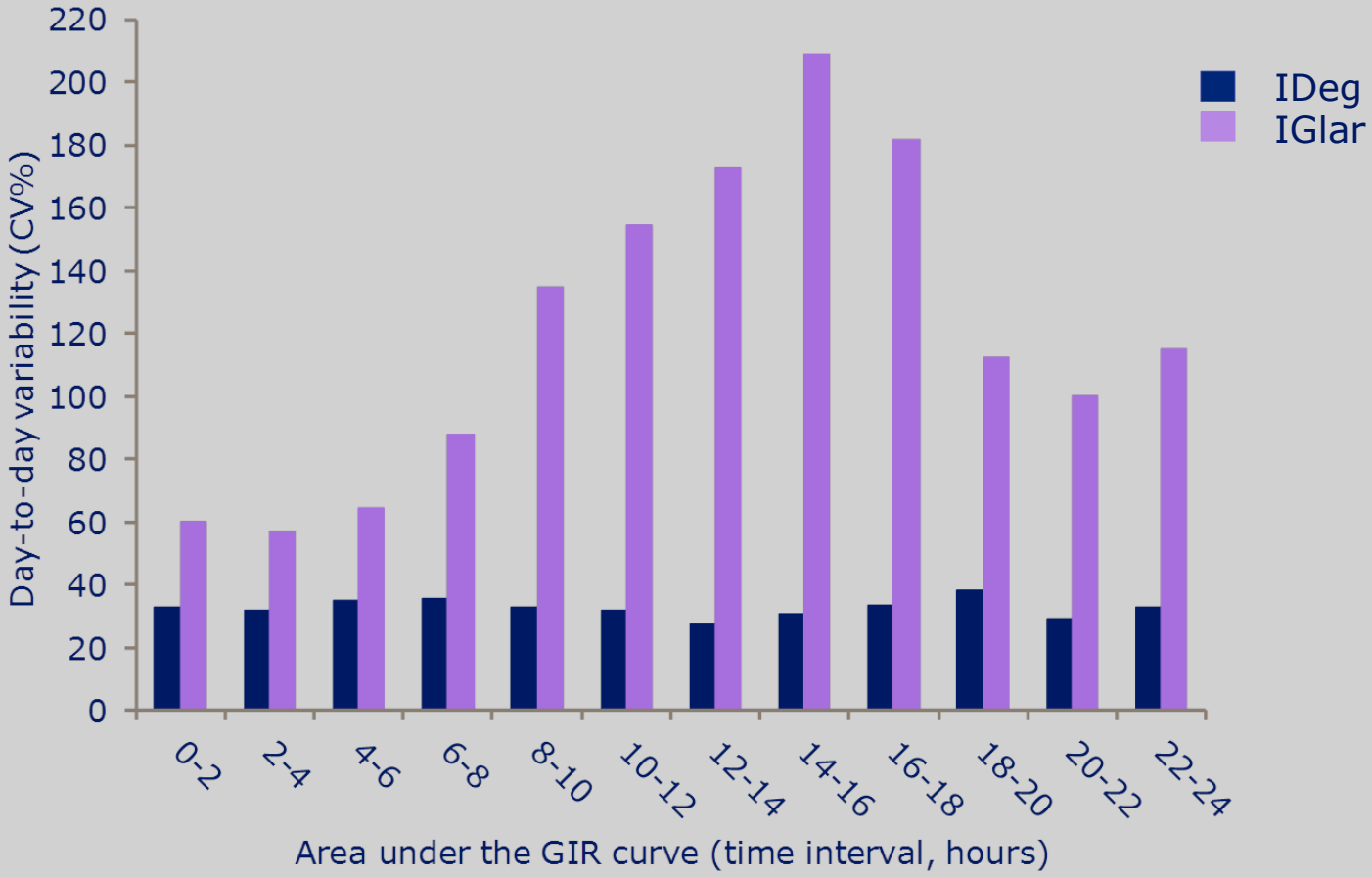
Concentrazione ematica ed emivita



	IDeg			IGlar		
	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	23.9	11.8	14.0	11.9
Mean half-life	**25.4**			**12.5**		

Kurtzhals P, Diabetes July 2011; vol 60 (Supplement 1): 42-LB. ADA 2011

Variabilità individuale

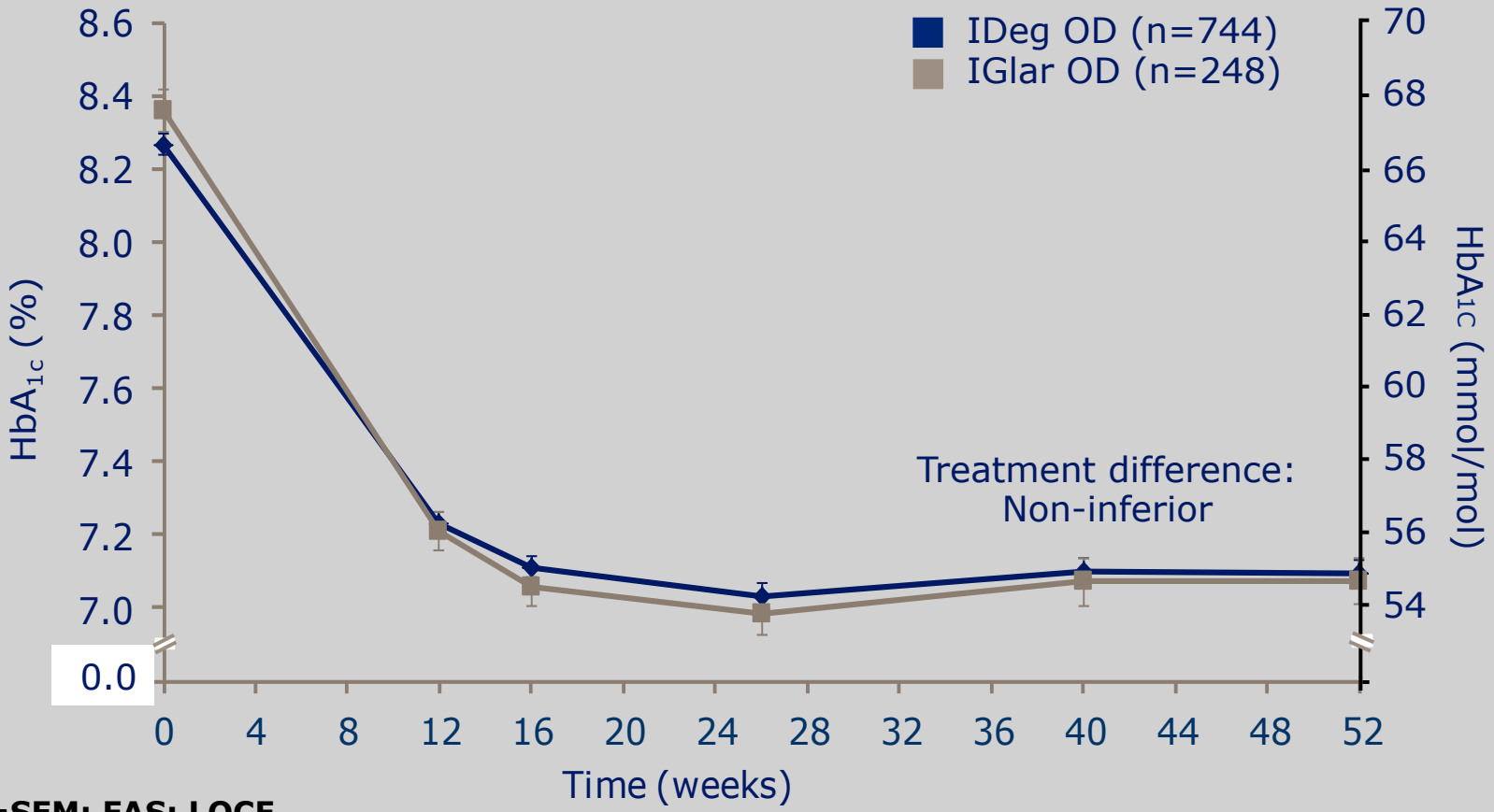


Heise et al. Diabetes 2011;60(Suppl. 1):A263

- **Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial.**
- **Garber AJ, et al.**
- **Lancet. 2012 Apr 21;379(9825):1498-507.**

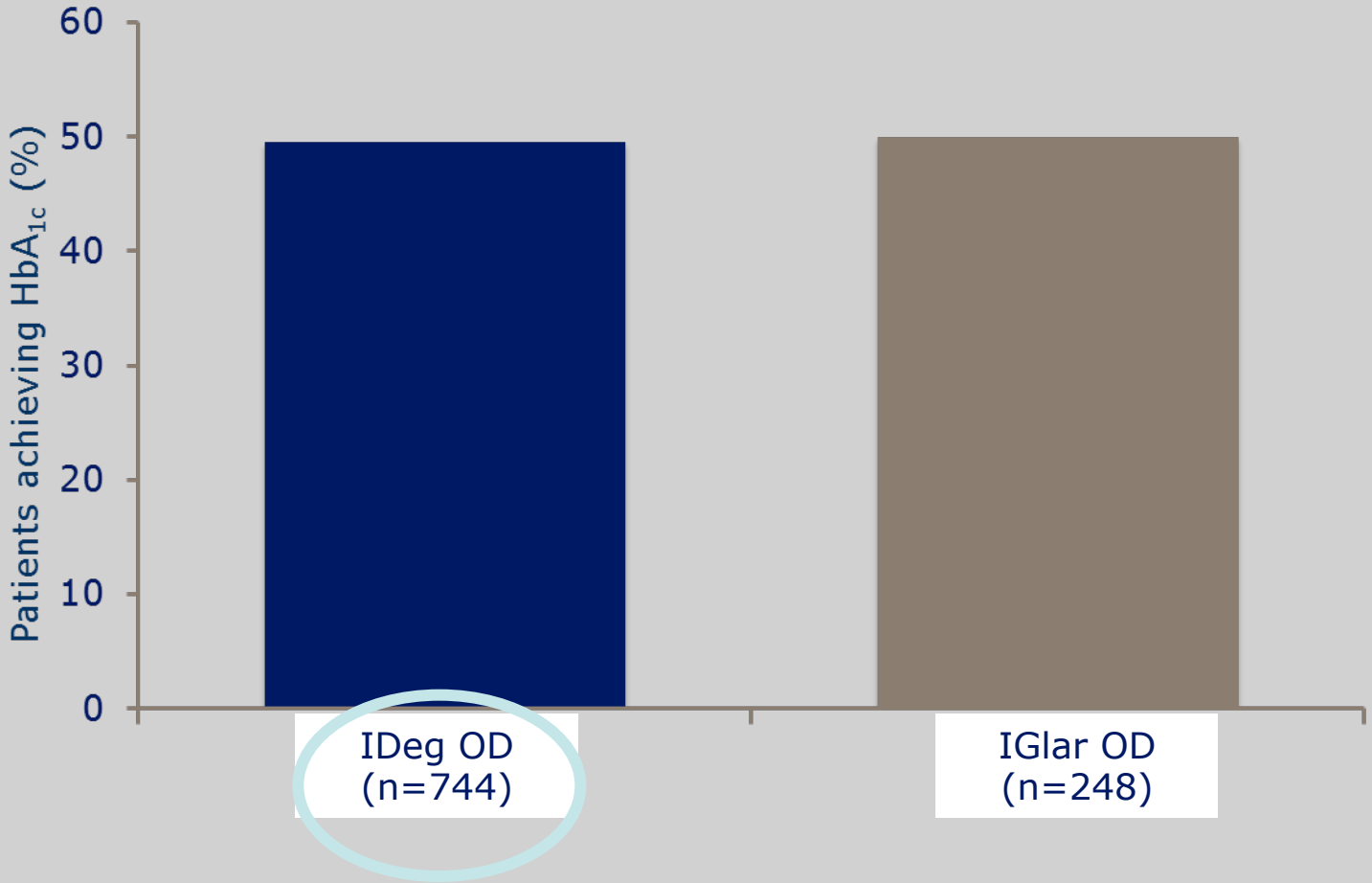
Valori di HbA1c durante lo studio a 52 settimane

Garber A *et al. Lancet* 2012;379:1498-507



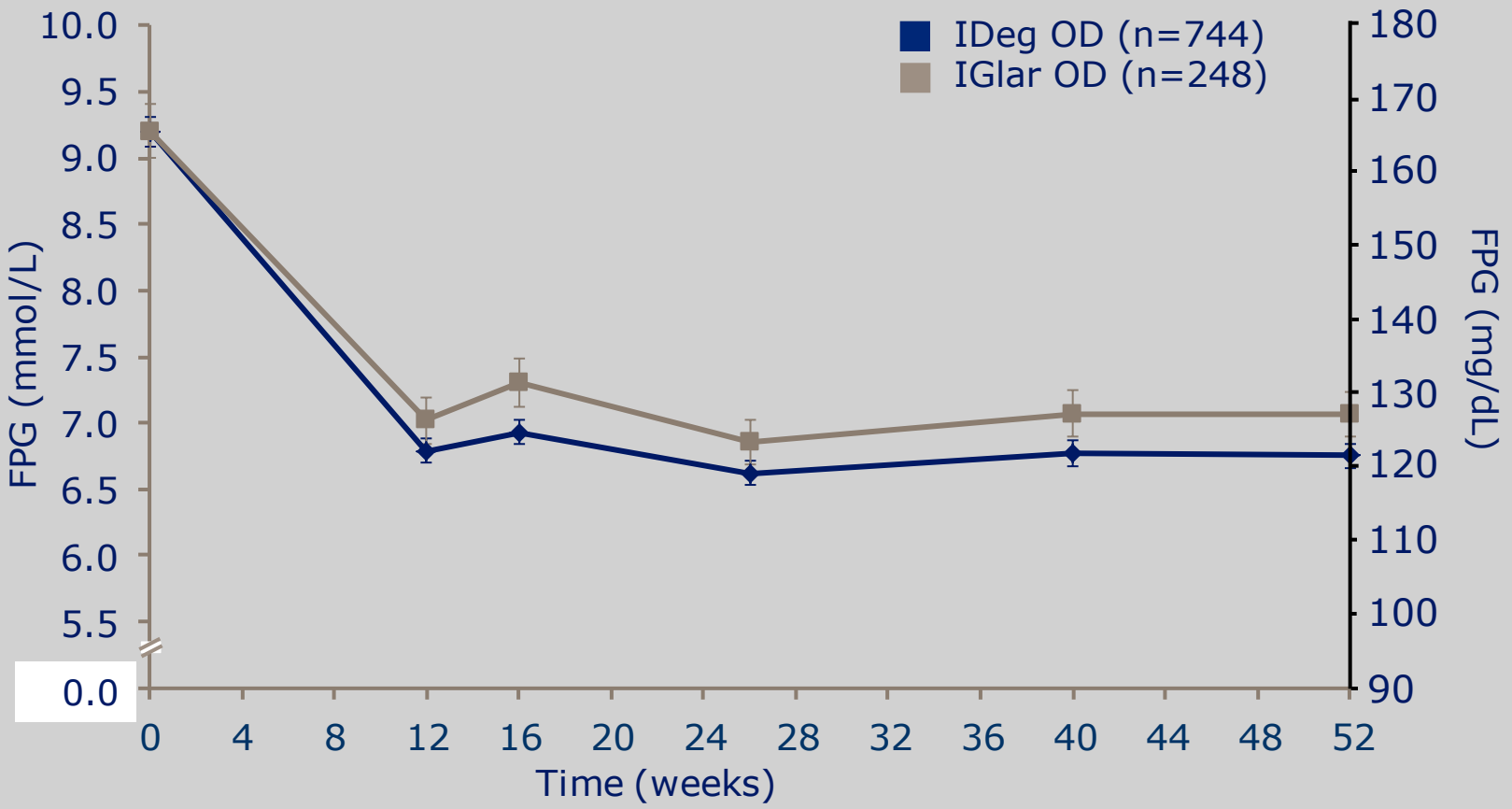
Mean±SEM; FAS; LOCF
Comparisons: Estimates adjusted for multiple covariates
In the following results presentations, p-values are shown for results that show statistically significant differences, and not for results that are not statistically significant

Pazienti che hanno raggiunto il target HbA1c <7.0%



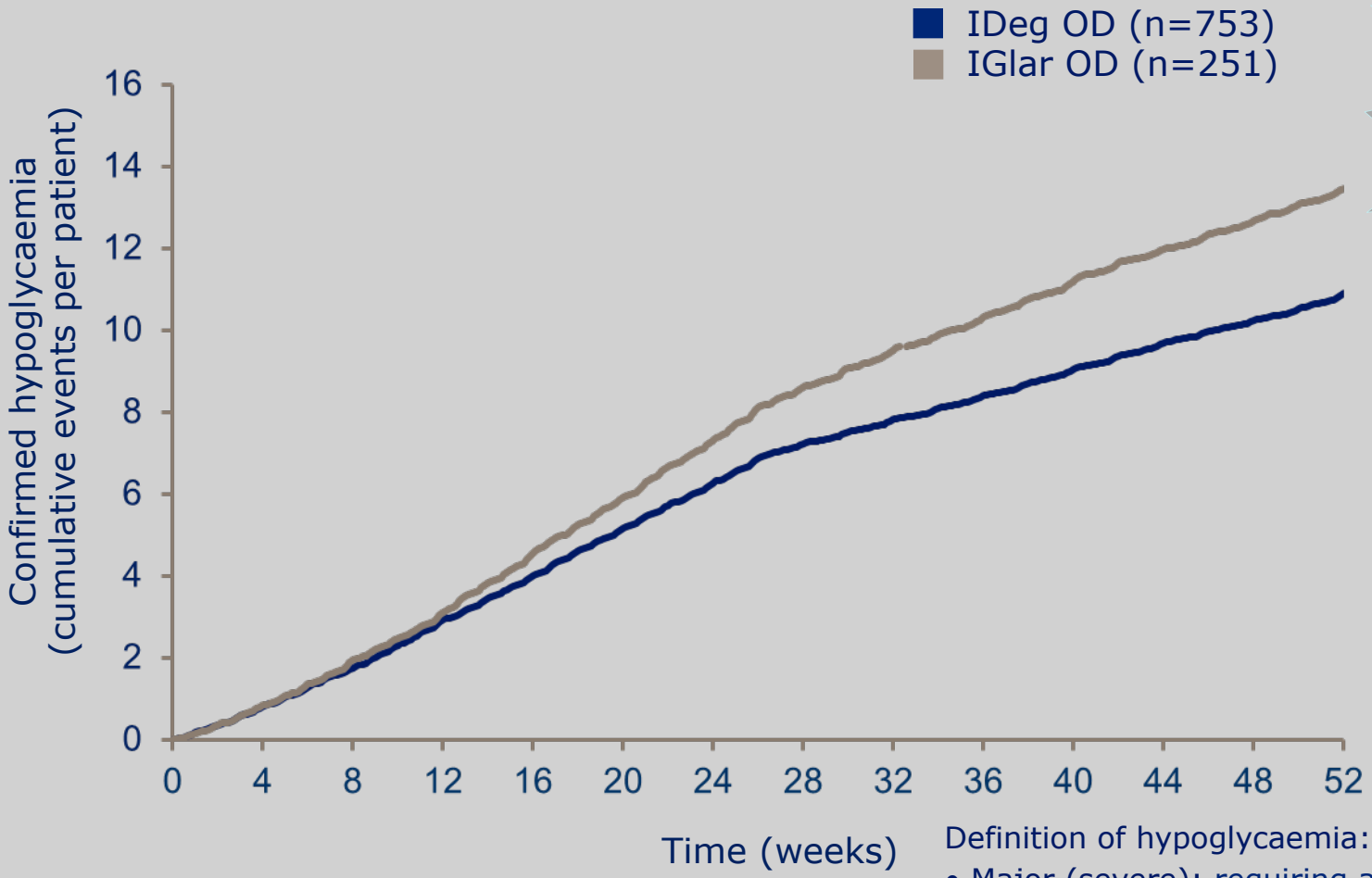
Garber A *et al. Lancet* 2012;379:1498-507

FPG durante lo studio a 52 settimane



Garber A *et al. Lancet* 2012;379:1498-507

Ipoglicemie



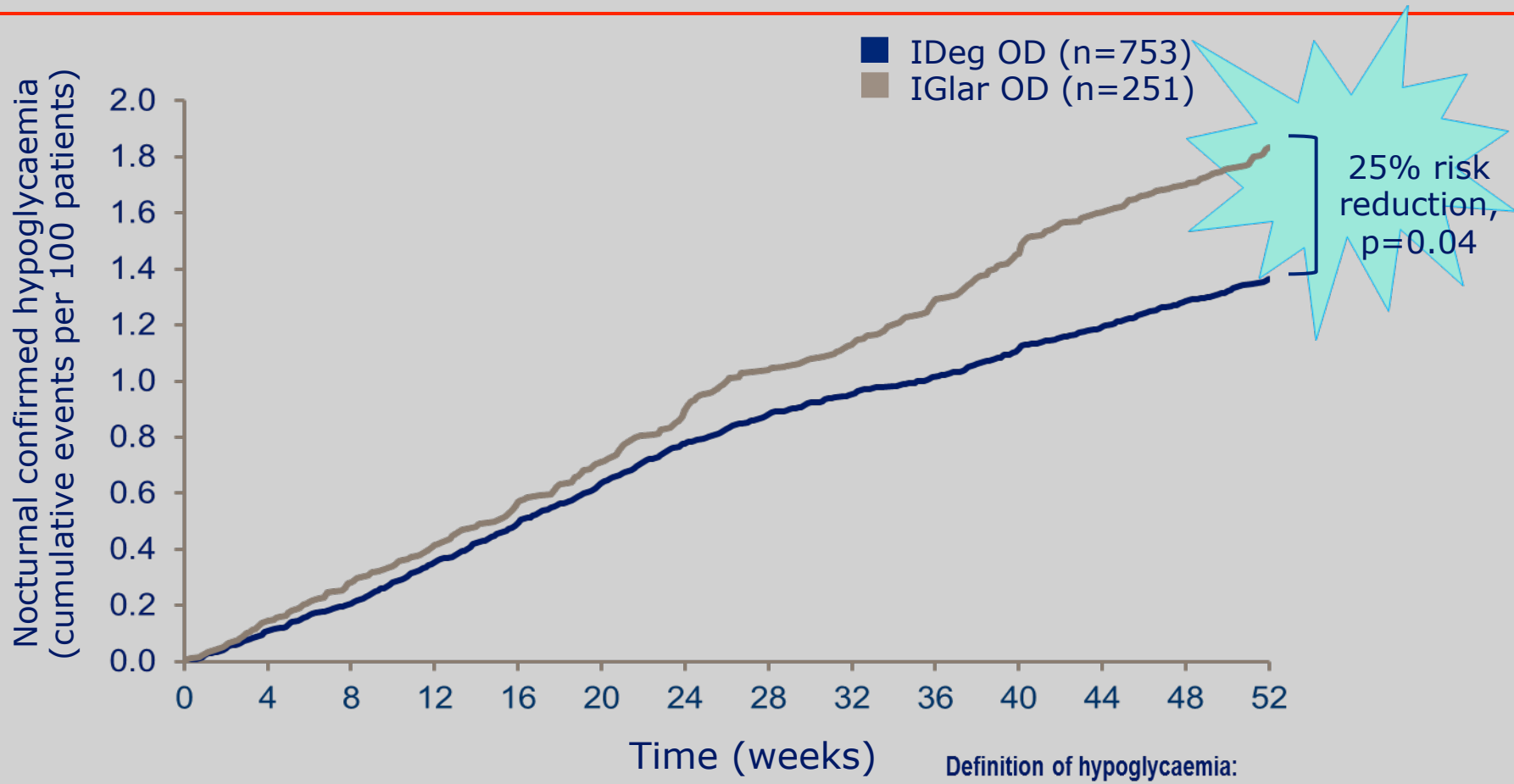
Definition of hypoglycaemia:

- Major (severe): requiring assistance
- Minor: plasma glucose <56 mg/dL (3.1 mmol/L) ± symptoms
- Symptoms only

Nocturnal: Episode with time of onset between 23:00 and 05:59 (inclusive)

Garber A et al. Lancet 2012;379:1498-507

Ipoglicemie notturne



Definition of hypoglycaemia:

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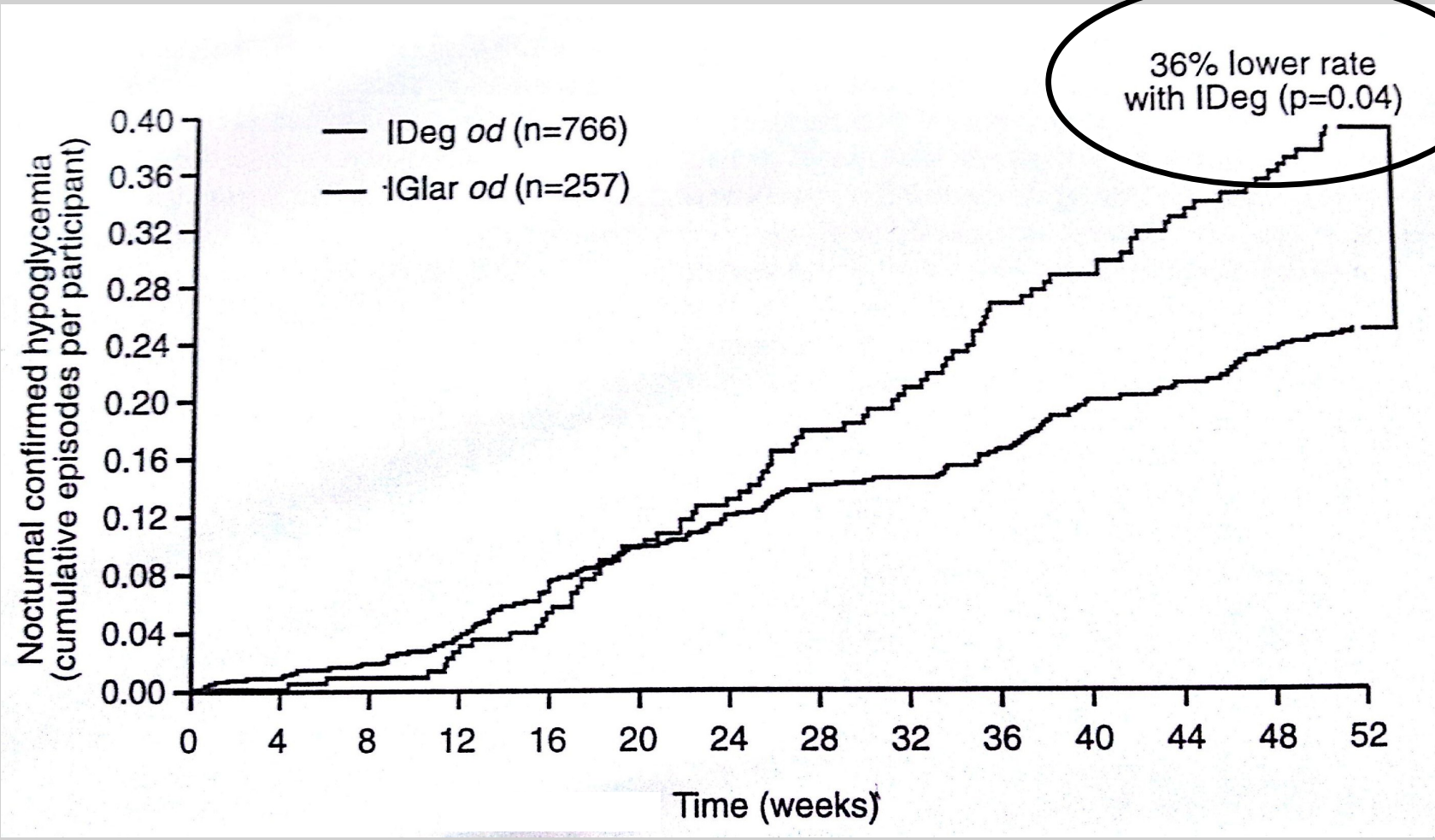
Nocturnal: Episode with time of onset between 23:00 and 05:59 (inclusive)

Garber A *et al. Lancet* 2012;379:1498-507

Comparisons: Estimates adjusted for multiple covariates

Insulin Degludec Versus Insulin Glargine in Insulin-Naive Patients With Type 2 Diabetes



Diabetes Care Publish Ahead of Print, published online October 5, 2012

A 26-week, treat-to-target trial comparing efficacy and safety of a flexible insulin degludec dosing regimen with fixed insulin degludec dosing and insulin glargine, each given once daily ± OAD therapy, in patients with type 2 diabetes mellitus

(BEGIN™: FLEX)

Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

Disegno dello studio

Patients with type 2 diabetes (n=687)

- **IDeg Flexible ±OADs (met, SU, pio) (n=229)**
- **IDeg Fixed ±OADs (met, SU, pio) (n=228)**
- **IGlar ±OADs (met, SU, pio) (n=230)**

0 — **26 weeks**

Randomised 1:1:1
Open label

Inclusion criteria

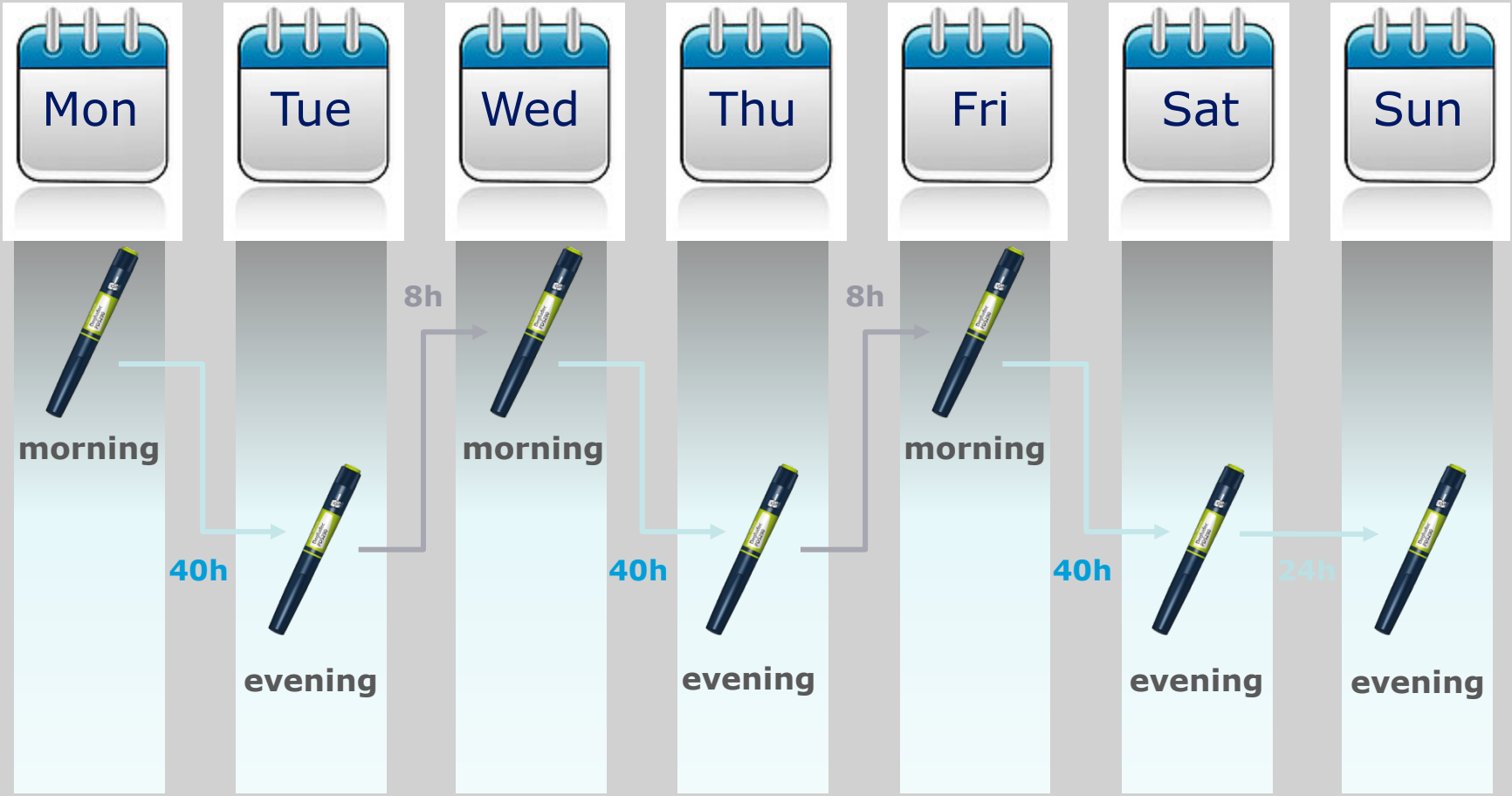
- Type 2 diabetes ≥6 months
- Previously treated with OADs and/or basal insulin
- HbA_{1c}:
  OADs only 7–11%
  Basal insulin ± OADs 7–10%
- BMI ≤40 kg/m^2
- Age ≥18 years

OAD: oral antidiabetic drug
met: metformin
pio: pioglitazone
SU: sulphonylurea
OD: once-daily

Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

IDeg vs IGlar in T2: dose flessibile

Roma,
9-11 novembre 2012



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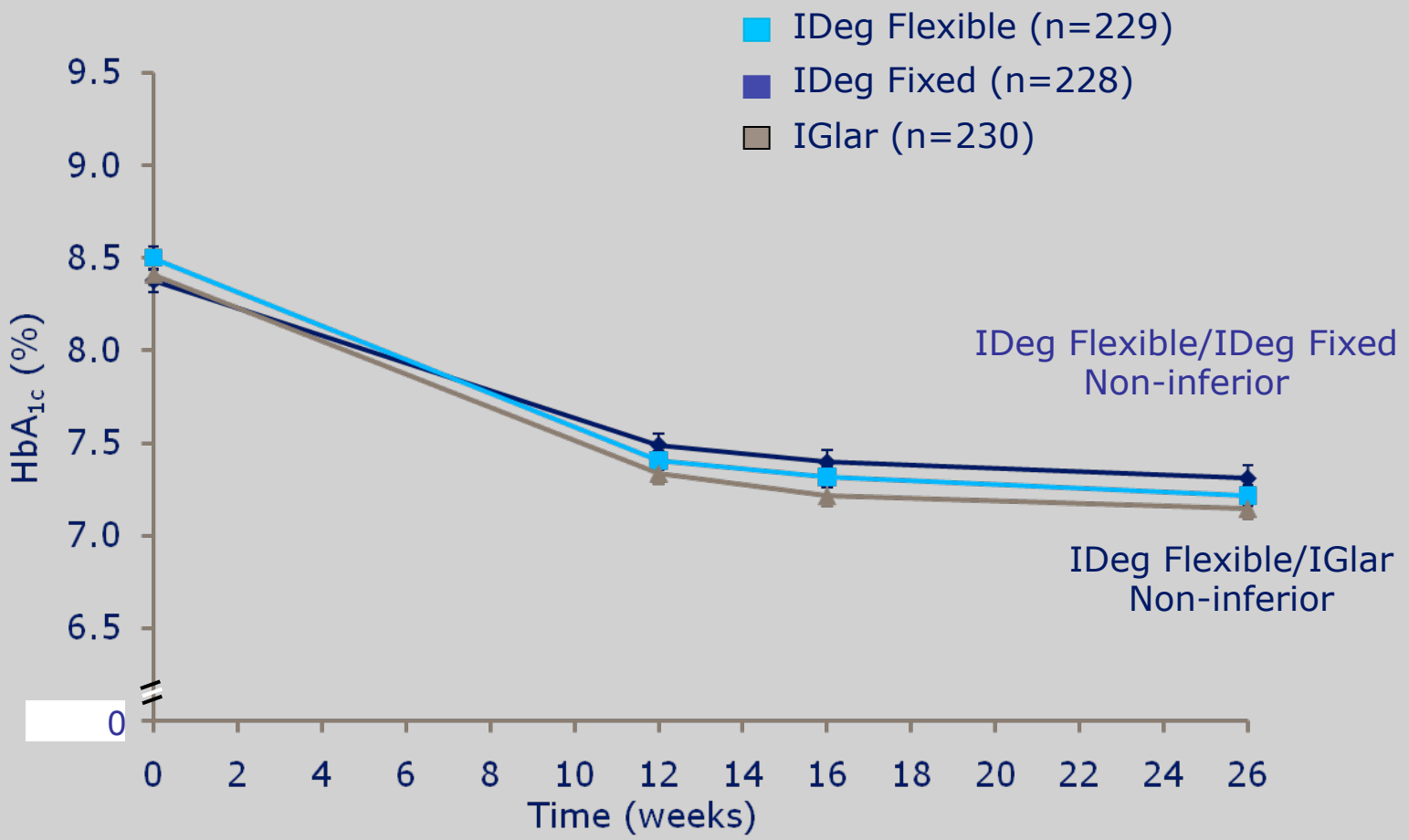
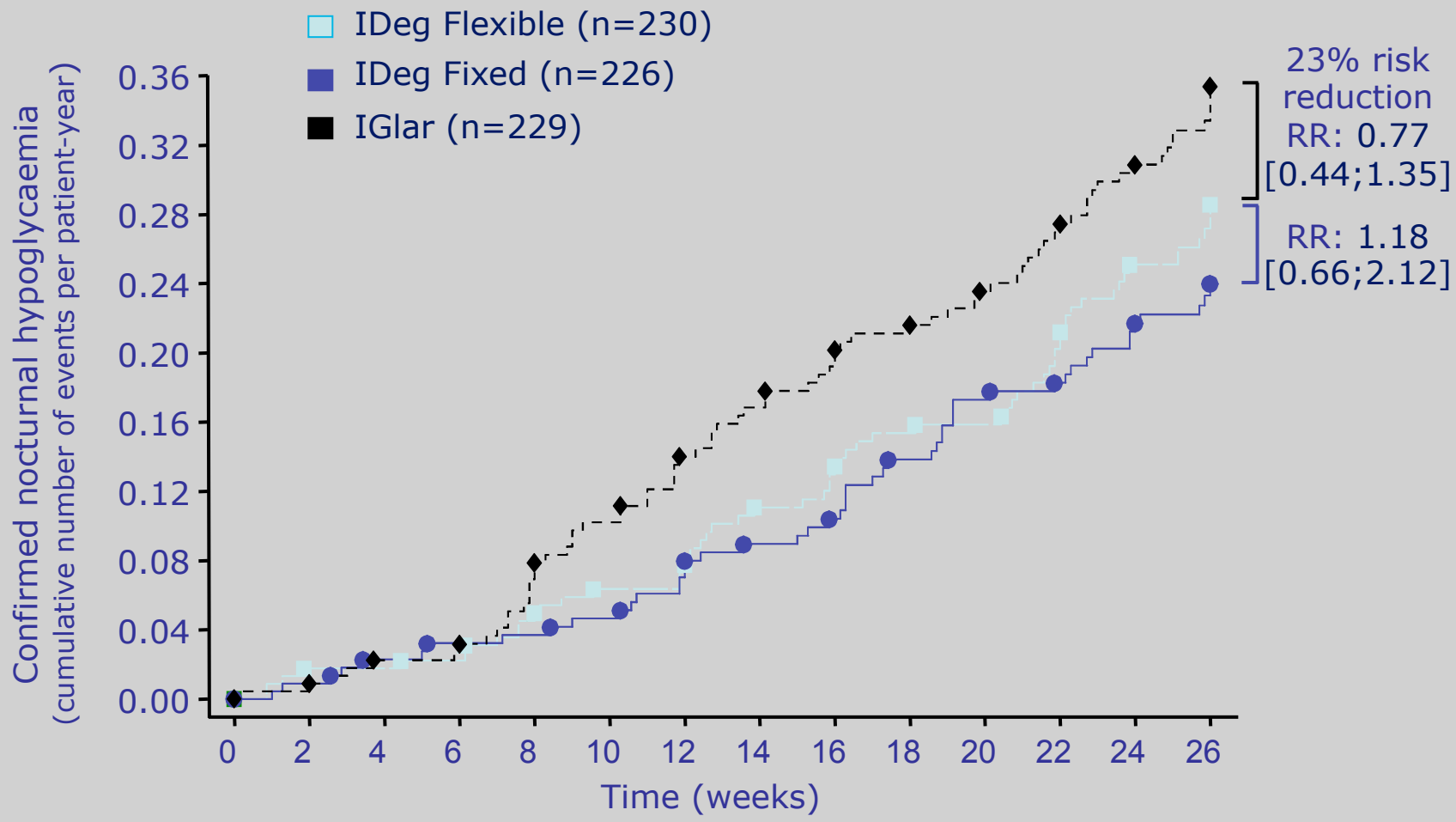
HbA1c



FAS; LOCF
Comparisons: Estimates adjusted for multiple covariates

Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

Ipoglicemie notturne



SAS
Comparisons: Estimates adjusted for multiple covariates

Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

Colpa Del Farmaco

- ✓ Concentrazione costante
- ✓ Priva di picchi
- ✓ Continua per 24 ore
- ✓ Bassa variabilità
- ✓ No aumento di peso
- ✓ No ipoglicemia
- ✓ No induzione mitogenica con i recettori non insulinici

Diabete tipo 1

Roma,
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Table 1 Summary of clinical trials in patients with type 1 diabetes

Study	N	Duration (weeks)	Mean baseline values Age (years); BMI (kg/m^2); HbA_{1c} (%); FPG (mg/dL)	Comparators	Basal insulin target goals FPG (mg/dL)	HbA_{1c}, %		FPG, mg/dL (laboratory measured)	
						Change (±SD) from baseline to end of study	ETD (95% CI)	Change (±SD) from baseline to end of study	ETD (95% CI)
Birkeland et al[‡,29] Phase II M, R, C, O	178	16	Age: 45.8; BMI: 26.9; HbA_{1c}: 8.4; FPG: 178.2	IDeg[†] vs IGlar	72–108	IDeg (A): –0.57 (±0.76) IDeg (B): –0.54 (±0.78) IGlar: –0.62 (±0.68)	IDeg (A) – IGlar: –0.10 (–0.1–0.3) IDeg (B) – IGlar: –0.18 (–0.06–0.4)	IDeg (A): –28.8 (±83.88) IDeg (B): –37.08 (±93.06) IGlar: –9.72 (±78.48)	IDeg (A) vs IGlar: –10.08 (–33.1–13.1) IDeg (B) vs IGlar: –13.68 (–36.7–9.4)
Hirsch et al[*,26,27] Phase III O, R, treat-to-target	548	26	Age: 41; HbA_{1c}: 8.3; FPG: 189	IDegAsp (70/30) vs detemir	Not reported	IDegAsp: –0.73 Detemir: –0.68	IDegAsp – detemir: –0.05 (–0.2–0.08)	IDegAsp: –28.8 Detemir: –43.2	IDegAsp vs detemir: 4.1 (–8.3–16.4)
Russell-Jones et al and Heller et al[*,26,28] Phase III O, R, treat-to-target	629	52	Age: 43; HbA_{1c}: 7.7; FPG: not reported	IDeg vs IGlar	<90	IDeg: –0.4 IGlar: –0.4	IDeg – IGlar: –0.01 (–0.14–0.11)	IDeg: –23 IGlar: –25	IDeg vs IGlar: –5.94 (–18.6–6.5)

Notes: [†]Trials using two formulations of insulin degludec (IDeg (A), 600 µmol/L, 1 unit/6 nmol; IDeg (B), 900 µmol/L, 1 unit/9 nmol); IDeg (B) was discontinued following study (mean dose was decreased over the trial suggesting the starting dose for this higher strength was too high); [‡]Abstract; [*]Full publication.

Abbreviations: M, multicenter; R, randomized; C, controlled; P, parallel-group; O, open-label; BMI, body-mass index; HbA_{1c}, glycosylated hemoglobin; FPG, fasting plasma glucose; IDeg, insulin degludec; IGlar, insulin glargine; IDegAsp is a soluble co-formulation of IDeg (70%) and insulin aspart (IAsp; 30%); ETD, estimated mean treatment difference.

Insulin degludec as an ultralong-acting basal insulin once a day: a systematic review.
Wang F, Surh J, Kaur M. Diabetes Metab Syndr Obes. 2012;5:191-204. Epub 2012 Jul 5.

Ipoglicemie DMT1

Roma,
9-11 novembre 2012

Table 3 Incidence of hypoglycemia in type 1 diabetes

Study	Weeks	Confirmed hypoglycemia < 56 mg/dL (3.0 mmol/L)		Nocturnal hypoglycemia[II]	
		Events/patient-year	vs IGlar (ERR (95% CI))	Events/patient-year	vs IGlar (ERR (95% CI))
Birkeland et al[11,29]	16	47.9, 59.5, 66.2 IDeg (A), IDeg (B), IGlar	IDeg (A): −28% (0.72 (0.52–1.00))[‡] IDeg (B): −10% (0.90 (0.65–1.24))	5.1, 8.8, 12.3 IDeg (A), IDeg (B), IGlar	−58% (0.42 (0.25–0.69))[‡] −29% (0.71 (0.44–1.16))
Russell-Jones et al, Heller et al[24,28]	52	42.5 vs 40.2 IDeg vs IGlar	No Change (1.07 (0.89–1.28))	4.4 vs 5.9	−25% (0.75 (0.59–0.96))[‡]
			vs insulin detemir		
Hirsch et al[†,26,27]	26	39 vs 44 IDegAsp vs detemir	0.9 (0.76–1.09)	3.7 vs 5.7	−37% (0.63 (0.49–0.81))[‡]

Notes: [‡]Statistically significant ($P < 0.05$); [†]Trials using two formulations of insulin degludec (IDeg (A), 600 µmol/L, 1 unit/6 nmol; IDeg (B), 900 µmol/L, 1 unit/9 nmol); [a]IDegAsp (IDeg 70%; IAsp 30%); ERR, estimated rate ratio; IGlar, insulin glargine; [II]Nocturnal hypoglycemic episodes was defined as confirmed hypoglycemia < 56 mg/dL occurring between 2300 and 0559 hours (inclusive)[19,26,27] and not defined in the following studies.[16,28]

Insulin degludec as an ultralong-acting basal insulin once a day: a systematic review.
Wang F, Surh J, Kaur M. Diabetes Metab Syndr Obes. 2012;5:191-204. Epub 2012 Jul 5.

perché

- ✓ Analoghe caratteristiche

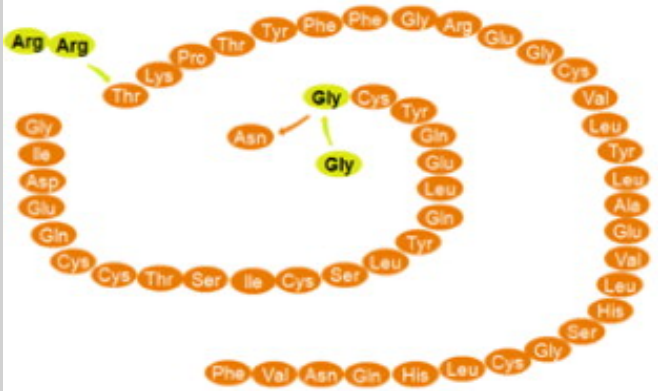
  - ✓ **Efficacia**
  - ✓ **Sicurezza**
  - ✓ **Tollerabilità**
  - ✓ **-- DMT1, DMT2**

- L' Insulina degludec può essere dosata ad ogni ora del giorno ed a differente orario,
- Migliora il controllo glicemico dei pazienti con diabete mellito
- FPG è ridotta in misura maggiore con insulina deglutec a dose fissa rispetto all'insulina glargine
- Il tasso di ipoglicemia non cambia sia con il dosaggio flessibile che con la dose fissa, vi è inoltre una diminuzione delle ipoglicemie notturne rispetto a glargine.
- L'intervallo di somministrazione può essere dalle 8 alle 40 ore, evitando che il paziente possa dimenticare o saltare una dose.

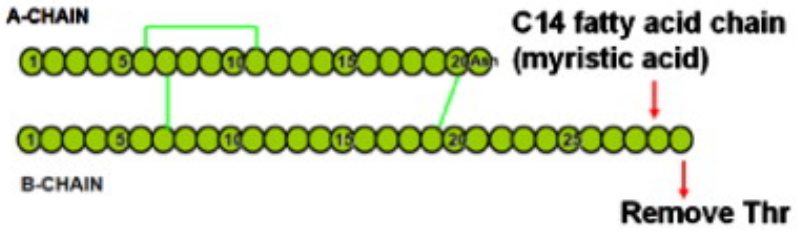
Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

(a)

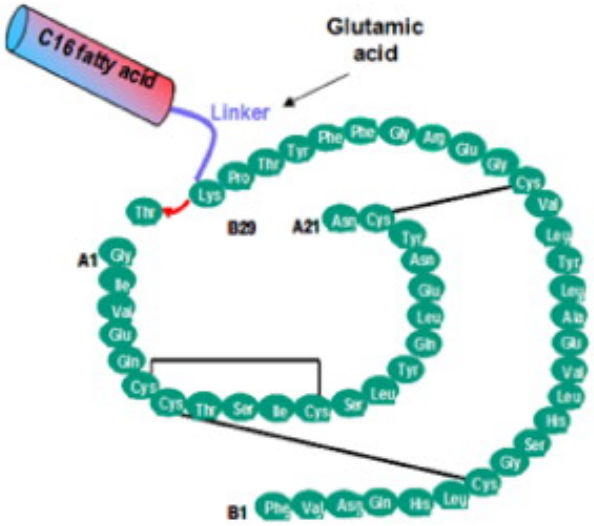
(a) Insulin Glargine



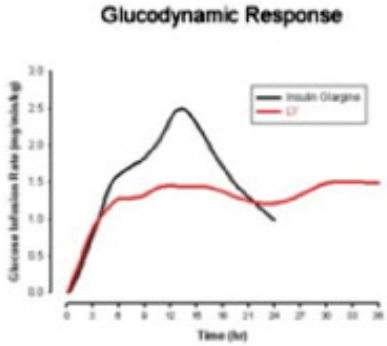
(b) Insulin Detemir



(c) Insulin Degludec



(d) Lilly's Basal Insulin: LY2605541



Derived From Phase 1 Data

Novel engineered insulin goals:

- Less patient variability
- Less hypoglycemia risk
- Better patient control

Status: Phase 1 studies

(b)

www.clinicaltrials.gov

Roma,
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2	Recruiting	A Study of LY2605541 in Participants With Type 2 Diabetes Mellitus **Condition:** Diabetes Mellitus, Type 2 **Interventions:** Drug: LY2605541; Drug: Insulin glargine
3	Recruiting	A Study in Patients With Type 2 Diabetes Mellitus **Condition:** Diabetes Mellitus, Type 2 **Interventions:** Drug: Glargine; Drug: LY2605541
4	Recruiting	A Study in Patients With Type I Diabetes Mellitus **Condition:** Diabetes Mellitus, Type 1 **Interventions:** Drug: Glargine; Drug: LY2605541; Drug: Insulin Lispro
5	Recruiting	A Study in Participants With Type 1 Diabetes Mellitus **Condition:** Diabetes Mellitus, Type 1 **Interventions:** Drug: Glargine; Drug: LY2605541; Drug: Insulin Lispro

PUBMED- LY 2605541

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http://www.ncbi.nlm.nih.gov/pubmed/22787177

A Randomized, Controlled ...

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Diabetes Care. 2012 Jul 11. [Epub ahead of print]

A Randomized, Controlled Study of Once Daily LY2605541, a Novel Long-Acting Basal Insulin, Versus Insulin Glargine in Basal Insulin-Treated Patients With Type 2 Diabetes.

Bergenstal RM, Rosenstock J, Arakaki RF, Prince MJ, Qu Y, Sinha VP, Howey DC, Jacober SJ.

International Diabetes Center at Park Nicollet, Minneapolis, Minnesota.

Abstract

OBJECTIVETo evaluate whether LY2605541 results in lower fasting blood glucose (FBG) versus insulin glargine (GL).RESEARCH DESIGN AND METHODSThis 12-week, randomized, open-label, Phase 2 study enrolled patients with type 2 diabetes (hemoglobin A(1c) [A1C] ≤ 10.5%), taking metformin and/or sulfonylurea with GL or NPH insulin once daily. Patients converted to morning insulin administration during lead-in were randomized 2:1 from GL (n = 248) or NPH insulin (n = 39) to LY2605541 (n = 195) or GL (n = 95) once daily in the morning.RESULTSAt 12 weeks, FBG (mean ± SE) was similar with LY2605541 and GL (118.2 ± 2.0 mg/dL [6.6 ± 0.1 mmol/L] vs. 116.9 ± 2.7 mg/dL [6.5 ± 0.2 mmol/L], P = 0.433) as was A1C (7.0 ± 0.1 vs. 7.2 ± 0.1%, P = 0.279). Intraday blood glucose variability was reduced with LY2605541 (34.4 vs. 39.1 mg/dL [1.9 vs. 2.2 mmol/L], P = 0.031). LY2605541 patients had weight loss (-0.6 ± 0.2 kg, P = 0.007), whereas GL patients gained weight (0.3 ± 0.2 kg, P = 0.662; treatment difference: -0.8 kg, P = 0.001). The incidence and rate of both total hypoglycemia and nocturnal hypoglycemia were comparable between LY2605541 and GL, although, LY2605541 had a 48% reduction in nocturnal hypoglycemia after adjusting for baseline hypoglycemia (P = 0.021). Adverse events were similar across treatments. Alanine aminotransferase and aspartate aminotransferase remained within normal range but were significantly higher with LY2605541 (P ≤ 0.001).CONCLUSIONSIn patients with type 2 diabetes, LY2605541 and GL had comparable glucose control and total hypoglycemia rates, but LY2605541 showed reduced intraday variability, lower nocturnal hypoglycemia, and weight loss relative to GL.

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Mealtime 50/50 basal + prandial insulin analogue mixture with a l [Clin Ther. 2007]

Combination of oral antidiabetic agents with basal insulin [J Am Geriatr Soc. 2007]

Triple therapy in type 2 diabetes: insulin glargine or rosiglita: [Diabetes Care. 2006]

Review Insulin glargine: a systematic review of a long-acting in [Clin Ther. 2003]

Review Dosing of insulin glargine in the treatment of type 2 diabe [Clin Ther. 2007]

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1. **Insulin Degludec** Versus Insulin Glargine in Insulin-Naive Patients With Type 2 Diabetes: A 1-year, randomized, treat-to-target trial (BEGIN Once Long).
Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, Endahl L, Mathieu C; On behalf of the NN1250-3579 (BEGIN Once Long) Trial Investigators.
Diabetes Care. 2012 Oct 5. [Epub ahead of print]
PMID: 23043166 [PubMed - as supplied by publisher]
Related citations

2. Design of Non-Standard Insulin Analogs for the Treatment of Diabetes Mellitus.
Pandyarajan V, Weiss MA.
Curr Diab Rep. 2012 Sep 16. [Epub ahead of print]
PMID: 22983891 [PubMed - as supplied by publisher]
Related citations

3. IDegAsp : a novel soluble insulin analogs combination.
Ma Z, Parkner T, Christiansen JS, Laursen T.
Expert Opin Biol Ther. 2012 Nov;12(11):1533-40. doi: 10.1517/14712598.2012.722203. Epub 2012 Sep 4.
PMID: 22946603 [PubMed - in process]
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- Tresiba® (insulin degludec) and Ryzodeg® (insulin degludec/insulin aspart) receive positive opinions from the European regulatory authorities (19 October 2012)
- IDegLira (NN9068)

Conclusioni

- Gli analoghi attuali sono efficaci ma avremo a disposizione ulteriori analoghi.
- I potenziali miglioramenti includono:
- un nuovo analogo che avrà un profilo flat
- minima variabilità interindividuale
- La chiave di svolta del prossimo futuro dipende dal corretto utilizzo degli analoghi attuali con le nuove insuline,
- che hanno il vantaggio di essere dosate
  - » in maniera flessibile
  - » riducono il rischio di ipoglicemia.