YENİ İNSÜLİN FORMÜLLERİ, GÜNCEL UYGULADIĞIMIZ İNSÜLİNLERDEN İYİ Mİ?

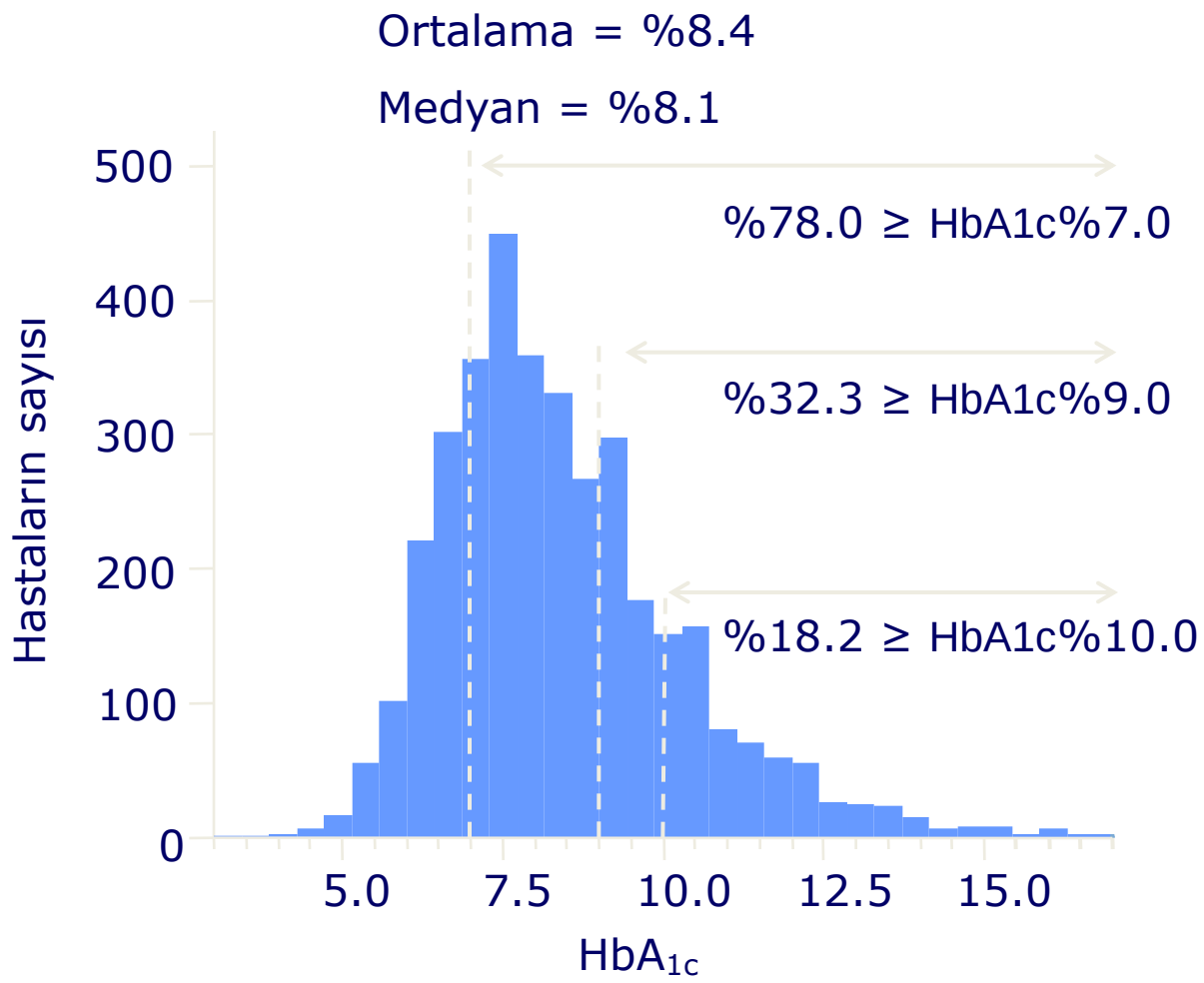
Prof Dr. Cumali Gökçe

Mustafa Kemal Üniv. Endokrinoloji ve Metabolizma Hast. BD. HATAY

Sunum Planı

- Kan şekerini kontrol edebiliyormuyuz?
- Neden yeni insülinlere gereksinim var?
- Yeni insülinler
- Yeni insülin formülleri güncel uyguladığımız insülinlerden iyi mi?

TOPLUMDA İNSÜLİN KULLANAN HASTALARDA DA GLİSEMİK KONTROL YETERSİZDİR



n = 3,658 İngiltere ve Almanya'da insülin kullanıcıları

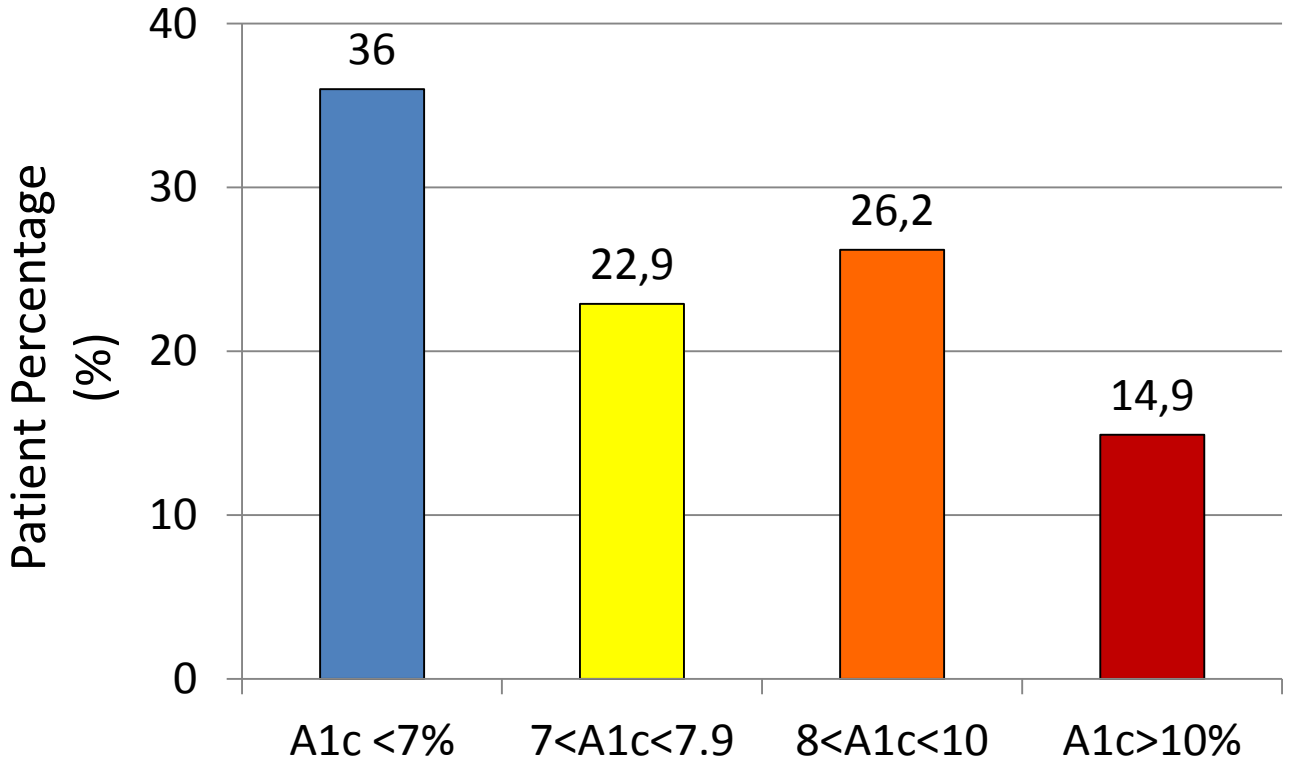
Gough et al.. ADA 2006

Glycemic Contol of Turkish Adult Diabetic Patients

Türkiye'de Tedavi Altındaki Diyabet Hastalarında Glisemik Kontrol

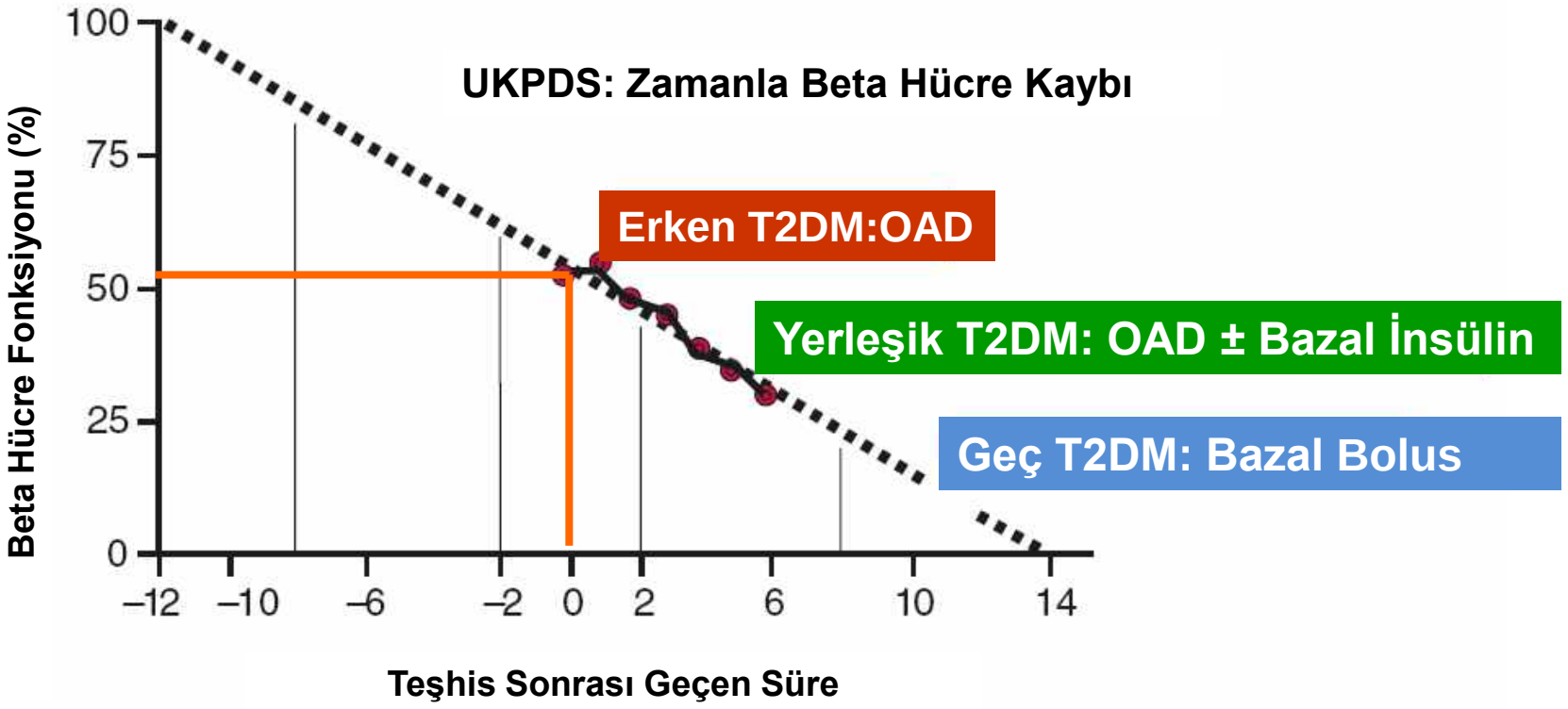
N:2358

İnsülin kullananlarda A1c <%7: %26.4



Turk Jem 2008; 12: 50-4

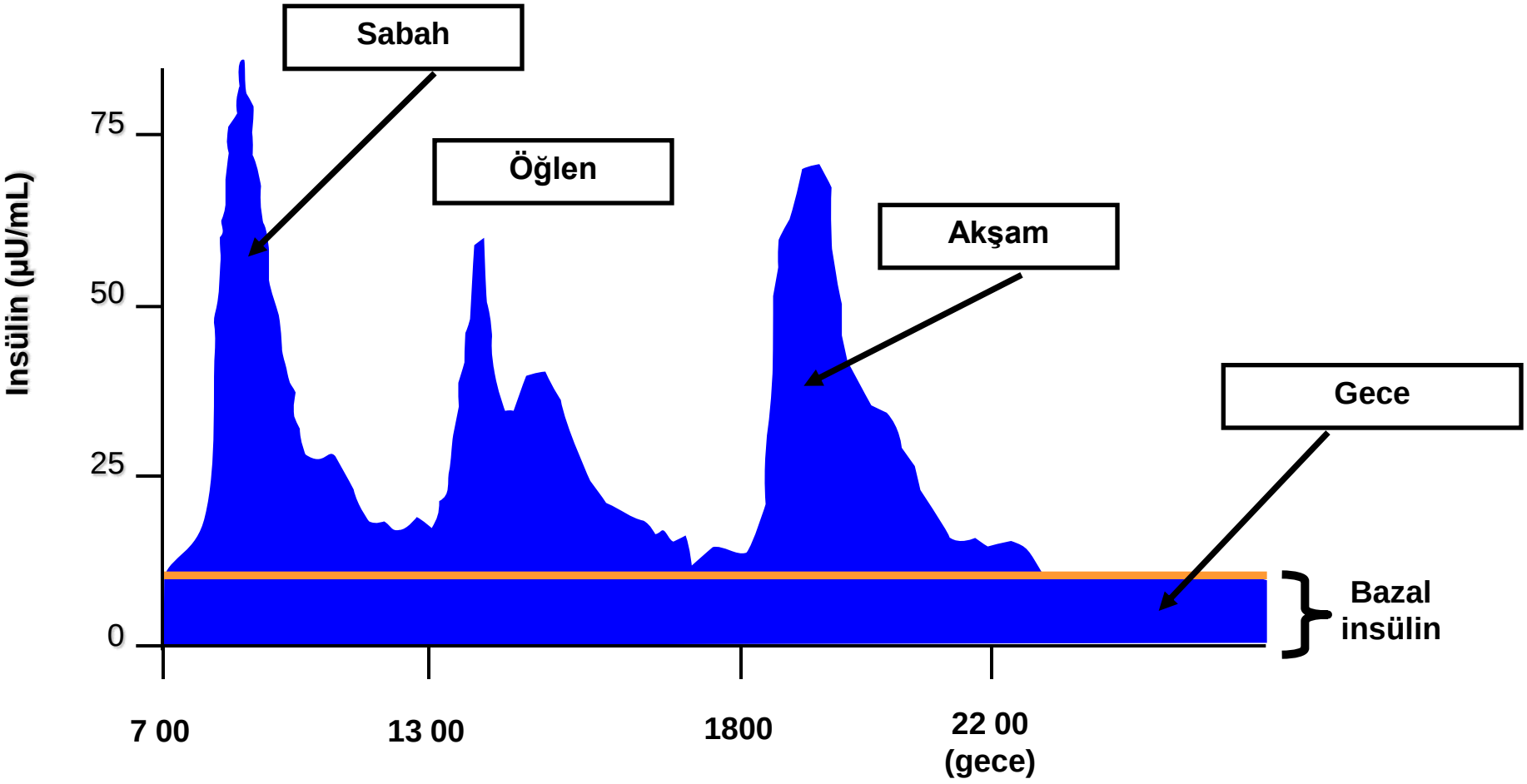
Tip 2 DM Progresif Bir Hastalık



- Zamanla tüm hastalar **insülin** tedavisine ihtiyaç duyacaktır.

Diabetes 44: 1249-1258, 1995

Diyabet/İnsülin tedavisindeki hedef fizyolojik insülin yanıtını taklit edebilmektir.

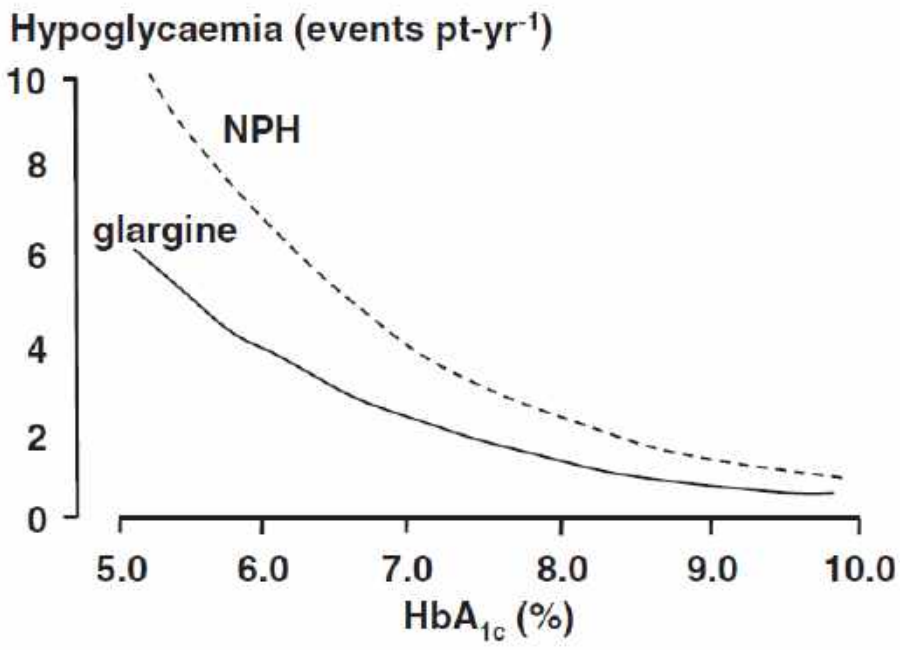


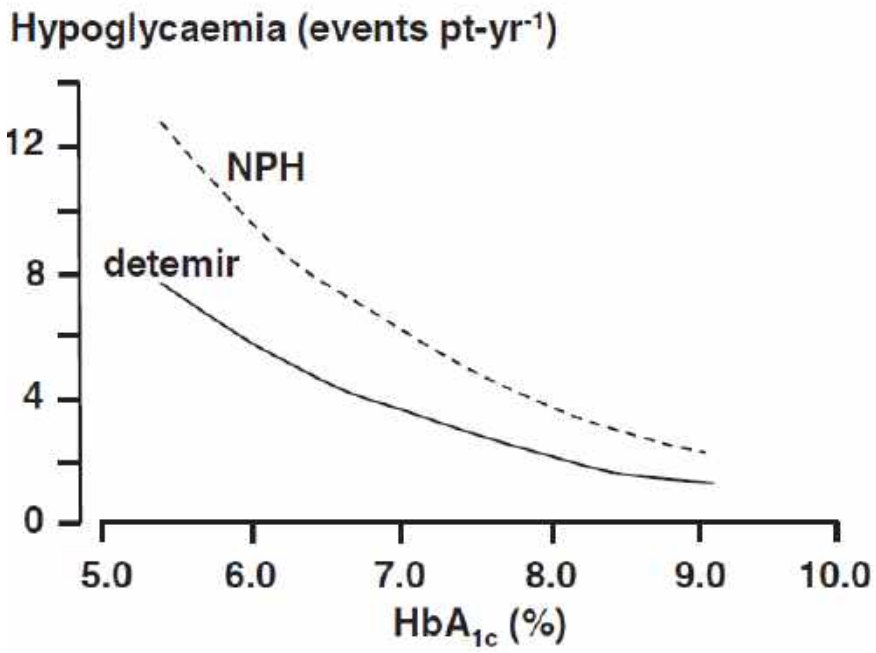
Kruszynska et al. Diabetologia 1987;30:16–21.

İnsülin Tedavisi-Problemler

- Hipoglisemi- Nokturnal hipoglisemi
- 24 saat etkinlik?
  - Hiperglisemi?
  - Etki değişkenliği?
- İdeal bazal insülin;
  - Uzun enj. süresi
  - Sabit FK, FD
  - Etkin glukoz düşürme
- Kilo artışı, enj. ve sayısı ……

Tip 2 DM- Hedefe Ulaşmak için Tedavi Çalışmalarında Hipoglisemi

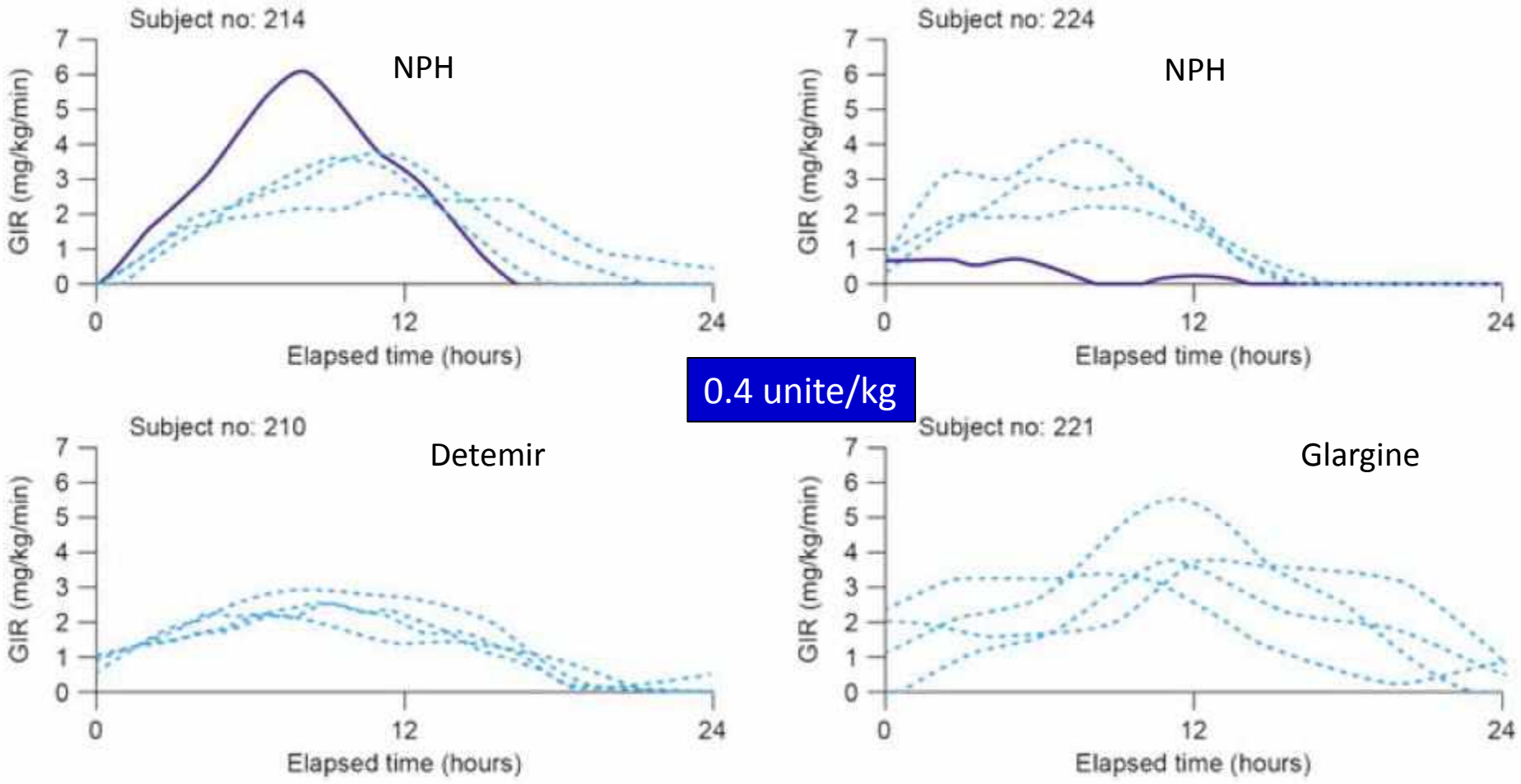




Hipoglisemi

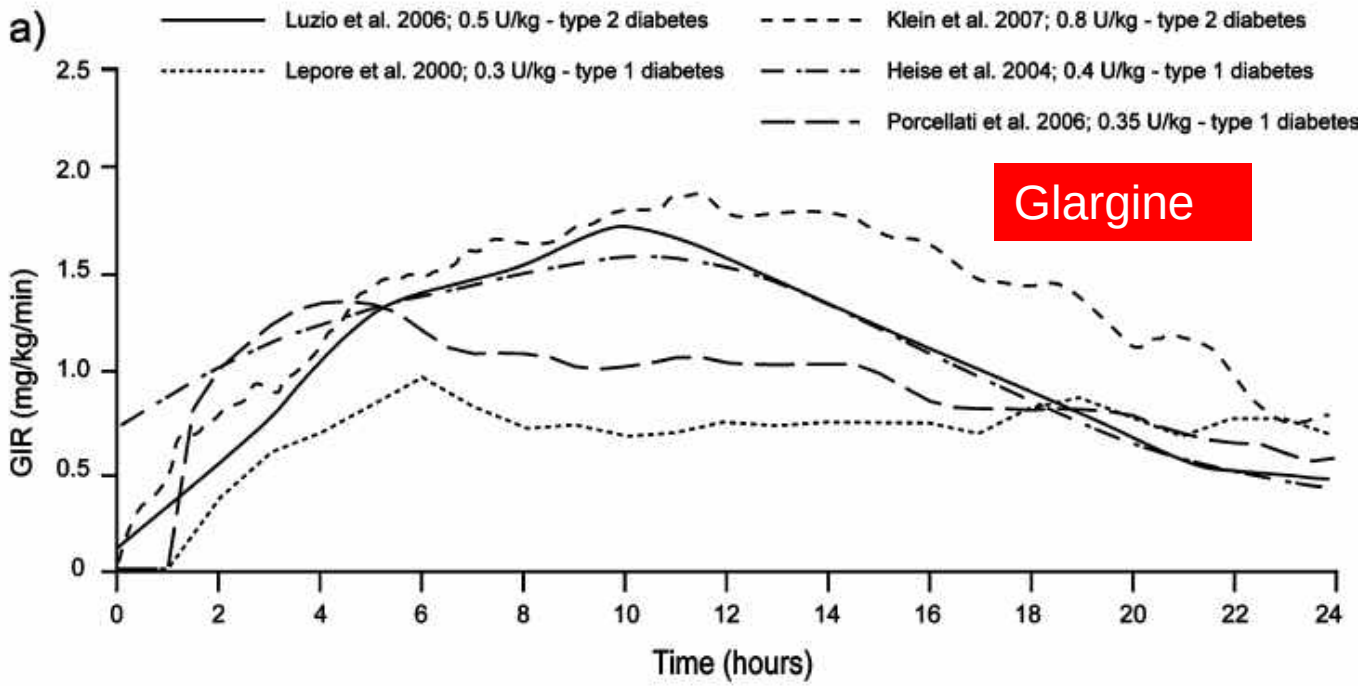
Little S, Shaw J, and Home P. DiabetesTechnology&Theurapeutics. 13, Supplement 1, 2011 S53-64

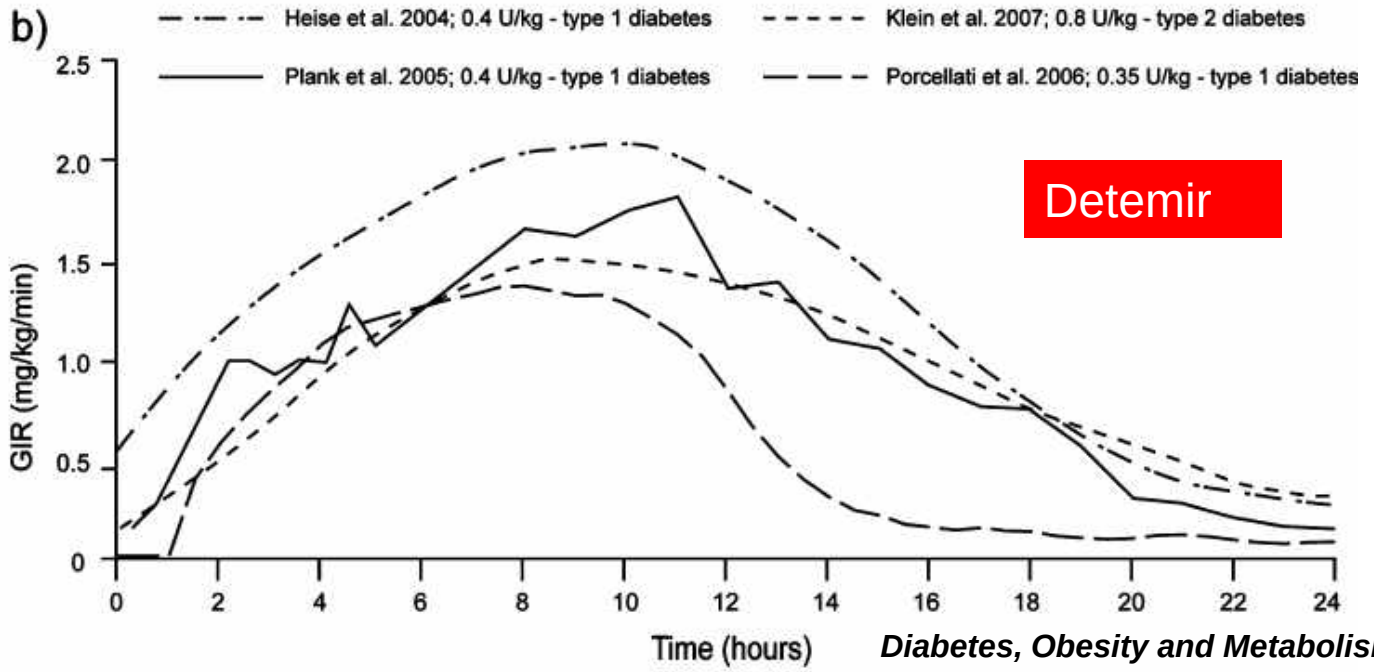
Bazal insülinlerin aynı kişide farklı enjeksiyonlardaki farmakodinamik değişkenliği



Heise Tet al. Diabetes 2004; 53:1614–1620

Vora J,Heise T. Diabetes, Obesity and Metabolism 2013. doi:10.1111/dom.12087

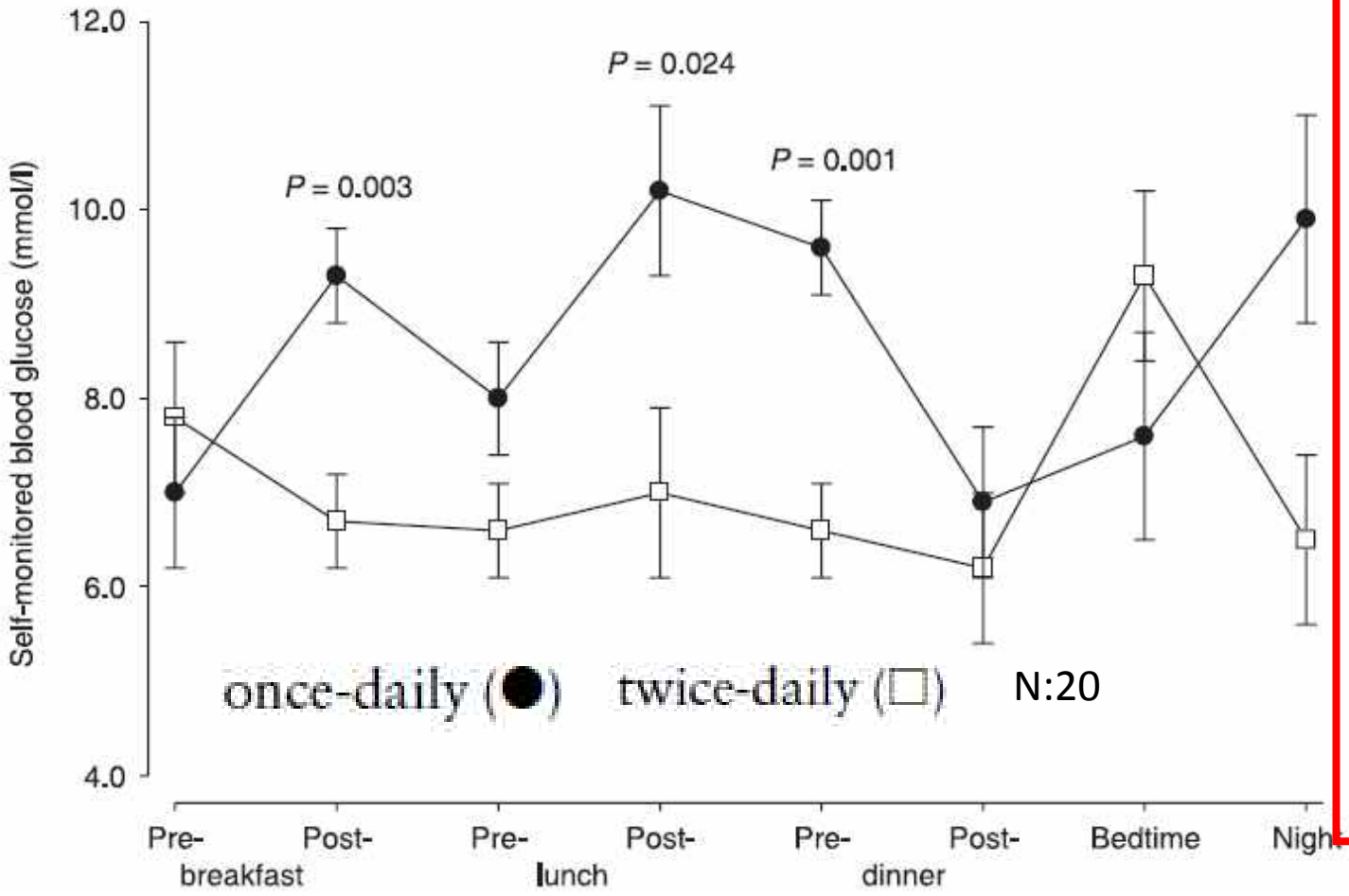




Diabetes, Obesity and Metabolism, 9, 2007, 648–659

DOI: 10.1111/j.1464-5491.2006.01913.x

Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart



- A1c ve Fruktozamin ölçümleri benzer
- Tek enjeksiyon ile 24 saatin sonuna doğru İnsülin ↓→ Glukoz ↑

S. G. Ashwell, J. Gebbie and P. D. Home. Diabet. Med. 23, 879–886 (2006)

Yeni insülinler

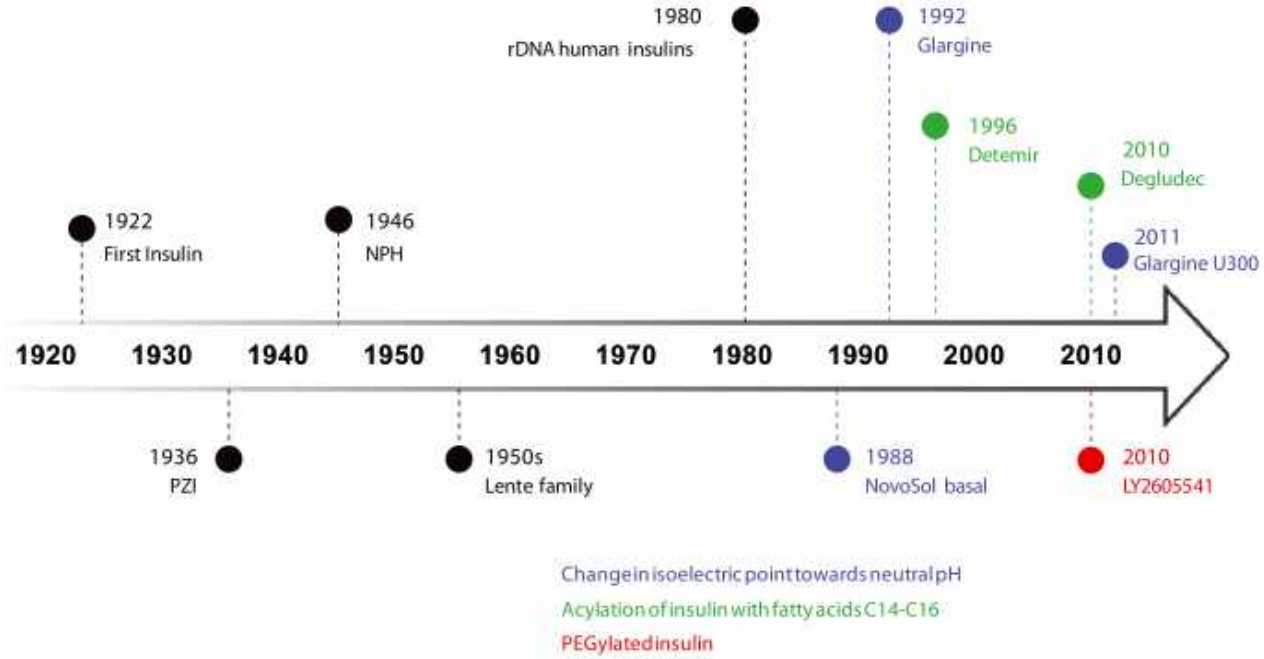


Figure 1. Timeline for the development of novel human insulin analogues. NPH, neutral protamine Hagedorn; PZI, protamine zinc insulin; rDNA, recombinant DNA

Diabetes Metab Res Rev 2014; **30**: 104–119.
DOI: 10.1002/dmrr

Ultra-Uzun etkili İnsülinler

Etki süreleri kullanımda olan uzun etkili insülinlerden daha uzun, bir enjeksiyonla sabit, tahmin edilebilir glukoz düşürücü etkiye sahip olmaları bekleniyor.

Source	Insulin Agent	Patient Characteristics	Insulin Comparator	Design	Outcomes
Rosenstock et al, 2013[56]	LY2605541 (pegylated insulin lispro)	T1DM; basal-bolus therapy	Glargine	8-wk randomized, phase 2, open-label, 2×2 crossover study	Greater improvements in glycemic control, increased total hypoglycemia, reduced nocturnal hypoglycemia, reduced weight, and lowered insulin doses at mealtime
Bergenstal et al, 2012[57]	LY2605541 (pegylated insulin lispro)	T2DM (HbA_{1c} level ≤10.5%); metformin and/or sulfonylurea with glargine or NPH insulin once daily	Glargine	12-wk, randomized, open-label, phase 2 study	Comparable glucose control; total hypoglycemia rates, reduced intraday variability, and lower nocturnal hypoglycemia, as well as weight loss, relative to glargine
Birkeland et al, 2011[43]	Degludec	T1DM; mean HbA_{1c} level 8.4%	Glargine	16-wk randomized, phase 2 controlled trial	Comparable glucose control at similar doses, with reduced rates of hypoglycemia
Heise et al, 2011[45]	Degludec/ aspart	T2DM; background metformin therapy	Glargine	16-wk, open-label trial	Comparable glucose control at similar doses, similar low rates of hypoglycemia, and better glucose control after dinner
Zinman et al 2012[50]	Degludec	T2DM; background therapy for OAD; baseline HbA_{1c} level 7% to 10%	Glargine	1-year treat-to-target, open-label, randomized trial	Comparable glucose control, much lower rates of nocturnal hypoglycemia
Heller et al, 2012[46]	Degludec	T1DM; basal-bolus insulin therapy; HbA_{1c} level ≤10%	Glargine	1-year treat-to-target, open-label, randomized trial	Comparable glucose control and much lower rates of nocturnal hypoglycemia
Garber et al, 2012[44]	Degludec	T2DM; basal-bolus insulin; HbA_{1c} level, 7% to 10%	Glargine	1-year treat-to-target, open-label, randomized trial	Comparable glucose control and much lower rates of overall and nocturnal hypoglycemia
Niskanen et al, 2012[58]	Degludec/ aspart (twice daily) and an alternative formulation	T2DM; HbA_{1c} level 7% to 11%	Biphasic insulin aspart twice daily	16-wk, open-label, randomized, treat-to-target trial	Comparable glucose control and lower rates of hypoglycemia

The Journal of the American Osteopathic Association.113 (4); Supl 2) 2013

LY2605541-PEGylated LysB28

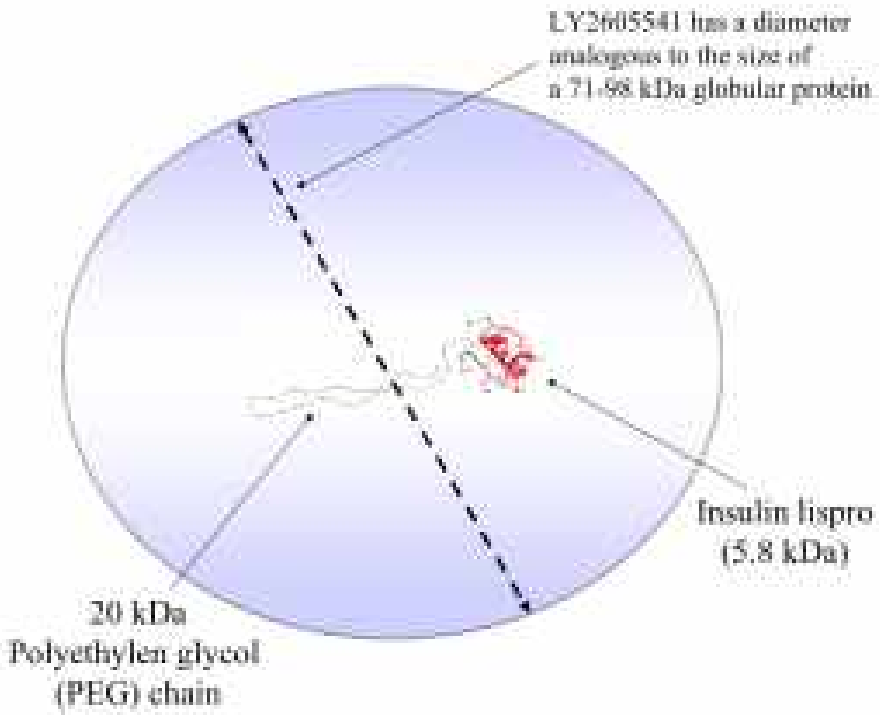
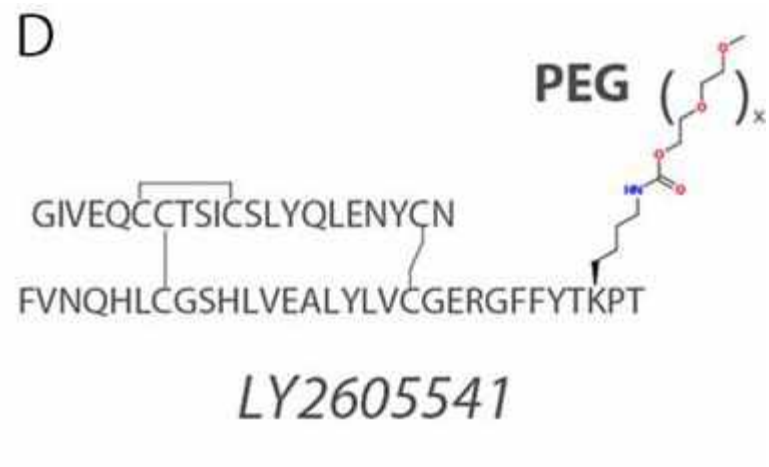


Figure 1—Insulin lispro is a 5.8-kilodalton (kDa) peptide hormone. PEG is a neutral linear, which is conjugated to insulin lispro to give rise to the basal analog LY2605541. It is able to bind three molecules of water, allowing it to become highly hydrated, thereby increasing the hydrodynamic size of the molecule, which delays the absorption and reduces renal filtration resulting in protracted half-life of LY2605541 (5). The PEGylation also protects against proteolytic degradation. PEGylation is novel in the context of insulin, but is a well-established strategy to improve the therapeutic properties of proteins.

LY2605541-PEGylated LysB28



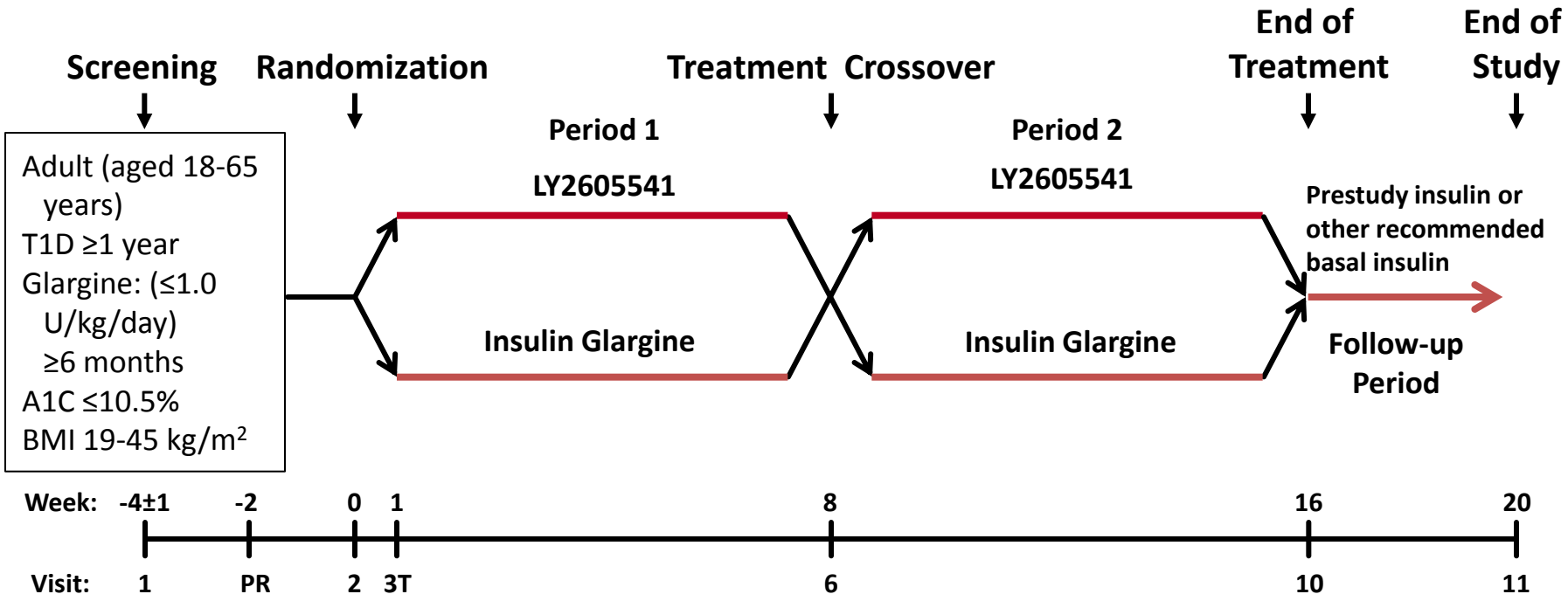
- 20 kDa polyethyleneglycol'ün(PEG) urathane bağı ile insülin lisproya bağlanması ile elde edilmiş.
- PEG bağlantısı ile 4 kat artmış hidrodinamik çapı hem SC depodan emilimini hem de renalklerensi azaltır.

Rosenstock et al, 2013[56]	LY2605541 (pegylated insulin lispro)	T1DM; basal-bolus therapy	Glargine	8-wk randomized, phase 2, open-label, 2×2 crossover study	Greater improvements in glycemic control, increased total hypoglycemia, reduced nocturnal hypoglycemia, reduced weight, and lowered insulin doses at mealtime
Bergenstal et al, 2012[57]	LY2605541 (pegylated insulin lispro)	T2DM (HbA_{1c} level ≤10.5%); metformin and/or sulfonylurea with glargine or NPH insulin once daily	Glargine	12-wk, randomized, open-label, phase 2 study	Comparable glucose control; total hypoglycemia rates, reduced intraday variability, and lower nocturnal hypoglycemia, as well as weight loss, relative to glargine

Diabetes Care. 2013;36(3):522-528.

Hansen RJ, Cutler JGB, Vick A, etal. LY2605541: 896-P. ADA72nd Scientific Sessions. Philadelphia, 2012.

T1DM'de Faz 2 LY2605541 ile Glargine Çalışma Planı



- Phase 2, multinational, randomized, open-label, crossover, clinical trial
- Morning once-daily AM basal insulin (LY2605541 or GL) plus prandial insulin for 8 weeks, then switched to the other basal insulin for 8 weeks

Primary outcome measure: Daily mean blood glucose as measured by 8-point SMBG profiles during 8 weeks of treatment

Rosenstock et al. *Diabetes Care* 2012

T1DM'de Faz 2 LY2605541 ile Glargine Bulgular

- Daha düşük ortalama kan glukoz değeri
- Kilo kaybı
- Azalmış prandiyal insülin dozu
- Daha düşük noktürnal hipoglisemi oranı
- Karaciğer enzimlerinde orta derecede artış
- Normal aralıkta olmasına rağmen daha yüksek TG ve LDL-K, daha düşük HDL-K (normal sınırlarda olmasına rağmen)
- GİS YE hariç diğer YE' ler aynı

Rosenstock et al. *Diabetes Care* 2012.

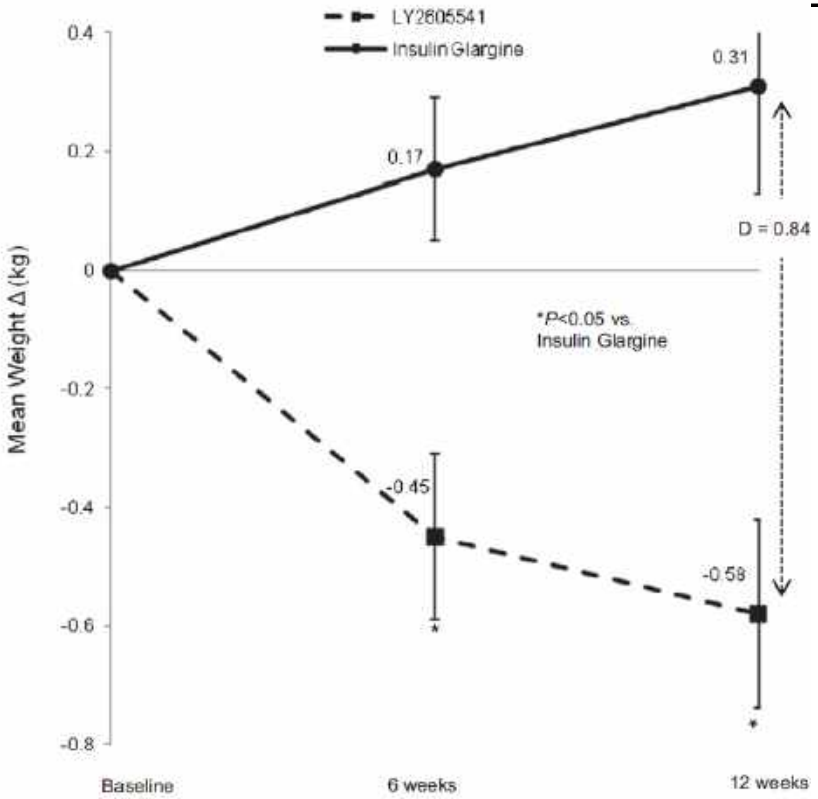
T1DM' de Faz 2 LY2605541 ile Glargine Sonuçlar

- Düzelmiş glisemik kontrol ve azalmış glukoz değişkenliği
- Kilo kaybı
- Daha düşük prandiyal insülin gereksinimi
  - Noktürnal hipoglisemide azalma
- LY2605541 daha farklı bir etki mekanizmasına sahip olabilir
- Faz 3 çalışmaları tespit edilen faydalar ve KC enzimleri ve lipidlerin yüksekliği için planlanmıştır.

Rosenstock et al. *Diabetes Care* 2012

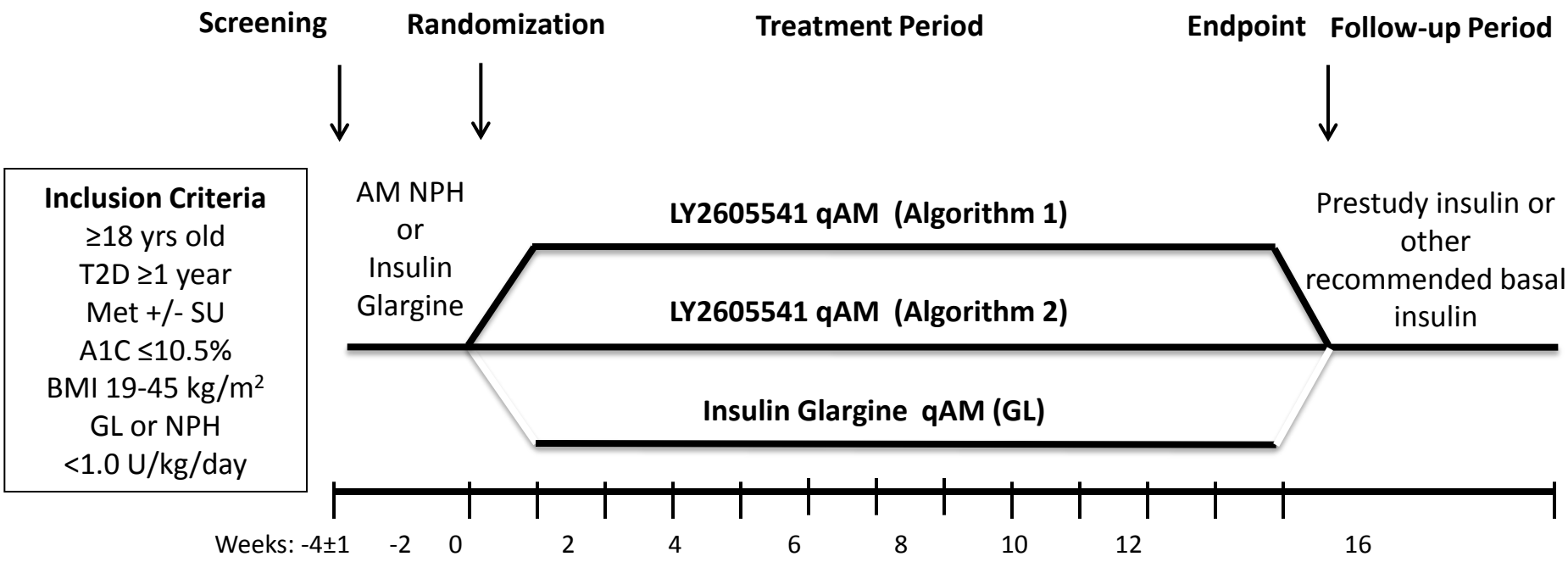
A Randomized, Controlled Study of Once-Daily LY2605541, a Novel Long-Acting Basal Insulin, Versus Insulin Glargine in Basal Insulin–Treated Patients With Type 2 Diabetes

	Combined LY2605541	GL	LS mean difference (90% CI)	*P* value
n	195	93		
FBG (SMBG) (mg/dL)				
Baseline	146.6 ± 2.9	140.3 ± 4.1	—	0.131
Week 12	118.2 ± 2.0	116.9 ± 2.7	—	0.433
Change from baseline	−25.9 ± 2.5	−24.5 ± 3.8	−3.6 (−10.6, 3.4)	0.388
FSG (laboratory) (mg/dL)				
Baseline	146.5 ± 3.2	151.3 ± 4.9	—	0.404
Week 12	122.9 ± 2.7	128.6 ± 4.1	—	0.347
Change from baseline	−23.2 ± 3.4	−22.2 ± 4.7	−0.9 (−9.9, 8.3)	0.882
Daily mean BG (mg/dL)				
Baseline	170.1 ± 3.1	164.7 ± 3.8	—	0.073
Week 12	138.9 ± 2.2	144.7 ± 3.4	—	0.741
Change from baseline	−27.4 ± 2.5	−19.6 ± 3.1	−8.8 (−15.0, −2.7)	0.017
A1C (%)				
Baseline	7.7 ± 0.1	7.8 ± 0.1	—	0.766
Week 12	7.0 ± 0.1	7.2 ± 0.1	—	0.279
Change from baseline	−0.7 ± 0.1	−0.7 ± 0.1	−0.1 (−0.2, 0.0)	0.197



Bergenstal RM, Rosenstock J, Arakaki RF, et al. Diabetes Care 35:2140–2147, 2012

T2DM'de Faz 2 LY2605541 ile Glargine Çalışma Planı



- Statistical Methods
  - Algorithm 1 and Algorithm 2 groups were combined for all analyses
  - All analyses are based on FAS, a slightly modified ITT population
  - Phase 2 trial, statistical significance is determined at p<.1
  - Continuous variables were analyzed by MMRM, except body weight, liver enzyme, and lipids, which were analyzed by ANCOVA

Bergenstal et al. *Diabetes Care* 2012;35(11):2140-7.

T2DM'de Faz 2 LY2605541 ile Glargine Bulgular

- Benzer AKŞ ve A1C
- Glkoz değişkenliğinde düzelme
- Kilo kaybı
- Daha düşük noktürnal hipoglisemi oranı
- YE benzer
- Karaciğer enzimlerinde minimal artış (N aralıkta)
- Normal aralıkta olmasına rağmen daha yüksek TG değerleri

Rosenstock et al. *Diabetes Care* 2012

T2DM'de Faz 2 LY2605541 ile Glargine Sonuçlar

- Gün içi azalmış glukoz değişkenliği
- Kilo kaybı
- Noktürnal hipoglisemide azalma
- LY2605541 daha farklı bir etki mekanizmasına sahip olabilir
  - Kilo alımı ve TG azalması- insülin tedavisinde
  - Kilo kaybı ve N TG-LY2605541 tedavisinde

Rosenstock et al. *Diabetes Care* 2012.

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Diabetes. 2014 Feb;63(2):494-504. doi: 10.2337/db13-0826. Epub 2013 Oct 2.

Novel PEGylated basal insulin LY2605541 has a preferential hepatic effect on glucose metabolism.

Moore MC[1], Smith MS, Sinha VP, Beals JM, Michael MD, Jacober SJ, Cherrington AD.

Author information

Abstract

The impact of the novel basal insulin LY2605541 (LY) on hepatic and nonhepatic glucose uptake (non-HGU) was evaluated. Conscious dogs underwent euglycemic clamps with tracer and hepatic balance measurements. Clamp period infusions were peripheral venous regular insulin (0.1 nmol · kg(-1) · h(-1) [control], n = 6) or LY (bolus [nmol/kg], continuous [nmol · kg(-1) · h(-1)]: 0.5, 0.5 [n = 6]; 0.375, 0.375 [n = 5]; 0.25, 0.25 [n = 4]), somatostatin, and glucose, as well as intraportal glucagon (basal). During the clamp, the dogs switched from net hepatic glucose output to uptake (rates reached 2.1 ± 1.2, 0.9 ± 2.1, 8.6 ± 2.3, and 6.0 ± 1.1 μmol · kg(-1) · min(-1) within 5 h in control, LY0.25, LY0.375, and LY0.5, respectively). Non-HGU in LY increased less than in control; the ratio of change from basal in non-HGU to change in net hepatic glucose balance, calculated when glucose infusion rates (GIRs) were ~20 μmol · kg(-1) · min(-1) in all groups, was higher in control (1.17 ± 0.38) versus LY0.25 (0.39 ± 0.33), LY0.375 (-0.01 ± 0.13), and LY0.5 (-0.09 ± 0.07). Likewise, the change from baseline in glucose Rd-to-Ra ratio was greatest in control (1.4 ± 0.3 vs. 0.6 ± 0.4, 0.5 ± 0.2, and 0.6 ± 0.2 in LY0.25, LY0.375, and LY0.5, respectively). In contrast to exogenously administered human insulin, LY demonstrated preferential hepatic effects, similar to endogenously secreted insulin. Therefore, the analog might reduce complications associated with current insulin therapy.

Comment in

LY2605541--a preferential hepato-specific insulin analogue. [Diabetes. 2014]

PMID: 24089512 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

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LY2605541--a preferential hepato-specific insulin analogue. [Diabetes. 2014]

Interaction of a selective serotonin reuptake inhibitor v [Am J Physiol Endocrinol Metab. 2005]

A comparison of the effects of selective increases in peripheral or portal [Diabetes. 1996]

Small amounts of fructose markedly augment net hepatic glucose uptake in th [Diabetes. 1998]

Inclusion of low amounts of fructose with an intraporta [Am J Physiol Endocrinol Metab. 2005]

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- Eksojen uygulanan insan insülinlerinin aksine, LY endojen insüline benzer hepatik olumlu etkiler göstermiştir. Mevcut insülinlerden kaynaklanan komplikasyonları azaltabilir...

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Diabetes Care. 2014 Mar;37(3):659-65. doi: 10.2337/dc12-2621. Epub 2013 Nov 6.

Lower glucose variability and hypoglycemia measured by continuous glucose monitoring with novel long-acting insulin LY2605541 versus insulin glargine.

Bergenstal RM[1], Rosenstock J, Bastyr EJ 3rd, Prince MJ, Qu Y, Jacober SJ.

Author information

Abstract

OBJECTIVE: To use continuous glucose monitoring (CGM) to evaluate the impact of the novel, long-acting basal insulin analog LY2605541 on hypoglycemia and glycemic variability in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS: Hypoglycemia and glucose variability were assessed with CGM of interstitial glucose (IG) in a subset of patients with type 2 diabetes from a phase II, randomized, open-label, parallel study of LY2605541 (n = 51) or insulin glargine (GL) (n = 25). CGM was conducted on 3 consecutive days (72-84 h) during the week before week 0, 6, and 12 study visits.

RESULTS: Measured by CGM for 3 days prior to the 12-week visit, fewer LY2605541-treated patients experienced hypoglycemic events overall (50.0 vs. 78.3%, P = 0.036) and nocturnally (20.5 vs. 47.8%, P = 0.027) and spent less time with IG ≤70 mg/dL than GL-treated patients during the 24-h (25 ± 6 vs. 83 ± 16 min, P = 0.012) and nocturnal periods (11 ± 5 vs. 38 ± 13 min, P = 0.024). These observations were detected without associated differences in the average duration of individual hypoglycemic episodes (LY2605541 compared with GL 57.2 ± 5.4 vs. 69.9 ± 10.2 min per episode, P = NS). Additionally, LY2605541-treated patients had lower within-day glucose SD for both 24-h and nocturnal periods.

CONCLUSIONS: By CGM, LY2605541 treatment compared with GL resulted in fewer patients with hypoglycemic events and less time in the hypoglycemic range and was not associated with protracted hypoglycemia.

PMID: 24198302 [PubMed - in process]

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A randomized, controlled study of once-daily LY2605541, a novel long-a [Diabetes Care. 2012]

Better glycemic control and weight loss with the novel long-acting basal ins [Diabetes Care. 2013]

Continuous Subcutaneous Insulin Infusion (CSII) Pumps fc [Ont Health Technol Assess Ser. 2009]

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

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

See reviews...

See all...

Related information

Related Citations

- CGMS ile, LY 2605541 vs Glargine
  - Daha düşük glukoz değişkenliği
  - Daha az hipoglisemi
  - Daha az hipoglisemide kalma süresi

Diabetes Obes Metab. 2014 Apr;16(4):351-6.

Contrasting weight changes with LY2605541, a novel long-acting insulin, and insulin glargine despite similar improved glycaemic control in T1DM and T2DM.

Jacober SJ, Rosenstock J, Bergenstal RM, Prince MJ, Qu Y, Beals JM.

Abstract

AIMS: The basal insulin analogue LY2605541, a PEGylated insulin lispro with prolonged duration of action, was previously shown to be associated with modest weight loss in Phase 2, randomized, open-label trials in type 2 (N=288) and type 1 (N=137) diabetes mellitus (T2DM and T1DM), compared with modest weight gain with insulin glargine. Exploratory analyses were conducted to further characterize these findings.

METHODS: Pearson correlations between change in body weight and other variables were calculated. Continuous variables were analysed using a mixed linear model with repeated measurements. Proportions of subjects with weight loss were analysed using Fisher's exact test for T2DM and Nagelkerke's method for T1DM.

RESULTS: Weight loss was more common in LY2605541-treated patients than in patients treated with insulin glargine (T2DM: 56.9 vs. 40.2%, p=0.011; T1DM: 66.1 vs. 40.3%, p<0.001). More LY2605541-treated patients experienced ≥5% weight loss compared to patients treated with glargine (T2DM: 4.8 vs. 0%, p=0.033; T1DM: 11.9 vs. 0.8%, p<0.001). In both the T1DM and T2DM studies, weight change did not correlate with baseline body mass index (BMI), or change in HDL-cholesterol in either treatment group. No consistent correlations were found across both studies between weight change and any of the variables assessed; however, weight change was significantly correlated with hypoglycaemia rate in glargine-treated T2DM patients.

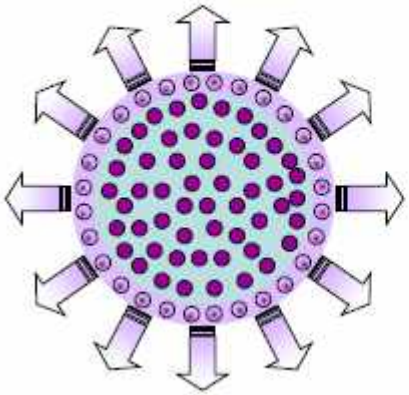
CONCLUSION: In two Phase 2 trials, improved glycaemic control with long-acting basal insulin analogue LY2605541 is associated with weight loss in previously insulin-treated patients. This weight change is independent of baseline BMI or hypoglycaemia.

PMID: 24719911 [PubMed - in process]

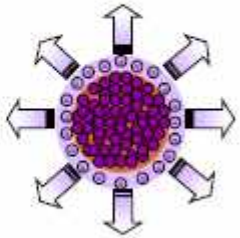
- Tip 1 DM ve Tip 2 DM ile yapılan Faz 2 Çalışmasında (LY vs GL)
  - LY ile daha önce insülin alanlarda kilo kaybı
  - Kilo kaybı BMI veya hipoglisemiden bağımsız

U-300 İnsülin Glargine: daha düz, daha stabil ve uzamış (FK/FD) profili

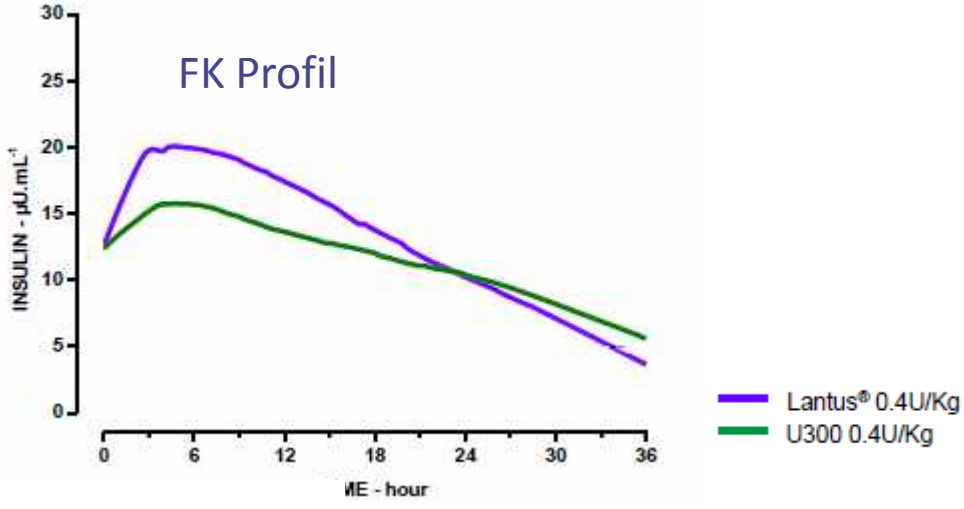
İnsülin Glargine

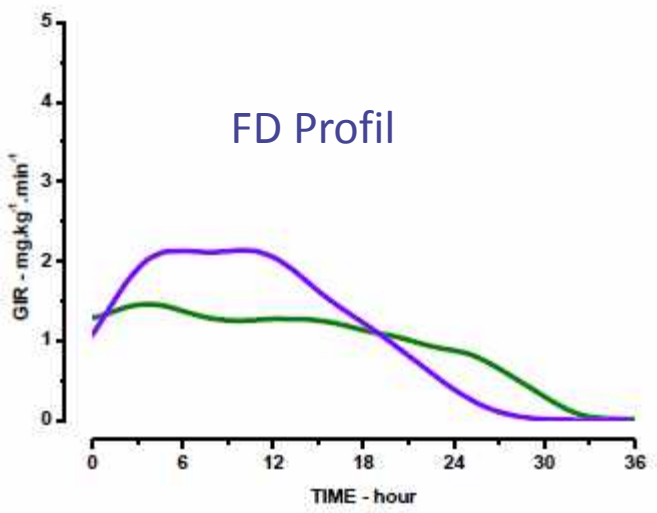


U300



- **Daha konsantre formülasyon(x3)**
- **Azalmış volüm (1/3) ve SC depoda insülin glargine'ninazalmış yüzey alanı (1/2)**
- **Glargine'nin daha yavaş salınımı**
- **Daha düz FK/FD profili dozdan bağımsızdır ve glikoz kontrolü enjeksiyondan sonra 36. saate (çalışma sonu) kadar sürmektedir.**





Dahmen R et al, ADA 2013, abstract no. 113-OR.

EDITION I: U 300,U100 (GL) ile benzer etkinlik ve daha az noktürnal hipoglisemi göstermektedir

- Hızlı etkili insülin + bazal insülin kullanan 807 T2DM'li hastada U 300'ün etkililik ve güvenirliğini GL (U100) ile karşılaştıran 6 aylık, çok merkezli, 1:1 randomize, açık etiketli, paralel grup çalışması

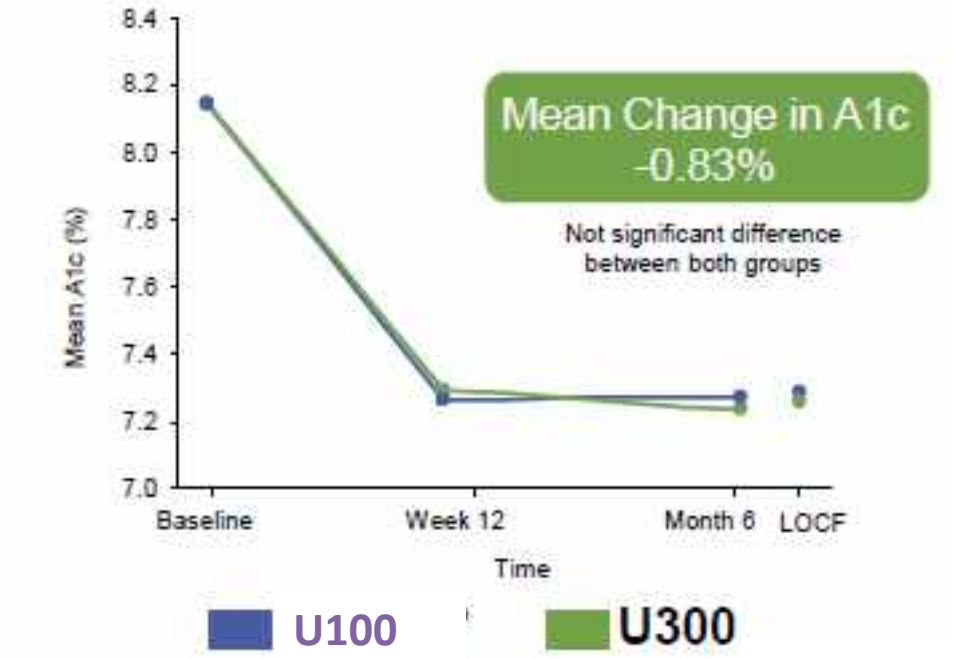
- Ort yaş 60 yıl, DM süresi 15.8 yıl, BMI 36.6 kg/m2, A1C % 8.15 , toplam insülin dozu 1.2 U/kg, bazal insulin dozu 0.67 U/kg

- Birincil sonlanım: 6 ayda A1c değişimi, İkincil sonlanım: 3-6 arası ≥1 ciddi veya konfirme noktürnal hipoglisemi geçiren hasta oranı

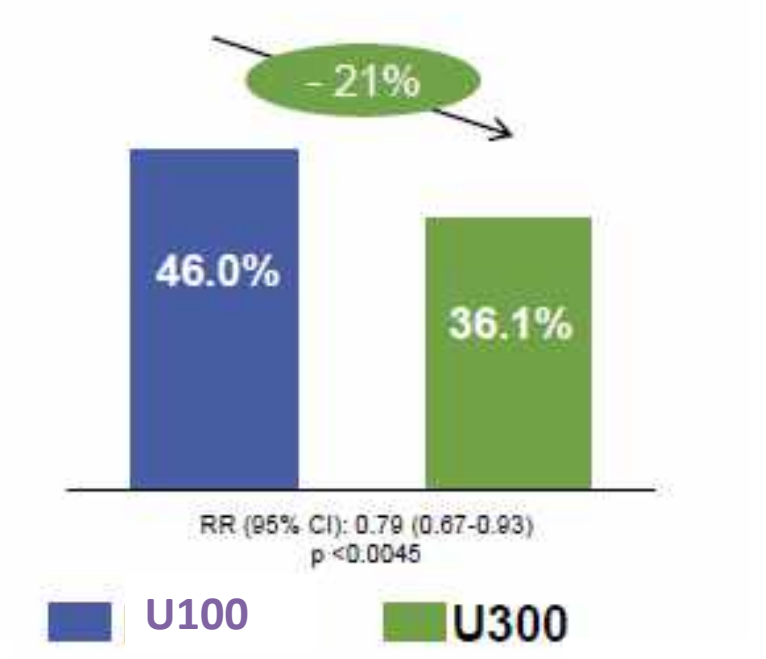
Riddle MC et al, ADA 2013, Late Breaking Poster 43-LB

EDITION I: U 300,U100 (GL) ile benzer etkinlik ve daha az noktürnal hipoglisemi göstermektedir

A1c değişimi



En az 1 ciddi ya da konfirme noktürnal hipoglisemi oranı



Riddle MC et al, ADA 2013, Late Breaking Poster 43-LB

EDITION II: U-300 ile daha az hipoglisemi ve daha az kilo alımı

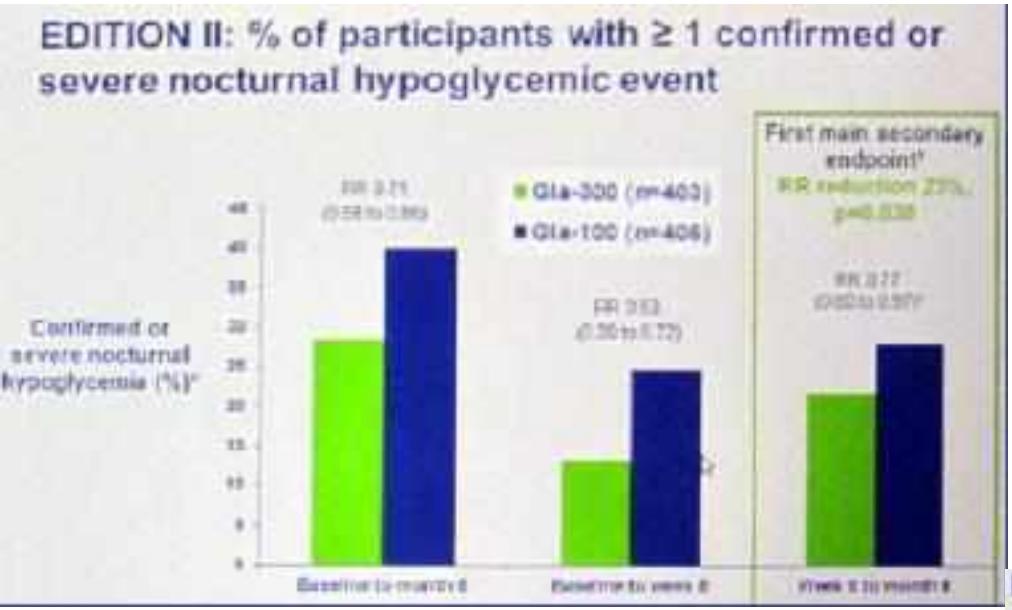
- 811 T2DM hastasında U-300 vs U-100 değerlendirildiği 6 aylık açık uçlu, randomize çalışma

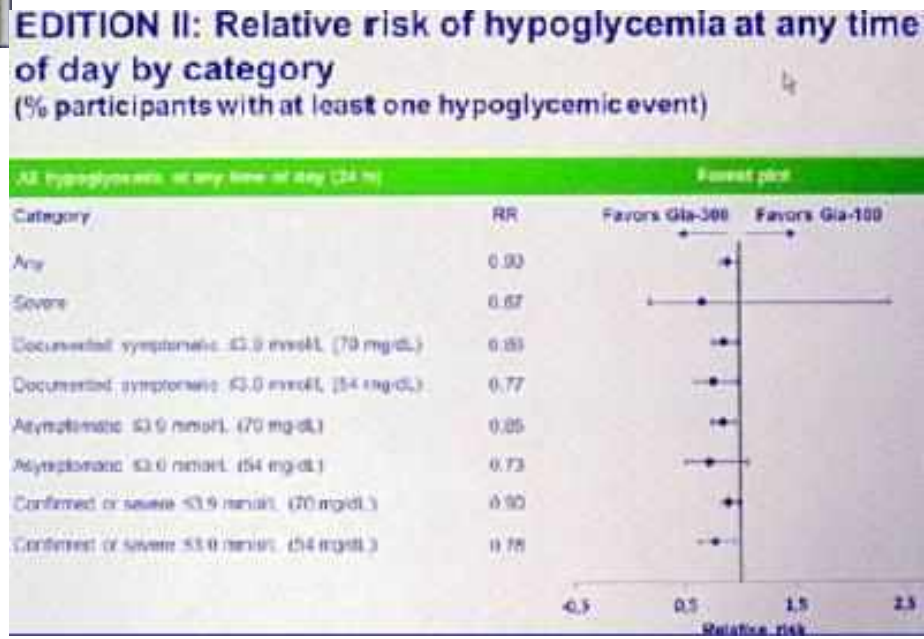
Sonuç: U-300 ile;

- Benzer A1c ve APG düşüşü
- Daha az ciddi ve konfirme noktürnal hipoglisemi
- Her A1c düzeyinde daha az hipoglisemi
- Daha az kilo artışı (0.08 vs 0.66 kg, p:0.01)
- Tüm bulgular EDITION I ile uyumlu

Yki-Jarvinen et al. WDC 2013 OP-0075

EDITION II: U-300 ile daha az hipoglisemi ve daha az kilo alımı

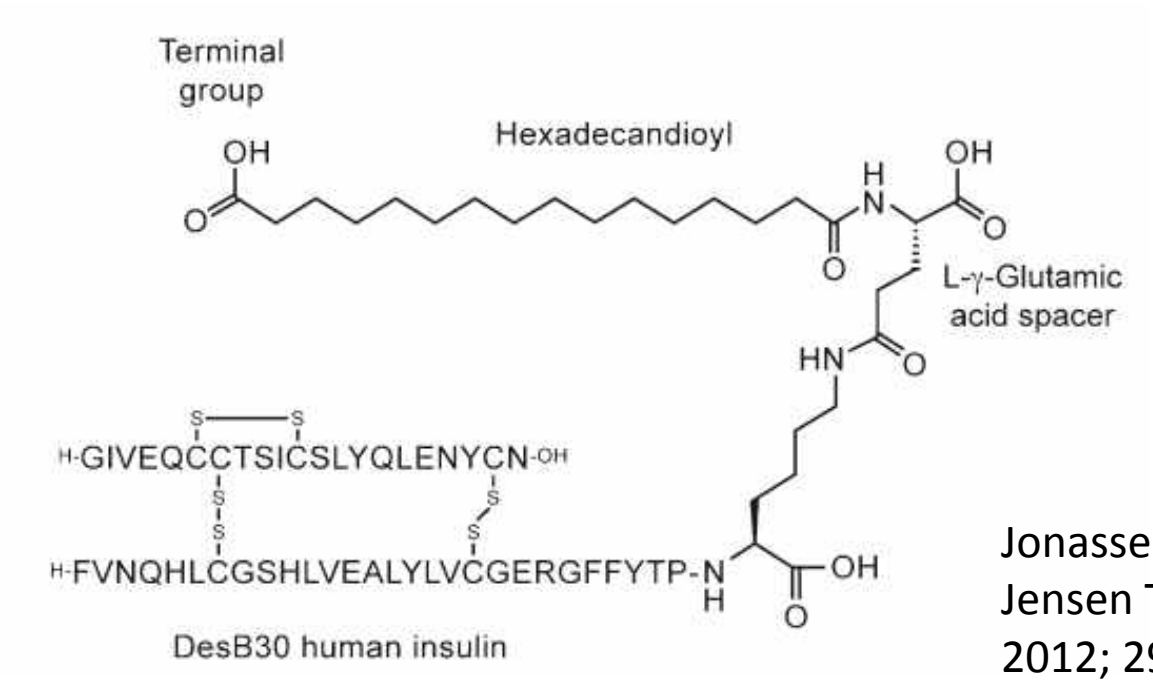




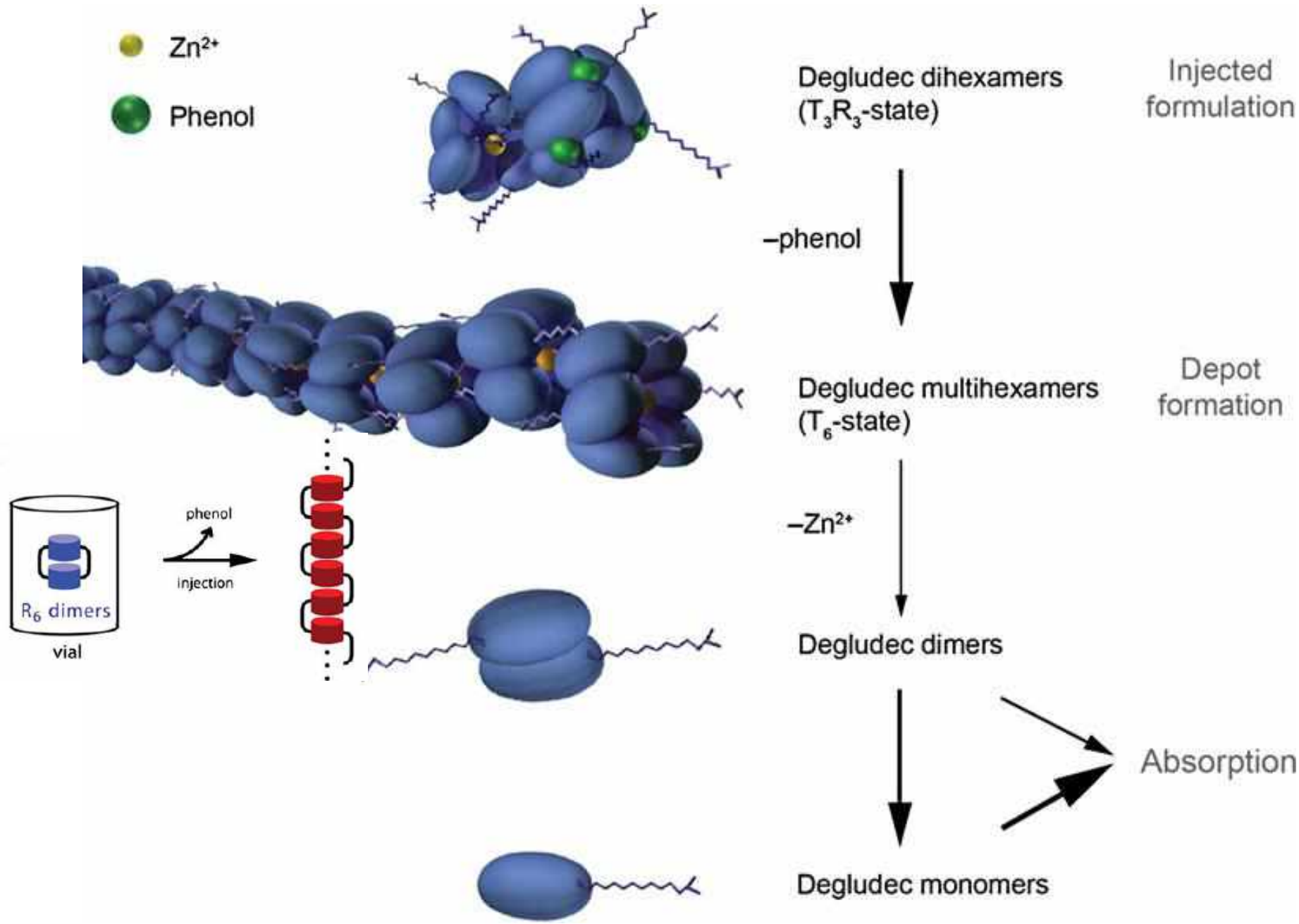
Yki-Jarvinen et al. WDC 2013 OP-0075

Degludec

- İnsülin degludec nötral, çözünür, ultra-uzun etkili bazal insülin analoğudur. İnsan insülini ile B30'daki threonin aminoasidinin çıkarılarak B29 daki Lysine' e glutamik asid aracılığı ile yağ asidi (hexadecanedioicacid) bağlanarak oluşturulmuştur.

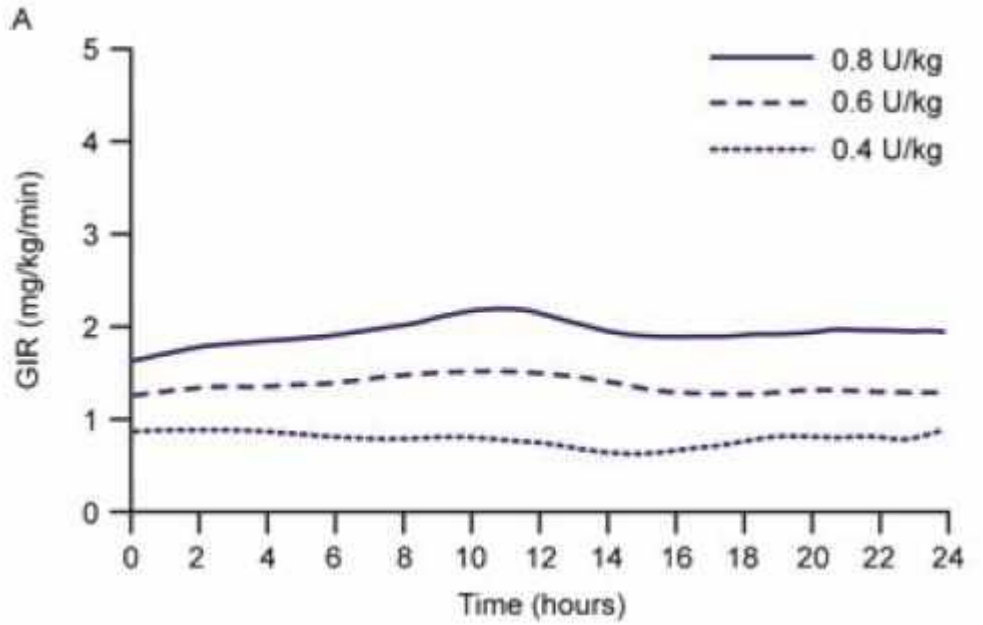


Jonassen I, Havelund S, Hoeg-Jensen T, et al. Pharm Res 2012; 29: 2104–2114.



Jonassen I, Havelund S, Hoeg-Jensen T, et al.Design of the novel protraction mechanism of insulin degludec,an ultra-long-acting basal insulin. Pharm Res 2012; 29: 2104–2114.

Farmakokinetik ve Farmakodinamik



- Tip 1 DM'da 0.6 ve 0.8 IU/kg/gün dozunda etki süresi >42 saat
- 100 IU/ml ve 200IU/ml benzer etkili
- İnsan insülinine benzer eliminasyon, insülin reseptöründe
- Ortalama yarılanma süresi 25 saat

Heise T, Nosek L, Bottcher SG, Hastrup H, Haahr H. Diabetes Obes Metab 2012; 14: 944–950.

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See 1 citation in Diabet Med by Bode Bw:

Diabet Med. 2013 Nov;30(11):1293-7. doi: 10.1111/dme.12243. Epub 2013 Jun 17.

Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN(®) Basal-Bolus Type 1): 2-year results of a randomized clinical trial.

Bode BW[1], Buse JB, Fisher M, Garg SK, Marre M, Merker L, Renard E, Russell-Jones DL, Hansen CT, Rana A, Heller SR; BEGIN® Basal-Bolus Type 1 trial investigators.

Collaborators (89)

Author information

Abstract

AIMS: The goal of this study was to compare the long-term safety and efficacy of the basal insulin analogue, insulin degludec with insulin glargine (both with insulin aspart) in Type 1 diabetes, over a 2-year time period.

METHODS: This open-label trial comprised a 1-year main trial and a 1-year extension. Patients were randomized to once-daily insulin degludec or insulin glargine and titrated to pre-breakfast plasma glucose values of 3.9-4.9 mmol/l.

RESULTS: The rate of nocturnal confirmed hypoglycaemia was 25% lower with insulin degludec than with insulin glargine (P = 0.02). Rates of confirmed hypoglycaemia, severe hypoglycaemia and adverse events, and reductions in glycated haemoglobin and fasting plasma glucose were similar between groups. Despite achieving similar glycaemic control, insulin degludec-treated patients used 12% less basal and 9% less total daily insulin than did insulin glargine-treated patients (P < 0.01).

CONCLUSIONS: Long-term basal therapy using insulin degludec in Type 1 diabetes required lower doses and was associated with a 25% lower risk for nocturnal hypoglycaemia than insulin glargine.

Comment in

Insulin degludec: a new insulin for today? [Diabet Med. 2013]

PMID: 23710902 [PubMed - in process] Free full text

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Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in t [Lancet. 2012]

Comparison of insulin degludec with insulin glargine in insulin-naive subje [Diabet Med. 2013]

Review Insulin degludec and insulin degludec/insulin aspart: a review of [Drugs. 2013]

Review Insulin glargine: a review of its therapeutic use as a long-acting ag [Drugs. 2001]

See reviews...

See all...

Cited by 1 PubMed Central article

Effects of switching from insulin glargine or detemir to insulin degludec [Diabetes Ther. 2013]

- Tip 1 DM'de 2 yıl süreli IDeg vs GL,
  - IDeg insülin dozu daha düşük
  - %25 daha az noktürnal hipoglisemi

Display Settings: Abstract

Send to:

Lancet. 2012 Apr 21;379(9825):1498-507. doi: 10.1016/S0140-6736(12)60205-0.

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[1], King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M, Rosenstock J, Endahl LA, Francisco AM, Hollander P; NN1250-3582 (BEGIN BB T2D) Trial Investigators.

Collaborators (132)

Author information

Abstract

BACKGROUND: Basal insulin therapy does not stop loss of β-cell function, which is the hallmark of type 2 diabetes mellitus, and thus diabetes control inevitably deteriorates. Insulin degludec is a new, ultra-longacting basal insulin. We aimed to assess efficacy and safety of insulin degludec compared with insulin glargine in patients with type 2 diabetes mellitus.

METHODS: In this 52 week, phase 3, open-label, treat-to-target, non-inferiority trial, undertaken at 123 sites in 12 countries, we enrolled adults (aged ≥18 years) with type 2 diabetes mellitus and a glycated haemoglobin (HbA(1c)) of 7·0-10·0% after 3 months or more of any insulin regimen (with or without oral antidiabetic drugs). We randomly allocated eligible participants in a 3:1 ratio to receive once-daily subcutaneous insulin degludec or glargine, stratified by previous insulin regimen, via a central interactive response system. Basal insulin was titrated to a target plasma glucose concentration of 3·9-<5·0 mmol/L self-measured before breakfast. The primary outcome was non-inferiority of degludec to glargine measured by change in HbA(1c) from baseline to week 52 (non-inferiority limit of 0·4%) by ANOVA in the full analysis set. We assessed rates of hypoglycaemia in all treated patients. This study is registered with ClinicalTrials.gov, number NCT00972283.

FINDINGS: 744 (99%) of 755 participants randomly allocated degludec and 248 (99%) of 251 allocated glargine were included in the full analysis set (mean age 58·9 years [SD 9·3], diabetes duration 13·5 years [7·3], HbA(1c) 8·3% [0·8], and fasting plasma glucose 9·2 mmol/L [3·1]); 618 (82%) and 211 (84%) participants completed the trial. After 1 year, HbA(1c) decreased by 1·1% in the degludec group and 1·2% in the glargine group (estimated treatment difference [degludec-glargine] 0·08%, 95% CI -0·05 to 0·21), confirming non-inferiority. Rates of overall confirmed hypoglycaemia (plasma glucose <3·1 mmol/L or severe episodes requiring assistance) were lower with degludec than glargine (11·1 vs 13·6 episodes per patient-year of exposure; estimated rate ratio 0·82, 95% CI 0·69 to 0·99; p=0·0359), as were rates of nocturnal confirmed hypoglycaemia (1·4 vs 1·8 episodes per patient-year of exposure; 0·75, 0·58 to 0·99; p=0·0399). Rates of severe hypoglycaemia seemed similar (0·06 vs 0·05 episodes per patient-year of exposure for degludec and glargine) but were too low for assessment of differences. Rates of other adverse events did not differ between groups.

INTERPRETATION: A policy of suboptimum diabetes control to reduce the risk of hypoglycaemia and its consequences in advanced type 2 diabetes mellitus might be unwarranted with newer basal insulins such as degludec, which are associated with lower risks of hypoglycaemia than insulin glargine.

- Tip 2 DM'de 1 yıl süreli IDeg vs GL,
  - HbA1c sonuçları benzer
  - "Confirmed" ve noktürnal hipoglisemi daha düşük
  - Non inferior

- Tip 1 DM'de 1 yıl süreli IDeg, IDeg Flex vs GL,
  - HbA1c sonuçları benzer ve güvenli
  - Bireysel gereksinime göre bazal insülin uyumunu (enj. zamanı açısından) sağlayabilir.
  - Non inferior

Efficacy and Safety of Insulin Degludec in a Flexible Dosing Regimen vs Insulin Glargine in Patients With Type 1 Diabetes (BEGIN: Flex T1): A 26-Week Randomized, Treat-to-Target Trial With a 26-Week Extension

Chantal Mathieu, Priscilla Hollander, Bresta Miranda-Palma, John Cooper, Edward Franek, David Russell-Jones, Jens Larsen, Søren Can Tamer, and Stephen C. Bain, on behalf of the NN1250-3770 (BEGIN: Flex T1) Trial Investigators

UZ Gasthuisberg (C.M.), KU Leuven, 3000 Leuven, Belgium; Baylor Endocrine Center (P.H.), Dallas, Texas 75246; Miller School of Medicine (B.M.-P.), University of Miami, Miami, Florida 33136; Department of Medicine (J.C.), Stavanger University Hospital, 4068 Stavanger, Norway; Central Clinical Hospital MSWiA and Medical Research Center (E.F.), Polish Academy of Sciences, 02-507 Warsaw, Poland; Royal Surrey County Hospital and University of Surrey (D.R.-J.), GU2 7XX Guildford, United Kingdom; Novo Nordisk A/S (J.L., S.C.T.), DK-2860 Søborg, Denmark; and Institute of Life Sciences (S.C.B.), Swansea University, SA2 8QA Swansea, United Kingdom

Objective: This study investigated the efficacy and safety of insulin degludec (IDeg) once daily (OD), varying injection timing day to day in subjects with type 1 diabetes.

Research Design and Methods: This 26-week, open-label, treat-to-target, noninferiority trial compared IDeg forced flexible (Forced-Flex) OD (given in a fixed schedule with a minimum 8 and maximum 40 hours between doses) with IDeg or insulin glargine (IGlar) given at the same time daily OD. In the 26-week extension, all IDeg subjects were transferred to a free-flexible (Free-Flex) regimen, which allowed any-time-of-day dosing, and compared with subjects continued on IGlar.

Results: After 26 treatment weeks, mean glycosylated hemoglobin was reduced with IDeg Forced-Flex (−0.40%), IDeg (−0.41%), and IGlar (−0.58%). IDeg Forced-Flex noninferiority was achieved. Fasting plasma glucose reductions were similar with IDeg Forced-Flex and IGlar but greater with IDeg (−2.54 mmol/L) than IDeg Forced-Flex (−1.28 mmol/L) ($P = .021$). At week 52, IDeg Free-Flex subjects had similar glycosylated hemoglobin but greater fasting plasma glucose reductions than IGlar subjects (−1.07 mmol/L) ($P = .005$). Confirmed hypoglycemia rates (plasma glucose <3.1 mmol/L or severe hypoglycemia) were similar at weeks 26 and 52. Nocturnal confirmed hypoglycemia was lower with IDeg Forced-Flex vs IDeg (37%; $P = .003$) and IGlar (40%; $P = .001$) at week 26 and 25% lower with IDeg Free-Flex vs IGlar ($P = .026$) at week 52.

Conclusions: IDeg can be administered OD at any time of day, with injection timing varied without compromising glycemic control or safety vs same-time-daily IDeg or IGlar. This may improve basal insulin adherence by allowing injection-time adjustment according to individual needs. (*J Clin Endocrinol Metab* 98: 1154–1162, 2013)

Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial

Bernard Zinman, Greg Fulcher, Paturi V Rao, Nihal Thomas, Lars A Endahl, Thue Johansen, Rebecka Lindh, Andrew Lewin, Julio Rosenstock, Michel Pinget, Chantal Mathieu

Lancet 2011; 377: 924–31

- Tip 2 DM' de 16 hafta süreli IDeg (3 kez hafta), IDeg vs GL,
  - HbA1c sonuçları benzer
  - Hipoglisemi benzer
  - Doz sıklığı?

Summary

Background Insulin degludec is a new basal insulin that forms soluble multihexamer assemblies after subcutaneous injection, resulting in an ultra-long action profile. This study aimed to assess efficacy and safety of insulin degludec injected once a day or three times a week compared with insulin glargine once a day in insulin-naive people with type 2 diabetes, who were inadequately controlled with oral antidiabetic drugs.

Methods In this 16-week, randomised, open-label, parallel-group phase 2 trial, participants aged 18–75 years with type 2 diabetes and glycosylated haemoglobin (HbA_{1c}) of 7·0–11·0% were enrolled and treated at 28 clinical sites in Canada, India, South Africa, and the USA. Participants were randomly allocated in a 1:1:1:1 ratio by computer-generated block randomisation to receive insulin degludec either once a day or three times a week or insulin glargine once a day, all in combination with metformin. Investigators were masked to data until database release. The primary outcome was HbA_{1c} after 16 weeks of treatment. Analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00611884.

Findings Of 367 patients screened, 245 were eligible for inclusion. 62 participants were randomly allocated to receive insulin degludec three times a week (starting dose 20 U per injection [1 U=9 nmol]), 60 to receive insulin degludec once a day (starting dose 10 U [1 U=6 nmol]; group A), 61 to receive insulin degludec once a day (starting dose 10 U [1 U=9 nmol]; group B), and 62 to receive insulin glargine (starting dose 10 U [1 U=6 nmol]) once a day. At study end, mean HbA_{1c} levels were much the same across treatment groups, at 7·3% (SD 1·1), 7·4% (1·0), 7·5% (1·1), and 7·2% (0·9), respectively. Estimated mean HbA_{1c} treatment differences from insulin degludec by comparison with insulin glargine were 0·08% (95% CI –0·23 to 0·40) for the three dose per week schedule, 0·17% (–0·15 to 0·48) for group A, and 0·28% (–0·04 to 0·59) for group B. Few participants had hypoglycaemia and the number of adverse events was much the same across groups, with no apparent treatment-specific pattern.

Interpretation Insulin degludec provides comparable glycaemic control to insulin glargine without additional adverse events and might reduce dosing frequency due to its ultra-long action profile.

Çalışmalar

Table 1. Summary of findings from phase III trials with insulin degludec and degludec/aspart combination

Category and treatments	Trial ID	R ratio	No. patients	Duration, m	HbA_{1c} difference versus comparator	FPG reduction versus comparator	Confirmed hypoglycaemia events[a]		
							Severe	Overall	Nocturnal[b]
Insulin degludec									
Type 1 diabetes									
IDeg OD + IAsp *versus* IGlar OD + IAsp [68]	3583	3:1	629	12	Non-inferior	Equal	Equal	Equal	↓25%
IDeg OD + IAsp *versus* IDet OD + IAsp [69]	3585	2:1	456	6	Non-inferior	↓	Equal	Equal	↓34%
IDegFlex[c] + IAsp *versus* IGlar OD + IAsp *versus* IDeg OD + IAsp [70]	3770	1:1:1	493	6	Non-inferior	Equal	Equal	Equal	↓40%[d]
Type 2 diabetes									
IDeg OD *versus* IGlar OD [71]	3579	3:1	1030	12	Non-inferior	↓13%	↓86%	Equal	↓36%
IDeg OD + IAsp *versus* IGlar OD + IAsp [72]	3582	3:1	1006	12	Non-inferior	Equal	Equal	↓18%	↓25%
IDeg OD *versus* IGlar OD [73]	3586	2:1	435	6	Non-inferior	Equal	Equal	Equal	Equal
IDegFlex[c] *versus* IGlar *versus* IDeg OD + OAD [74]	3668	1:1:1	687	6	Non-inferior	↓	Equal	Equal	Equal[d]
IDeg (U200[e]) OD *versus* IGlar OD [75]	3672	1:1	468	6	Non-inferior	↓	Equal	Equal	Equal
IDeg 3W morning dose *versus* IGlar OD [76]	3718	1:1	467	6	Not non-inferior	Equal	Equal	Equal	↑212%
IDeg 3W evening dose *versus* IGlar OD [76]	3724	1:1	468	6	Not non-inferior	Equal	Equal	↑58%	Equal
IDeg OD *versus* sitagliptin OD [77]	3580	1:1	458	6	Superior	↓	Equal	↑381%	Equal
Insulin degludec/aspart (IDegAsp Plus)									
Type 1 diabetes									
IDegAsp OD *versus* IDet OD + IAsp [78]	3594	2:1	548	6	Non-inferior	Equal	Equal	Equal	↓37%
Type 2 diabetes									
IDegAsp OD *versus* IGlar OD [79]	3896	1:1	296	6	Superior	Equal	Equal	Equal	Equal
IDeglAsp OD *versus* IGlar OD [69]	3590	1:1	530	6	Non-inferior	↑	Equal	↑217%	↓71%
IDegAsp BD *versus* BIAsp 30 BD [82]	3592	1:1	447	6	Non-inferior	↓	Equal	↓32%	↓73%
IDegAsp OD *versus* IGlar OD + OAD [69]	3593	1:1	465	6	Non-inferior	Equal	Equal	↑43%	Equal
IDegAsp BD *versus* BIAsp 30 BD [83]	3597	2:1	424	6	Non-inferior	↓	Equal	Equal	Equal

R ratio, randomization ratio; ↓and ↑ refer to statistically significant reductions and increases compared with comparator; percentages are reported where available; HbA_{1c}, haemoglobin A_{1c}; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; NR, not reported; and OD, once daily.

[a]Confirmed hypoglycaemia events comprised severe events requiring assistance from another person to actively administer carbohydrate, glucagon or other resuscitative actions, along with episodes with plasma glucose of <3.1 mmol/L (56 mg/dL), irrespective of symptoms.

[b]Nocturnal confirmed hypoglycaemic events were defined as confirmed episodes occurring between 00:01 and 05:59 h (both inclusive).

[c]IDegFlex refers to the flexible dosing arm of IDeg, a regimen with fixed dosing intervals alternating between 8 and 40 h for the administration of IDeg.

[d]IDegFlex *versus* IGlar.

[e]U200 formulation of IDeg is twice as concentrated as traditional U100 insulin formulations, allowing smaller injection volume. 3W, three times weekly; FPG, fasting plasma glucose.

HbA1c

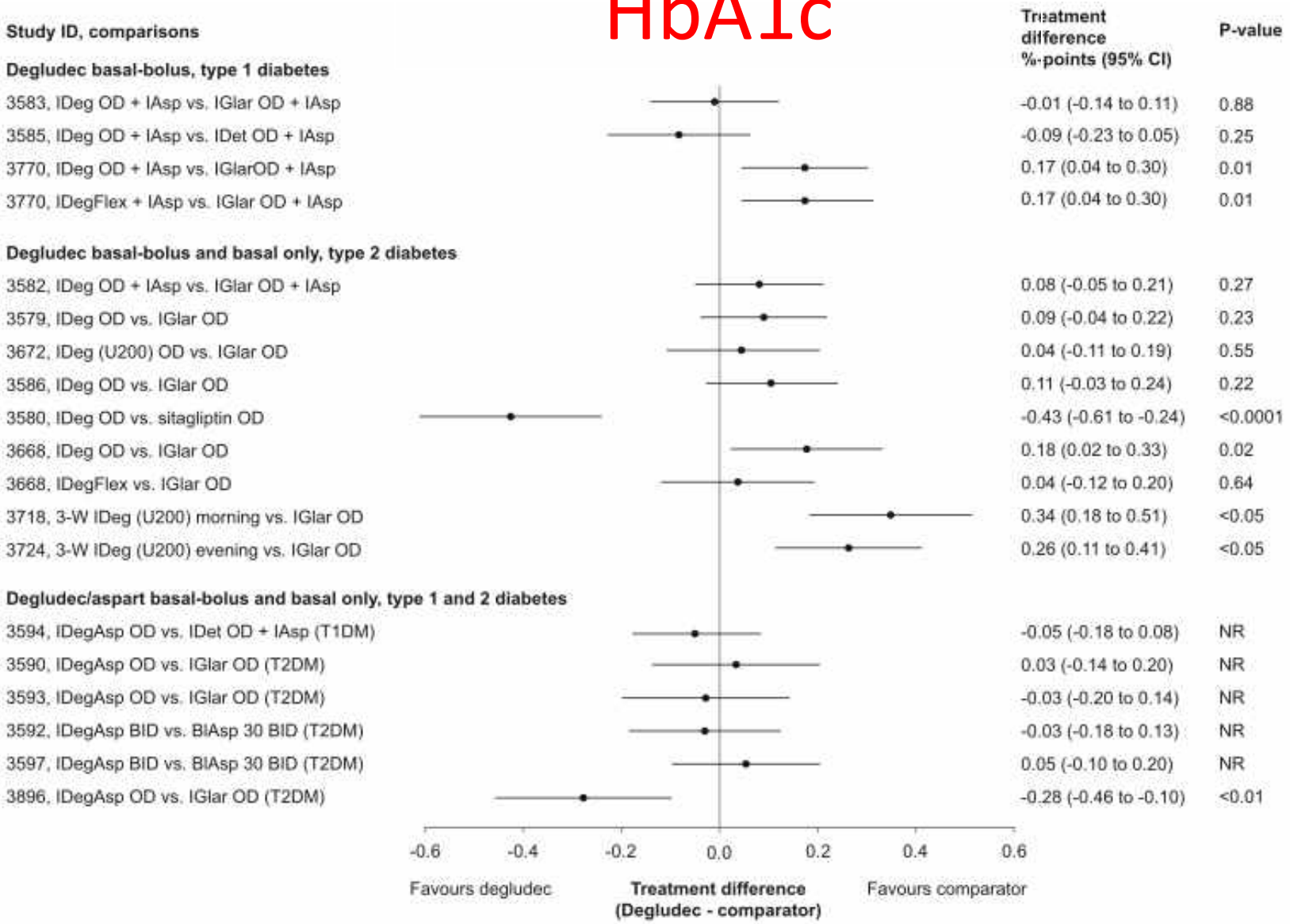
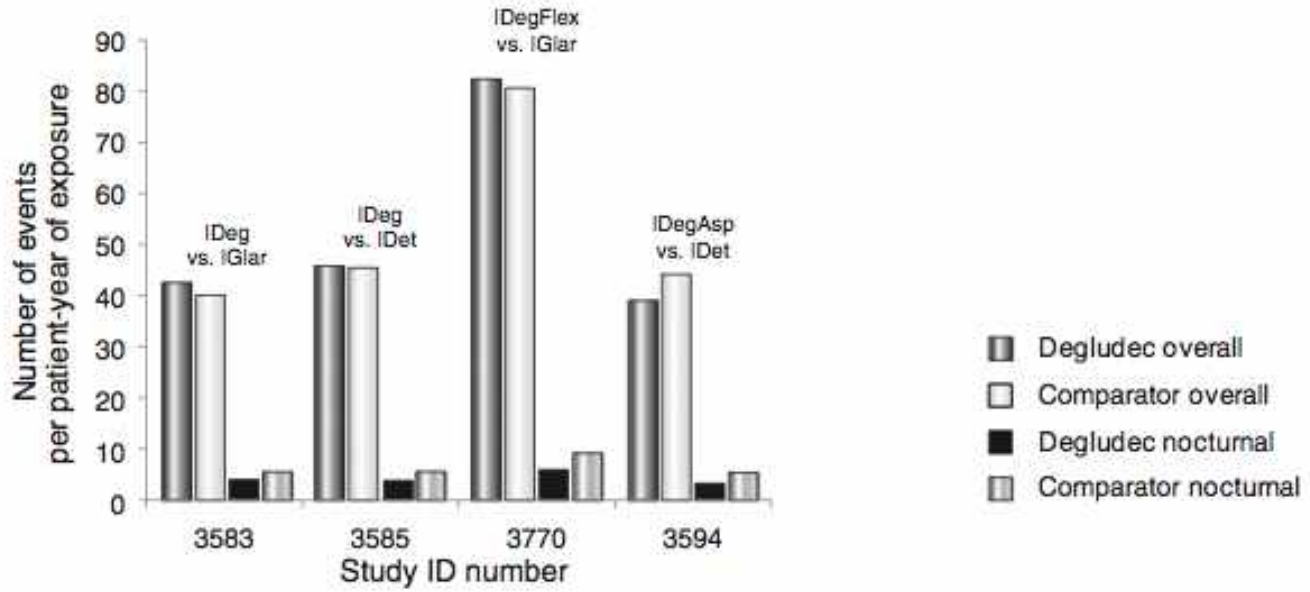
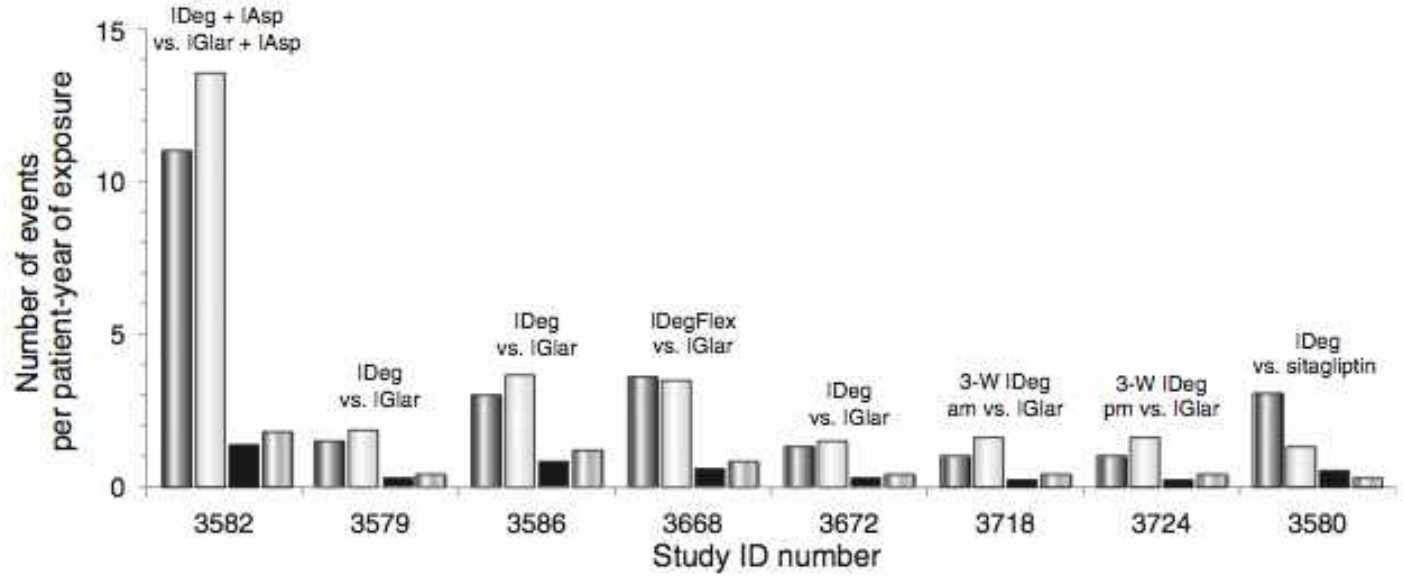


Figure 2. Difference in HbA_{1c} (%-points) at end of treatment (primary outcome) between degludec or degludec/aspart *versus* comparators in individual phase III trials. Treatment difference in study 3770 (IDeg OD + IAsp *versus* IGlar OD + IAsp) was based on data reported by FDA [84]. The *p*-values are based on data reported by FDA [84] except for studies 3718 [76], 3724 [76] and 3896 [79]. 3W, three times weekly; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; OD, once-daily; NR, not reported; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus

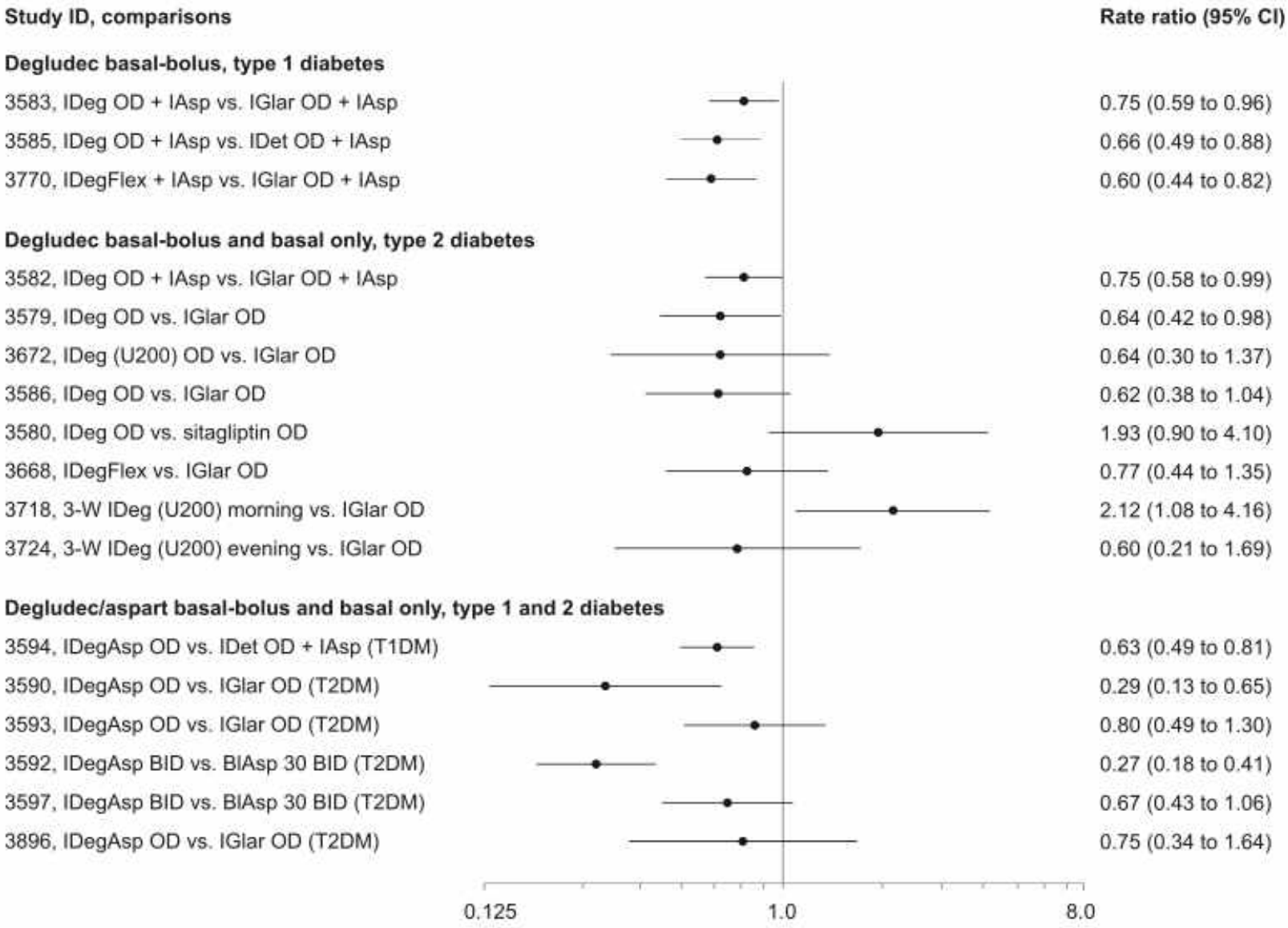
Type 1 Diabetes



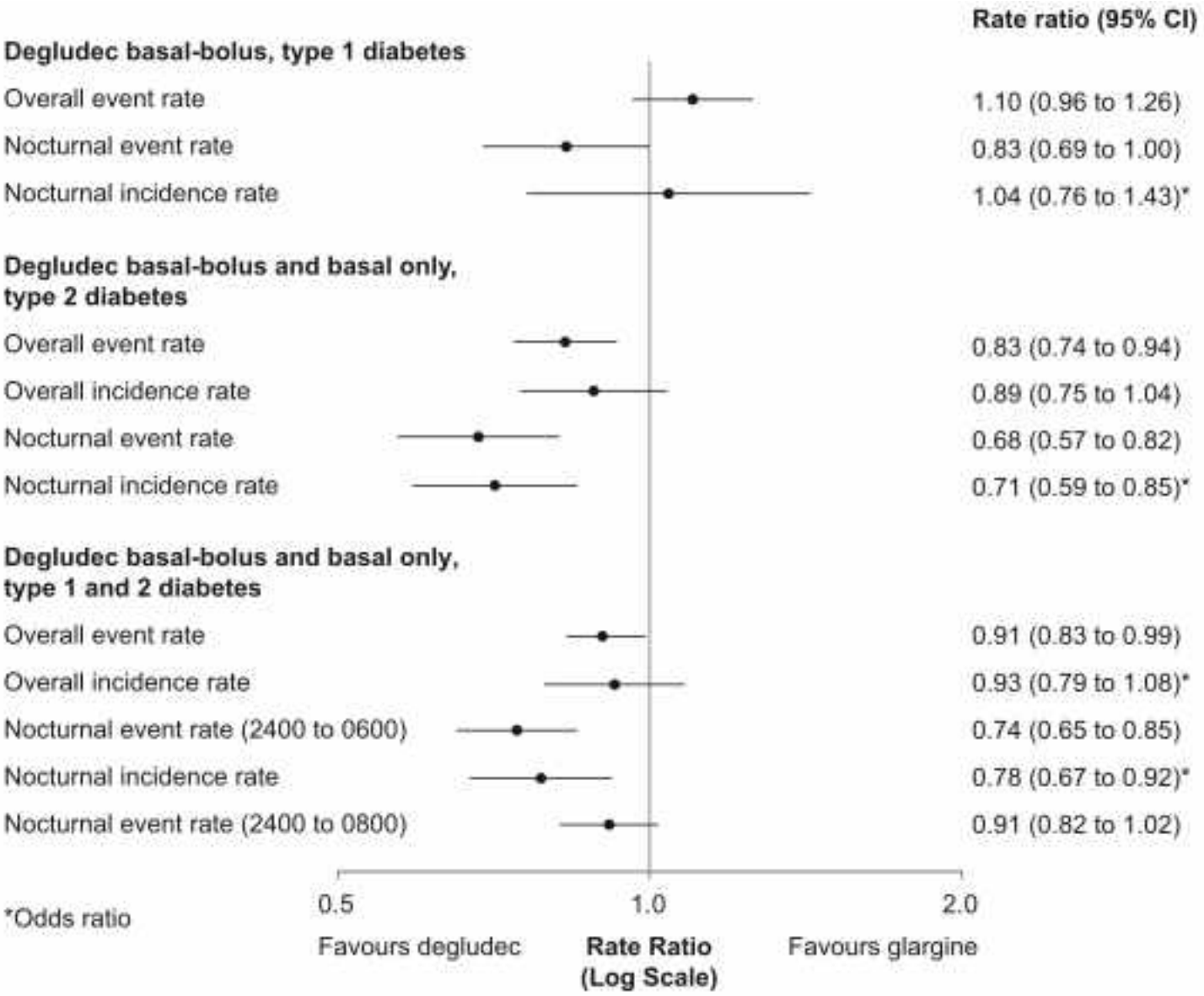
Type 2 Diabetes



Hipoglisemi-Çalışmalar



Hipoglisemi-Meta analiz



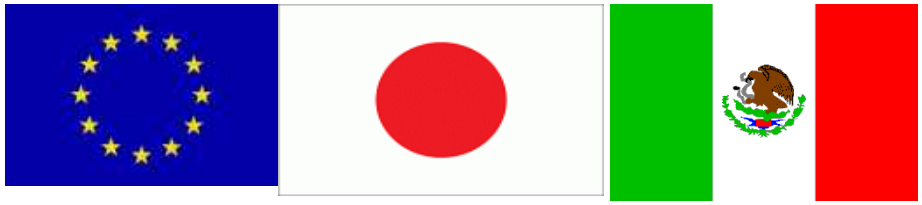
IDeg-Güvenlik

- Faz 3 çalışmalarına 5500 hasta katılmış.
- IGF-1 reseptörleri için düşük afinite
- Düşük mitojenik aktivite (insan insülininin %4-14'ü)
- Kilo alımı GL'e ile benzer
- Major Adverse Kardiyovasküler Olay 1.48 olay/100 hasta yılı vs 1.44/100 hasta yılı (85 olay 9806 hasta)

Nishimura E, Sorensen A, Hansen B, et al. Diabetologia2010; 53: 388.
Ratner RE, Gough S, Mathieu C et al. Diabetes 2012; **61**(Suppl 1): A101.
Goldman-Levine JD, Patel DK, Schnee DM. *Ann Pharmacother*2013;47:269-77.

İnsülin Degludec

- Faz III, FDA onayı yok, CV verileri eksik



- Avrupa, Japonya, Meksika'da onaylı
- Tresiba (IDeg)
- Ryzodeg (IDeg/asp: 70/30)

Diabetes Obes Metab. 2013 Mar;15 Suppl 1:6-10.
Ann Pharmacother. 2013 Feb;47(2):269-77.
Diabetes Care. 2013 Apr;36(4):858-64.

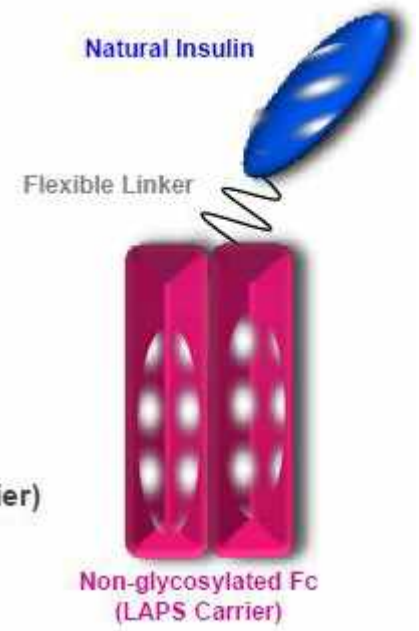
IDeg-Sonuçlar (1)

- Yeni bir formül
- Düşük mitojenite (vs RHI)
- $T_{1/2}$ 25 s, 42s stabil-125 s
- U100=U200
- Çalışmalardaki insülin dozu daha düşük (IDet, GL)
- IDeg OD, Flex ve 3kez/hafta
- IDeg OD, Flex, non-inferior (IDet, GL)
- IDeg 3kez/hafta inferior (GL)
- AKŞ daha düşük (IDet, GL)
- Kilo alımı benzer (IDet, GL)
- IDegAsp non-inferior (IDet, GL, bifazik asp)

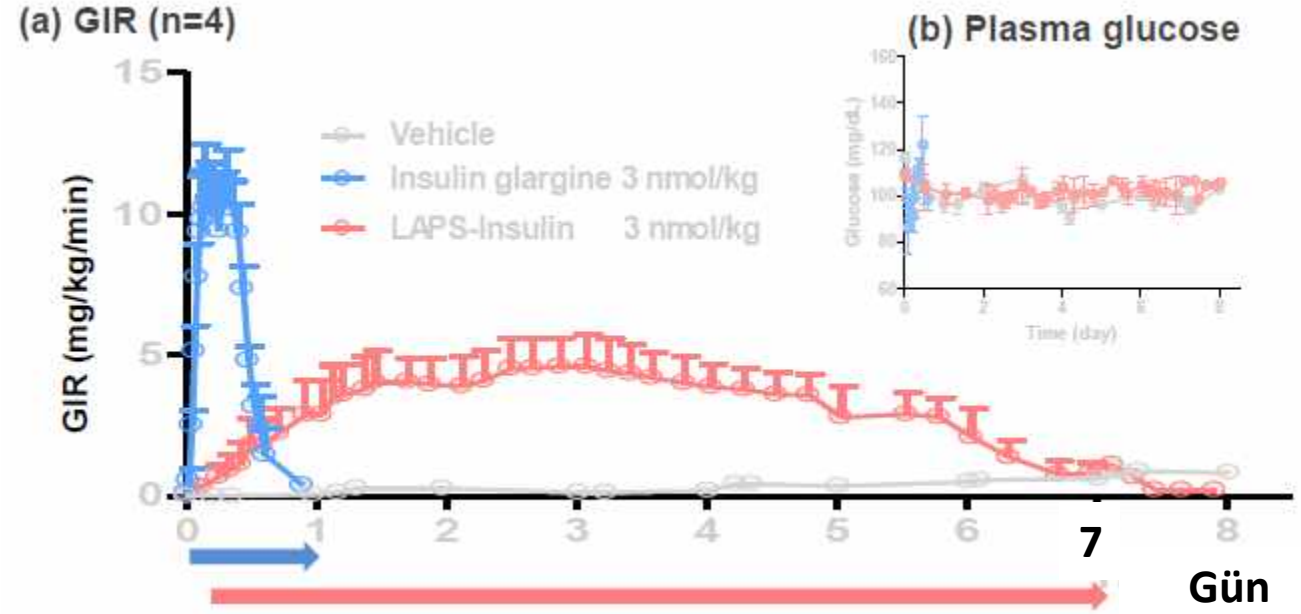
IDeg-Sonuçlar (1)

- HG ve NHG oranı daha düşük (IDet, GL)
- Bias
  - Pik etki
  - Veri toplama
  - HG tanımı
  - Klinik heterojenite
  - Ağır hastaların alınmaması
  - .....
- FDA onayı yok-KVS verileri
- EMA, Japonya, Meksika

LAPS İnsülin-HM12460A



Euglycemic clamp study in normal dogs



Haftada bir etkili, rekombinant insan insülini ve globulin G4 fragmanına bağlanarak elde edilmiş.

Ratlarda etkin ve stabil glisemik kontrol (vs GL)

LAPS İnsülin-HM12460A

Receptor pharmacology of LAPS-Insulin

Table 1. Potencies of LAPS-Insulin and insulin analogs in various *in vitro* assays

Parameter	Human insulin (HI)	Insulin glargine (% relative to HI)	LAPS-Insulin (% relative to HI)
Insulin Receptor binding (SPR/Human insulin receptor)	100	-	17
IGF-1 Receptor binding (Competition assay/Human IGF-1R)	100	1,603	12
Cellular metabolic potency (3T3-L1/Glucose uptake)	100	28	15
Cellular mitogenic potency (SaOs-2 proliferation)	100	702	8
Mitogenic/Metabolic potency	1	25	≤1

1. LAPS-Insulin showed the comparable metabolic potency with glargine, but the relative IGF-IR binding affinity and mitogenic potency were much lower than insulin glargine
2. Confirmed MOA / Low risk of cancer via low IGF-1R Binding

Çok Hızlı Etkili İnsülinler

- ÇHI yakın zamanda, HI lerin yerini alabilir.
- Yemekler sonrası olan ani KŞ yükselmelerini önleyebilir.
- Diabetik olmayan bireylerde faz 1 insülin yanıtını taklit edebilir.
- Prandiyal KŞ yükselmelerini ve gecikmiş hipoglisemileri kontrol edebilir-dolayısıyla kilo artışı azalır.
- Daha fizyolojik kontrol-suni pankreas

BIOD-090, 100, 123, 125

- RHI daki Zn şelasyonu (EDTA ile) insülin hexamer' oluşumunu önler ve destabilize eder.
- RHI agregasyonunu önlemek için, monomer yüzey yükleri sitrat ile önlenir.
- Bu iki esasa dayanarak BIOD-090 (25U/ml) insülin geliştirildi.BIOD-100 (100U/ml)
- Lokal enj. intoleransı-özl ağrı
  - BIOD-125: Ca ilavesi
  - BIOD-123: MgSO4 ilavesi

BIOD-090

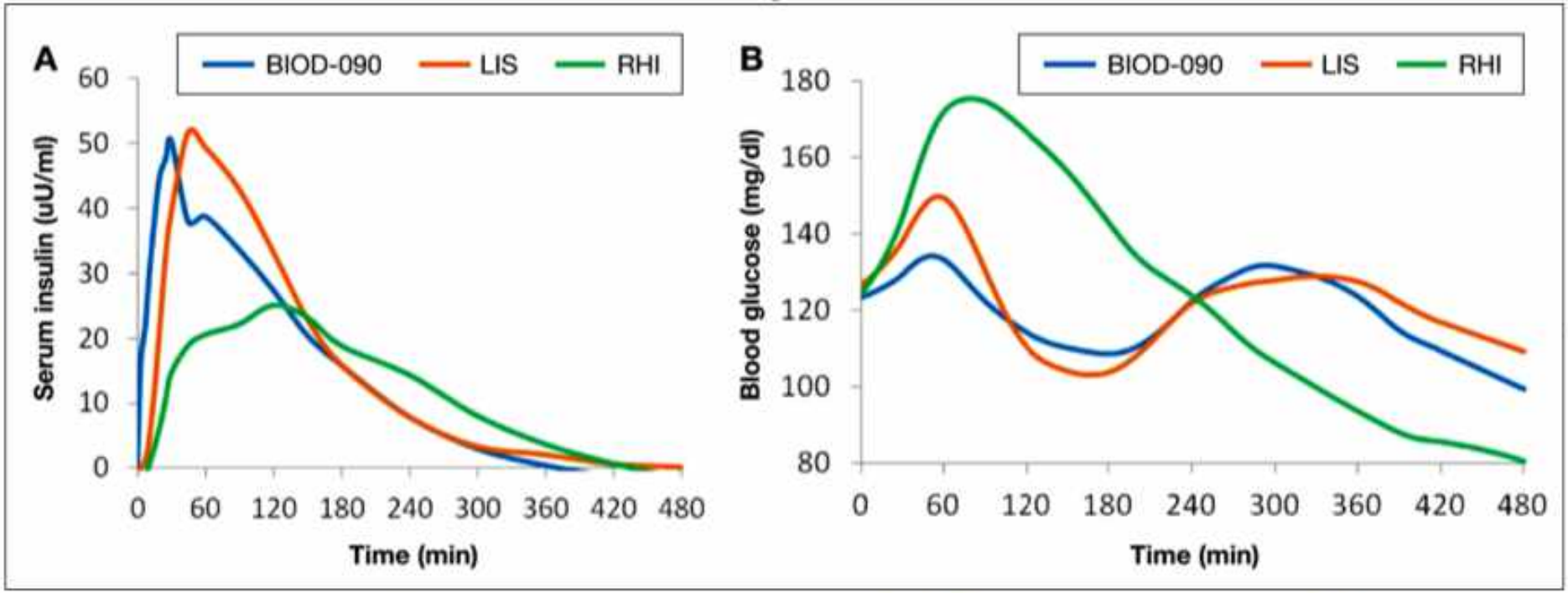


Figure 3. Mean plasma insulin profiles **(A)** with baseline correction (mean of the last three samples prior to injection), and mean blood glucose profiles **(B)** measured by the Biostator, obtained after SC injection of RHI, LIS, and BIOD-090 in 18 patients with type 1 diabetes.

BIOD-090

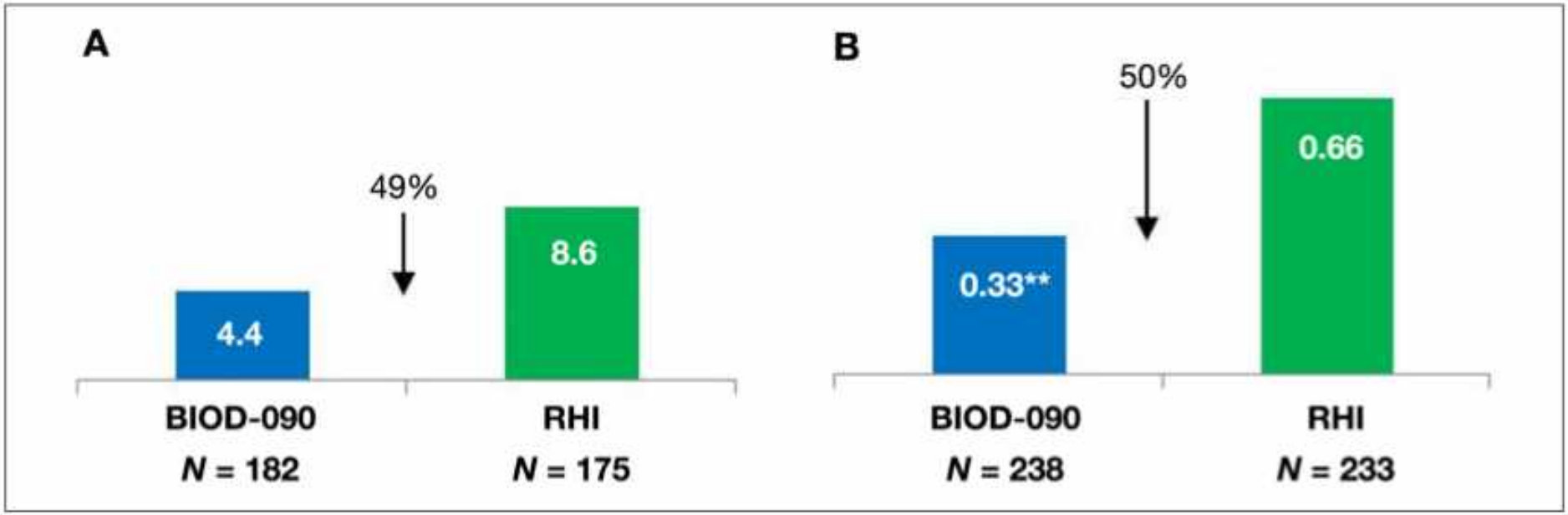


Figure 5. (A) Proportion of patients with at least one severe hypoglycemic event in phase 3 study in patients with type 1 diabetes, $p = .1324$. Severe hypoglycemia was defined as requiring the assistance of a third party. **(B)** Median hypoglycemic event rates in phase 3 study in patients with type 2 diabetes. Double asterisks indicate $p = .018$. Hypoglycemia was defined as home glucose readings <70 mg/dl or symptomatic episodes resolving with treatment.

BIOD-090

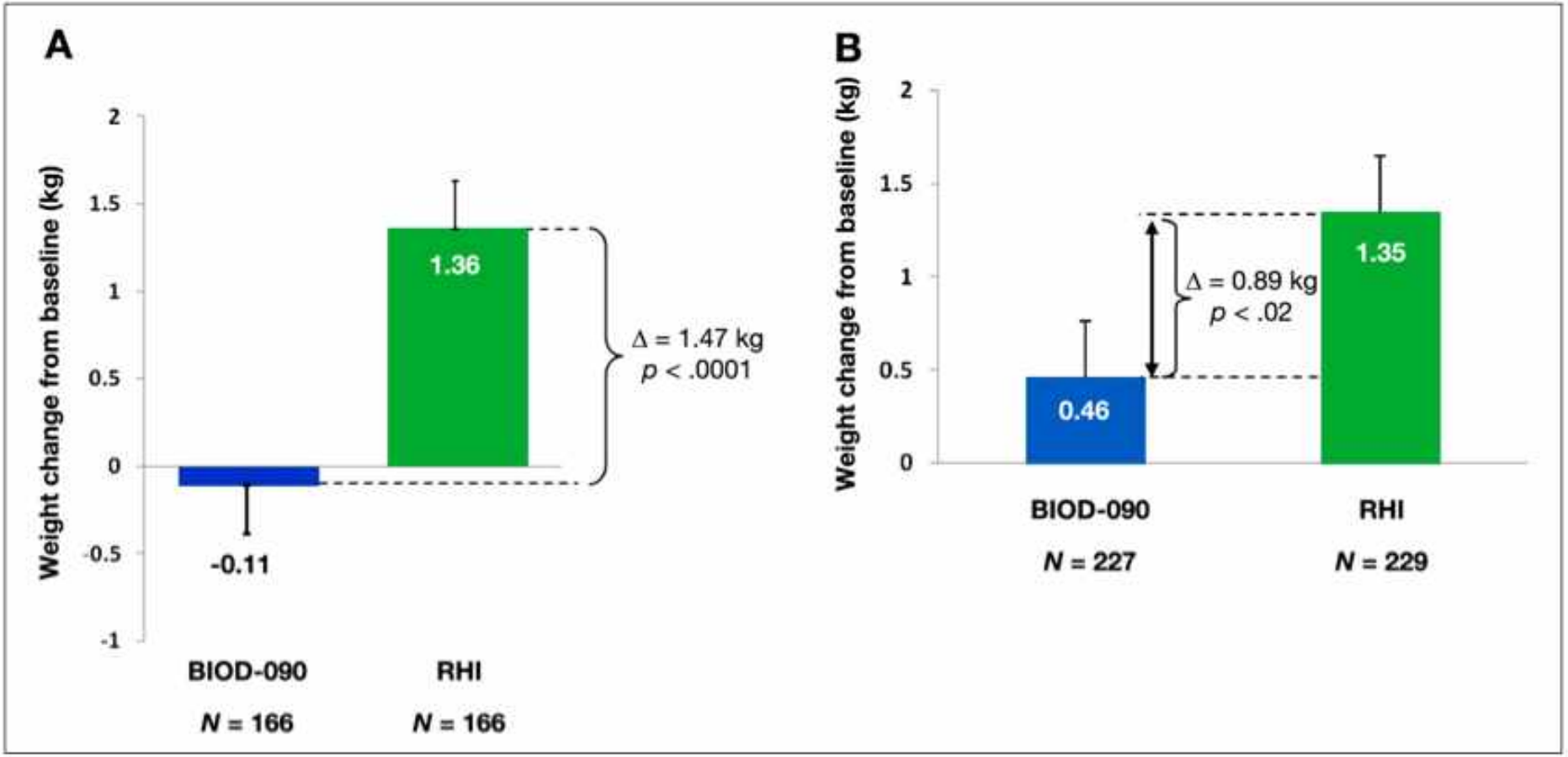


Figure 6. Weight change in phase 3 study of (A) type 1 diabetes and (B) type 2 diabetes.

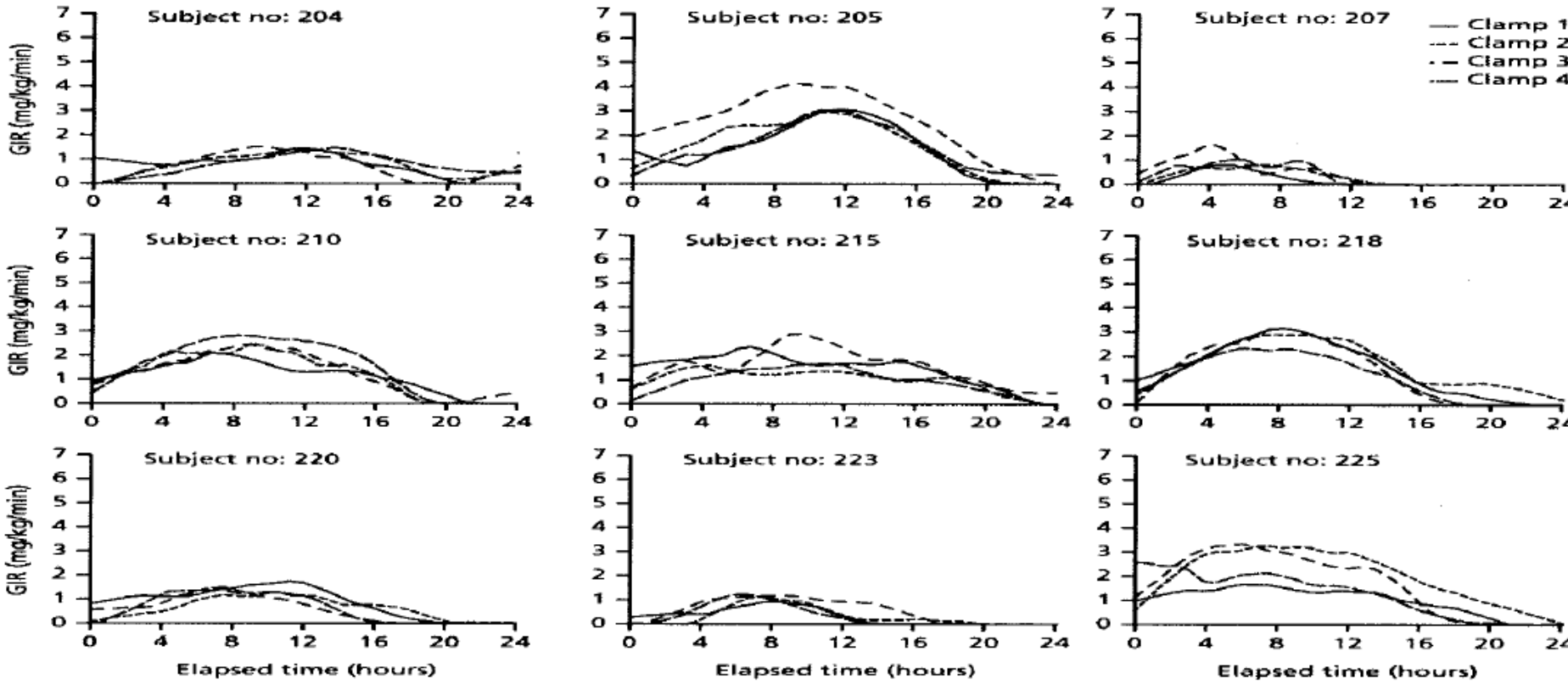
Teşekkür Ederim

Source	Insulin Agent	Patient Characteristics	Insulin Comparator	Design	Outcomes
Rosenstock et al, 2013[56]	LY2605541 (pegylated insulin lispro)	T1DM; basal-bolus therapy	Glargine	8-wk randomized, phase 2, open-label, 2×2 crossover study	Greater improvements in glycemic control, increased total hypoglycemia, reduced nocturnal hypoglycemia, reduced weight, and lowered insulin doses at mealtime
Bergenstal et al, 2012[57]	LY2605541 (pegylated insulin lispro)	T2DM (HbA_{1c} level ≤10.5%); metformin and/or sulfonylurea with glargine or NPH insulin once daily	Glargine	12-wk, randomized, open-label, phase 2 study	Comparable glucose control; total hypoglycemia rates, reduced intraday variability, and lower nocturnal hypoglycemia, as well as weight loss, relative to glargine
Birkeland et al, 2011[43]	Degludec	T1DM; mean HbA_{1c} level 8.4%	Glargine	16-wk randomized, phase 2 controlled trial	Comparable glucose control at similar doses, with reduced rates of hypoglycemia
Heise et al, 2011[45]	Degludec/ aspart	T2DM; background metformin therapy	Glargine	16-wk, open-label trial	Comparable glucose control at similar doses, similar low rates of hypoglycemia, and better glucose control after dinner
Zinman et al 2012[50]	Degludec	T2DM; background therapy for OAD; baseline HbA_{1c} level 7% to 10%	Glargine	1-year treat-to-target, open-label, randomized trial	Comparable glucose control, much lower rates of nocturnal hypoglycemia
Heller et al, 2012[46]	Degludec	T1DM; basal-bolus insulin therapy; HbA_{1c} level ≤10%	Glargine	1-year treat-to-target, open-label, randomized trial	Comparable glucose control and much lower rates of nocturnal hypoglycemia
Garber et al, 2012[44]	Degludec	T2DM; basal-bolus insulin; HbA_{1c} level, 7% to 10%	Glargine	1-year treat-to-target, open-label, randomized trial	Comparable glucose control and much lower rates of overall and nocturnal hypoglycemia
Niskanen et al, 2012[58]	Degludec/ aspart (twice daily) and an alternative formulation	T2DM; HbA_{1c} level 7% to 11%	Biphasic insulin aspart twice daily	16-wk, open-label, randomized, treat-to-target trial	Comparable glucose control and lower rates of hypoglycemia

The Journal of the American Osteopathic Association.113 (4); Supl 2) 2013

Detemir

A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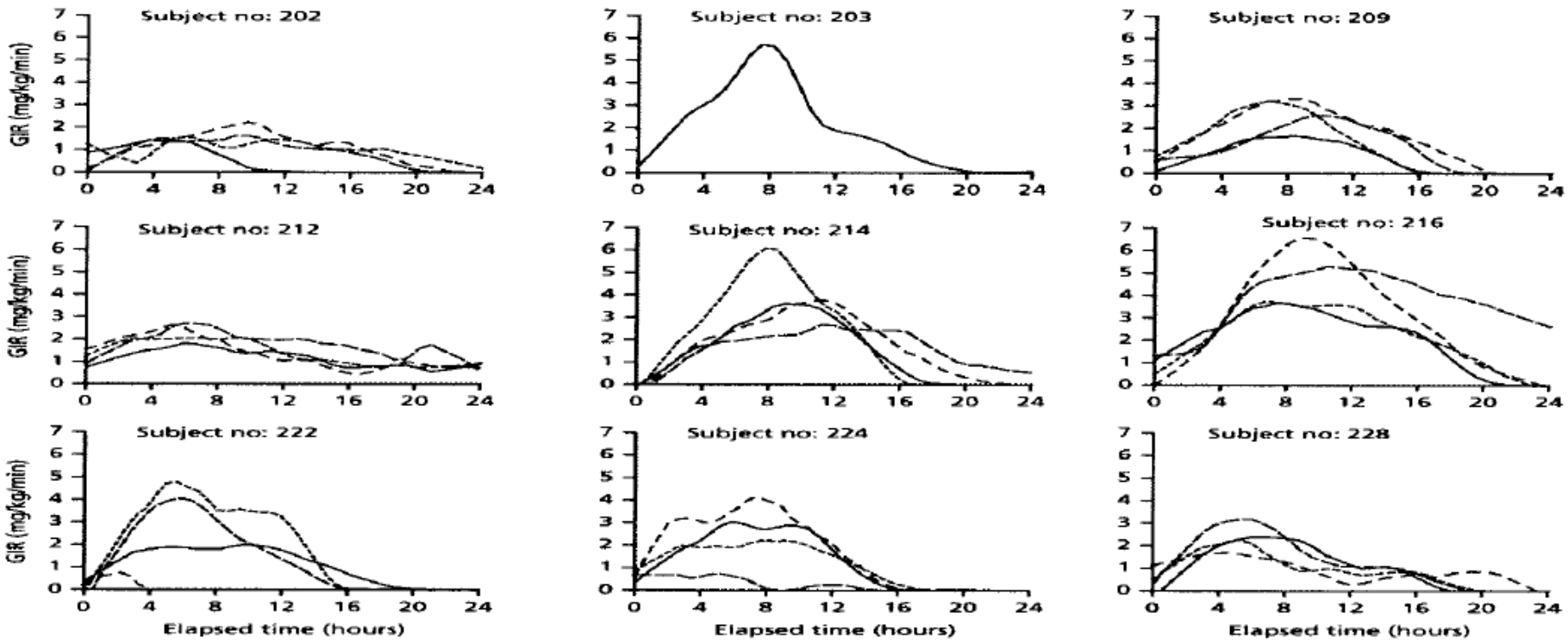
Subject no: 205
Subject no: 207
Clamp 1
Clamp 2
Clamp 3
Clamp 4
Subject no: 210
Subject no: 215
Subject no: 218
Subject no: 220
Subject no: 223
Subject no: 225
GIR (mg/kg/min)
Elapsed time (hours)

NPH

B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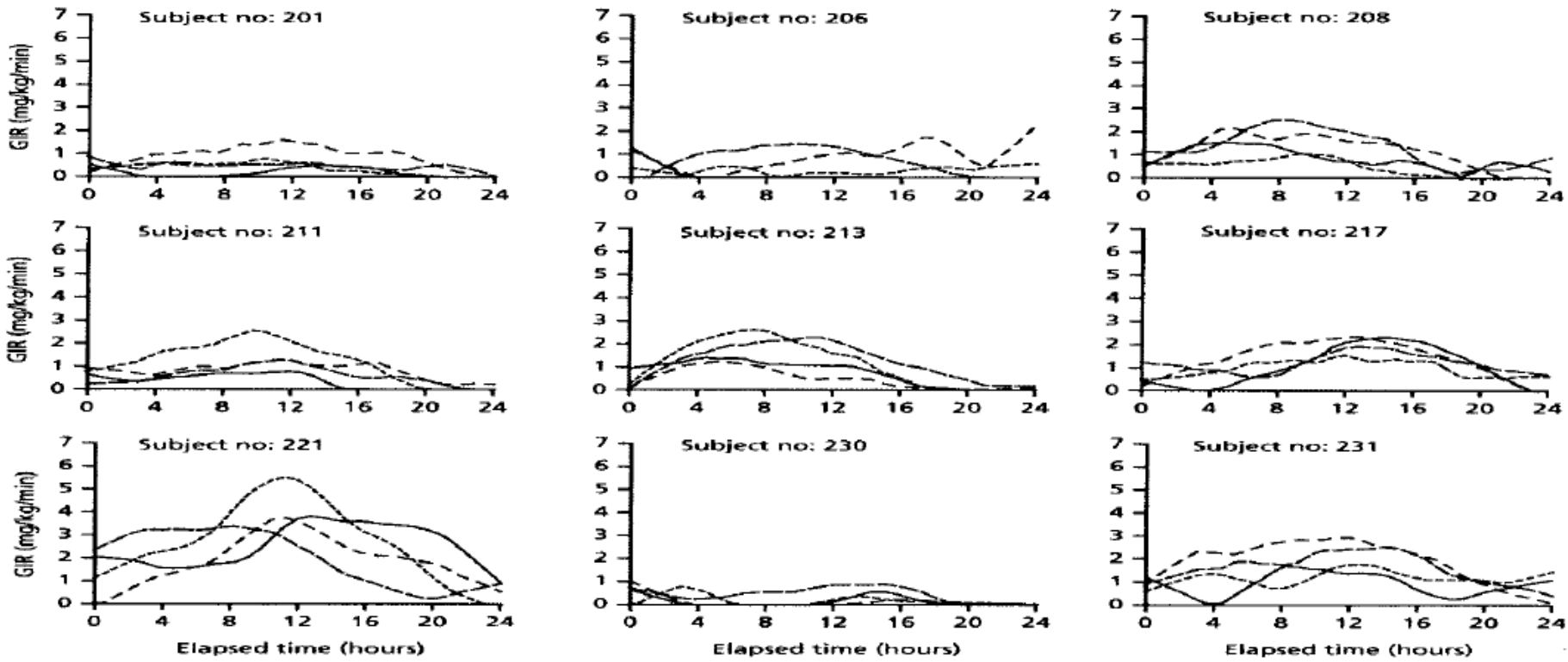
Subject no: 216
Subject no: 222
Subject no: 224
Subject no: 228
GIR (mg/kg/min)
Elapsed time (hours)

Glargine

C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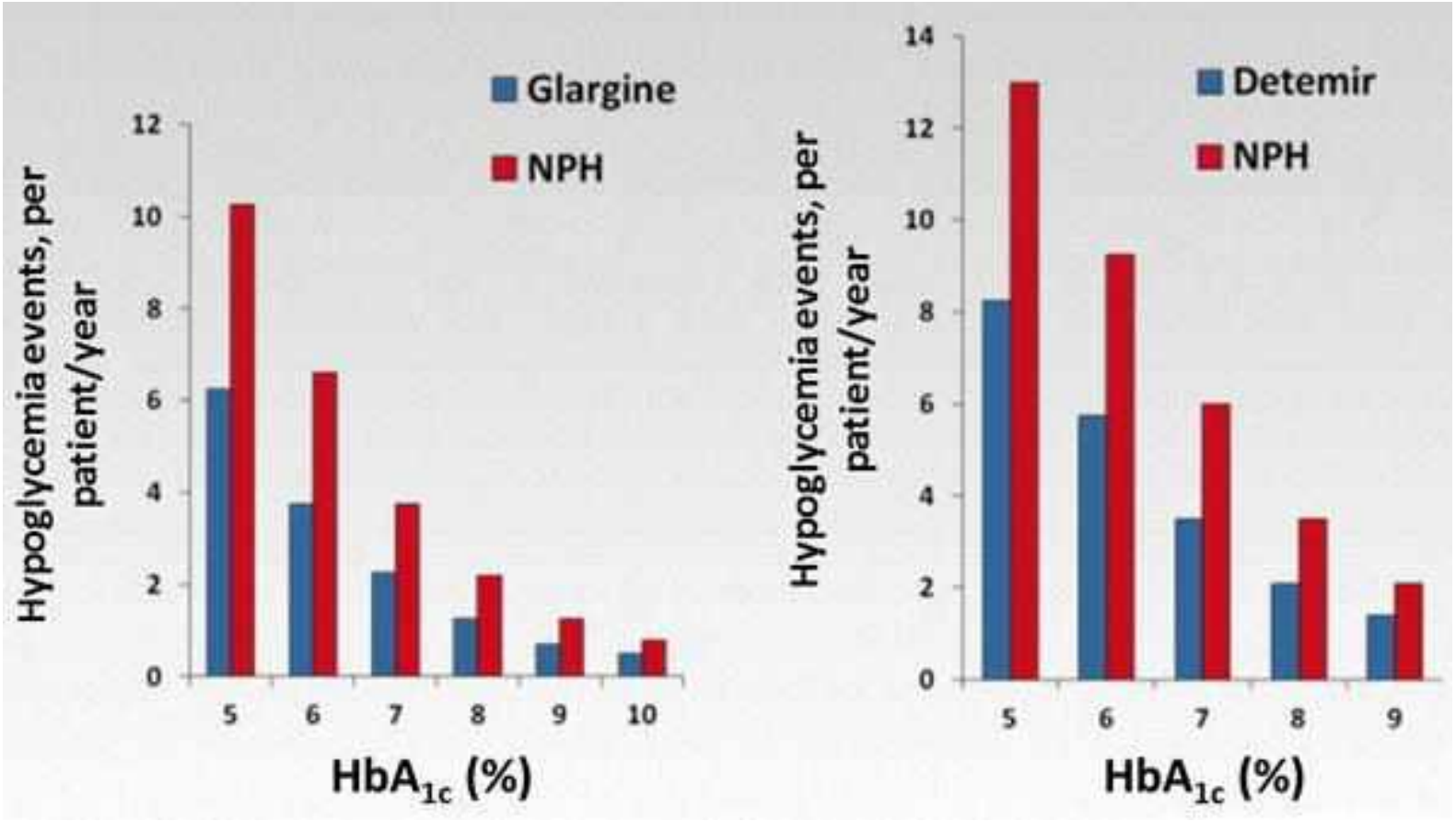
Subject no: 213
Subject no: 217
Subject no: 221
Subject no: 230
Subject no: 231
GIR (mg/kg/min)
Elapsed time (hours)

Bazal insülin[1,2]	Prandial insülin[1,2]
Öğün aralarında ve gece boyunca uyku sırasında besin tüketilmeyen dönemlerde sürekli salgılanır.	Besin tüketimine yanıt olarak salgılanır.
Öğün aralarında ve gece boyunca glukoz üretimini azaltır.	Besin tüketimi sonrası glukoz artışını sınırlar
Tüm gün boyunca normale yakın glukoz seyrini sağlar .	Besin alımından hemen sonra artar ve yaklaşık 1 -2 saat sonra zirve yapar

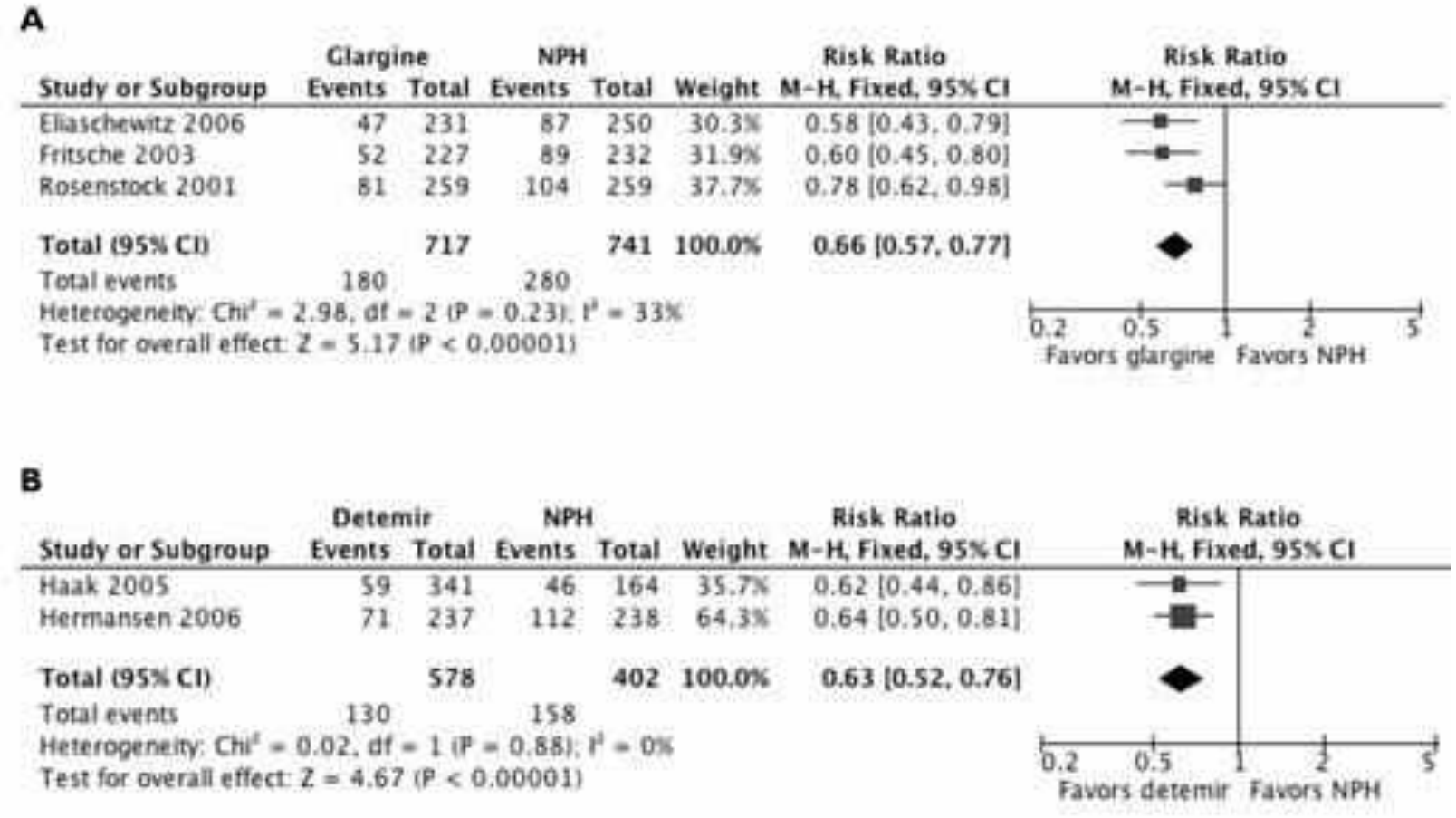
1. Rosenstock J.*Clin Cornerstone*. 2001;4:50-64.
2. White JR Jr et al. *Postgrad Med*. 2003;113:30-36.

Tip 2 DM- Hedefe Ulaşmak için Tedavi Çalışmalarında Hipoglisemi



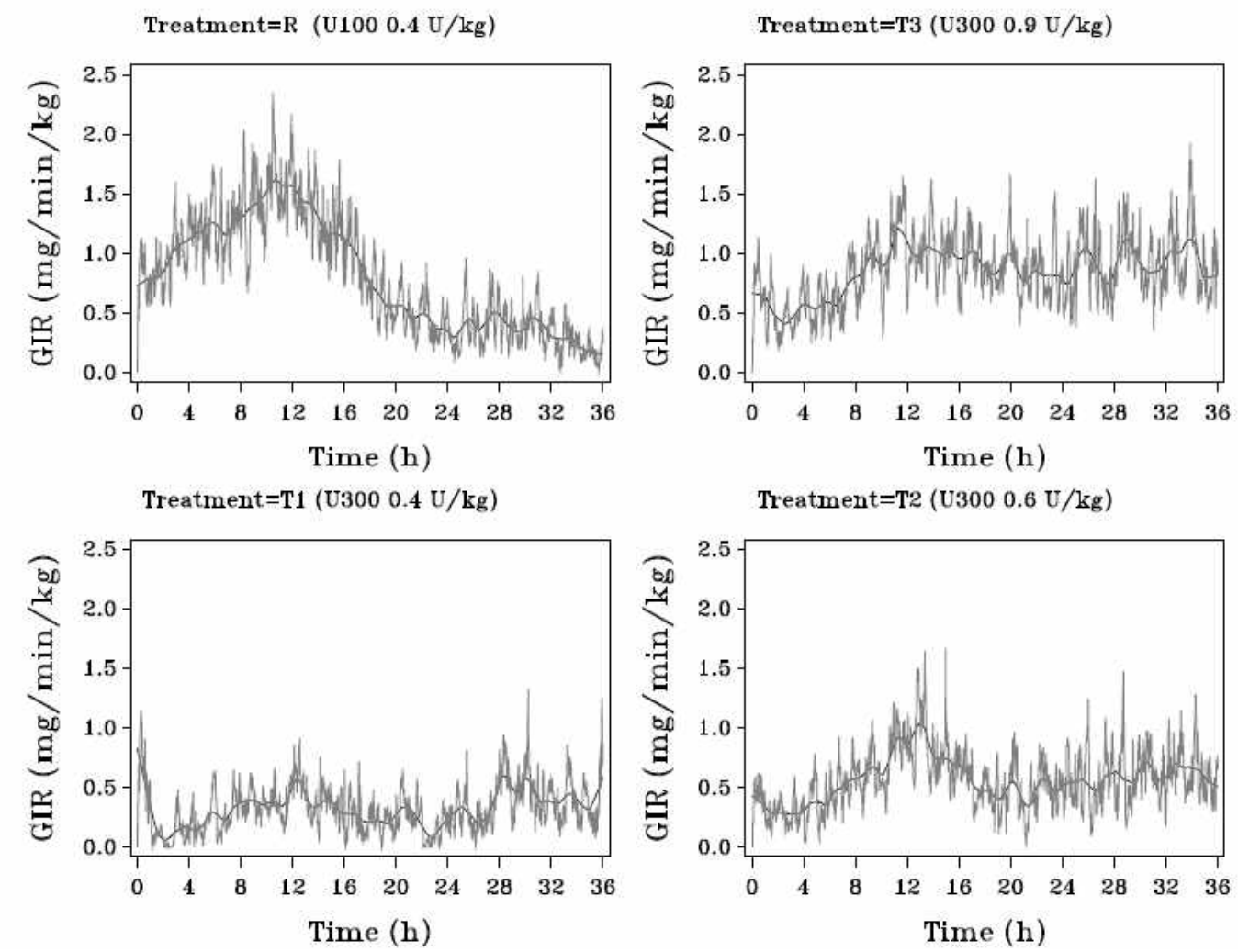
Little S, Shaw J, and Home P. DiabetesTechnology&Theurapeutics. 13, Supplement 1, 2011 S53-64

Noktürnal Hipoglisemi Riski Uzun Etkili Analoglar (A) glargine, (B) detemirvsNPH insülin



Horvath K, et al.Long-acting insulin analogues versus NPH insulin (humanisophaneinsulin) for type 2 diabetes mellitus. CochraneDatabase Syst Rev 2007;(2):CD005613.)

Glargine U300



http://en.sanofi.com/img/content/study/PKD11627_summary.pdf

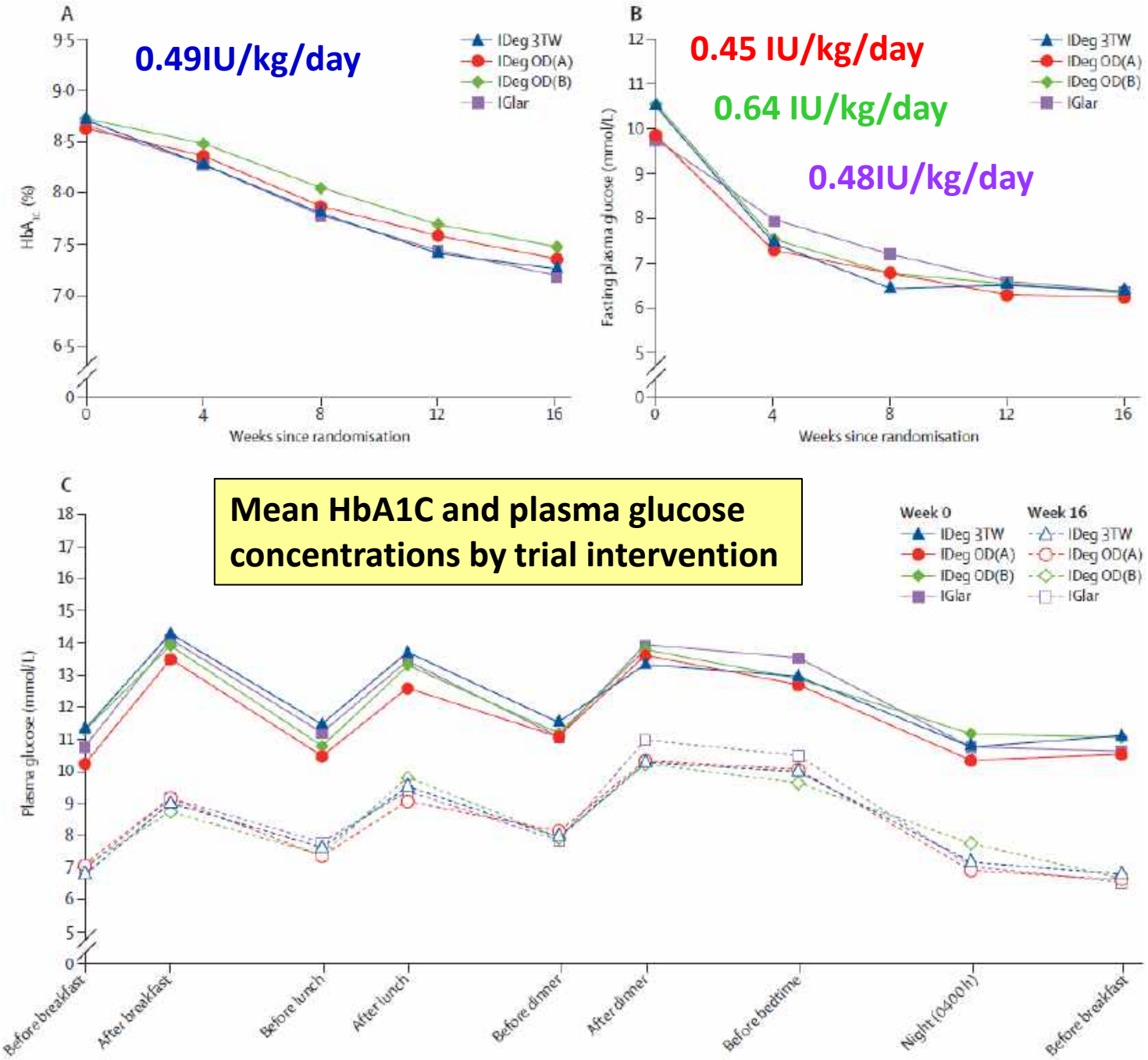
Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial

Bernard Zinman, Greg Fulcher, Paturi V Rao, Nihal Thomas, Lars A Endahl, Thue Johansen, Rebecka Lindh, Andrew Lewin, Julio Rosenstock, Michel Pinget, Chantal Mathieu

Lancet 2011; 377: 924–31

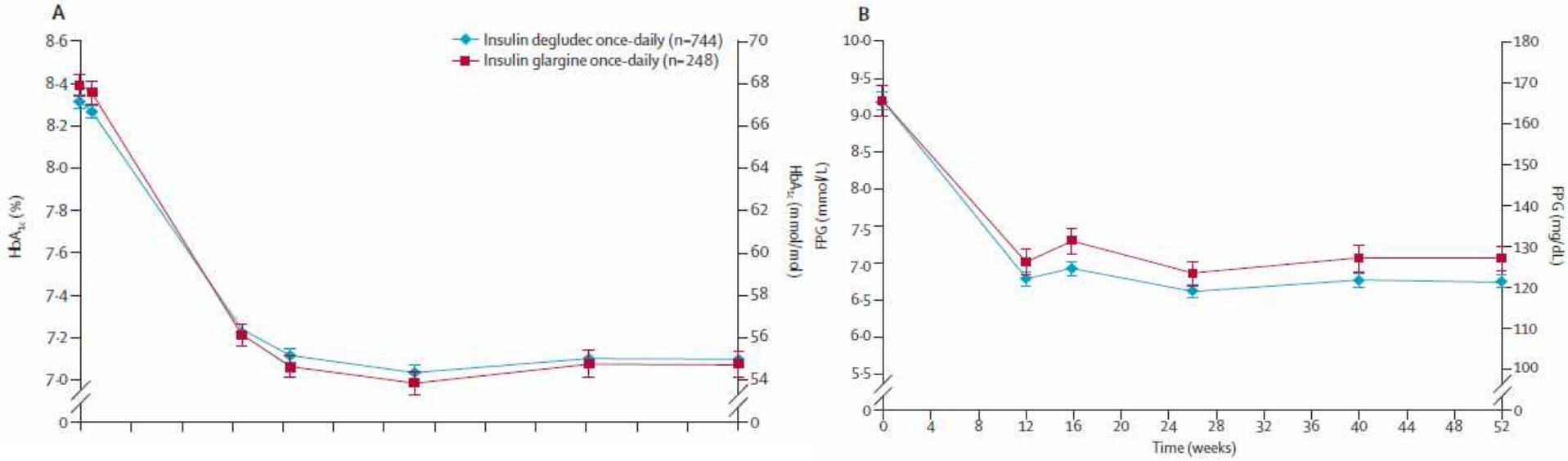
- İnsülin kullanmamış, OAD ile kontrolde olmayan Tip 2 DM'lu bireylerde insülin Degludec günde bir kez/haftada 3 kez vs insülin glargine günde bir kez etkinlik ve güvenilirlik karşılaştırması

Insulin degludec provides comparable glycaemic control to insulin glargine without additional adverseevents and might reduce dosing frequency due to its ultra-long action profile.


A
0.49IU/kg/day
IDeg 3TW
IDeg OD(A)
IDeg OD(B)
IGlar
HbA1c (%)
Weeks since randomisation
B
0.45 IU/kg/day
0.64 IU/kg/day
0.48IU/kg/day
Fasting plasma glucose (mmol/L)
Weeks since randomisation
C
Mean HbA1C and plasma glucose concentrations by trial intervention
Week 0
Week 16
Plasma glucose (mmol/L)
Before breakfast
After breakfast
Before lunch
After lunch
Before dinner
After dinner
Before bedtime
Night (0400 h)
Before breakfast

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

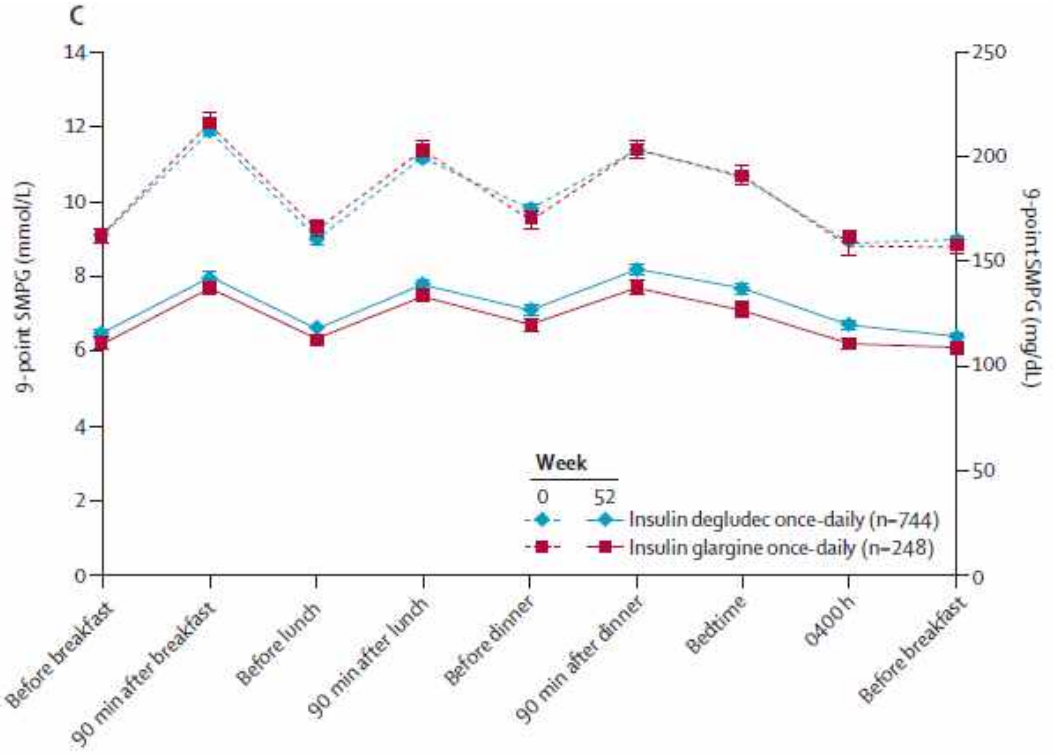
*Alan J Garber, Allen B King, Stefano Del Prato, Seamus Sreenan, Mustafa K Balci, Manuel Muñoz-Torres, Julio Rosenstock, Lars A Endahl, Ann Marie Ocampo Francisco, Priscilla Hollander, on behalf of the NN1250-3582 (BEGIN BB T2D) Trial Investigators**



Lancet 2012; 379: 1498–507

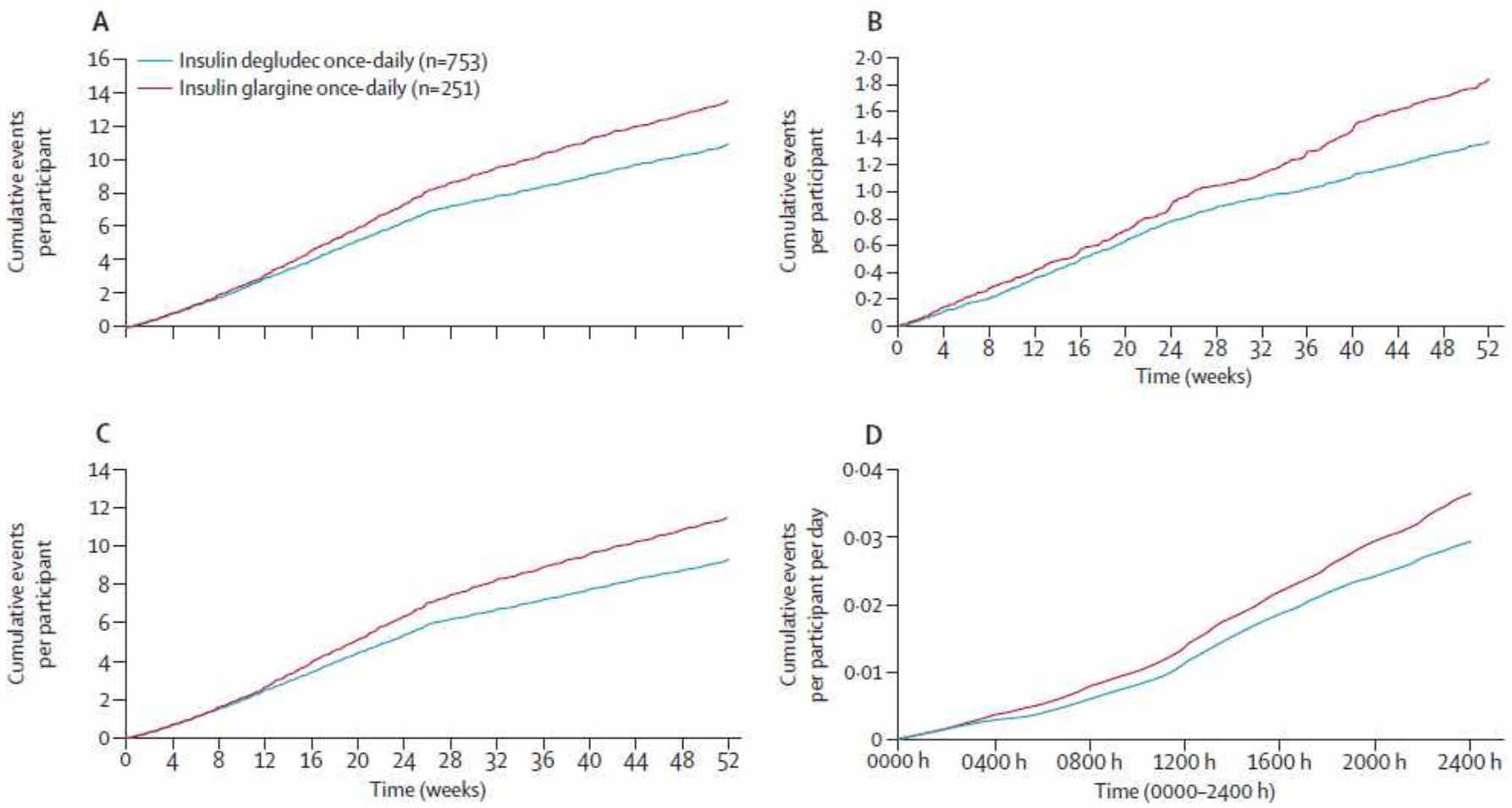
Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial

*Alan J Garber, Allen B King, Stefano Del Prato, Seamus Sreenan, Mustafa K Balci, Manuel Muñoz-Torres, Julio Rosenstock, Lars A Endahl, Ann Marie Ocampo Francisco, Priscilla Hollander, on behalf of the NN1250-3582 (BEGIN BB T2D) Trial Investigators**



Lancet 2012; 379: 1498–507

Hipoglisemik Olaylar
Güvenlik Analiz Serisi



Lancet 2012; 379: 1498–507

	Insulin degludec once-daily group, U/kg (n=753)			Insulin glargine once-daily group, U/kg (n=251)			Estimated rate ratio insulin degludec:insulin glargine (95% CI)	p value
	Participants (%)	Episodes	Rate per PYE	Participants (%)	Episodes	Rate per PYE		
Severe*	34 (5%)	41	0·06	11 (4%)	12	0·05	..	..
Overall confirmed	609 (81%)	7437	11·09	206 (82%)	3120	13·63	0·82 (0·69–0·99)	0·0359
Nocturnal confirmed	298 (40%)	930	1·39	119 (47%)	422	1·84	0·75 (0·58–0·99)	0·0399

PYE=patient-year of exposure. *Insufficient episodes for statistical assessment.

Table 3: Hypoglycaemic episodes

	Age, years	Sex	Trial day of adverse event onset	Cause of death
Insulin degludec group (n=753)				
Patient 1	65	Male	78	Arteriosclerosis and hypertensive heart disease
Patient 2	58	Male	82	Myocardial infarction
Patient 3	69	Male	86	Intracranial haemorrhage
Patient 4	63	Male	10	Cardiorespiratory arrest
Patient 5	68	Male	227	Haematemesis
Patient 6	67	Female	34	Cardiac arrest
Patient 7	54	Male	45	Rectal haemorrhage, anaemia, and myocardial infarction
Patient 8	58	Male	20	Road traffic accident
Insulin glargine group (n=251)				
Patient 9	61	Male	123	Metastatic neoplasm
Patient 10	48	Male	336	Myocardial infarction*

%1

%1

*Investigator assessed this event as possibly related to trial products.

Table 5: Causes of death in the safety analysis set

Lancet 2012; 379: 1498–507

T1DM'de Faz 2 LY2605541 ile Glargine Bulgular

- Daha düşük ortalama kan glukoz değeri
- Kilo kaybı
- Azalmış prandiyal insülin dozu
- Daha düşük noktürnal hipoglisemi oranı
- Karaciğer enzimlerinde orta derecede artış
- Normal aralıkta olmasına rağmen daha yüksek TG ve LDL-K, daha düşük HDL-K (normal sınırlarda olmasına rağmen)
- GİS YE hariç diğer YE' ler aynı

Rosenstock et al. *Diabetes Care* 2012.

T2DM'de Faz 2 LY2605541 ile Glargine Bulgular

- Benzer AKŞ ve A1C
- Glkoz değişkenliğinde düzelme
- Kilo kaybı
- Daha düşük noktürnal hipoglisemi oranı
- YE benzer
- Karaciğer enzimlerinde minimal artış (N aralıkta)
- Normal aralıkta olmasına rağmen daha yüksek TG değerleri

Rosenstock et al. *Diabetes Care* 2012