# INSULINA DEGLUDEC

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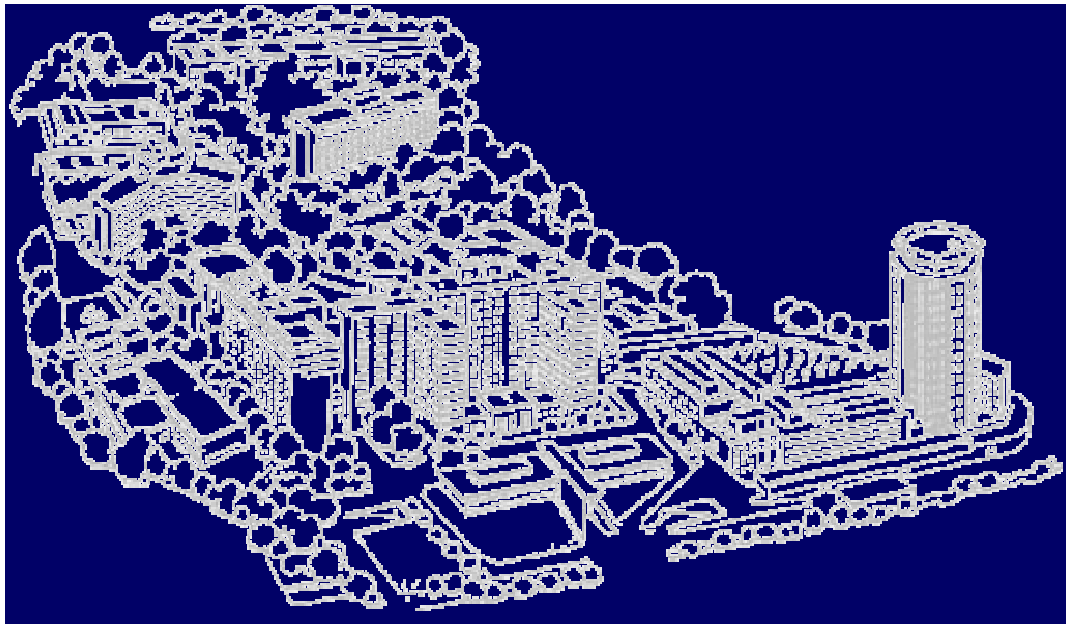


Vall d'Hebron
Hospital

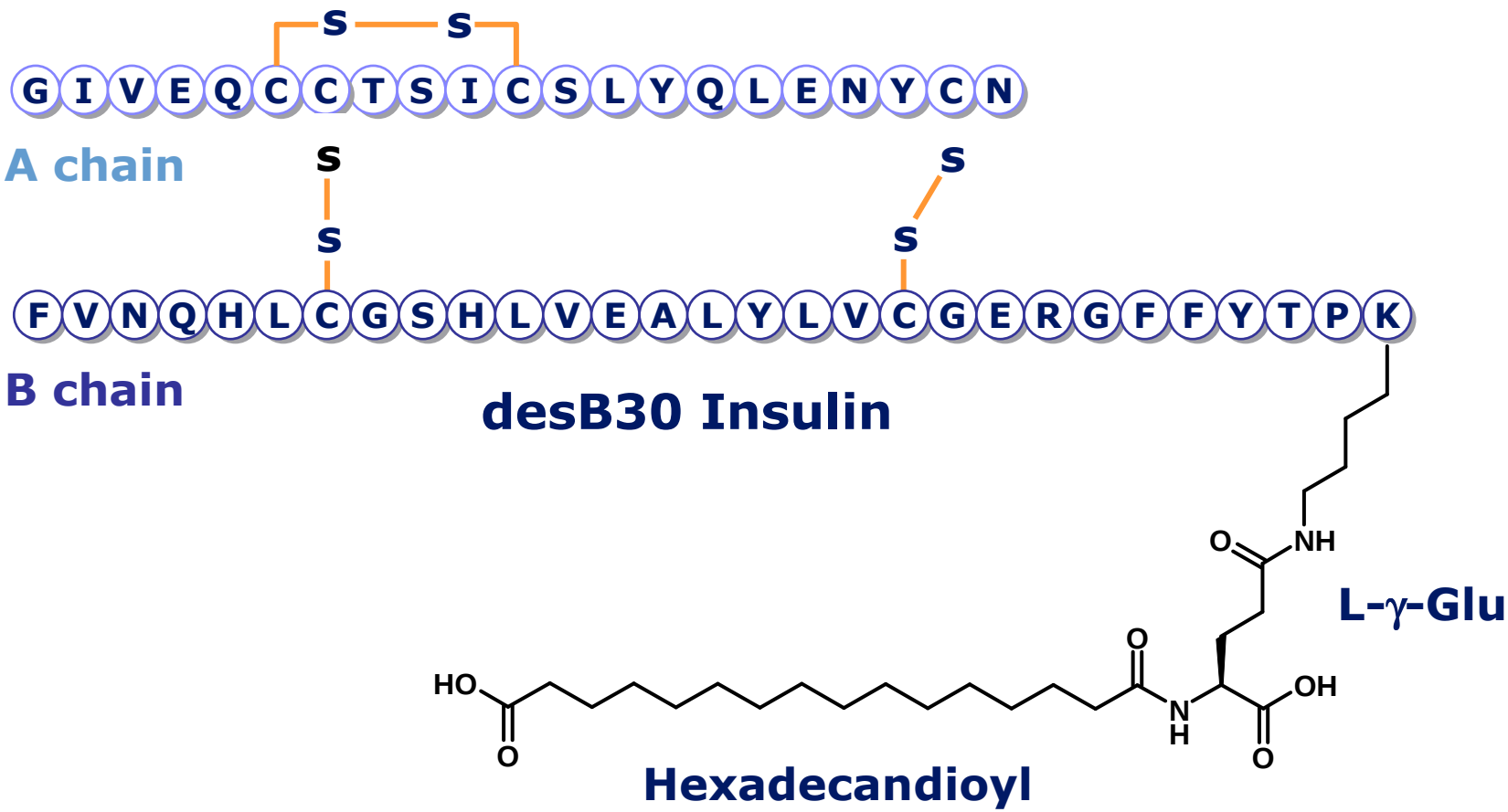
# ¿Cuál sería la insulina de acción lenta ideal?

- Efectiva y con larga duración de acción → Control de glucemia basal con una sola inyección
- Seguridad → Baja tasa de hipoglucemias
- Poca variabilidad → Niveles de glucosa estables
- Adaptabilidad al estilo de vida del paciente
- Dispositivo de administración de fácil manejo

# TRESIBA®

insulina degludec

# Insulin degludec : Structure

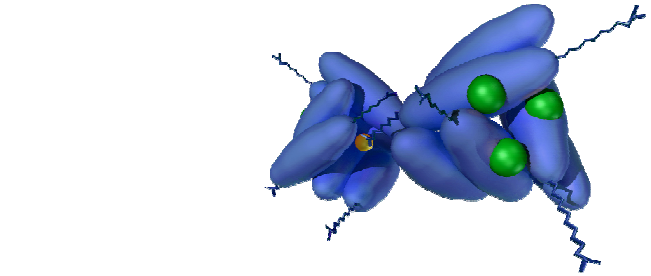




Jonassen et al. Diabetes 2010; 59 (Suppl. 1): A11 (39-OR)
Jonassen et al. Diabetologia 2010;53 (Suppl 1): S388 (Poster 972)

# Insulin degludec association

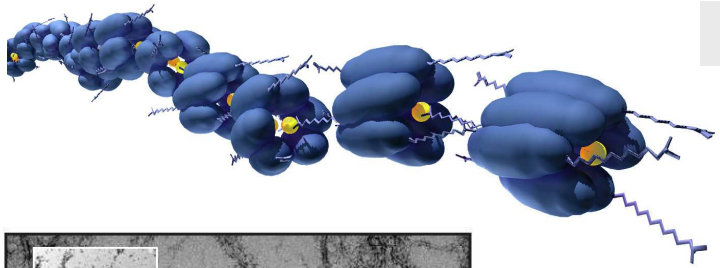
## Proposed steps from injection to absorption



**Insulin degludec di-hexamers**

**Injected formulation**

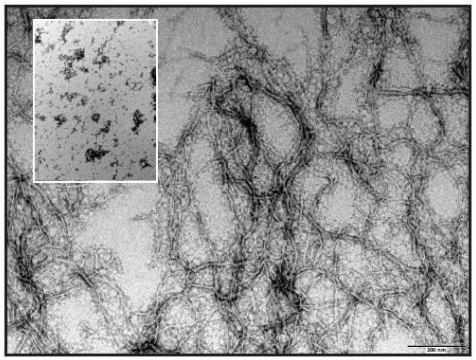
**-Phenol** ↓ ↑ **+Phenol**

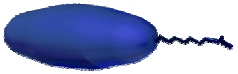


**Insulin degludec multi-hexamers**

**s.c. depot formation**

**-$Zn^{2+}$** ↓ ↑ **+$Zn^{2+}$**





**Insulin degludec monomers**

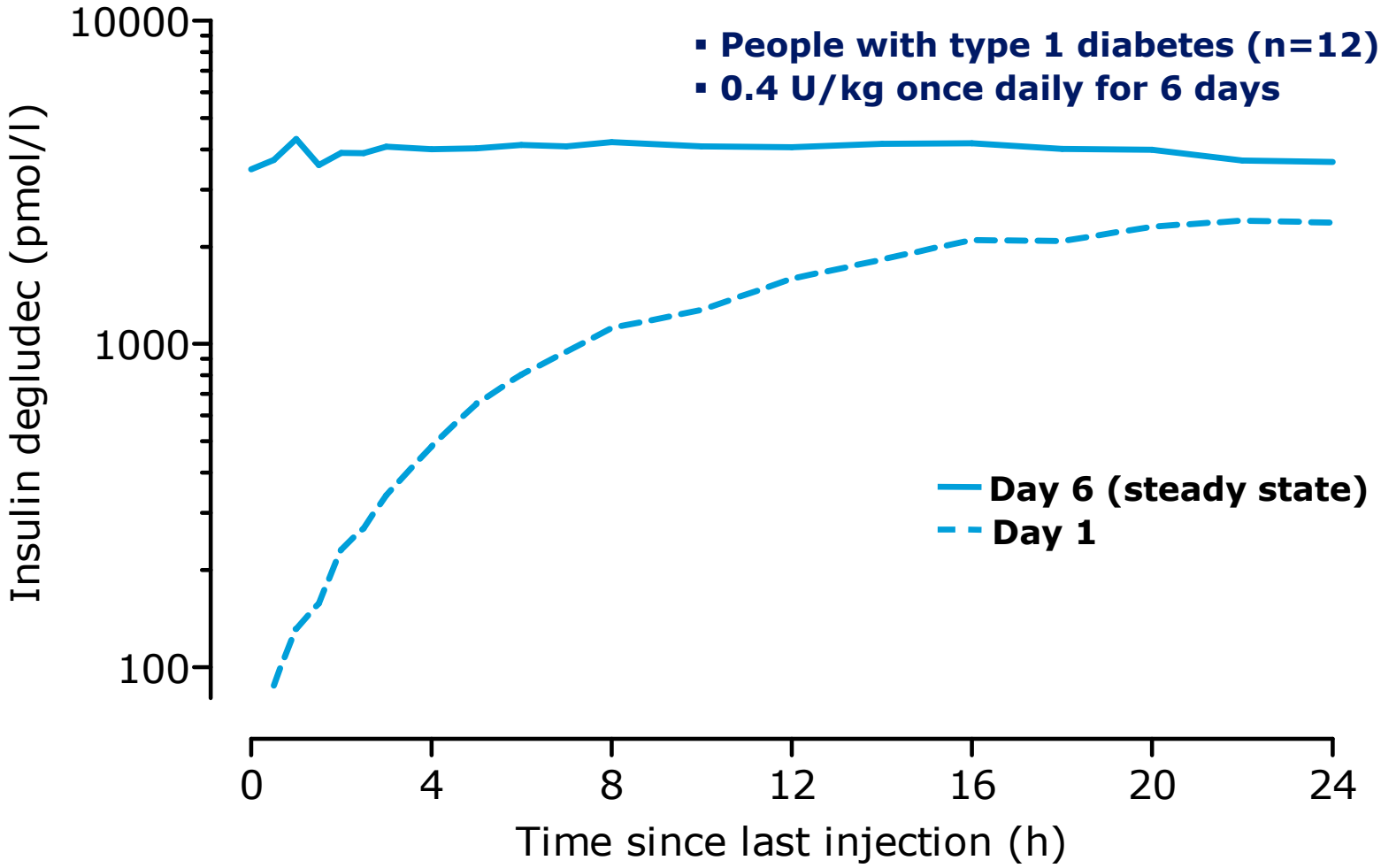
**Absorption**

**[ Phenol; $Zn^{2+}$ ]**


**Jonassen et al. Diabetes 2010; 59 (Suppl. 1): A11 (39-OR)**
**Jonassen et al. Diabetologia 2010;53 (Suppl 1): S388 (Poster 972)**

# Insulin degludec:pharmacokinetic profile

## Single dose and steady state

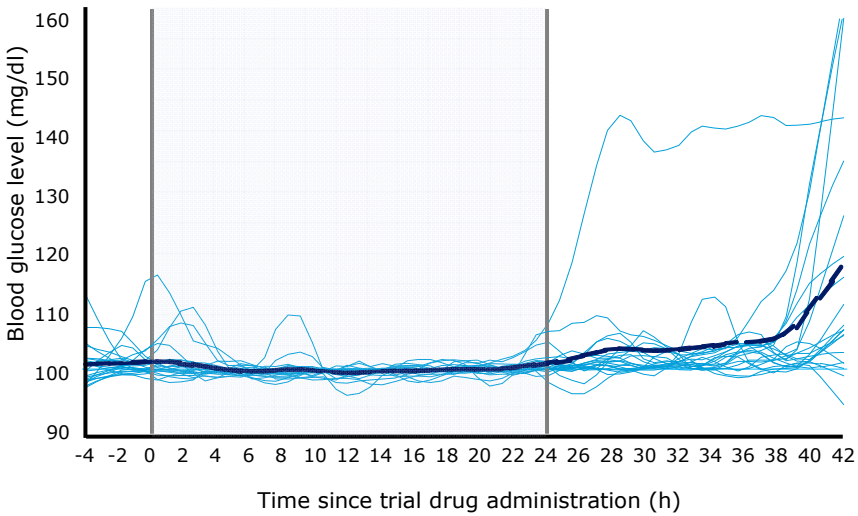



Jonassen et al. Diabetes 2010; 59 (Suppl. 1): A11 (39-OR)
Jonassen et al. Diabetologia 2010;53 (Suppl 1): S388 (Poster 972)

# Degludec shows longer duration of action

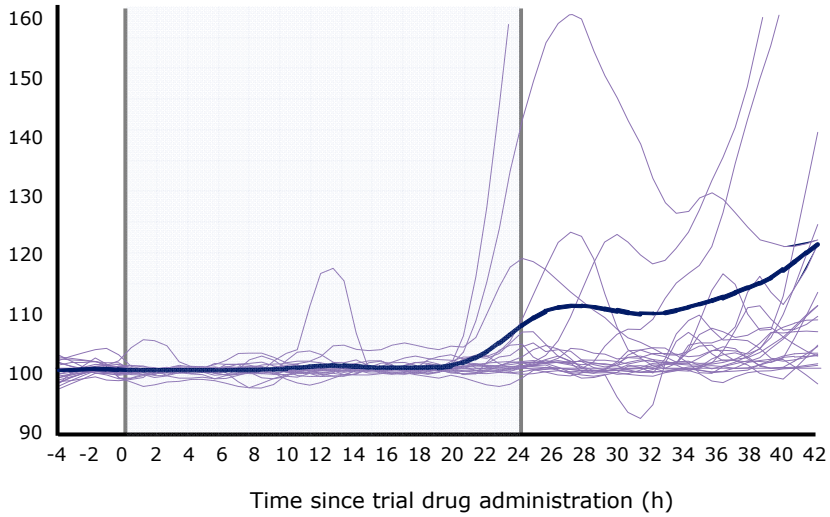
Earlier glucose escape with glargine

IDeg
0.57 U/kg




dose

IGlar
0.60 U/kg

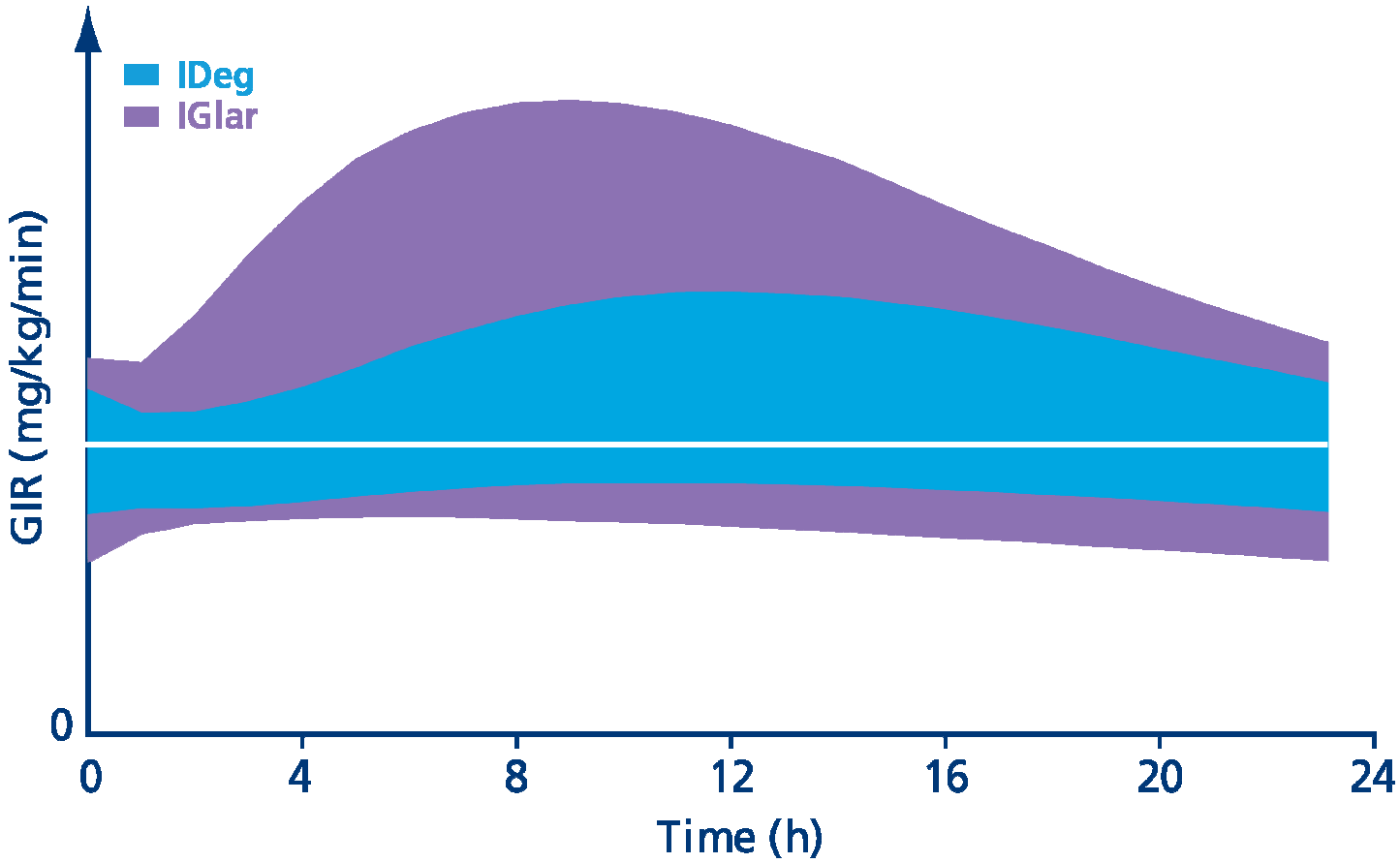



dose

Heise *et al.* IDF 2011:P-1444; *Diabetologia* 2011;54(Suppl. 1):S425; *Diabetes* 2011;60(Suppl. 1A):LB11

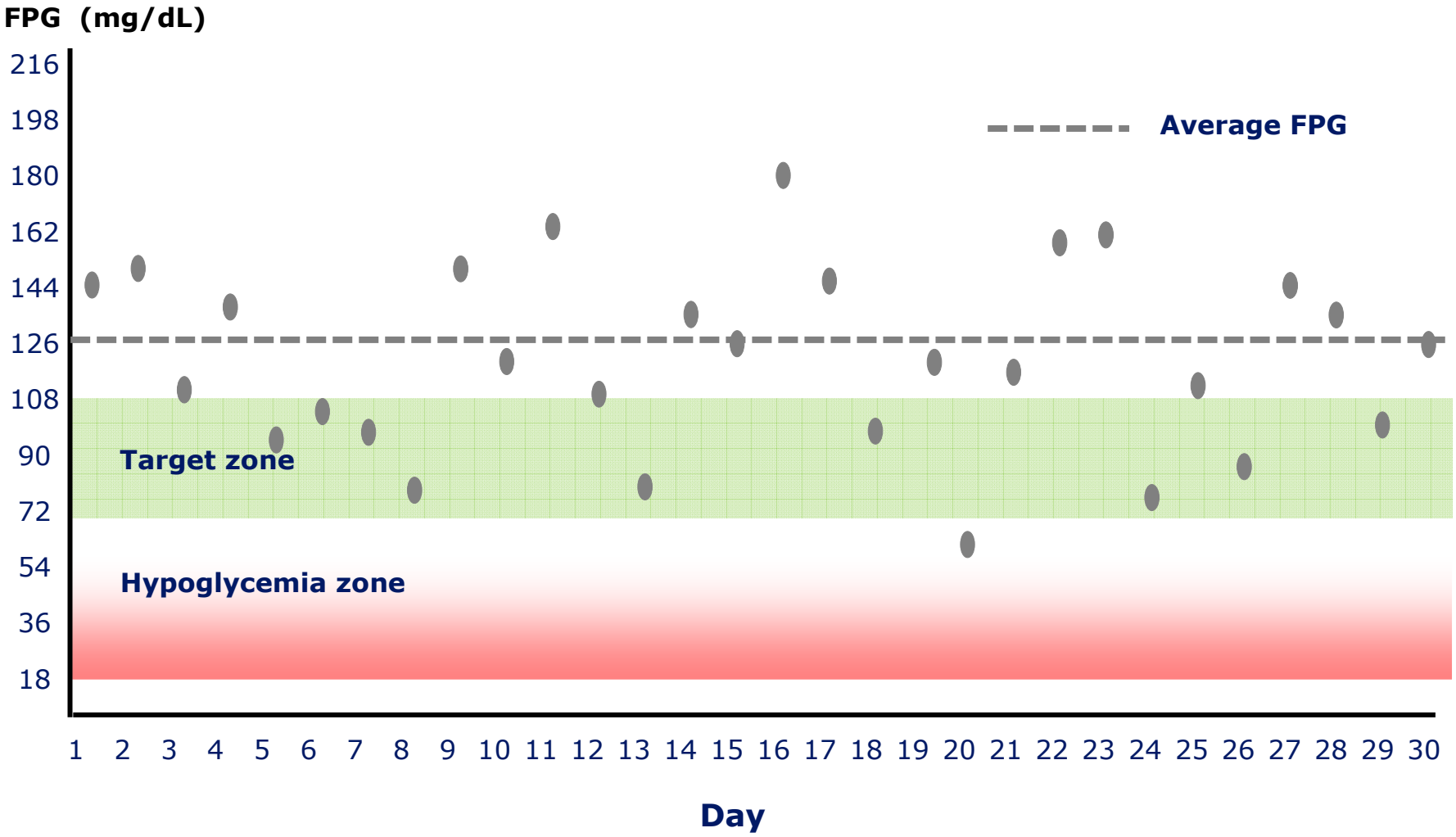
# Insulin degludec: Less variability

## Potential to decrease hypo- and hyperglycaemia

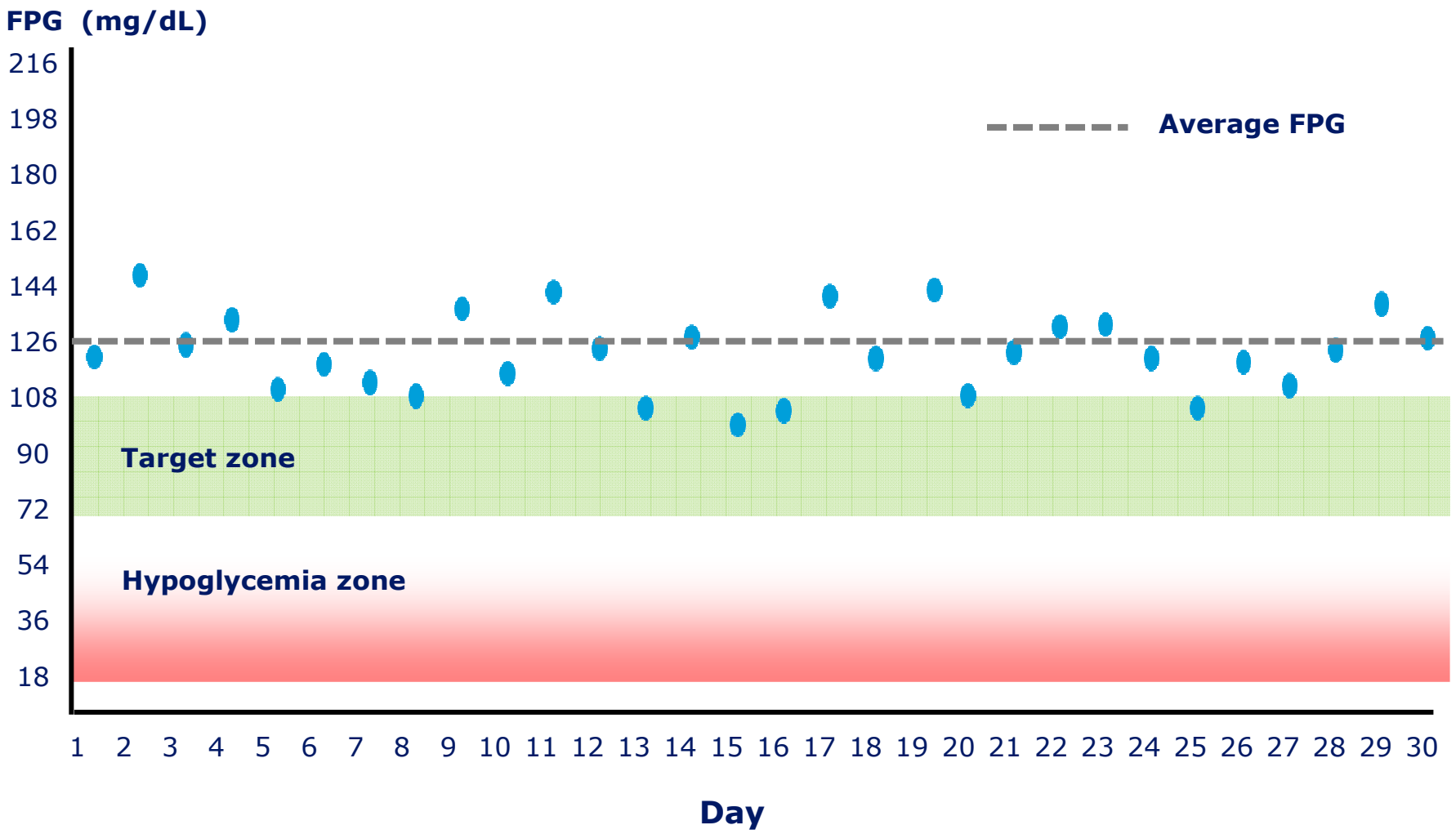



Heise et al. Diabetologia 2010;53(Suppl.1):S387 (Poster 971)

# Targeting fasting plasma glucose: currently available insulins



# Targeting fasting plasma glucose



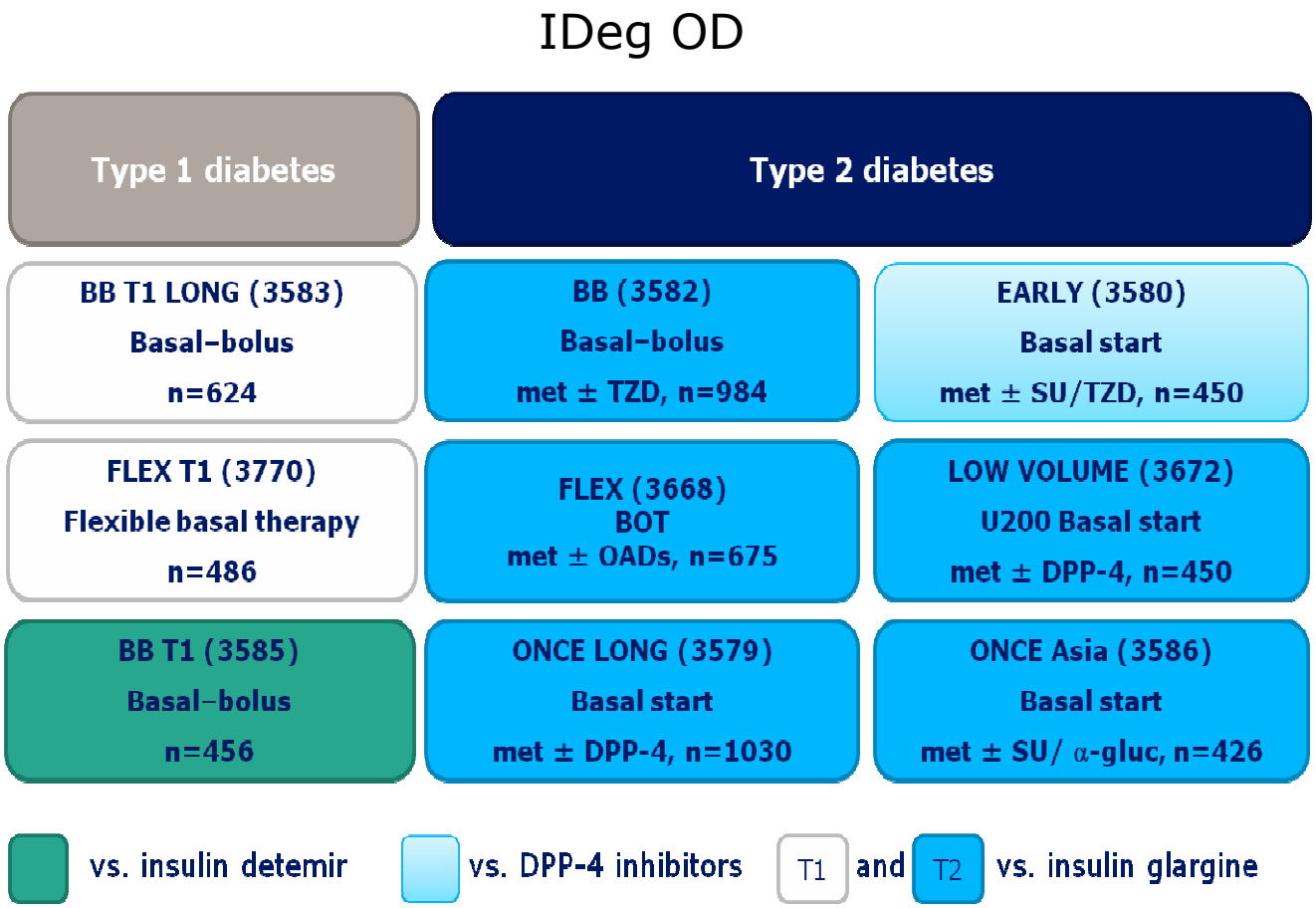
# Insulin degludec has lower relative affinity for the IGF-1 receptor compared to human insulin.

| Parameter | Human Insulin | B10Asp (X10) (% relative to Human Insulin) | Insulin Degludec (% relative to Human Insulin) |
|---|---|---|---|
| Insulin receptor binding | 100 | 205 | 15 |
| IGF-1 receptor binding | 100 | 587 | 2 |
| Insulin receptor binding off-rate | 100 | 14 | ~100 |
| Cellular metabolic potency | 100 | 207 | 8-21* |
| Cellular mitogenic potency | 100 | 975 | 5-9# |
| Mitogenic/metabolic potency | 1 | ~5 | ≤1 |

* Range from various cell types: Rat liver cells & MCF-7 tested with no added albumin
# Range from various cell types: HMEC, MCF-7, L6-HIR, COLO-205 tested with no added albumin
Data for X10 from Kurtzhals *et al*. *Diabetes* (2000) 49:999-1005

Nishimura et al. Diabetes 2010; 59 (Suppl. 1): A375 (1406-P)
Nishimura et al. Diabetologia 2010;53 (Suppl. 1):S388 (Poster 974)

# Degludec once-daily phase 3a



# Phase 3a titration algorithm in T2D: insulin degludec and insulin glargine

| Pre-breakfast plasma glucose[a] | | Adjustment |
|---|---|---|
| mmol/L | mg/dL | U |
| <3.1[b] | <56[b] | –4<br>(If dose >45 U, reduce by 10%) |
| 3.1–3.9[b] | 56–70[b] | –2<br>(If dose >45 U, reduce by of 5%) |
| 4.0–4.9 | 71–89 | 0 |
| 5.0–6.9 | 90–125 | +2 |
| 7.0–7.9 | 126–143 | +4 |
| 8.0–8.9 | 144–161 | +6 |
| ≥9.0 | ≥162 | +8 |

[a] Mean of 3 consecutive days' measurements for up titration
[b] Unless there is obvious explanation for the low value, such as a missed meal

# I. Degludec una vez al día vs. I Glargina

## Estudios de Fase III

- Niveles similares de reducción de la HbA1c
- Mayor reducción de glucosa plamática en ayunas
- Menos hipoglucemias (especialmente las nocturnas [26-36%])

## Otras ventajas

- Flexibilidad (amplia ventana en la hora de administración)
- Presentación 200 UI/ml (22% de los T2DM requieren más de 80 UI/día)
- Dispositivo de fácil manejo (sólo pulsando un botón se libera carga de insulina)
- Combinación con análogo de acción rápida ⟶ Degludec Plus

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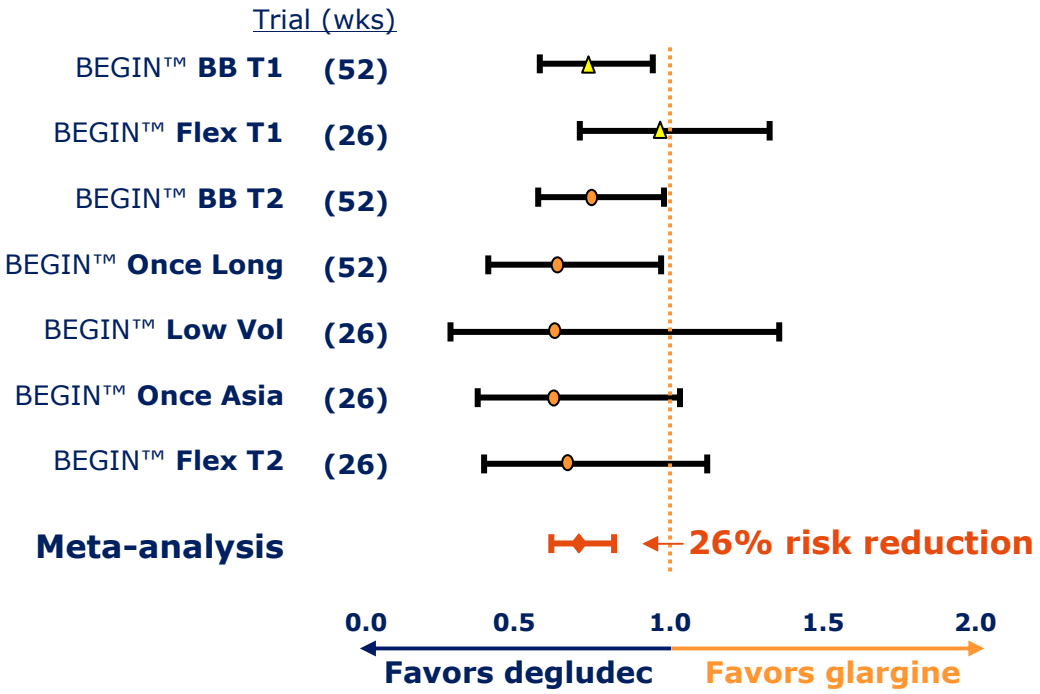
# Hypoglycemia results consistent with BEGIN™ pre-specified meta-analyses

## Nocturnal hypoglycemia

(all degludec vs glargine studies, T1 and T2)




## Reduction in confirmed hypoglycemia with degludec

(all degludec vs glargine studies)

| | |
|---|---|
| **Nocturnal** | |
| T1 and T2 | **26%*** |
| T2 basal only | **36%*** |
| **Overall** | |
| T1 and T2 | **9%*** |
| T2 basal only | **17%*** |

*: Statistically significant improvement

The **meta-analyses** were pre-specified as part of the BEGIN™ phase 3a trials for insulin degludec

Reference: http://www.novonordisk.com/images/investors/investor_presentations/2011/CMD2011/04_Diabetes_treatment_tomorrow_CMD2011.pdf

# Hypoglycemia in T2DM

## The magnitude of the problem

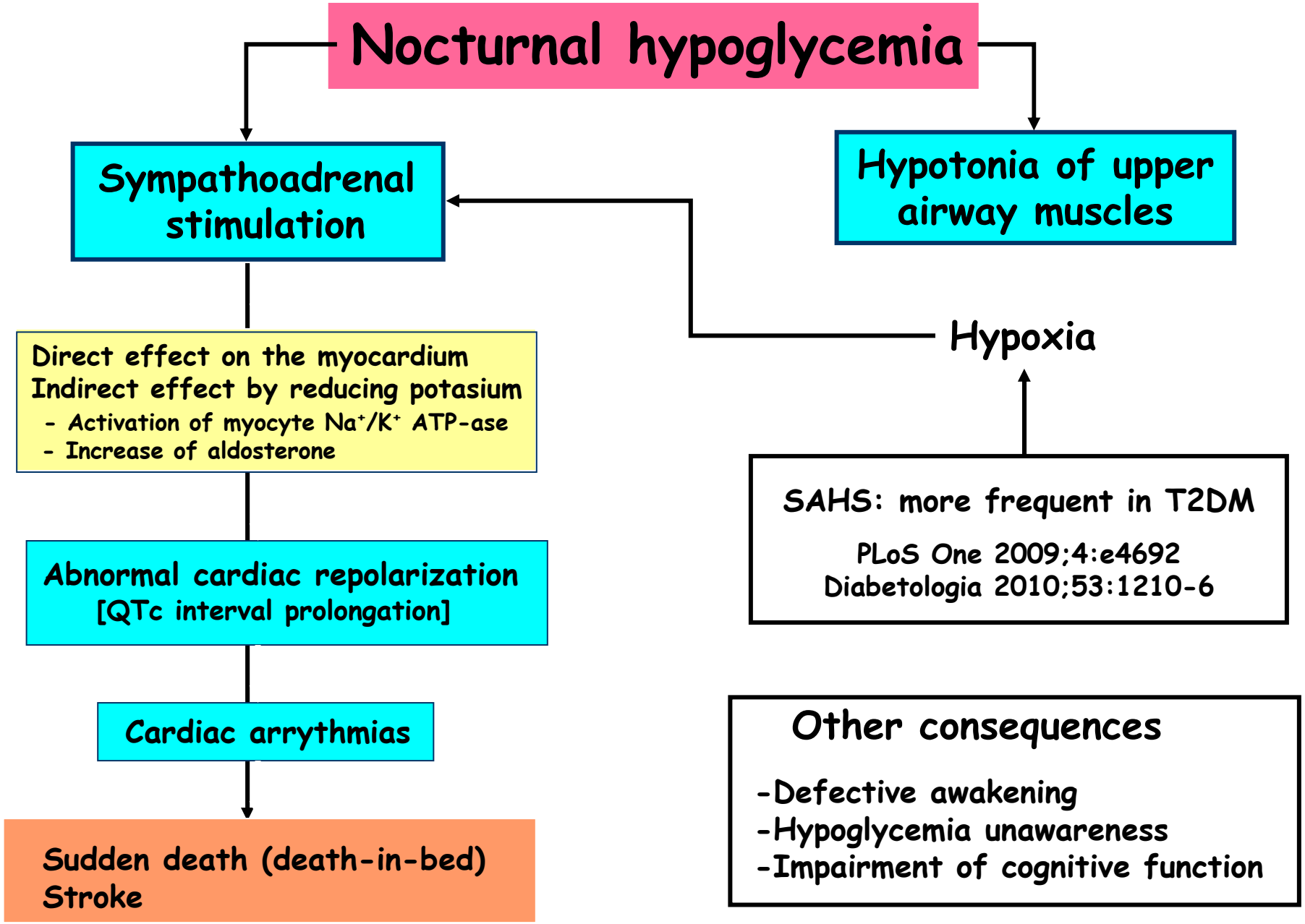
- Hypoglycemia is less frequent in T2DM than in T1DM.

- Because the prevalence of T2DM is ~20-fold greater than that T1DM and beacuse many patients ultimately require treatment with insulin, most episodes of hypoglycemia, including severe hypoglycemia, occur in persons with T2DM

*Cryer et al. JCEM 2009;94:709-728*

## The meaning of nocturnal hypoglycemia in T2DM

- Little is known about the frequency of and responses of nocturnal hypoglycemia in T2DM. However it seem clear that episodes of nocturnal hypoglycemia are particularly dangerous in older population


Nocturnal hypoglycemia
Sympathoadrenal stimulation
Hypotonia of upper airway muscles
Direct effect on the myocardium
Indirect effect by reducing potasium
- Activation of myocyte Na+/K+ ATP-ase
- Increase of aldosterone
Hypoxia
SAHS: more frequent in T2DM
PLoS One 2009;4:e4692
Diabetologia 2010;53:1210-6
Abnormal cardiac repolarization
[QTc interval prolongation]
Cardiac arrythmias
Other consequences
-Defective awakening
-Hypoglycemia unawareness
-Impairment of cognitive function
Sudden death (death-in-bed)
Stroke

# SUBSTUDIES IN TYPE 2 DIABETIC POPULATION

## IDeg vs IGlar in T2DM requiring high doses (>60 UI of basal insulin)

Lower rates of both overall (21%) and nocturnal confirmed hypoglycaemia (52%) with IDeg vs. IGlar

## Diabetes duration > 10 years for IDeg vs IGlar in T2DM

21% lower rate of confirmed hypoglycaemia (*p*=0.004) and 29% lower rate of nocturnal confirmed hypoglycaemia (*p*=0.0057) with IDeg vs. IGlar

## BMI > 30 kg/m$^2$ for IDeg vs IGlar in T2DM

22% lower rate of confirmed hypoglycaemia (*p*=0.0021) and 37% lower rate of nocturnal hypoglycaemia (*p*=0.0003) with IDeg vs. IGlar

# Impact of severe hypoglycaemic event

**Cost of severe hypoglycaemic event in Spain: €2.882**

**After a major hypoglycaemic episode:**

**20,0% (T1) and 26,3% (T2) stayed home the next day**

**63,6% (T1) and 84,2% (T2) feared future hypoglycaemia**

**78,2% (T1) and 57,9% (T2) changed their dose**

***Ministerio de Sanidad, Politica Social e Igualdad - Grupos Relacionados de Diagnóastico (GRD) - 2008, Leiter et al. (2005)***

# Impact of non-severe hypoglycaemic event

**Not as well-established as the severe hypoglycaemic events**

**88% of all hypoglycaemic events are non-severe**

**Impact assessed in a survey of 1,404 respondents**

***Brod et al. The Impact of Non-Severe Hypoglycaemic Events on Work Productivity and Diabetes Management Value in Health, 14(5) 2011, 665-671***

# Impact of NSHE on productivity per month

| | NSHE during work hrs | NSHE outside work hrs | Nocturnal NSHE |
|---|---|---|---|
| **NSHE** (N) | 963 | 1,046 | 612 |
| **Missed work time** (%) | 18.3% | 14.3% | 22.7% |
| **Missed work time** (mean hours) | 9.9 hours | 12.6 hours | 14.7 hours |
| **Missed a meeting/ appointment or deadline** (%) | 23.8% | 16.4% | 31.8% |

# Diabetes management after last NSHE

| | |
|---|---|
| **Extra BG measurements 7 days after NSHE** (mean) | 5.6 |
| **Contacted a health care professional** (%) | 24.9% |
| **Decrease in dose** (%) | 25.0% |
| **Total decrease in dose** (mean) | 6.5 units |
| **Days decreased** (mean) | 3.6 days |

***Brod et al. The Impact of Non-Severe Hypoglycaemic Events on Work Productivity and Diabetes Management Value in Health, 14(5) 2011, 665-671***

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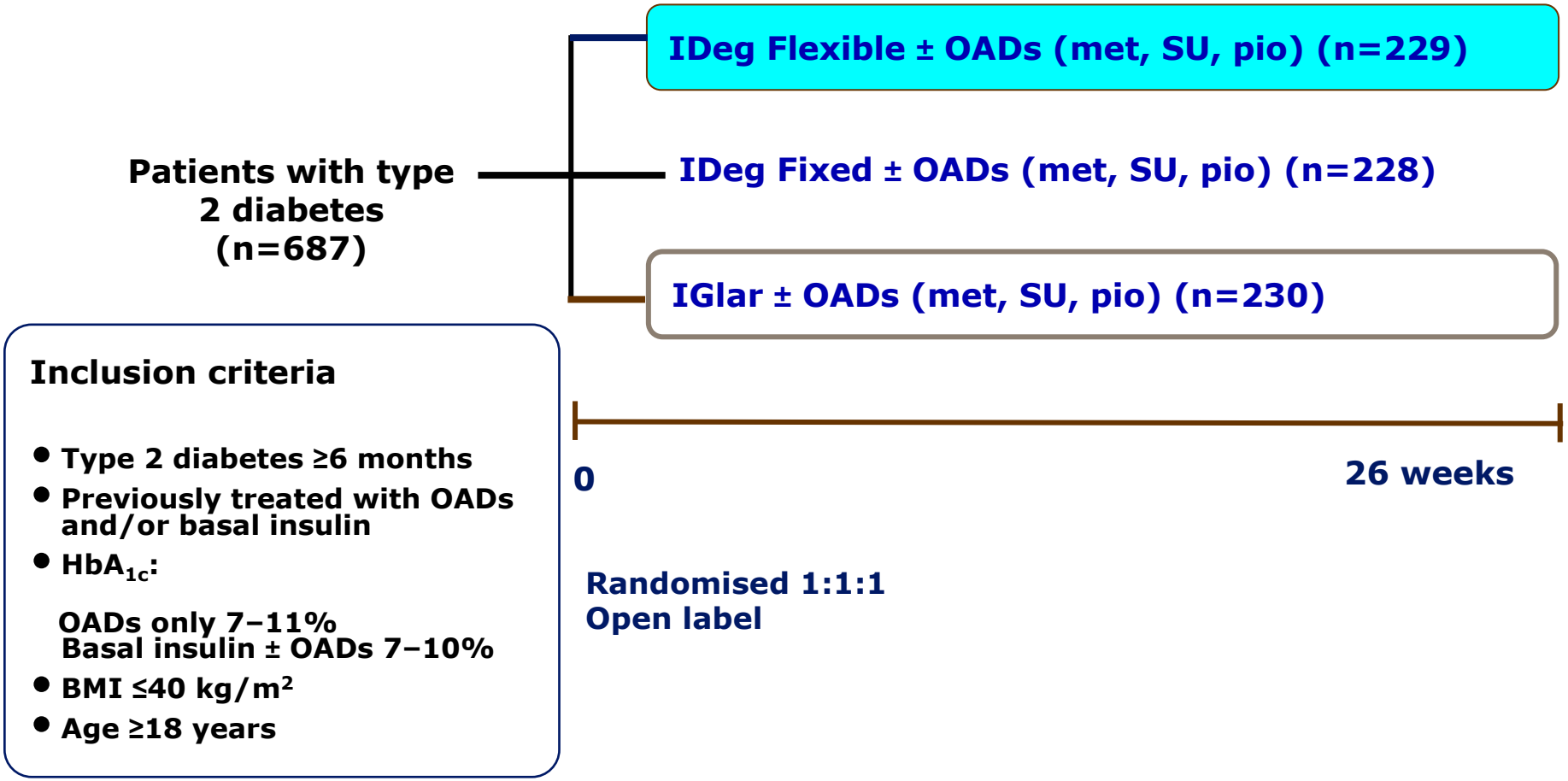
# Insulin omission/non-adherence
## Days per month by country

| Country | % with ≥1 day of insulin omission/non-adherence per month | Unadjusted days of insulin omission/non-adherence per month | Adjusted days of insulin omission/non-adherence per month† |
|---|---|---|---|
| China | 33.5% | 1.35 | 1.96 |
| France | 19.9% | 0.62 | 0.62 |
| Germany | 39.7% | 0.74 | 1.34 |
| Japan | 44.0% | 1.29 | 2.30 |
| Spain | 22.8% | 0.84 | 0.87 |
| Turkey | 23.9% | 1.36 | 6.01* |
| UK | 41.5% | 1.18 | 1.63 |
| USA | 42.0% | 1.56 | 2.34 |
| Overall | 34.6% | 1.18 | – |

†Adjusted for all patient characteristics; adjustment maintains lowest rate (France) and adjusts other countries relative to lowest *$p<0.05$

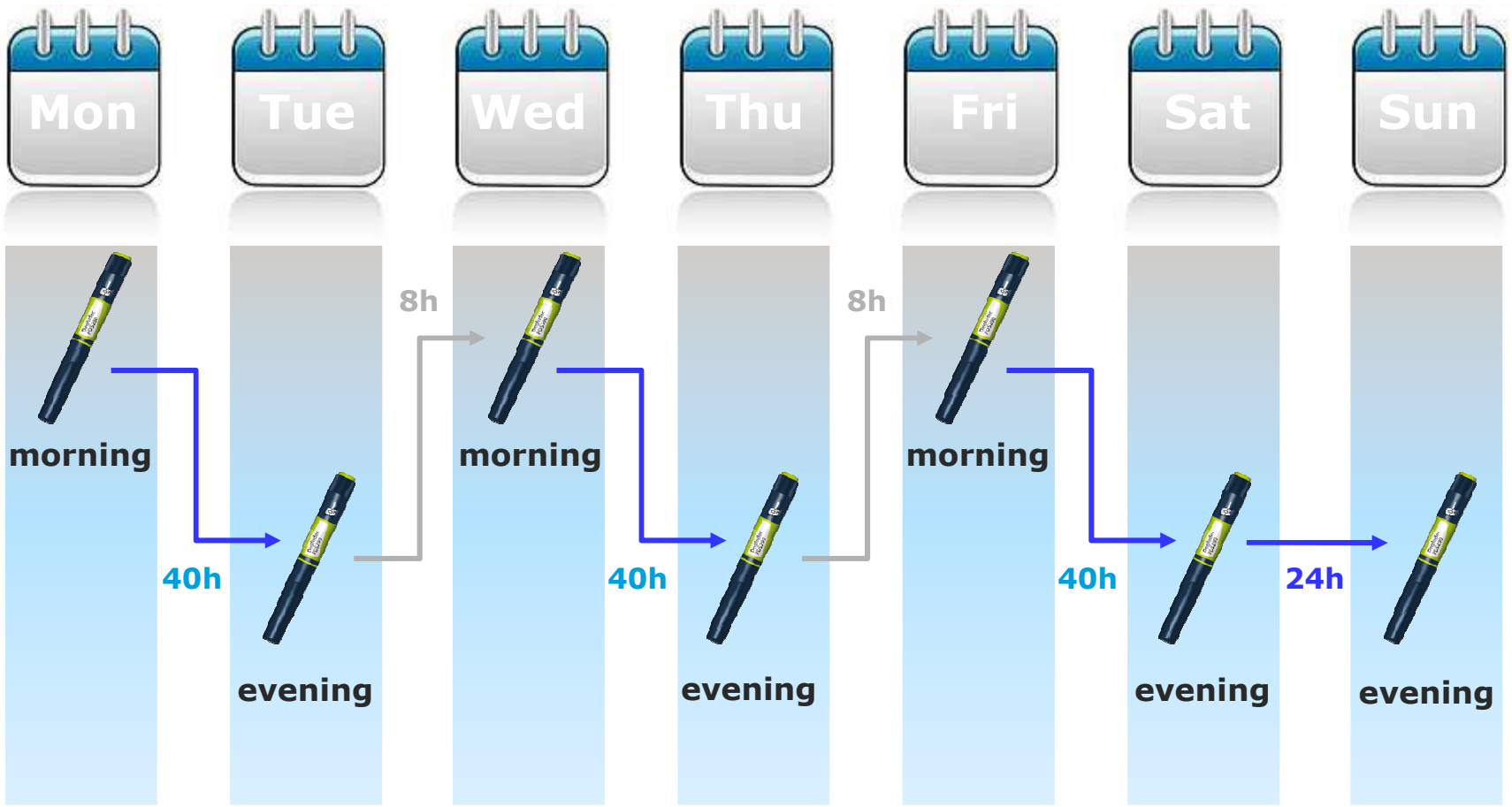
*Peyrot et al. ADA 2011; 830-P*

# Study design



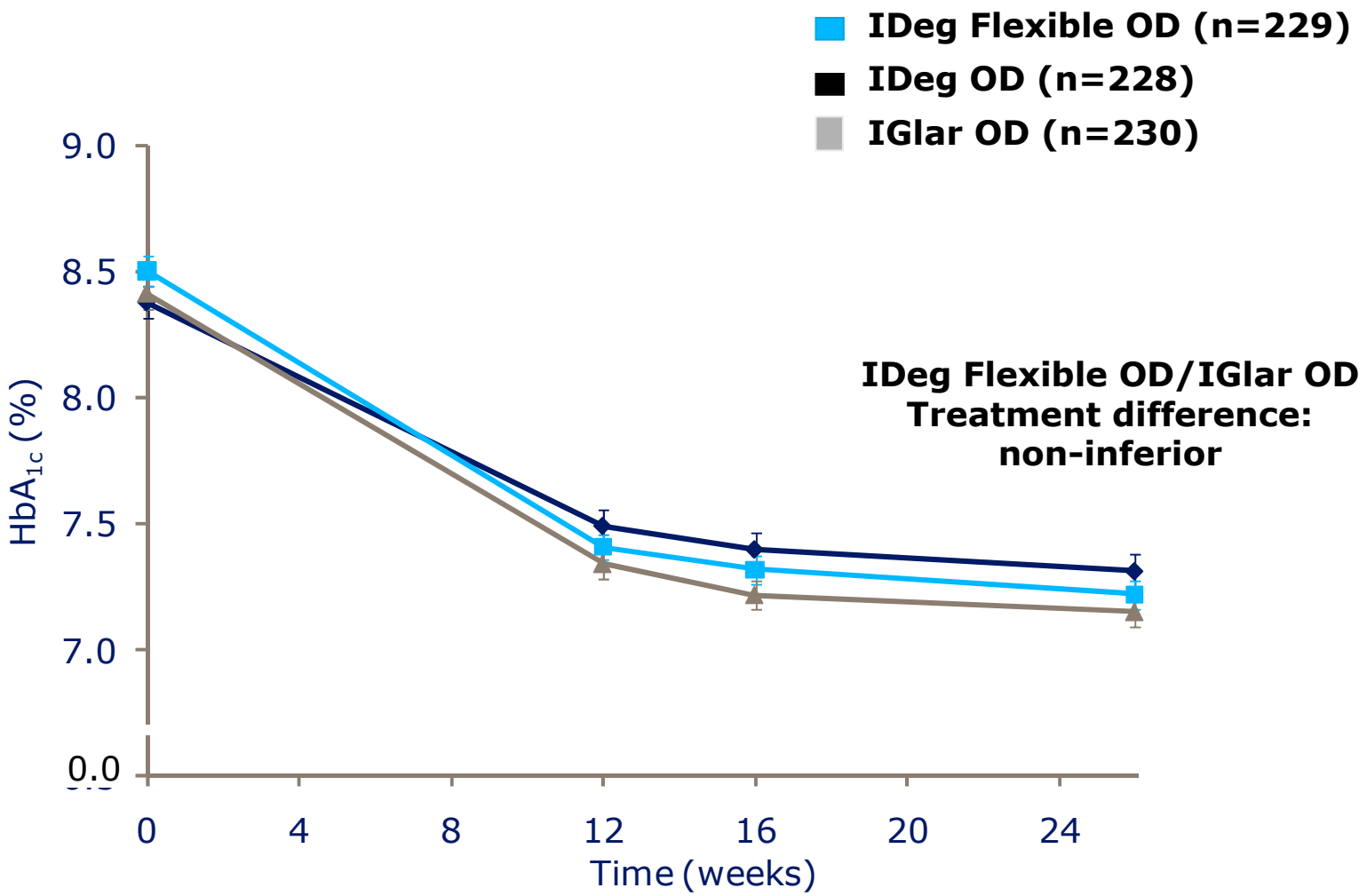

*Birkeland et al. IDF 2011:P-1443; Bain et al. IDF 2011:O-0508; Birkeland et al. Diabetologia 2011;54(Suppl. 1):S423; Atkin et al. Diabetologia 2011;54(Suppl. 1):S53; Meneghini et al. Diabetes 2011;60(Suppl. 1A):LB10*

# Dosing schedule for the IDeg Flexible arm




*Meneghini et al. ADA 2011; 35-P LB (NN1250-3668)*

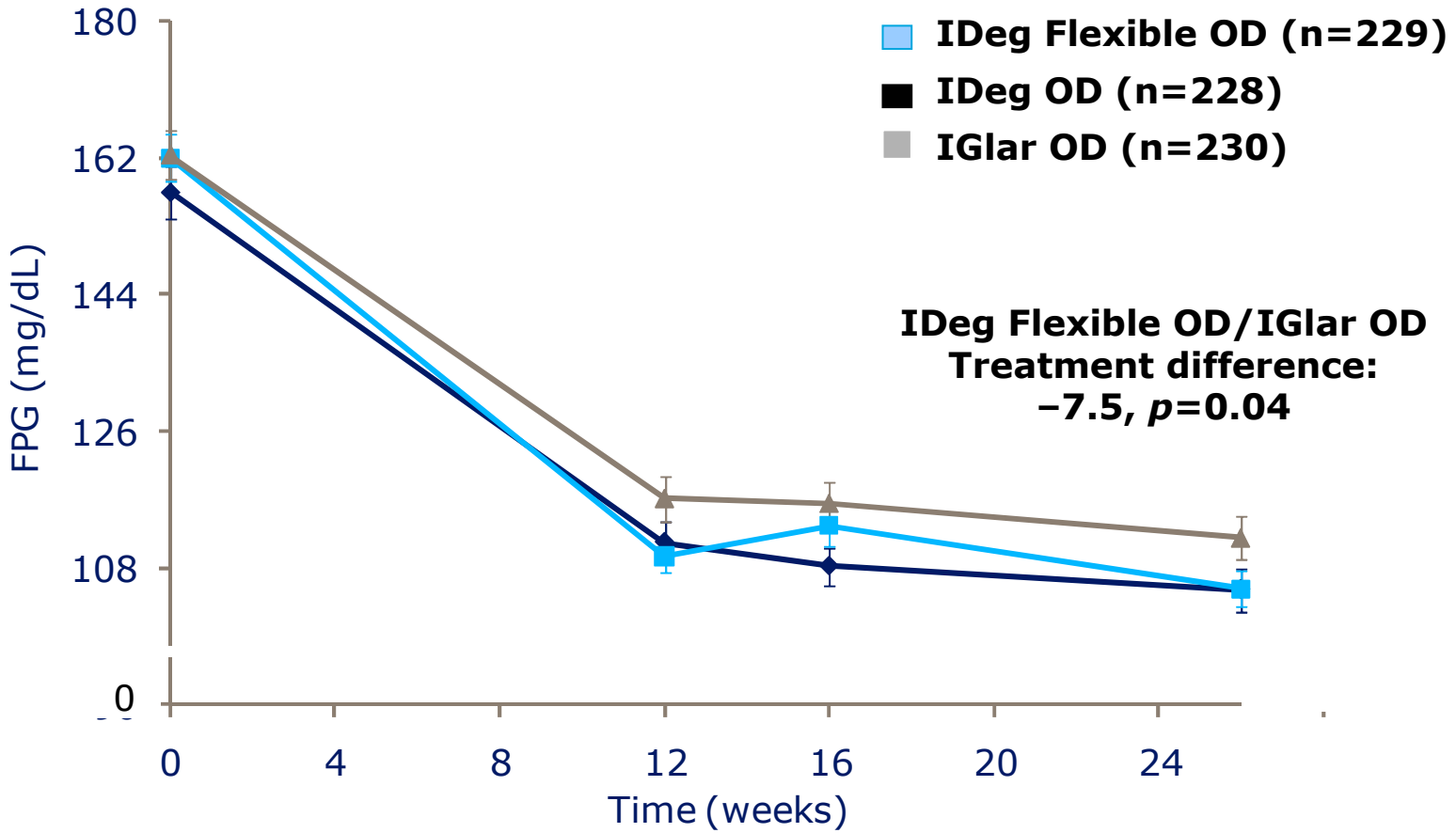
# $HbA_{1c}$ over time




**Mean±SEM; FAS; LOCF**
**Comparisons: Estimates adjusted for multiple covariates**

***Meneghini et al. ADA 2011; 35-P LB (NN1250-3668)***

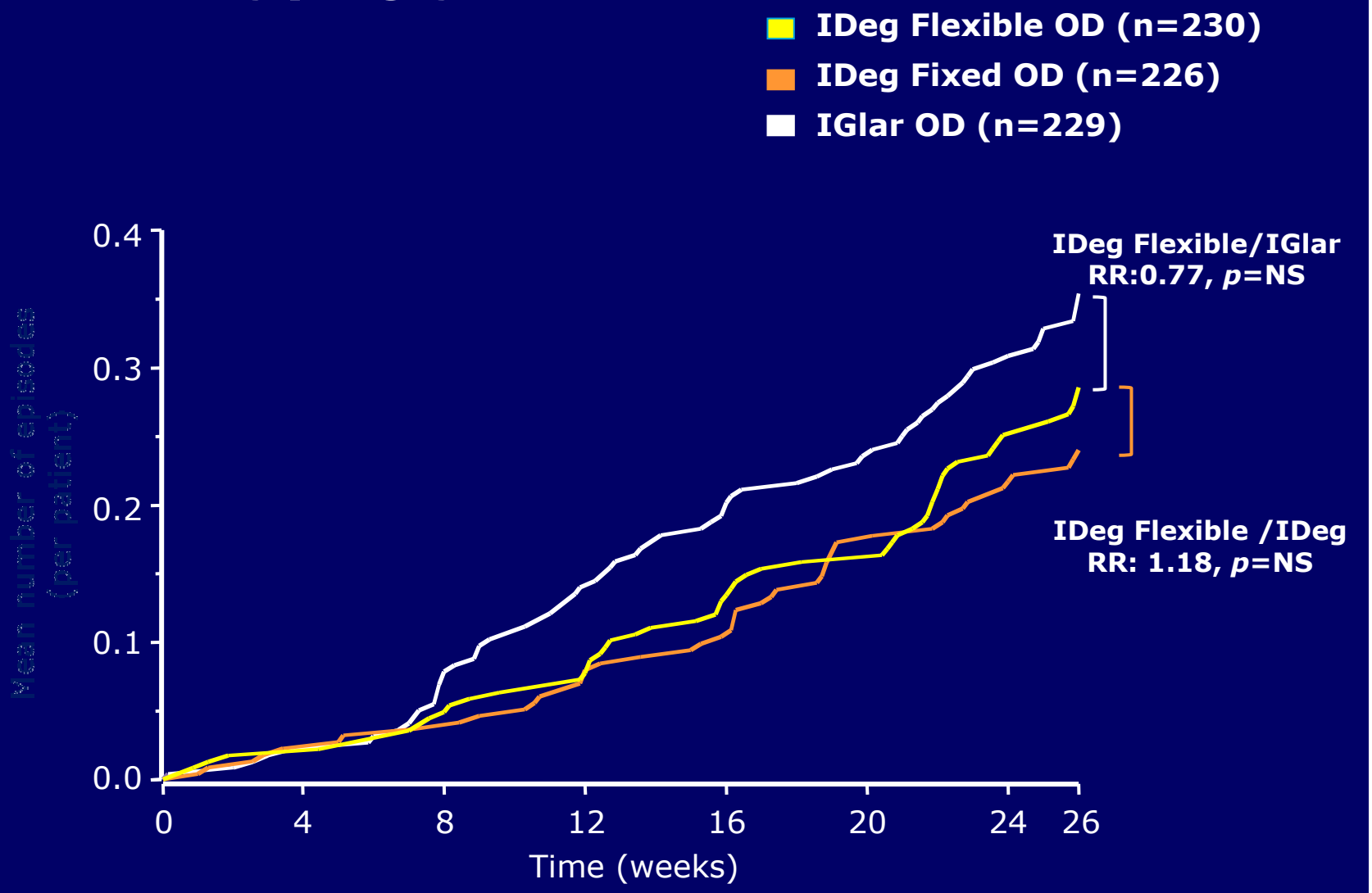
# Fasting plasma glucose over time




**Mean±SEM; FAS; LOCF**
**Comparisons: Estimates adjusted for multiple covariates**

*Meneghini et al. ADA 2011; 35-P LB (NN1250-3668)*

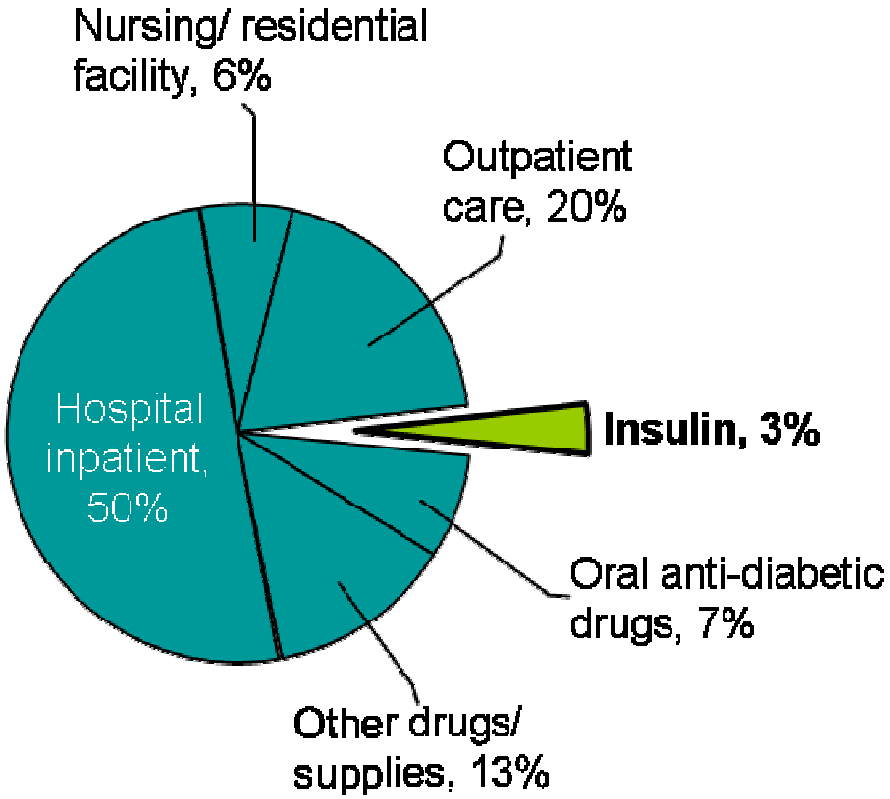
# Nocturnal hypoglycemia



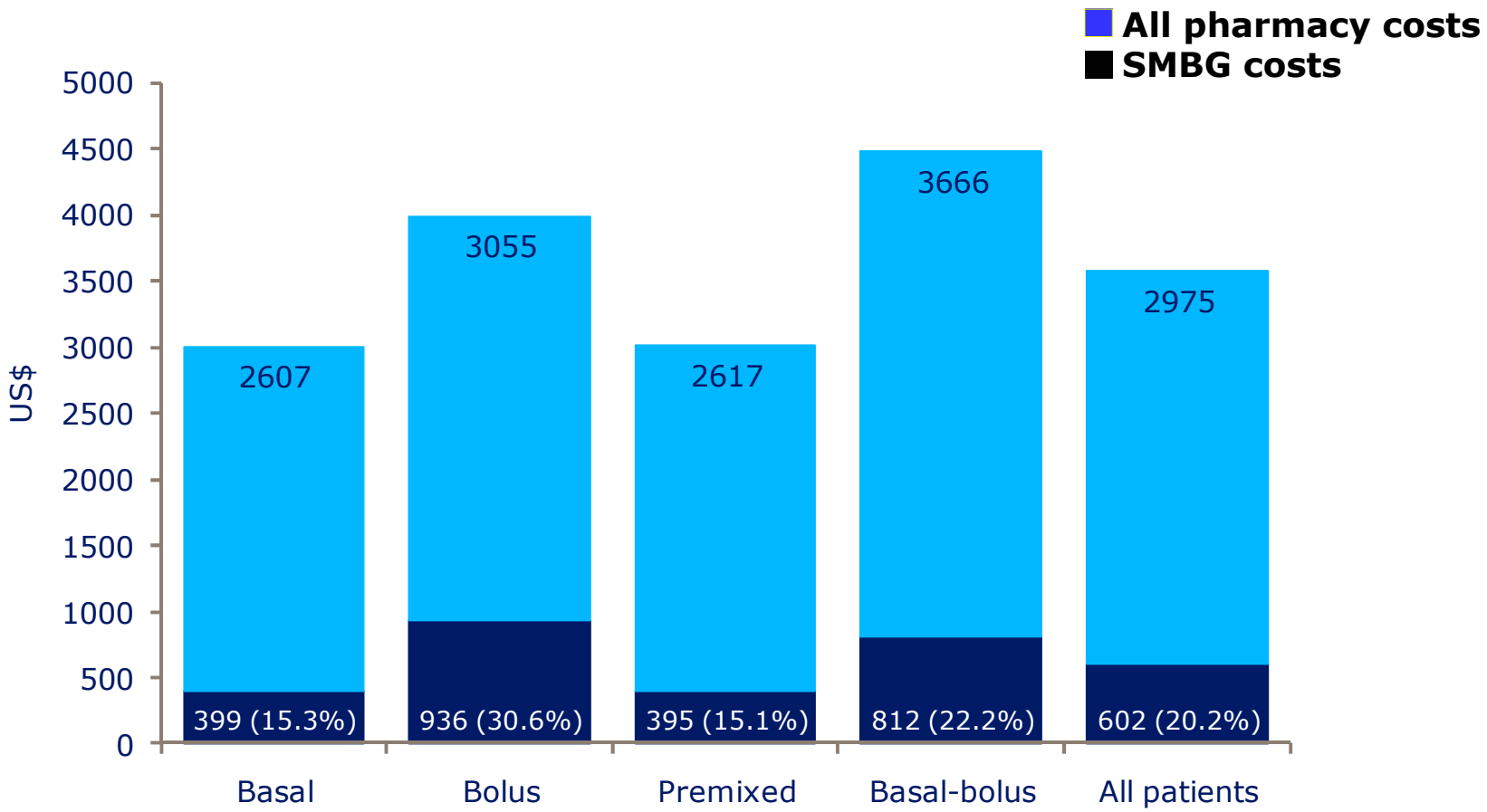

**SAS**
**Comparisons: Estimates adjusted for multiple covariates**
**RR: relative risk for IDeg Flexible OD/IGlar OD [CI: 95% confidence interval]**

Meneghini et al. ADA 2011; 35-P LB (NN1250-3668)

# Cost of insulin is the ”tip of the iceberg”



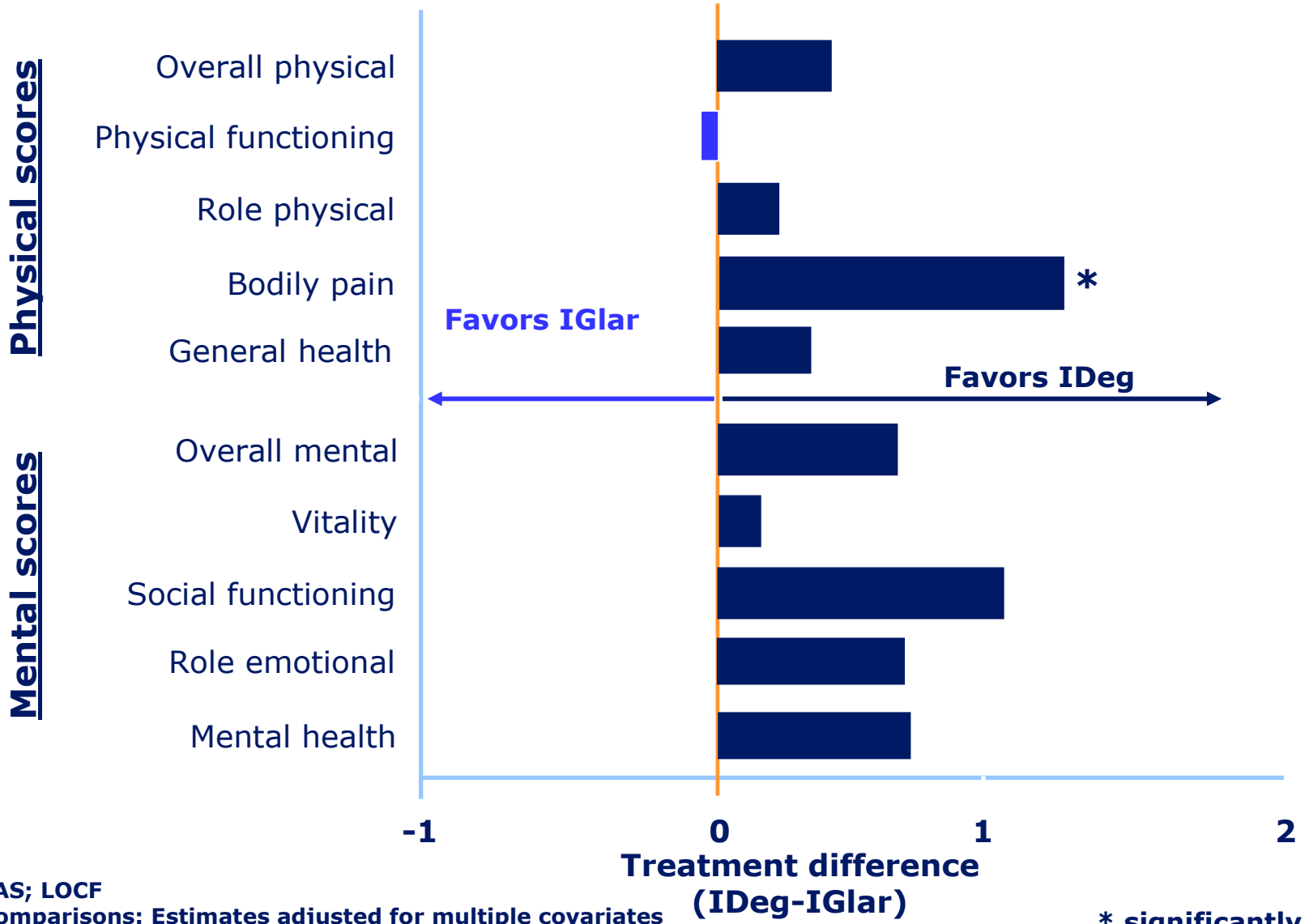

# SMBG testing costs relative to diabetes-related pharmacy costs




**SMBG: self-measured blood glucose**

Yeaw et al. ADA 2011; 1183-P

# Quality of life
# SF-36 Physical and Mental scores




FAS; LOCF
Comparisons: Estimates adjusted for multiple covariates

* significantly better

Garber et al. ADA 2011; 74-OR (NN1250-3582)

# CONCLUSION

El nuevo análogo de acción lenta (Insulina Degludec) es eficaz en una sola dosis y ofrece una gran seguridad. Además, permite una mayor flexibilidad de horario en su administración.

↓

*Facilita el inicio del tratamiento insulínico.*

**Thank you for your attention !**