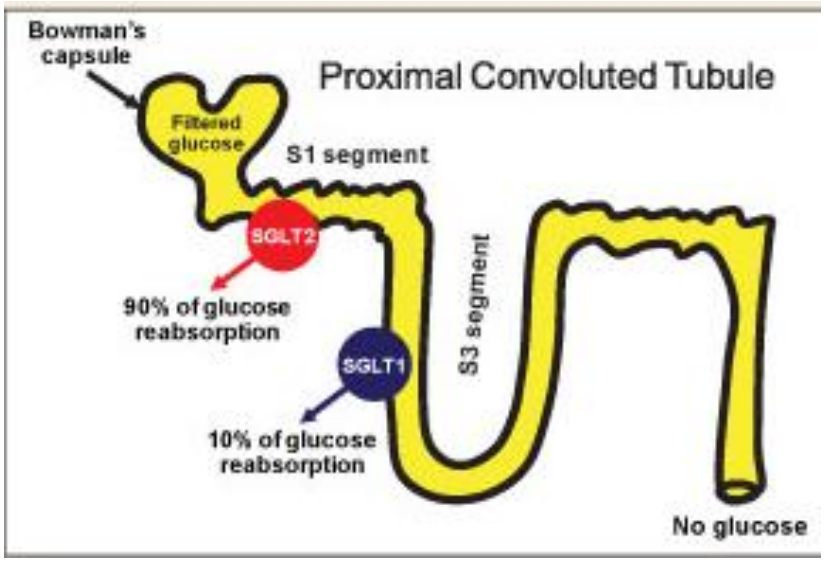
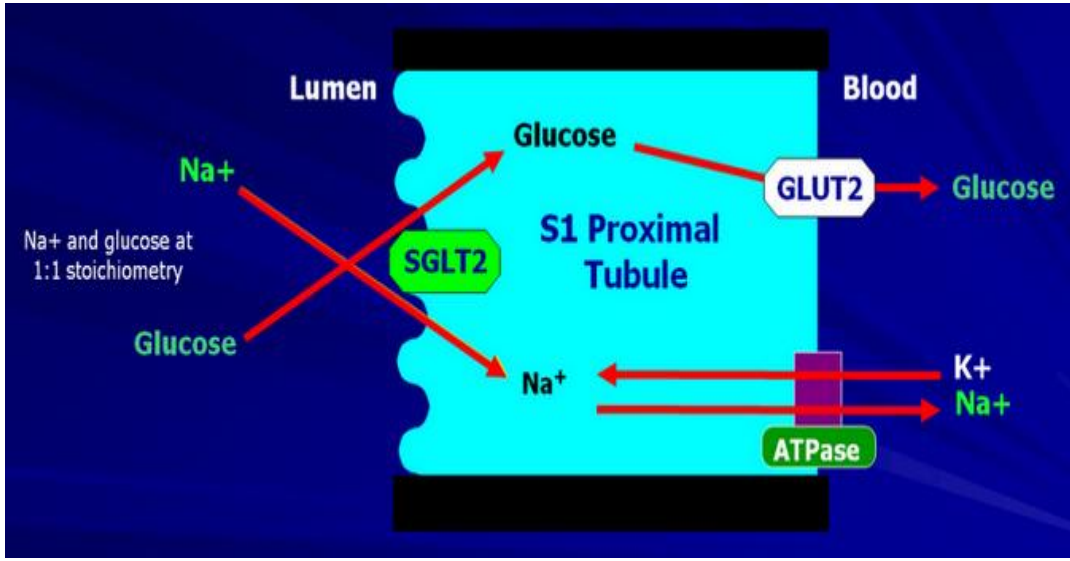




Endocrine Today on PDA.

Physiology Behind SGLT2 Inhibitors

Posted on January 20, 2012 n/a *George Bakris*

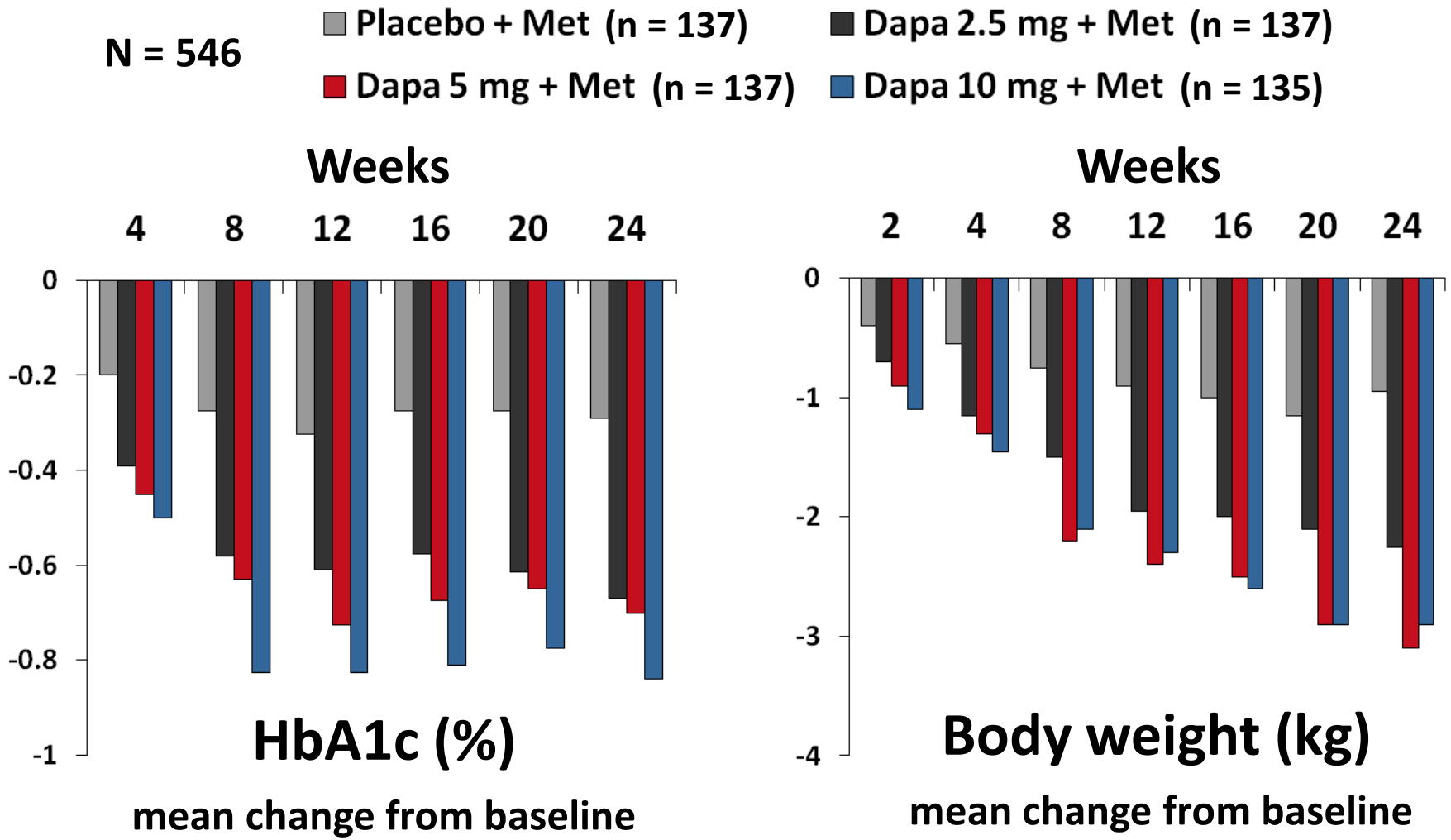
Table 1. Comparison of Sodium-Glucose Cotransporters.

	SGLT1	SGLT2
Site	Mostly in small intestine, some kidney, heart	Almost exclusively kidney
Renal Location	Late proximal straight tubule (S3 segment)	Early proximal convoluted tubule (S1 segment)
Affinity for Glucose	High Km = 0.4 mM	Low Km = 2 mM
Capacity for Glucose Transport	Low	High
% of Renal Glucose Reabsorption	10%	90%

Note: A comparison of selected traits of two of the major sodium-glucose cotransporters, SGLT-1 and SGLT-2. Adapted from Lee YJ, Lee YJ, Han HJ. Regulatory mechanisms of Na+/glucose cotransporters in renal proximal tubule cells. *Kidney Int* 106(Suppl):S27-S35, 2007.

Dapagliflozin Added to Metformin

Mean Change in HbA1c (%) and Body Weight (kg)



Week 24 (LOCF) change from baseline

From Bailey et al. *Lancet.* 2010;375:2223-33.

Mit szeretne elkerülni a kutató, a gyógyszercég, klinikus és főként a beteg?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction And Death from Cardiovascular Causes

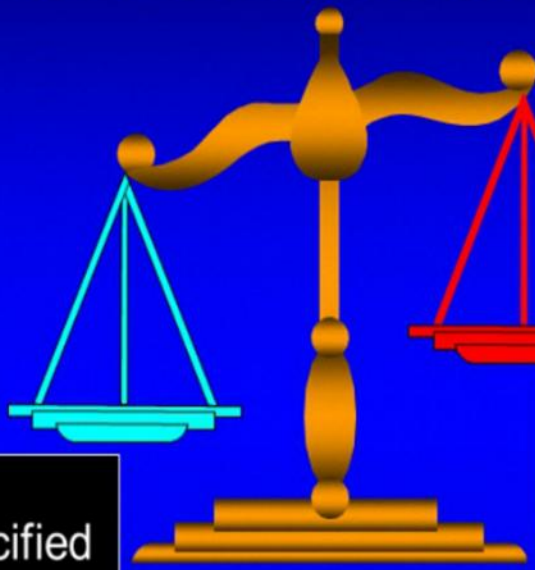
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death…that had borderline significance.

Benefit-Risk in Drug Development

Asymmetry in Assessment of Efficacy & Safety



Efficacy

- RCTs
- Anticipated, prespecified
- Adequate power
- Adjudicated
- Precisely measured and quantified (P values)

Safety

- Non-clinical data, PK/PD studies, meta-analyses, observational databases, AERS/Sentinel
- RCTs: limited exposure, narrow population
- Unanticipated, not prespecified
- Not adjudicated (after the fact)
- Delayed/late onset events missed (after withdrawal)
- Not precisely measured and quantified (r/o unacceptable risk)

Dr. Sanjay Kaul – OP – EASD, 2013, Barcelona

O'Neill RT, Drug Information Journal 2008;*42;235–245*

SGLT2 Inhibitors for Treatment of Diabetes

Balancing Benefits and Risks

Benefit

- Effective glycemic control (-0.66% HbA1c c/w placebo)
- ↓ hypoglycemia (-SU, insulin)
- Weight loss (-1.8Kg)
- BP lowering (-4.5 mmHg)

Risk

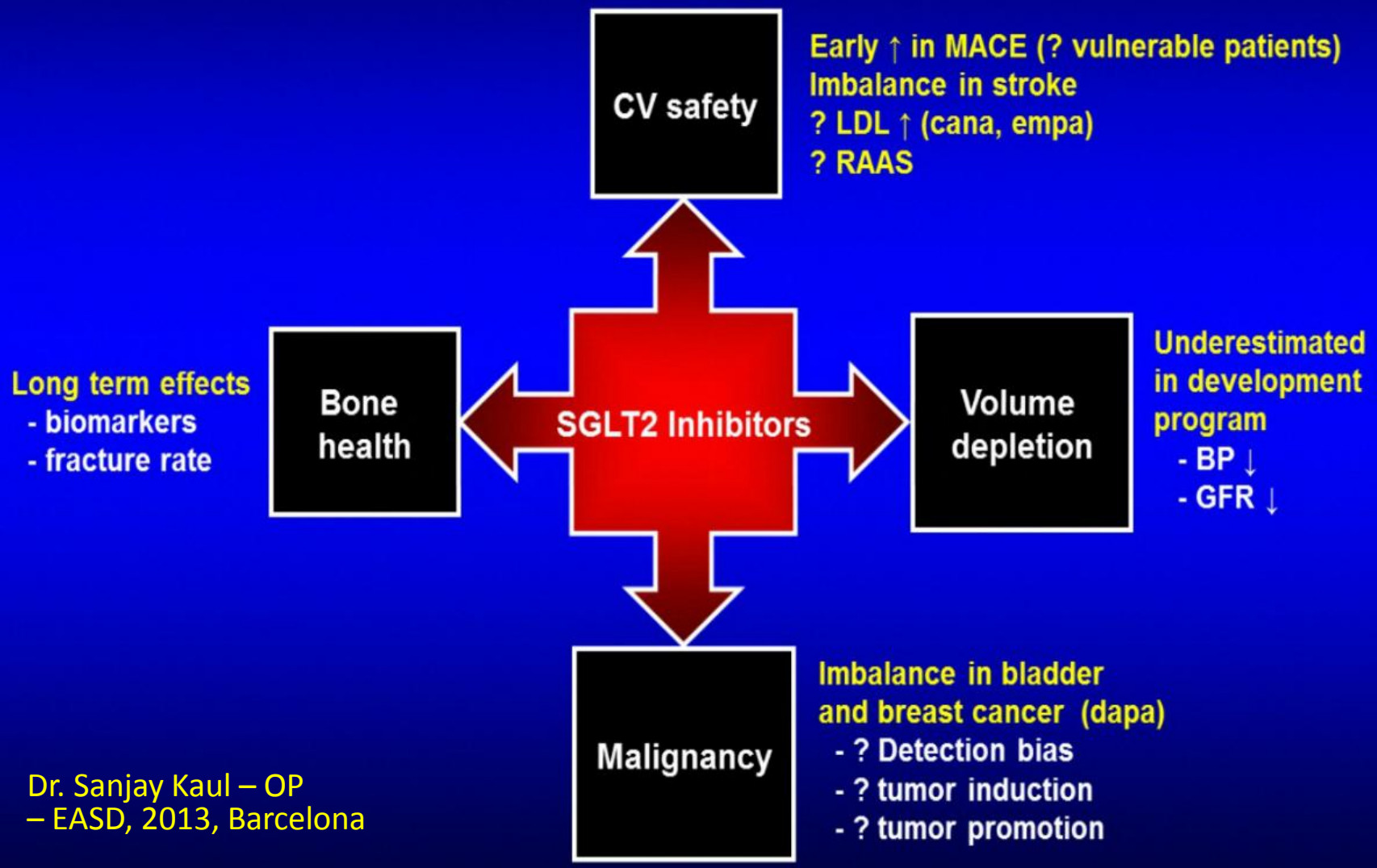
- Mycotic genital infection (OR 5.0)
- UTI (OR 1.4)
- Polyuria, nocturia, dysuria
- Volume depletion, thirst, ↑ Hct
- Dyslipidemia (↑ LDL, non-HDL)

Uncertainty about CV & renal effects, bone health, malignancy

Adapted from Vasilakou et al, Ann Intern Med 2013;159;262-274

Dr. Sanjay Kaul – OP – EASD, 2013, Barcelona

SGLT2 Inhibitors: Areas of Uncertainty



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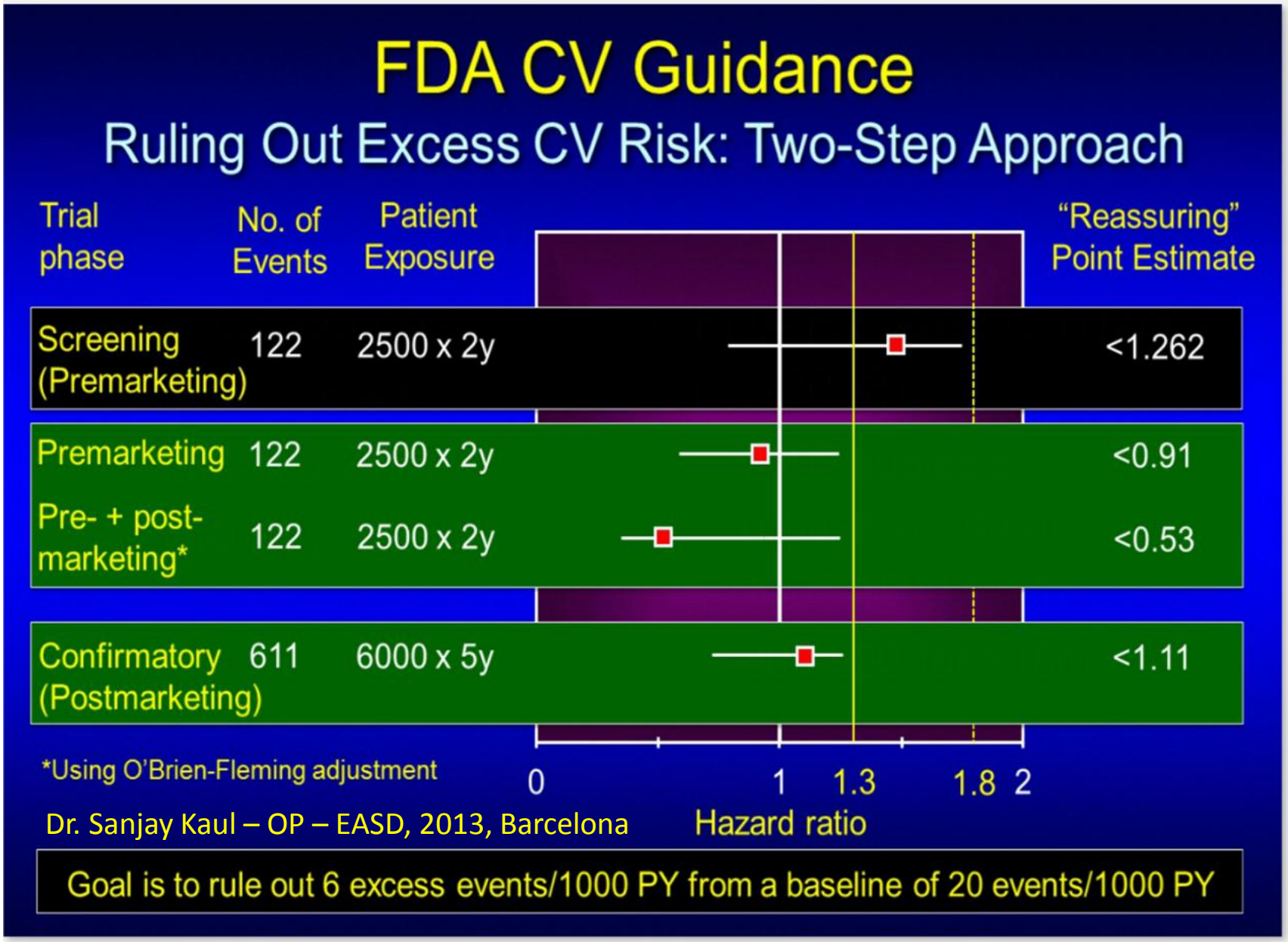
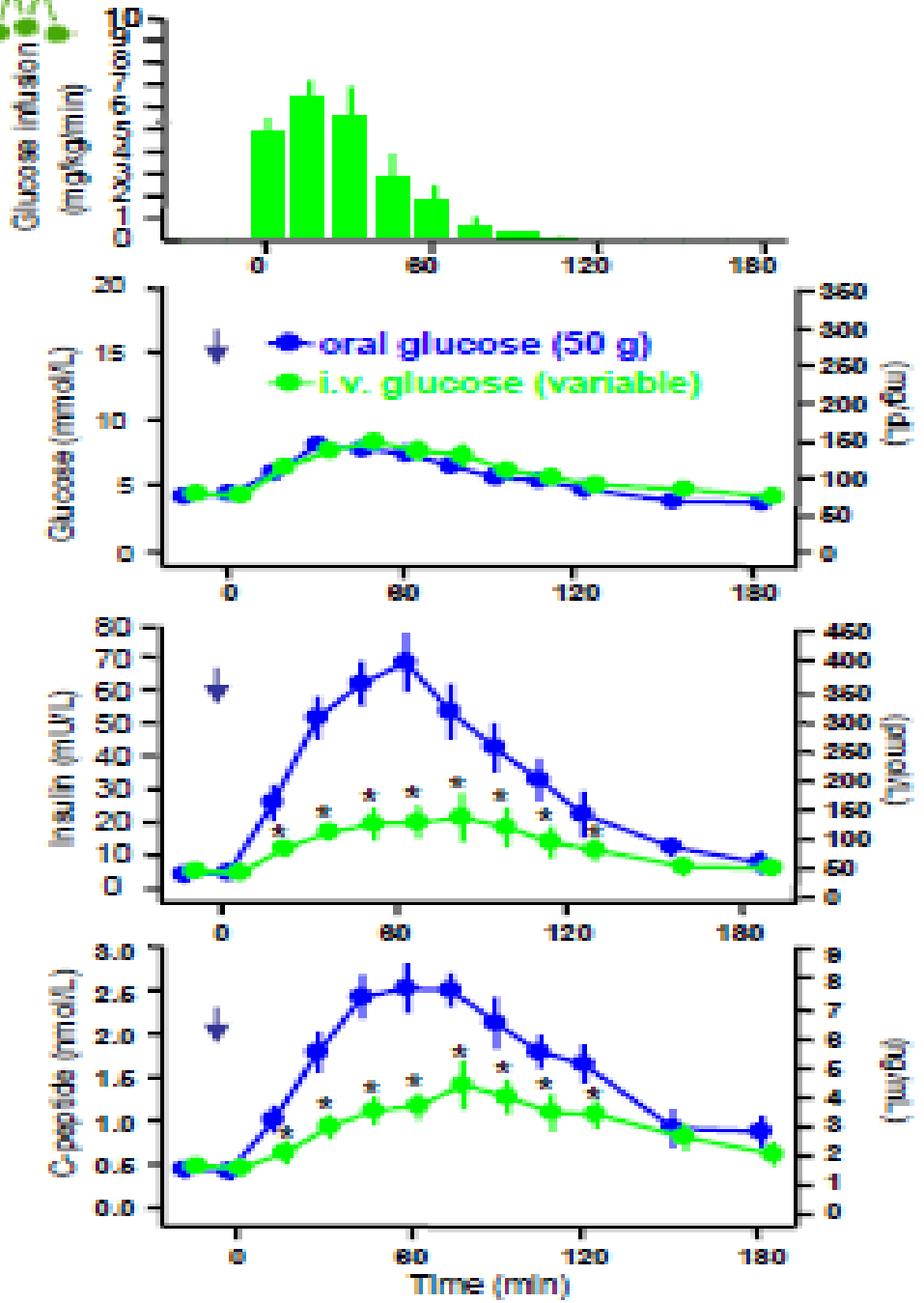
– EASD, 2013, Barcelona

FDA 2 lépcsős szűrés CV kockázathoz: HR 1.8x, majd HR 1.3x de (!)
pl. 1.1x-es HR kizárásához 6000 ember 5 éves utánkövetése szükségeltetene



Az Incretin Effektus



Nauck M, et al.: Diabetologia. 1986 Jan;29(1):46-52.

A DIPEPTIDYL PEPTIDASE IV (DPP IV) JELENTŐSÉGE AZ INCRETIN-HORMONOK INAKTIVÁLÁSÁ-BAN

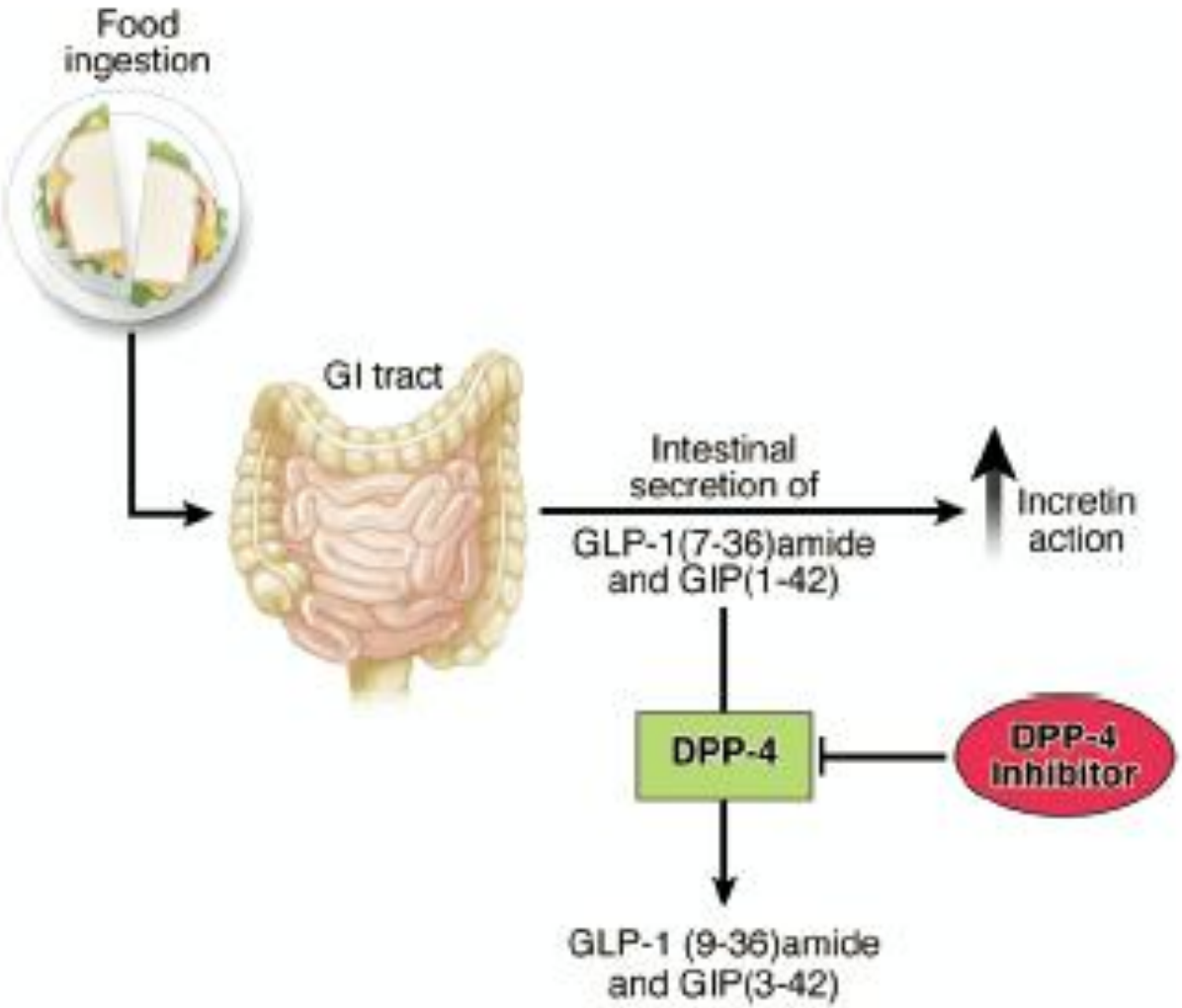


Figure 2. Bioactive GLP-1(7-36)amide and GIP (1-42) are released from the small intestine after meal ingestion and enhance glucose-stimulated insulin secretion (incretin action). DPP-4 rapidly converts GLP-1 and GIP to their inactive metabolites GLP-1 (9-36) and GIP (3-42) in vivo. Inhibition of DPP-4 activity prevents GLP-1 and GIP degradation, thereby enhancing incretin action.

Baggio LL, Drucker DJ: Gastroenterology2007;132:2131–2157
Biology of Incretins

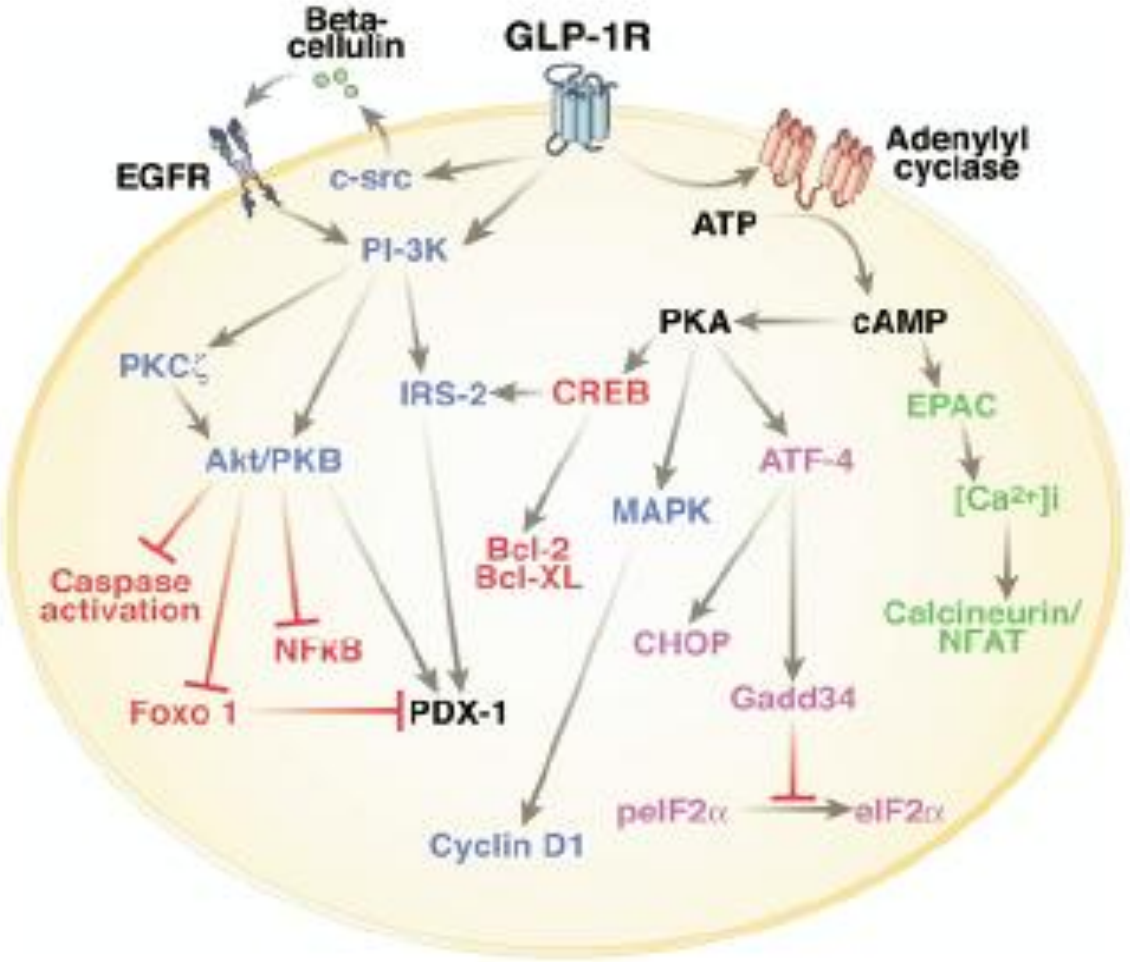
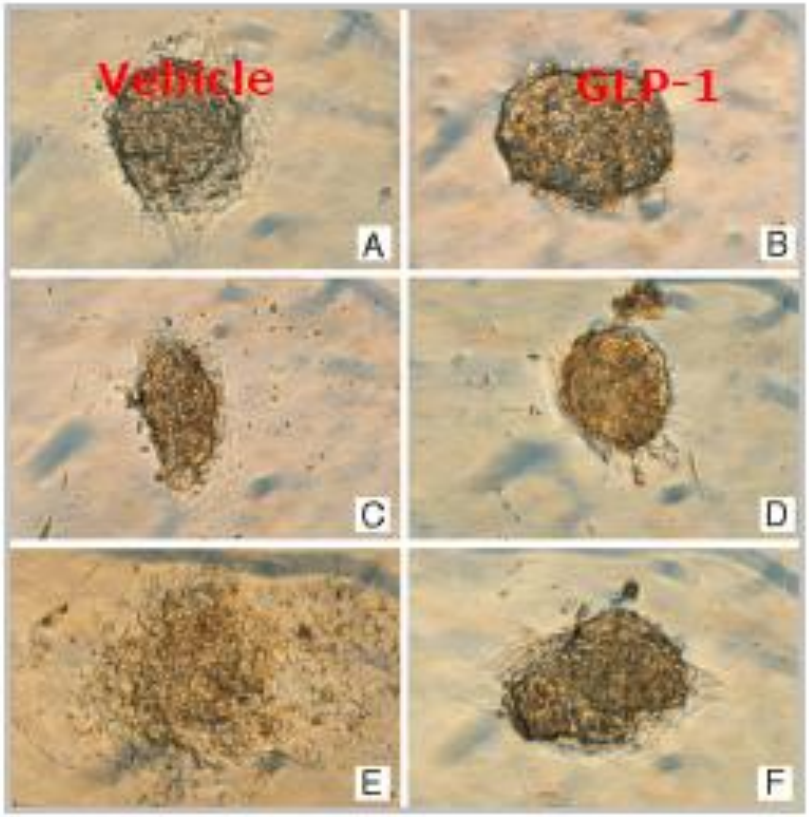


Figure 4. GLP-1R–dependent intracellular signal transduction pathways in the pancreatic β-cell. Although there is considerable overlap between pathways, the major effectors that couple GLP-1R activation to insulin secretion and biosynthesis (*green*), β-cell proliferation and neogenesis (*blue*), inhibition of apoptosis (*red*), and ER stress reduction (*purple*) are highlighted.

Baggio LL, Drucker DJ: Gastroenterology2007;132:2131–2157
Biology of Incretins

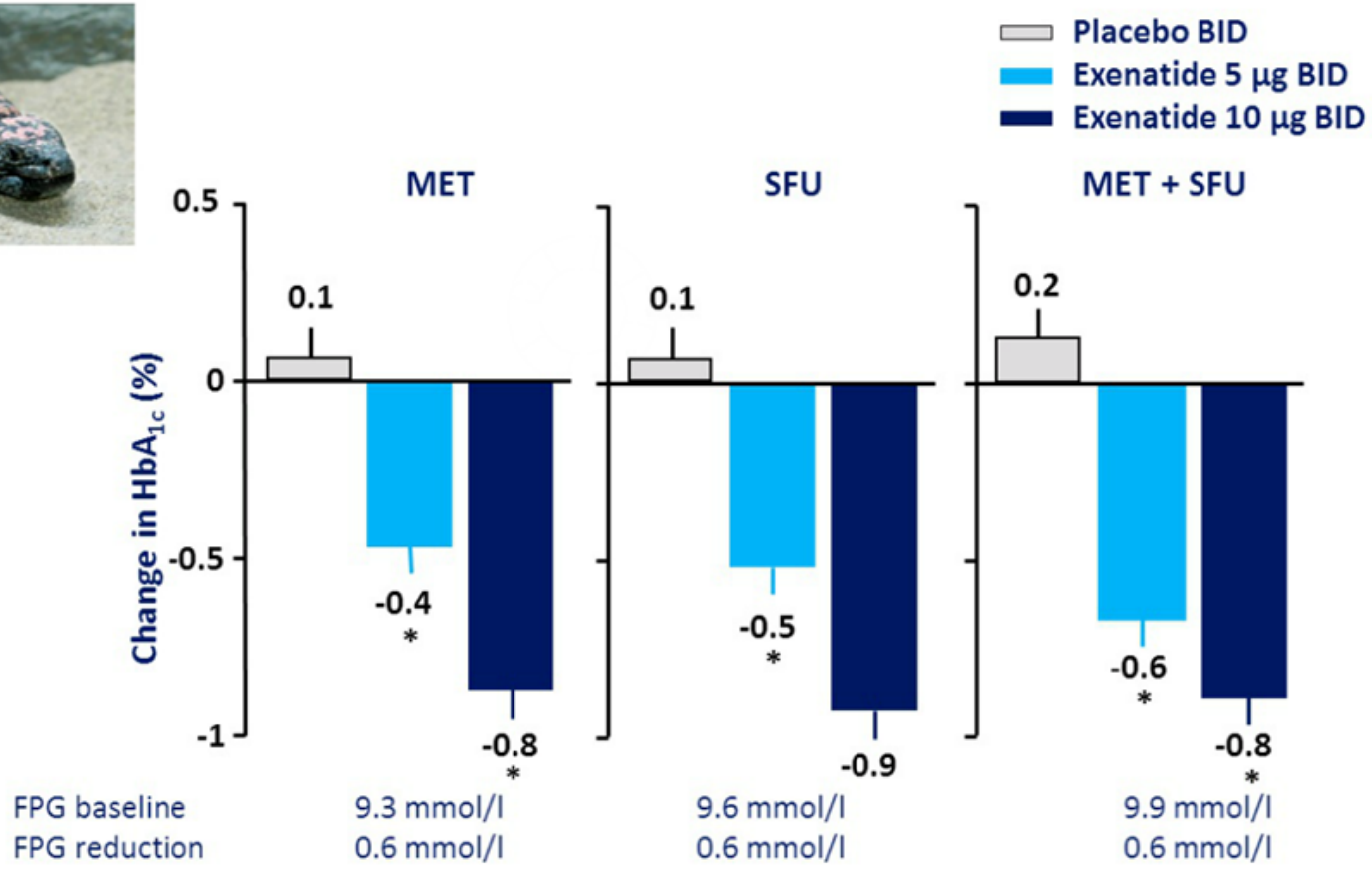
GLP-1 Effects in Isolated Human Islets



Farilla L et al. *Endocrinology* 2003;**144**:5149–58.

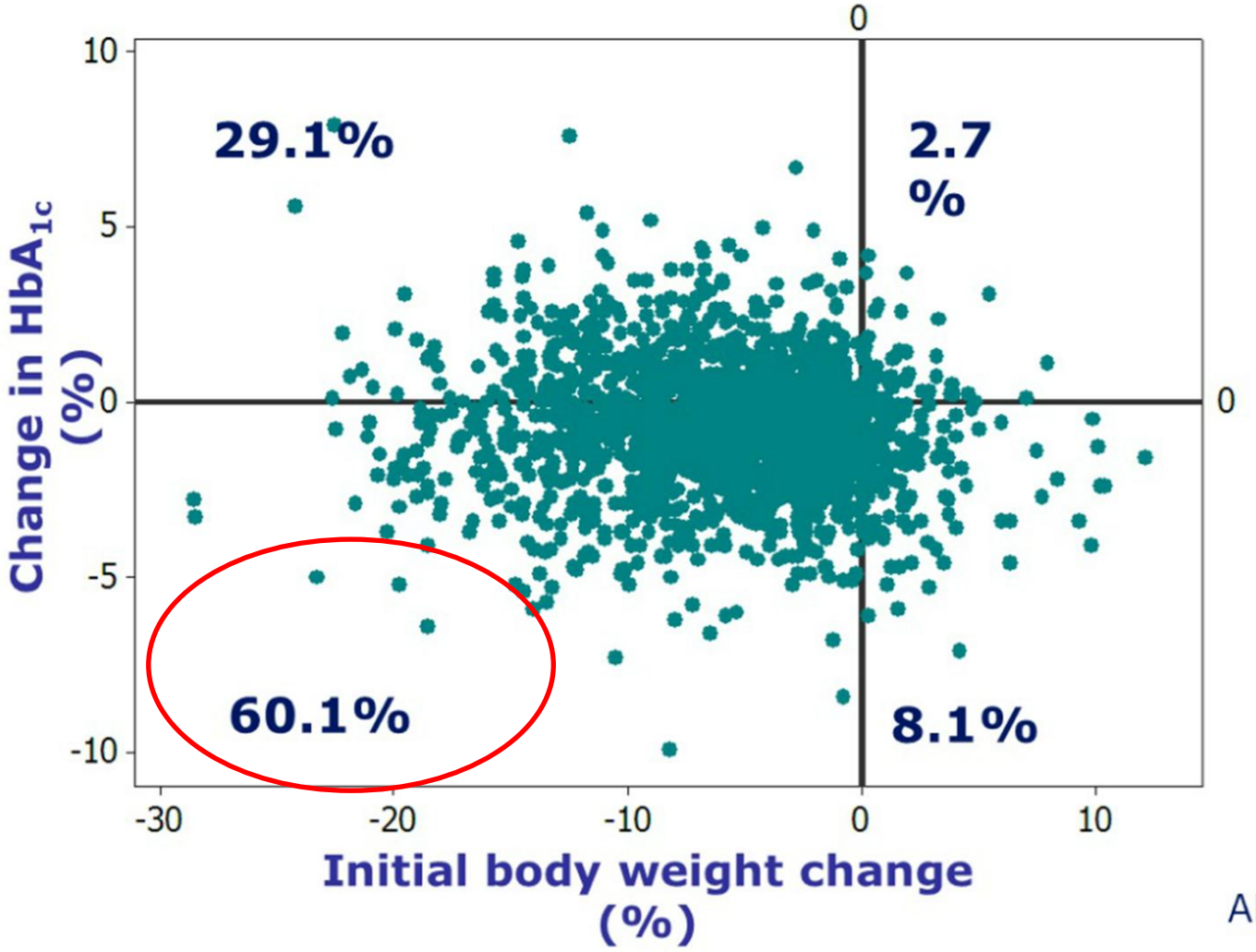
A KLINIKAI GONDOLKODÁS IS MEGVÁLTOZOTT – 2004-BEN

3 AMIGO trials in 2004-2005



ITT population; Mean (SE); MET (N = 336), SFU (N = 377), MET + SFU (N = 733); *P <.005 vs placebo.
Mean baseline HbA1c ranged from 8.2% to 8.7% across all trial arms.
DeFronzo RA, et al. *Diabetes Care*. 2005;28:1092-1100.; Buse JB, et al. *Diabetes Care*. 2004;27:2628-2635.; Kendall DM, et al. *Diabetes Care*. 2005;28:1083-1091.

A HbA1c értékek és a testsúly változása 6 hónap alatt 1882 Exenatiddal (GLP-1 RA) kezelt betegben



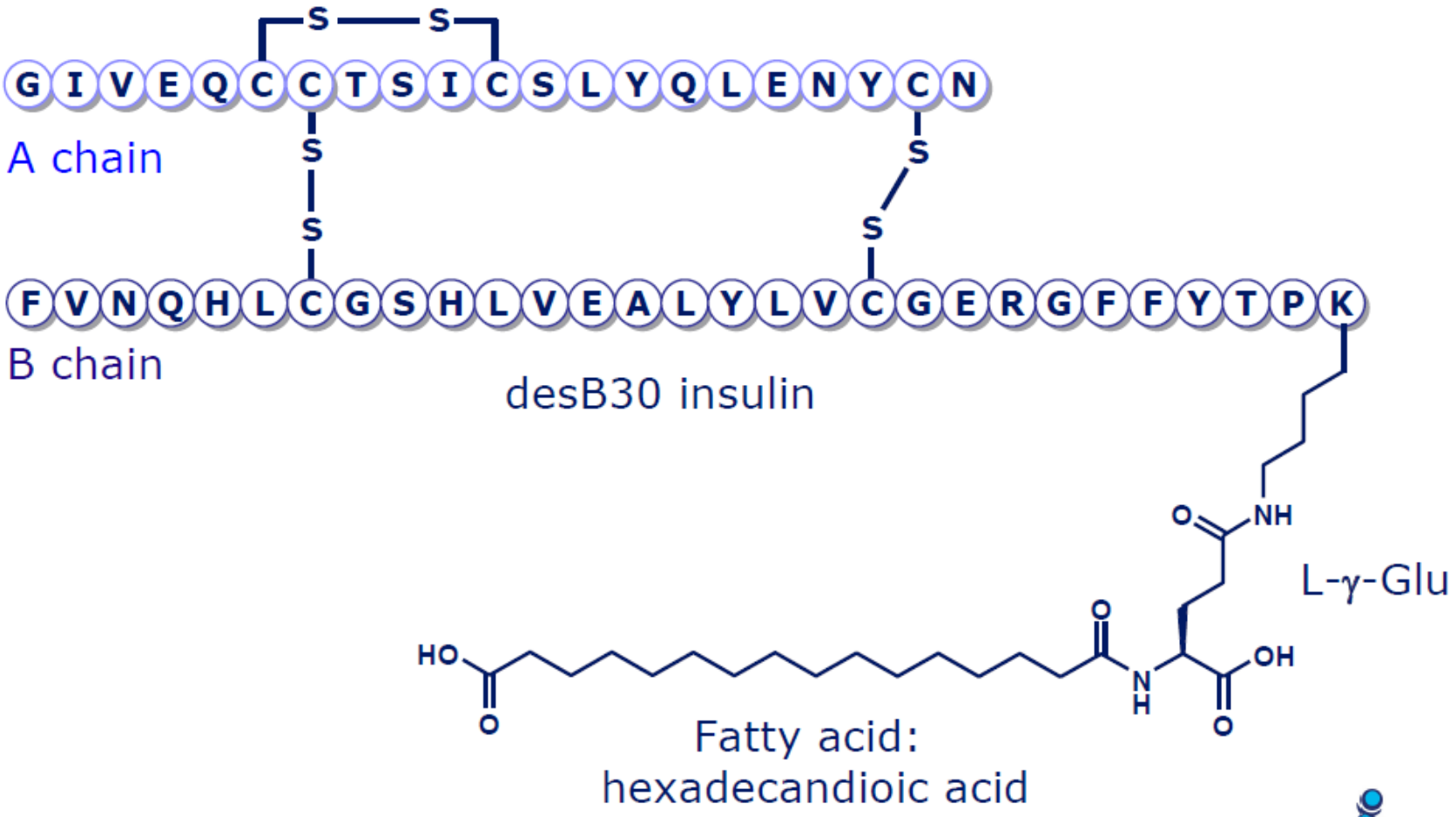
Stephen C.L. Gough – 2013, EASD, Barcelona

- **ÚJ INZULINOK:**

INZULIN DEGLUDEC

ULTRA HOSSZÚ (>42h) HATÁSÚ BÁZIS INZULIN

Molecular structure of Degludec



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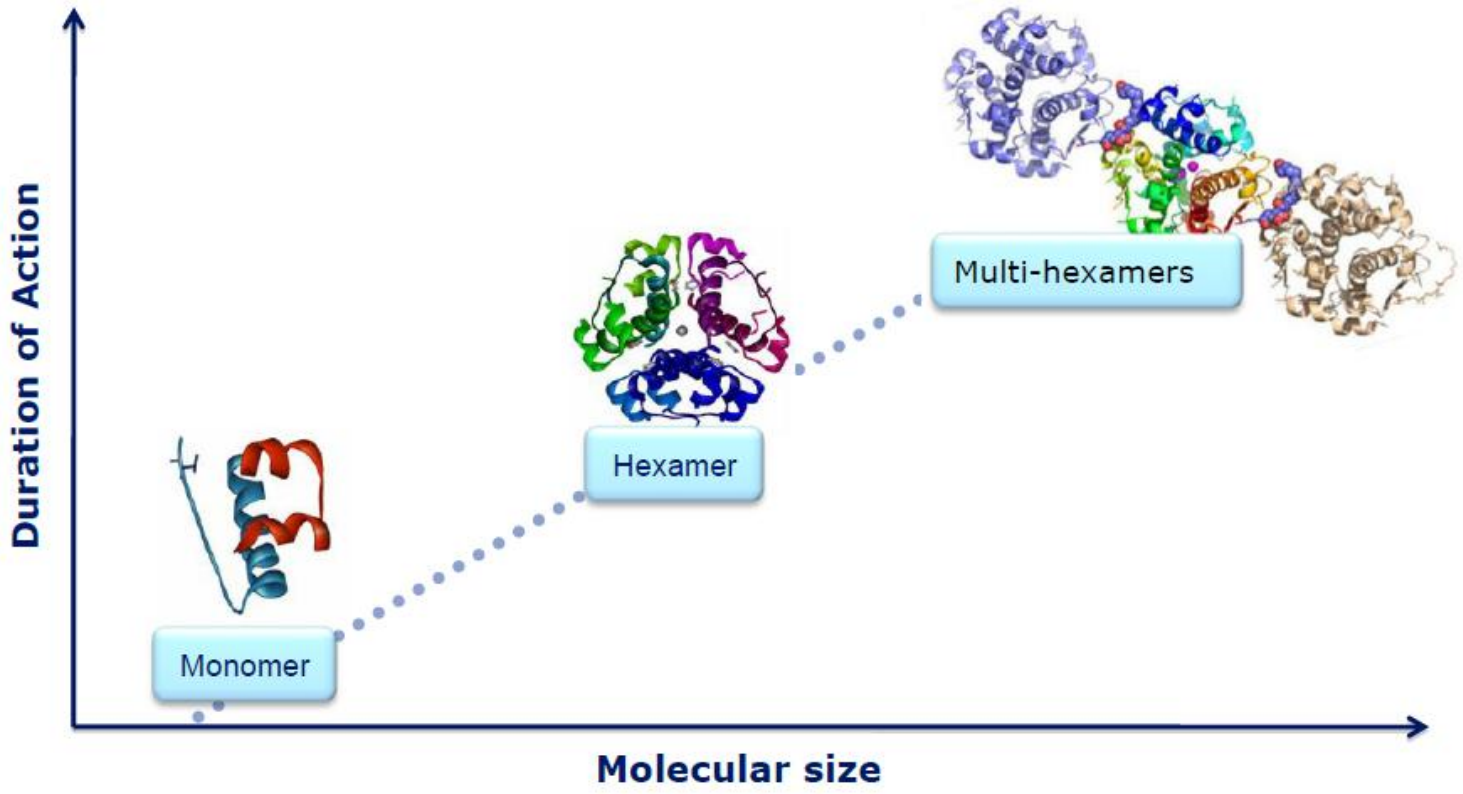
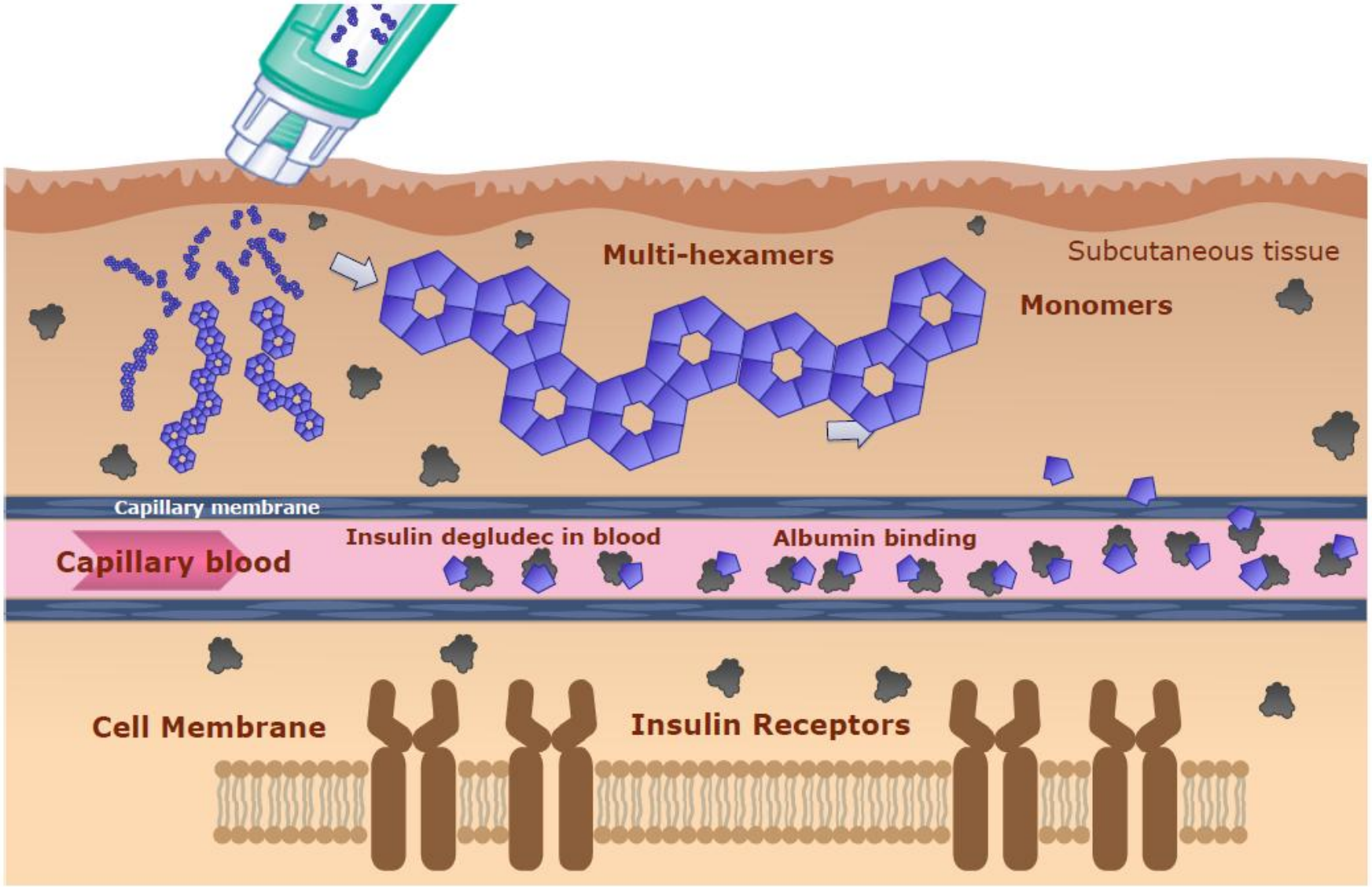
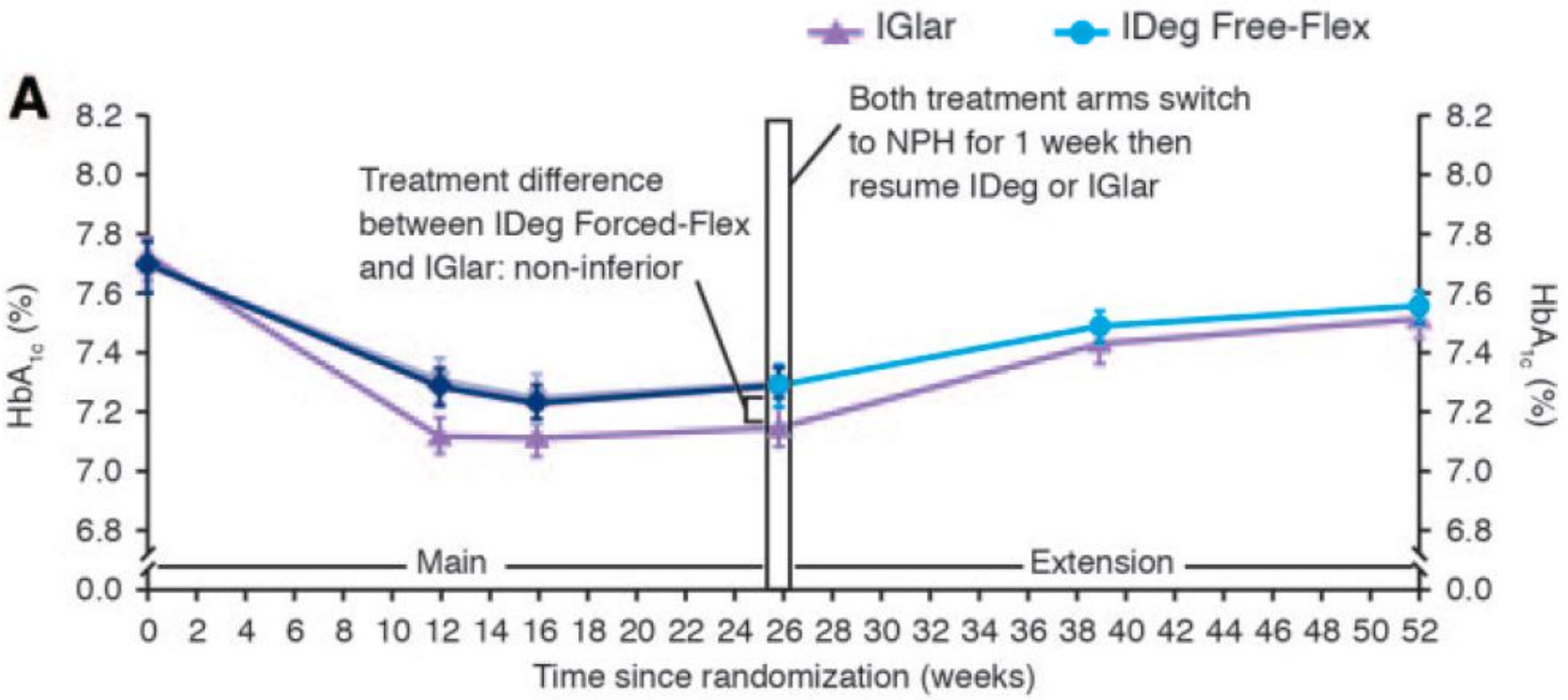
The protraction mechanism of Degludec is based on multi-hexamer formation



Protraction mechanism for Degludec



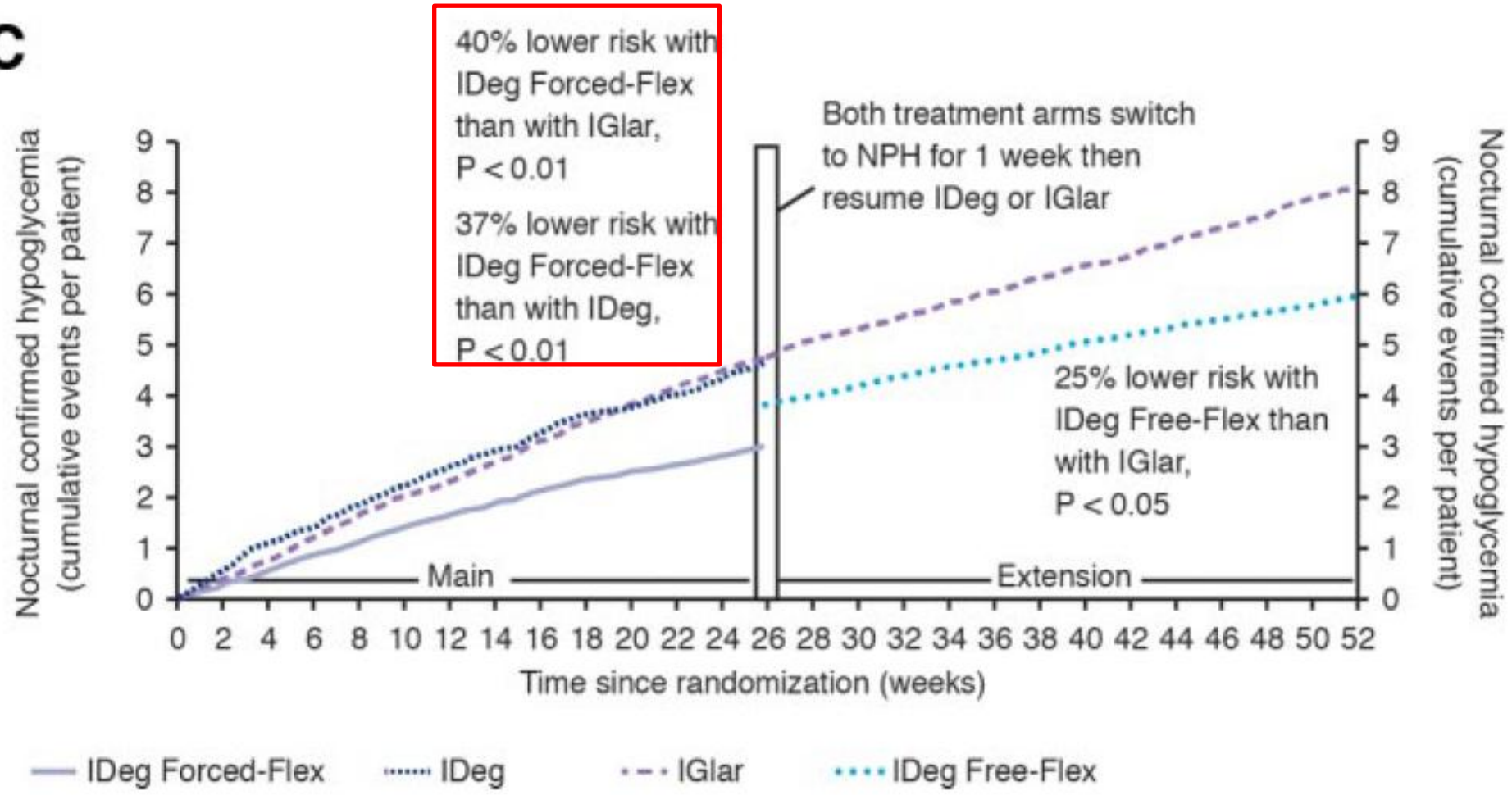
Mire jó?



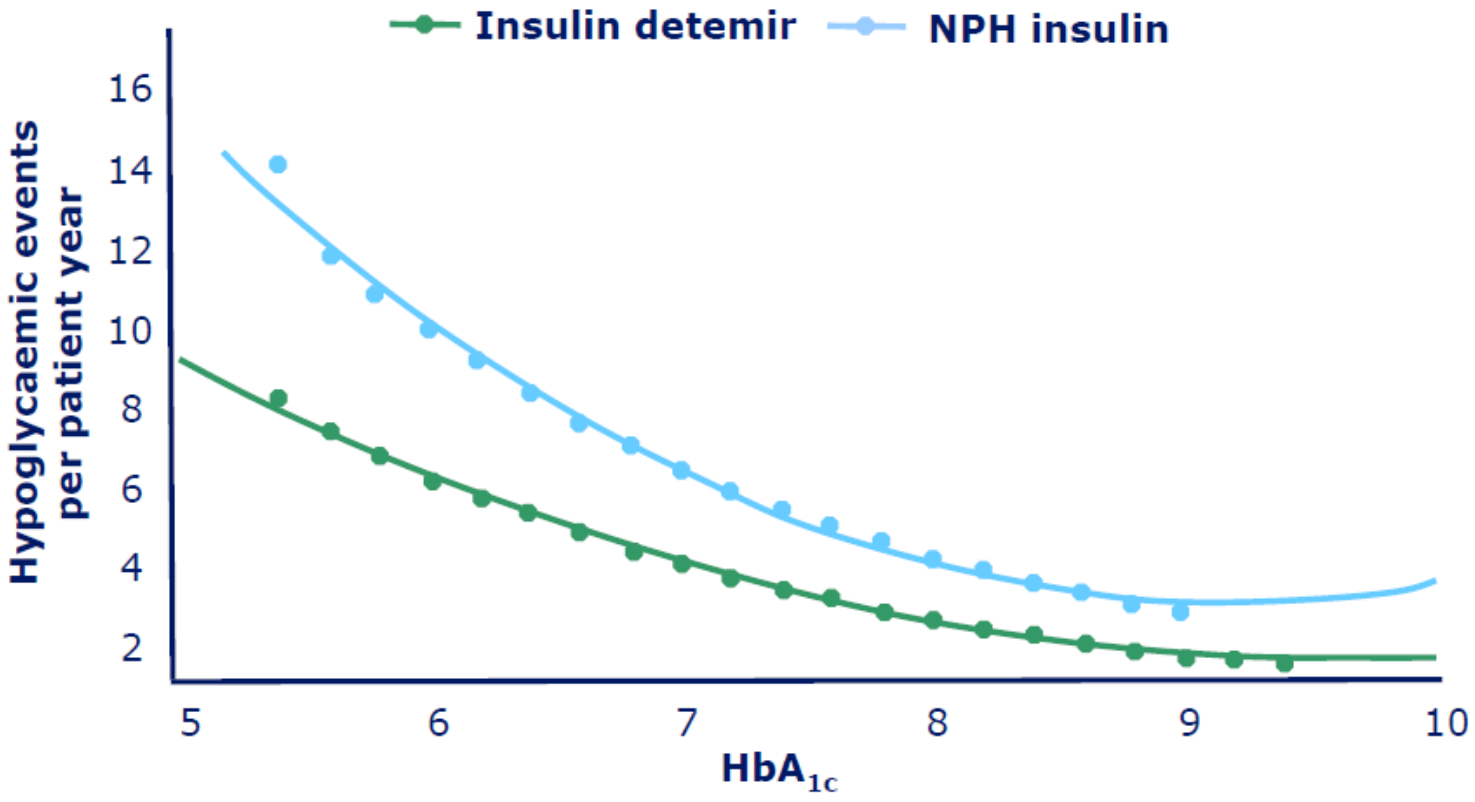
26-hetes, ‚open-label', ‚treat-to-target', ‚non-inferiority' vizsgálat:

- IDeg forced flexible (Forced-Flex) az inzulint forszírozottan váltakozó időközökkel adták: 8 és 40 óra (‚flexibilis' rendszer) vagy
- IDeg a nap azonos időpontjában
- Inzulin glargine (IGlar) a nap azonos időpontjában
- Az extenzió során minden Degludec inzulint kapó személyt átsoroltak egy ‚free-flexible' (Free-Flex) rendszerre.

Az éjszakai hypoglikémiák száma meglepően csökkent a flexibilis karon ‚megbocsátó inzulin' - nagyobb rugalmasság a betegnek



Reduced risk of hypoglycaemia in type 2 diabetes with modern insulins



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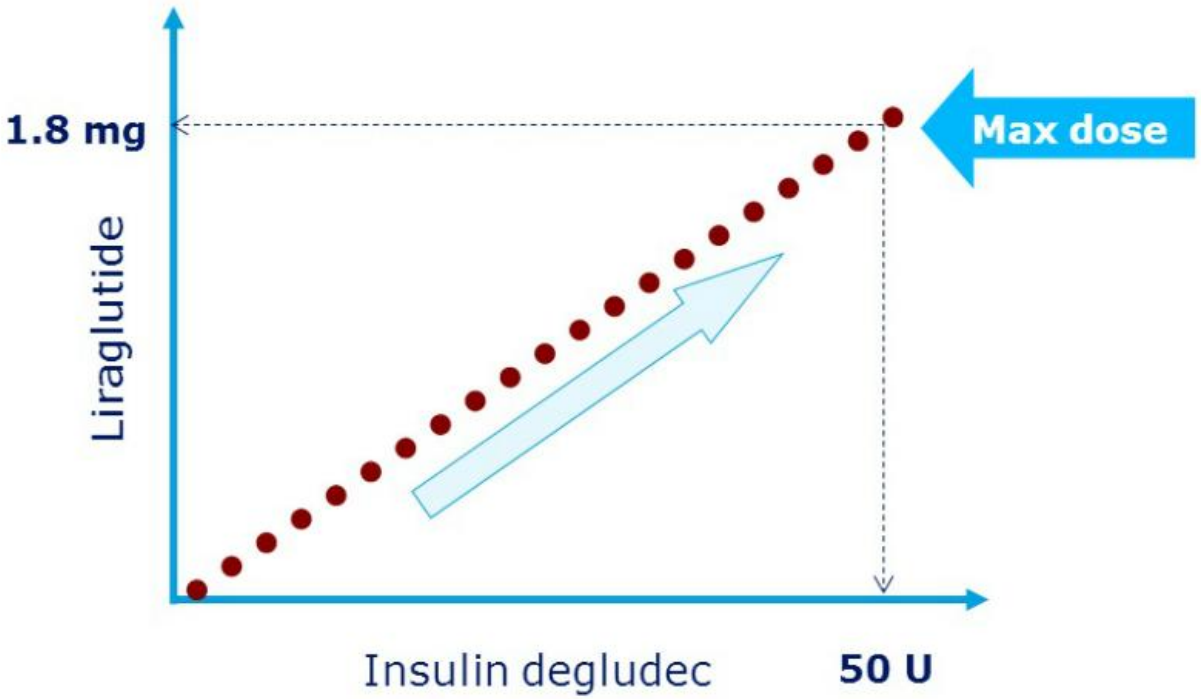
Source: Kolendorf and Kim, Lower Risk of Hypoglycemia at Each Level of Glycemic Control when Insulin Detemir is added to Oral Agents compared to NPH Insulin in Patients with Type 2 Diabetes, Poster nr 479, ADA 2005

Idén még GLP1-RA-val fix kombinációban történő alkalmazásról is született vizsgálat 2-es típusú cukorbetegekben

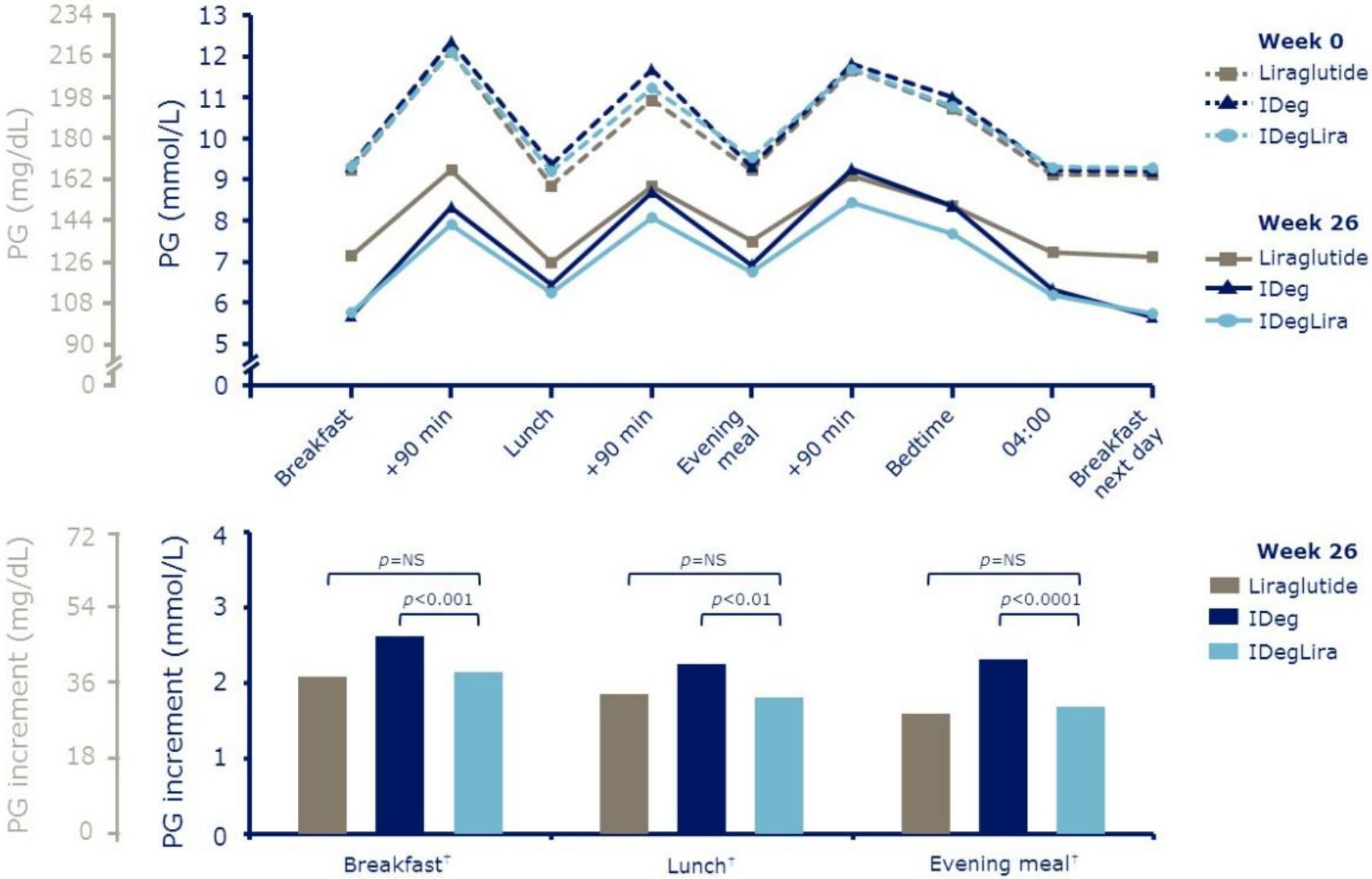
IDegLira

- Fixed ratio combination of insulin degludec and liraglutide



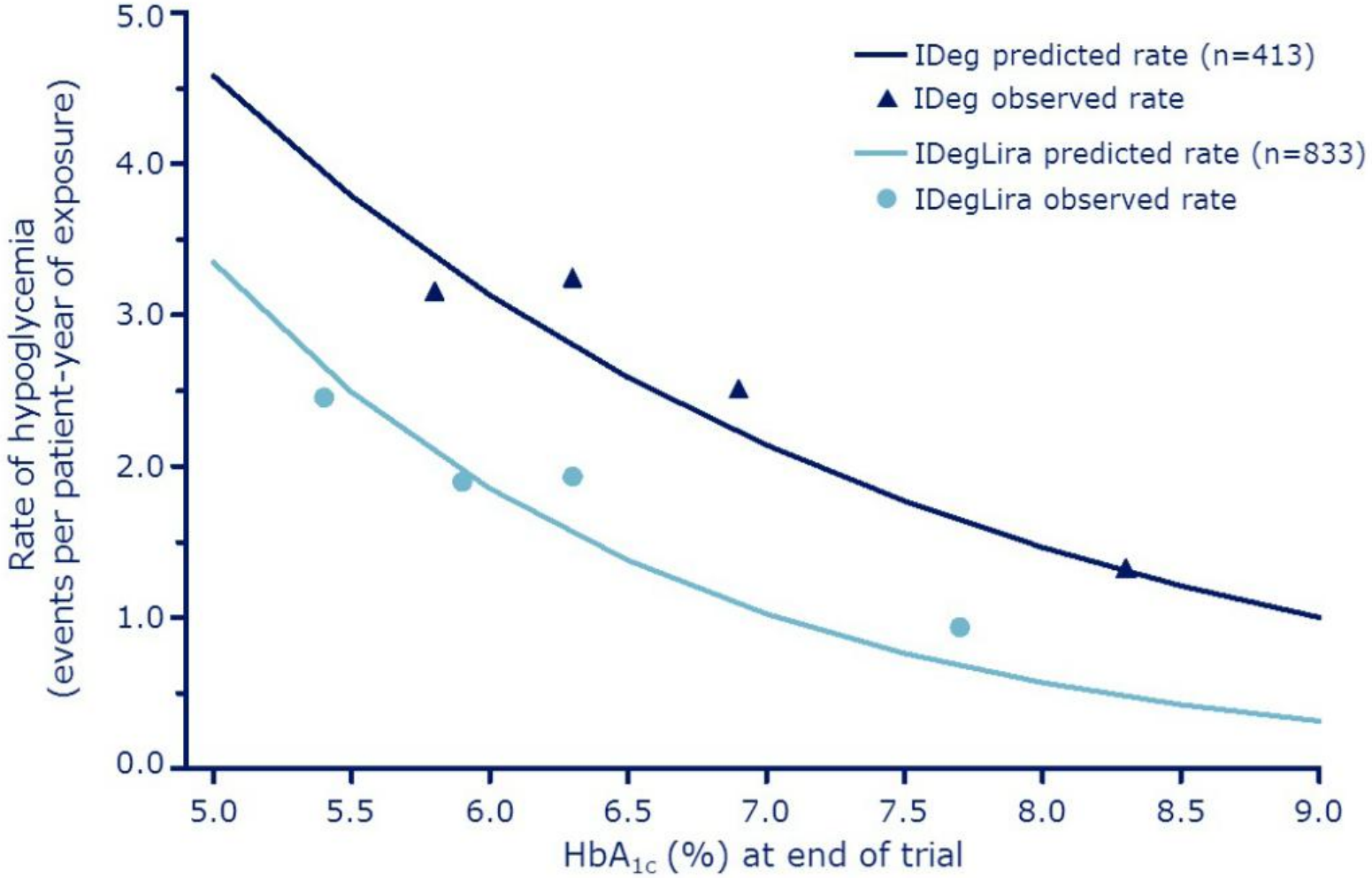
One dose step = 1 U insulin degludec and 0.036 mg liraglutide

9P-SMBG: Post-prandial PG increment



PG increment = change in pre-meal level to 90 min post-meal. Mean values based on FAS and LOCF-imputed data. *p*-values from separate ANCOVAs

Rate of confirmed hypoglycaemia by HbA_{1c}



Mean rates of hypoglycemia by HbA_{1c} at end of trial are predicted from a negative binomial model; symbols are observed hypoglycemia rates by mean HbA_{1c} quartiles based on FAS and LOCF-imputed data.

- **A kombinált alkalmazás lehetséges előnyei**

- **Jobb tolerálhatóság, kedvezőbb mellékhatás profil (hypoglycemia, testsúly, nausea)**

- **Jobb glikémiás kontroll (HbA1c, postprandialis vc)**