Yeni Diyabet İlaçları

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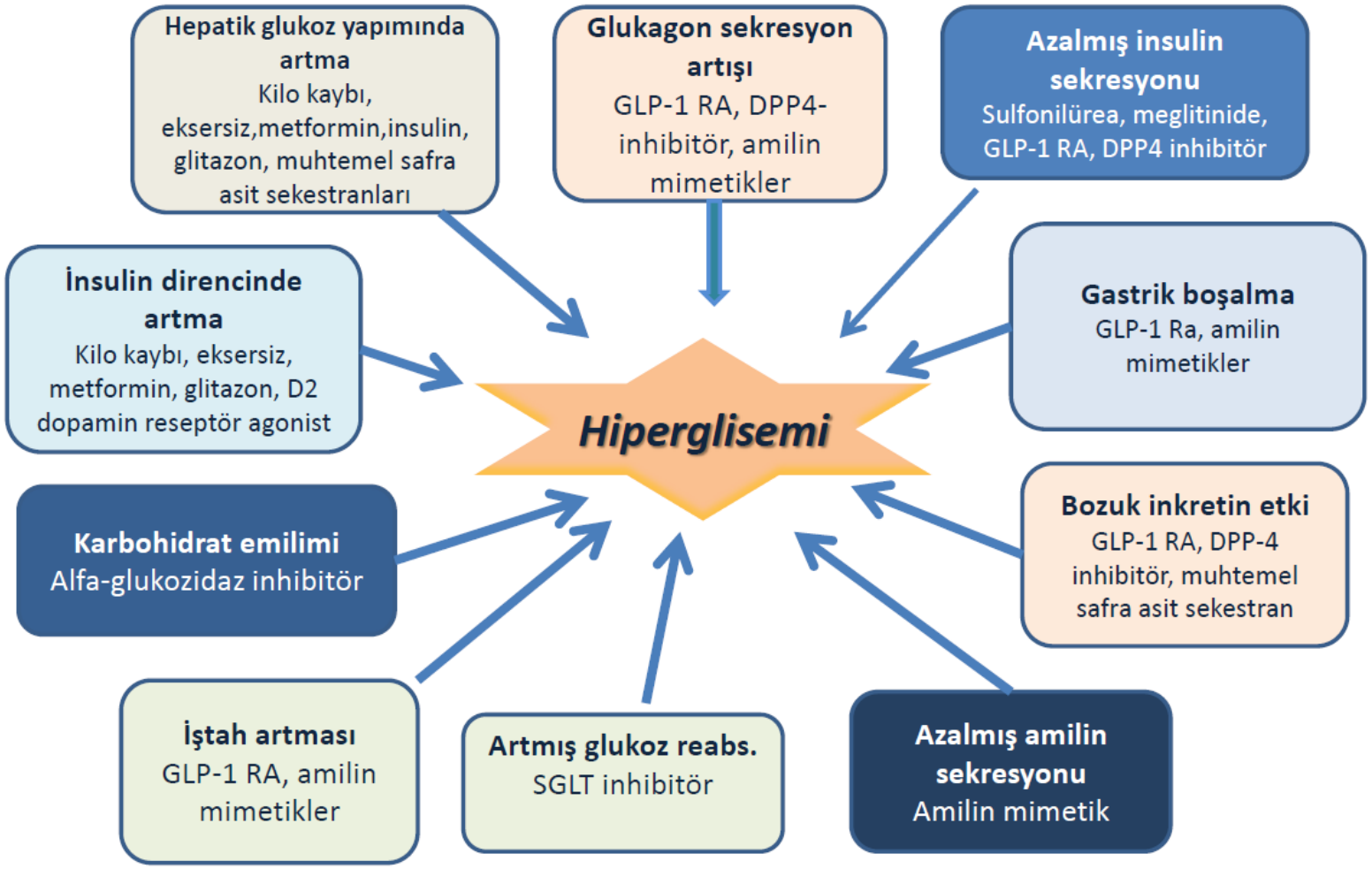
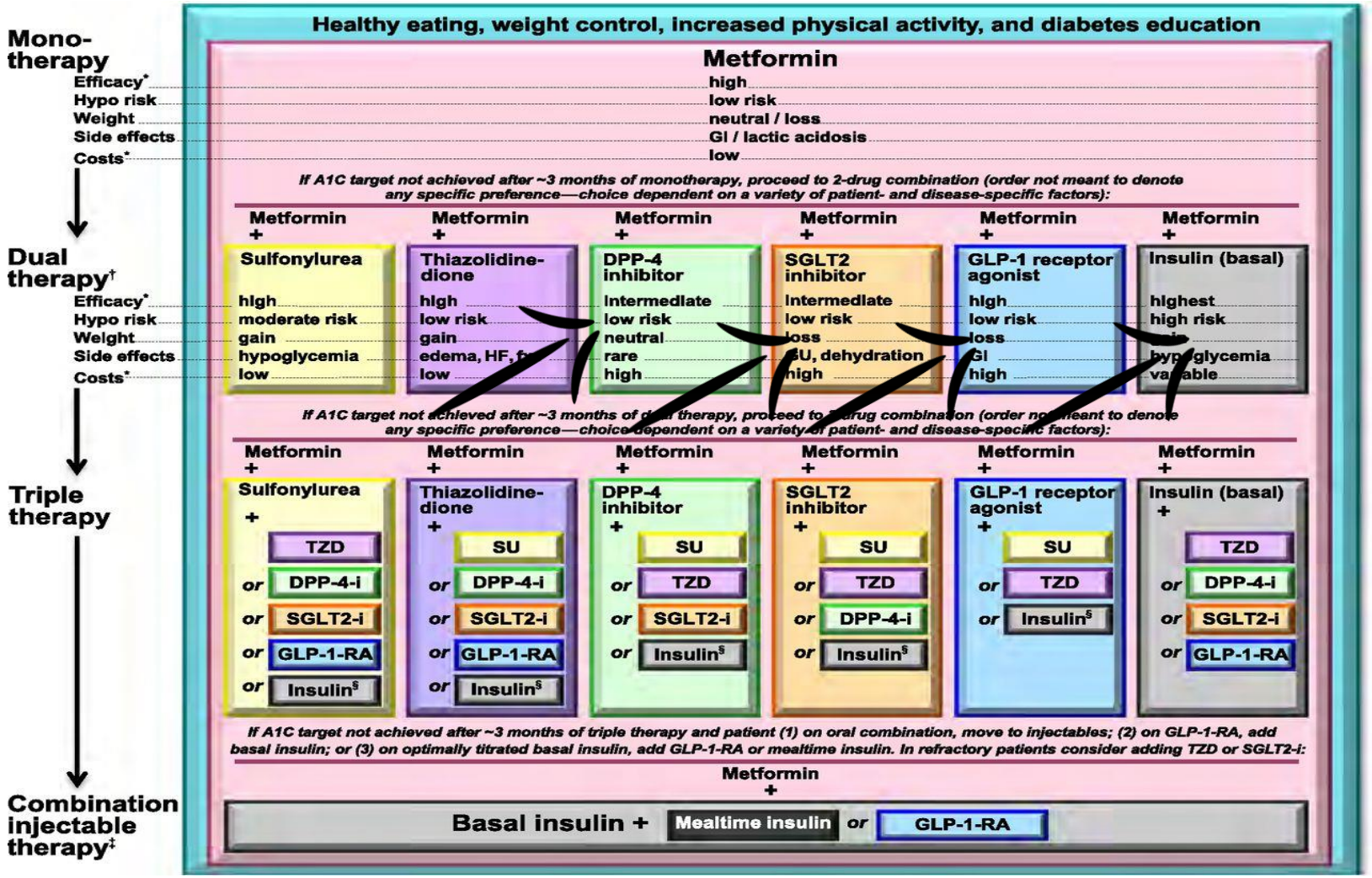
Yeditepe Üniversitesi Tıp Fakültesi, Endokrinoloji ve Metabolizma Hastalıkları B.D.

Patofizyoloji netleştikçe yeni tedaviler bulunmaktadır



İnsülin tip 2 diyabet tedavisinin her aşamasında gereklidir.



American Diabetes Association Diab Care 2016;39:S52-S59

Yeni Diyabet İlaçları

- Oral İlaçlar
  - DPP-4 İnhibitörleri
  - Safra asidi bağlayıcılar
  - Bromocriptin
  - Diğerleri
- Enjeksiyon ilaçlar
  - GLP-1 analogları
  - Amylin analogları
  - İnsülinler
    - Ultra uzun etkili insülinler
    - Kombinasyon insülinler
    - Biyobenzer insülinler
    - Biyonik pankreas

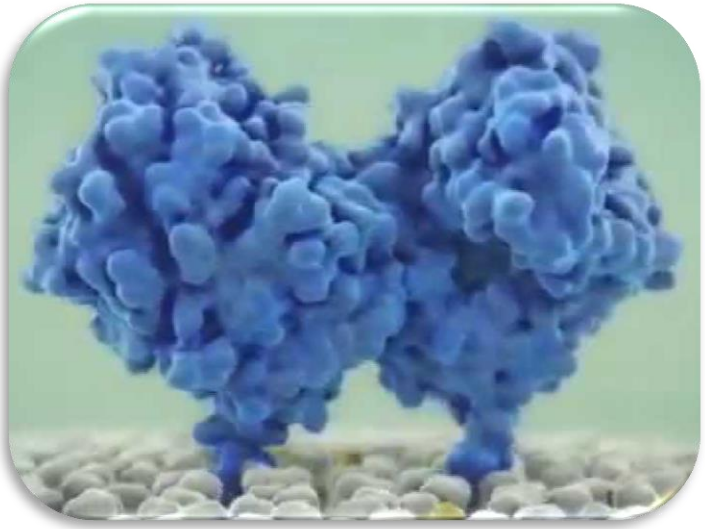
DPP-IV İnhibitörleri

Sitagliptin

Vildagliptin

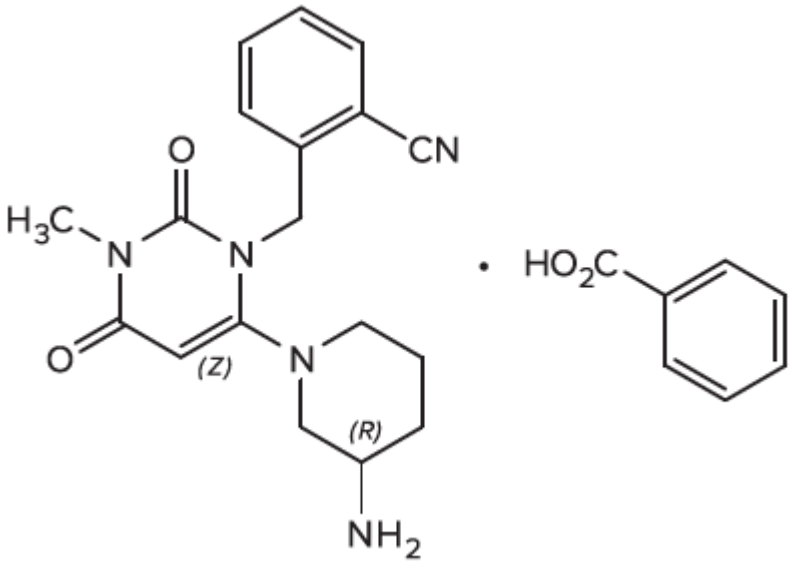
Saxagliptin

Alogliptin

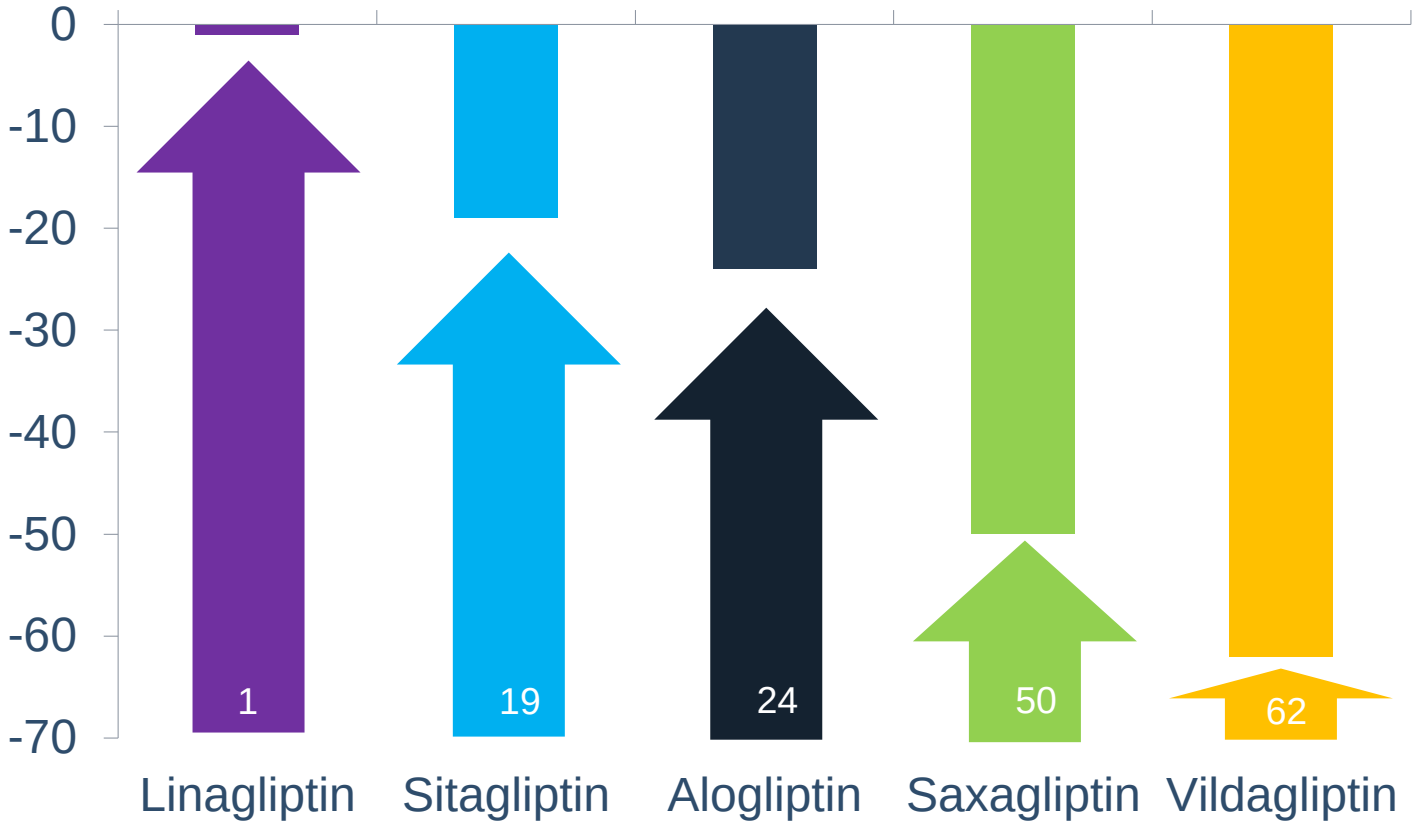


Linagliptin

Alogliptin



DPP4 inhibitörleri etkinlik



Linagliptin, 1 nanomolar miktar molekül ile DPP4 enzim aktivitesinin %50sini inhibe eder.

Grafik referanstan adapte edilmiştir. Thomas L, et al. *J Pharmacol Exp Ther*. 2008;325:175–182.

Alogliptin Klinik Çalışmaları

Reference Study Duration	Treatment (Number of Subjects)	Mean Baseline A1c (%)	Least–Squares Mean Change in A1c (%)
In Patients With No Prior Antihyperglycemic Therapy			
Defronzo et al. 2008[16] 26 weeks	Placebo (n = 64)	7.9	–0.02
	Alogliptin 12.5 mg (n = 133)		–0.56 ($P < 0.001$, vs. placebo)
	Alogliptin 25 mg (n = 131)		–0.59 ($P < 0.001$, vs. placebo)
Rosenstock et al. 2010[17] 26 weeks	Alogliptin 25 mg (n = 164)	8.80	–0.96
	Pioglitazone 30 mg (n = 163)	8.76	–1.15
	Alogliptin 12.5 mg + pioglitazone 30 mg (n = 164)	8.85	–1.56 ($P < 0.05$, vs. pioglitazone alone)
	Alogliptin 25 mg + pioglitazone 30 mg (n = 164)	8.80	–1.71 ($P < 0.05$, vs. pioglitazone alone, vs. alogliptin alone)
Pratley et al. 2012[8,18] 26 weeks	Placebo (n = 102)	8.5	0.1
	Alogliptin 12.5 mg b.i.d. (n = 104)	8.4	–0.6
	Metformin 500 mg b.i.d. (n = 103)	8.5	–0.7
	Metformin 1,000 mg b.i.d. (n = 108)	8.4	–1.1
	Alogliptin 12.5 mg + metformin 500 mg b.i.d. (n = 102)	8.5	–1.2 ($P < 0.001$, vs alogliptin 12.5 mg b.i.d., vs. metformin 500 mg b.i.d.)
	Alogliptin 12.5 mg + metformin 1,000 mg b.i.d. (n = 111)	8.4	–1.6 ($P < 0.001$, vs alogliptin 12.5 mg b.i.d., vs. metformin 1,000 mg b.i.d.)

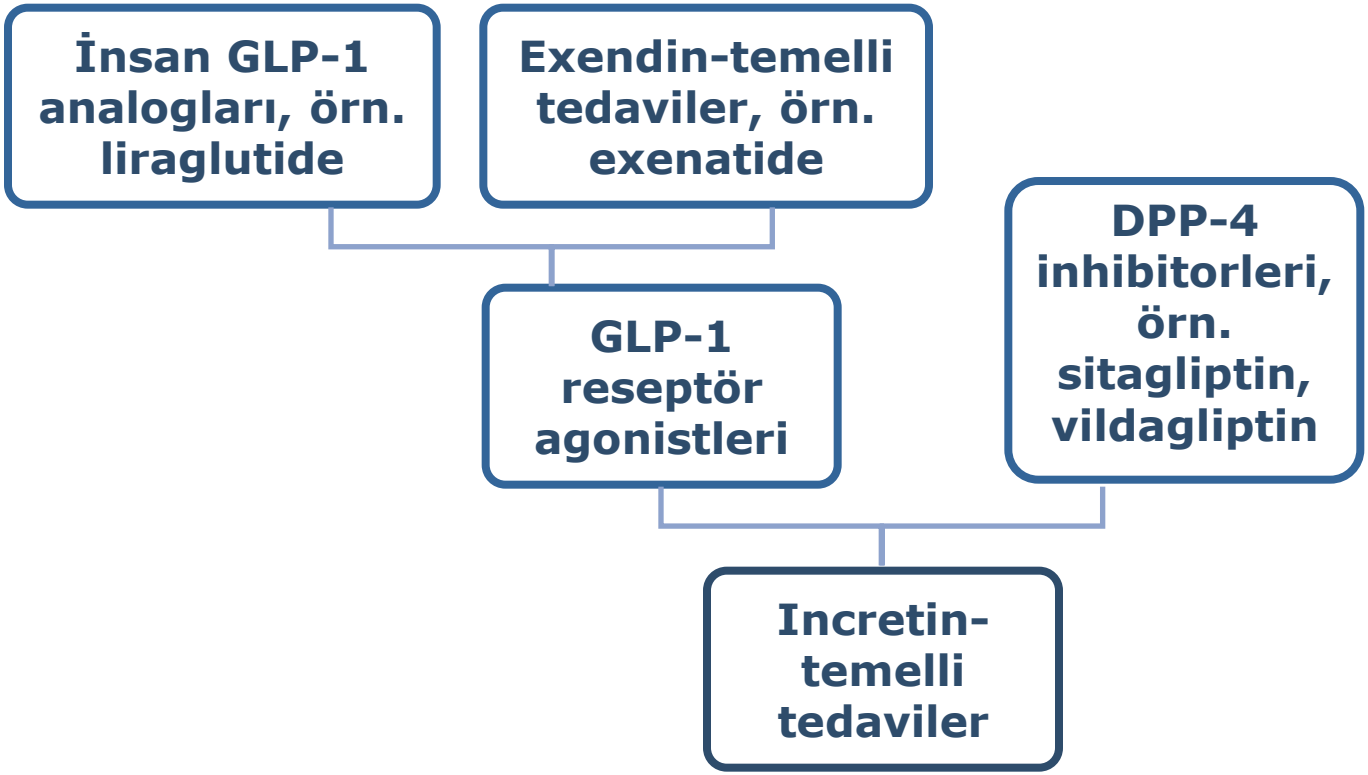
Alogliptin Klinik Çalışmaları

In Patients Receiving Thiazolidinedione			
Pratley et al. 2009[21] 26 weeks	Placebo + pioglitazone 30 or 45 mg (n = 97)	8.0	–0.19
	Alogliptin 12.5 mg + pioglitazone 30 or 45 mg (n = 197)	8.1	–0.66 ($P < 0.001$, vs. placebo)
	Alogliptin 25 mg + pioglitazone 30 or 45 mg (n = 199)	8.0	–0.80 ($P < 0.001$, vs. placebo)
In Patients Receiving Pioglitazone and Metformin			
Bosi et al. 2011[22] 52 weeks	Metformin (≥ 1,500 mg or MTD) + pioglitazone 30 mg + Alogliptin 25 mg (n = 404)	8.3	–0.70 (P < 0.001)
	Metformin (≥ 1,500 mg or MTD) + pioglitazone 30 mg + pioglitazone 15 mg (n = 399)	8.1	–0.29
In Patients Receiving Sulfonylurea			
Pratley et al. 2009[23] 26 weeks	Glyburide + placebo (n = 99)	8.1	+0.01
	Glyburide + alogliptin 12.5 mg (n = 203)	8.1	–0.39 ($P < 0.001$, vs. placebo)
	Glyburide + alogliptin 25 mg (n = 198)	8.1	–0.53 ($P < 0.001$, vs. placebo)
In Patients Receiving Insulin			
Rosenstock et al. 2009[24] 26 weeks	Insulin + placebo ± metformin (n = 130)	9.3	–0.13
	Insulin + alogliptin 12.5 mg ± metformin (n = 131)	9.3	–0.63 ($P < 0.001$, vs. placebo)
	Insulin + alogliptin 25 mg ± metformin (n = 129)	9.3	–0.71 ($P < 0.001$, vs. placebo)

DPP-4 İnhibitörleri

Product	Alogliptin (Nesina)	Linagliptin (Tradjenta)	Saxagliptin (Onglyza)	Sitagliptin (Januvia)
Cost (30 count)	6.25-, 12.5-, 25-mg tablets: $340.64	5-mg tablets: $340.62	2.5-, 5-mg tablets: $334.68	25-, 50-, 100-mg tablets: $340.61
Usual daily dose	25 mg once daily without regard to meals	5 mg once daily without regard to meals	2.5 to 5 mg once daily without regard to meals	100 mg once daily without regard to meals
Pregnancy category	B	B	B	B
Renal impairment	Dose adjustment required for CrCl < 60 mL/min	No dose adjustment required	Dose adjustment required for CrCl ≤ 50 mL/min	Dose adjustment required for CrCl < 50 mL/min
Hepatic impairment	No dosage adjustment required for mild to moderate hepatic impairment; not studied in severe impairment (Child-Pugh Grade C) Use with caution	No dose adjustment required	No dose adjustment required	No dosage adjustment required for mild to moderate hepatic impairment; not studied in severe impairment (Child-Pugh score > 9)
Warnings/ precautions	• Acute pancreatitis • Hypersensitivity • Hepatic effects • Hypoglycemia when added with insulin or insulin secretagogue	• Acute pancreatitis • Hypoglycemia when added with insulin or insulin secretagogue	• Acute pancreatitis • Hypersensitivity • Hypoglycemia when added with insulin or insulin secretagogue	• Acute pancreatitis • Acute renal failure • Hypersensitivity • Hypoglycemia when added with insulin or insulin secretagogue
Common adverse events	• Headache • Nasopharyngitis • Upper respiratory tract infection	• Hypoglycemia • Nasopharyngitis	• Hypoglycemia • Headache • Nasopharyngitis • Upper respiratory tract infection • Urinary tract infection • Peripheral edema	• Hypoglycemia • Headache • Nasopharyngitis • Upper respiratory tract infection
Drug interactions	No significant clinical interactions noted	P-glycoprotein and CYP3A4 inducers may decrease the efficacy of linagliptin	Strong CYP3A4/5 inhibitors increase saxagliptin exposure; limit saxagliptin to 2.5 mg	No significant clinical interactions noted
Combination products	• Kazano: with metformin • Oseni: with pioglitazone	Jentadueto: with metformin	Kombiglyze: with metformin	• Janumet: with metformin • Juvisync: with simvastatin

Incretin Temelli Tedavi Ailesi



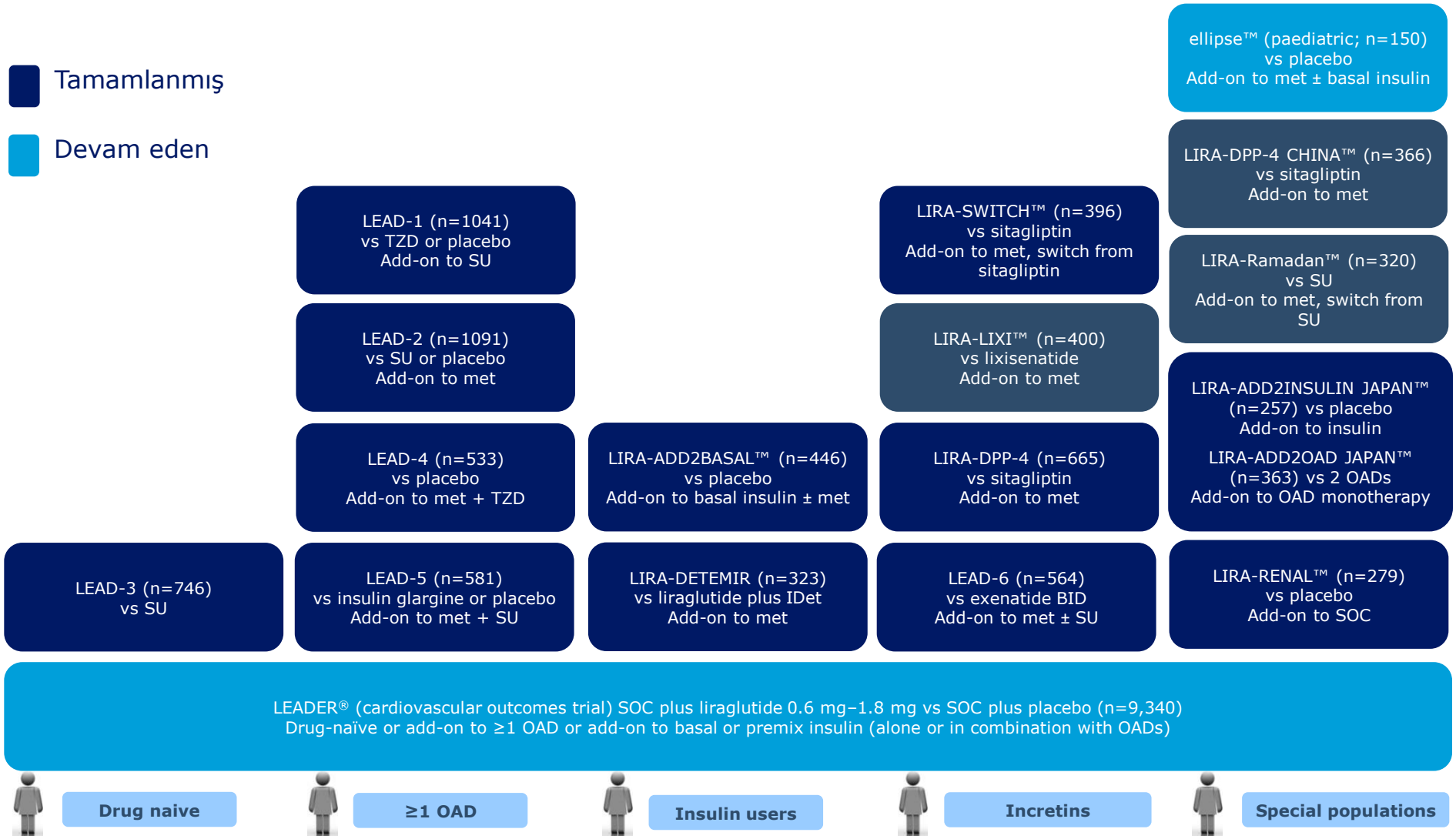
GLP-1 Reseptör Agonistleri: Kısa vs. Uzun etkili

Table 1 | Comparison of short-acting versus long-acting GLP-1 receptor agonists

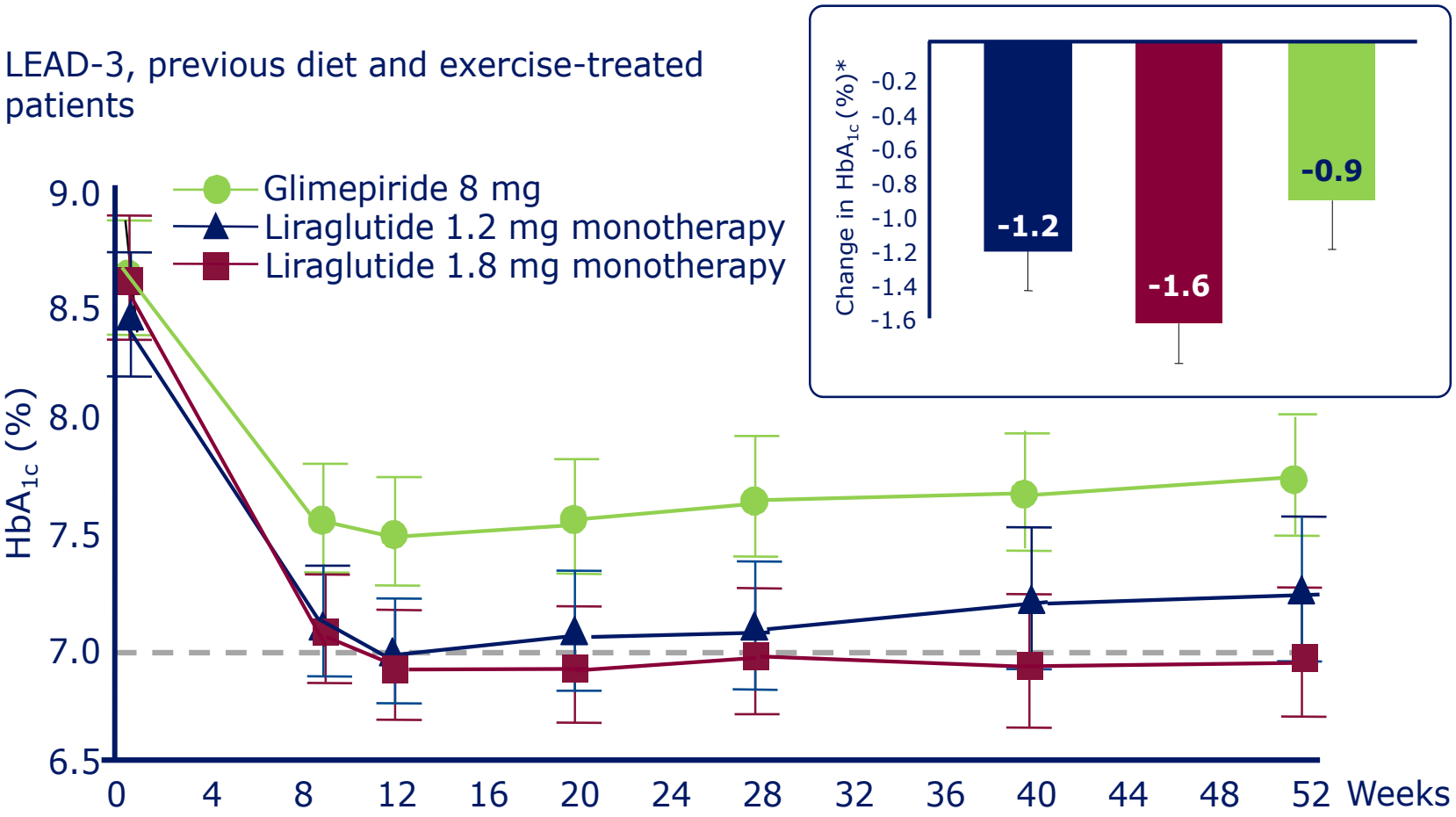
Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide-LAR Liraglutide
Half-life	2–5 h	12 h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

Liraglutide klinik çalışmaları: diyabetin tüm basamaklarında yeri vardır



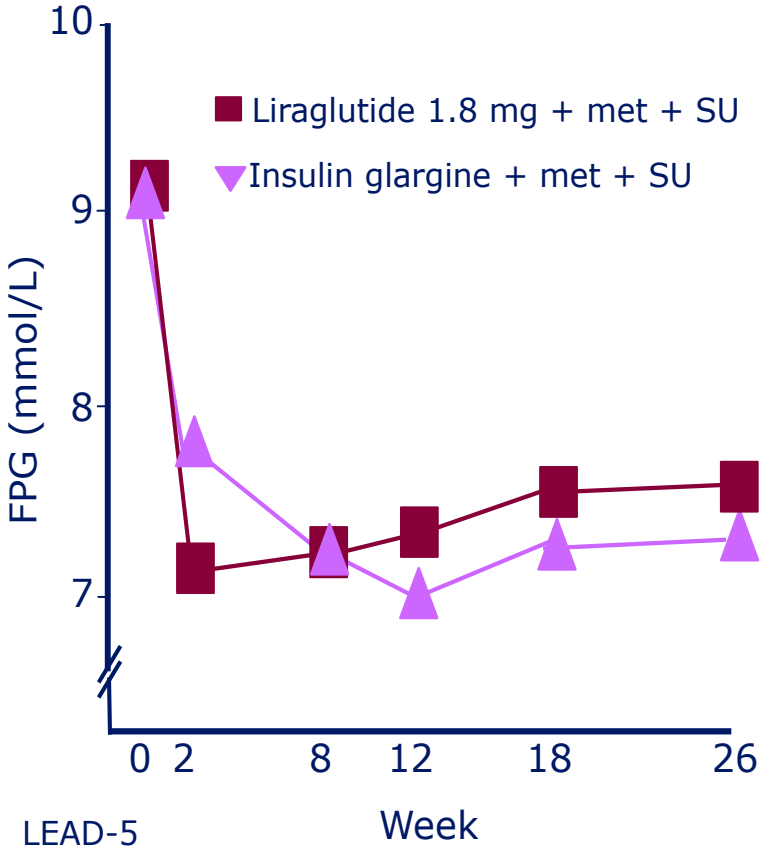
Liraglutide monoterapisi (A_{1c} <7.0%) uzun dönemli kontrol sağlar (52 hafta)



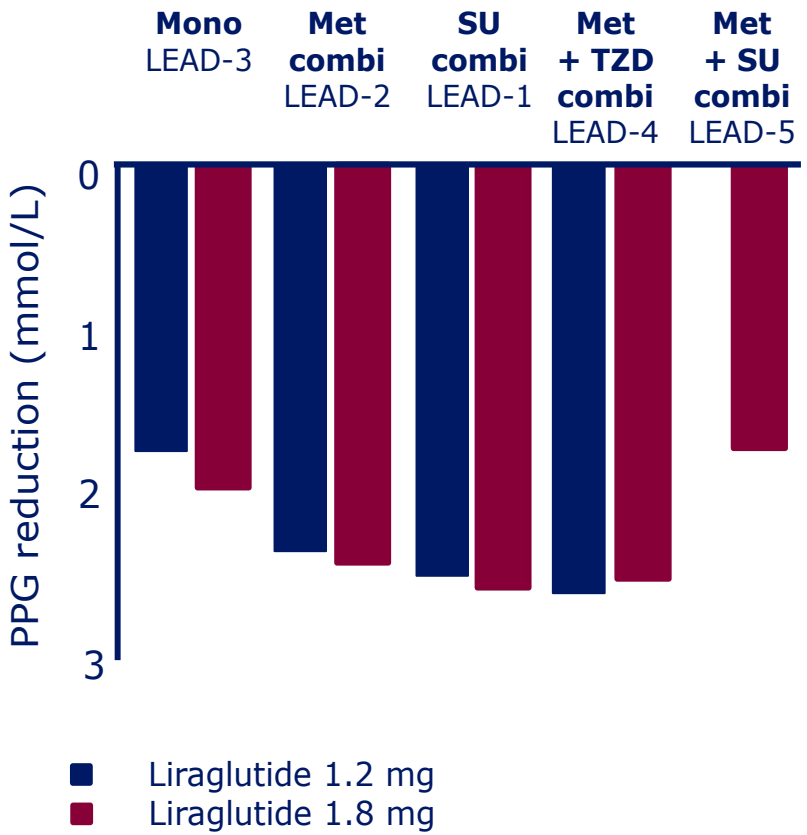
Garber *et al. Lancet* 2009;373:473–81 (LEAD-3). Data are mean (SD)

Liraglutide hem AKŞ hem de TKŞ etkilidir

Liraglutide reduces FPG (before 2 weeks)



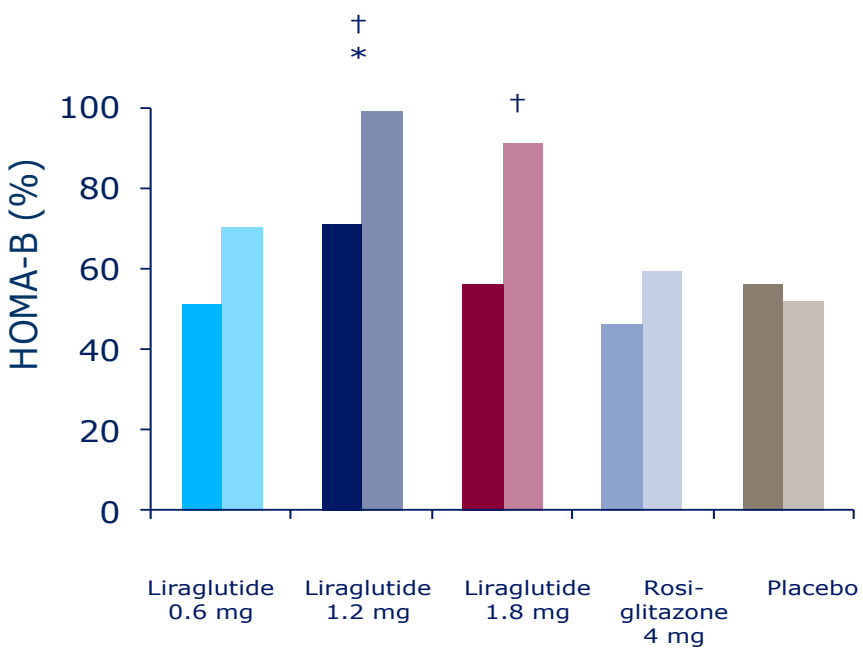
Mean PPG reduction over 3 meals

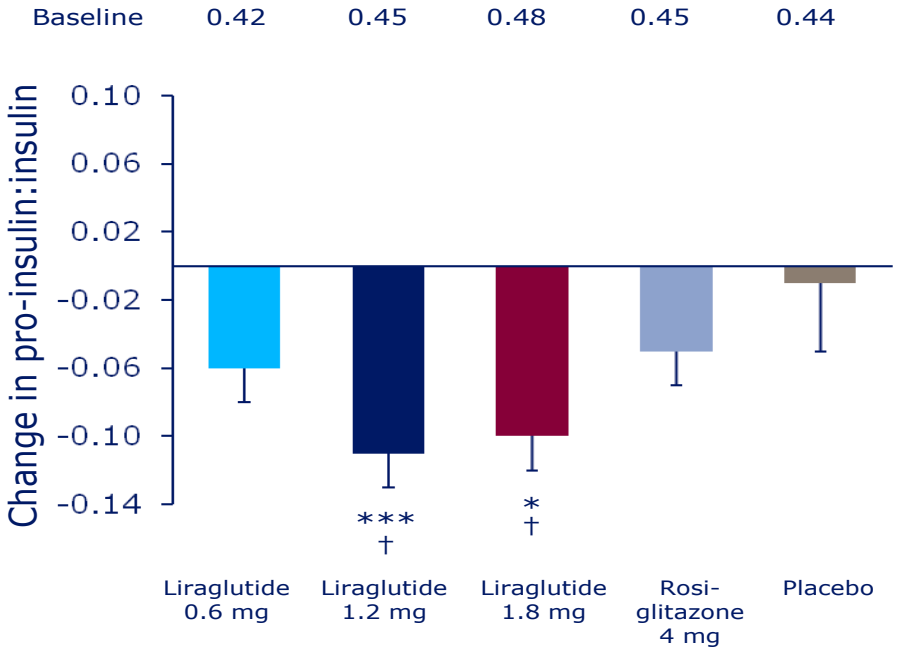


Marre *et al. Diabetic Medicine* 2009;26;268–78 (LEAD-1); Nauck *et al. Diabetes Care* 2009;32;84–90 (LEAD-2); Garber et al. *Lancet* 2009;373:473–81 (LEAD-3); Zinman *et al. Diabetes Care* 2009; DOI:10.2337/dc08-2124 (LEAD-4); Russell-Jones *et al. Diabetes* 2008;57(Suppl. 1):A159 (LEAD-5)

Liraglutide ve beta-hücre fonksiyonu: HOMA-B ve pro-insulin:insulin oranı

Treatment differences in changes:
*p<0.05, ***p<0.0001 vs. placebo;
†p<0.05, †††p<0.01 vs. rosiglitazone; NS for all other treatment comparisons



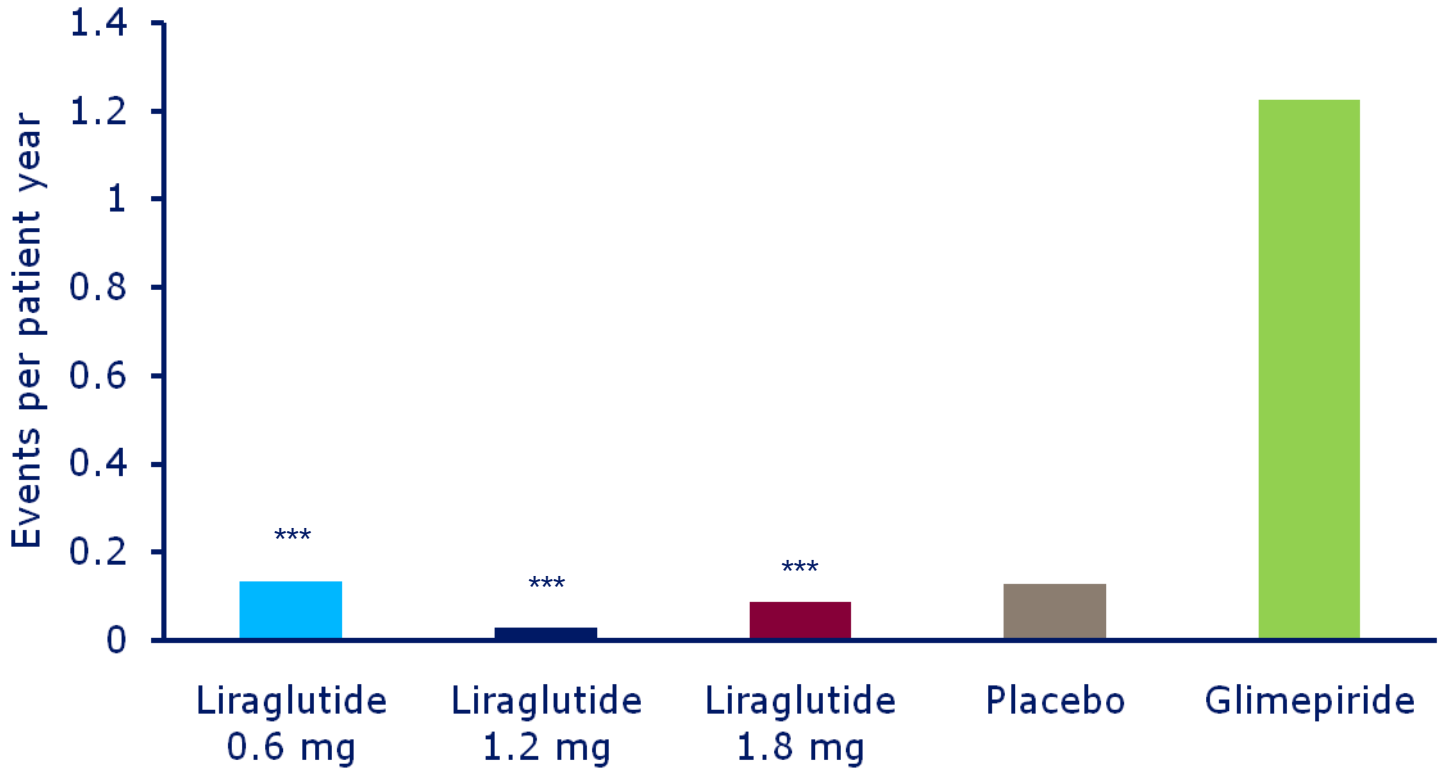


Darker bars = baseline values
Lighter bars = 26 weeks (LOCF)
(Statistical analysis [ANCOVA] performed on change in beta-cell function)

Marre *et al. Diabetic Medicine* 2009;26:268–78 (LEAD-1)

Liraglutide metformin ile kombinasyonda düşük hipoglisemi riski taşır

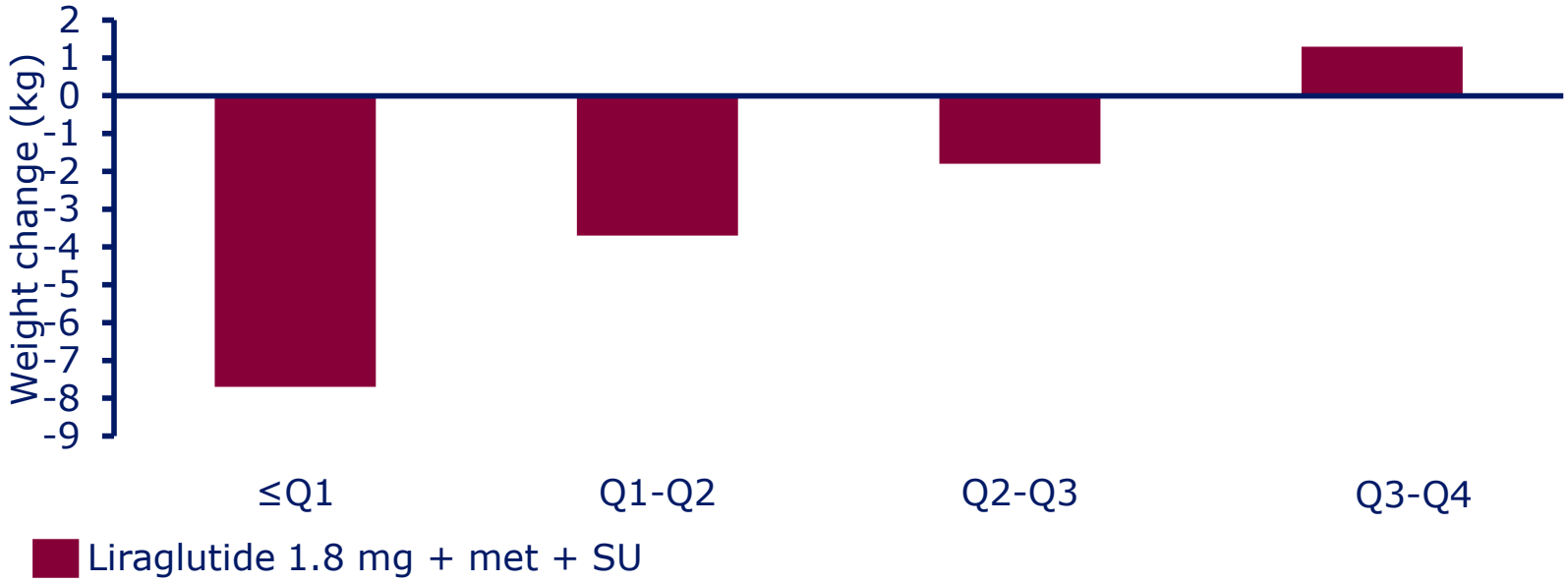
***p<0.0001 for treatment differences in changes versus glimepiride



- Minor hypoglycaemic events are at the placebo level (LEAD-2, above)
- There is a small but increased risk of minor hypoglycaemia when combined with SUs (1.0 events per subject every second year; LEAD-1)

Marre *et al. Diabetic Medicine* 2009;26;268–78 (LEAD-1); Nauck *et al. Diabetes Care* 2009; 32; 84–90 (LEAD-2)

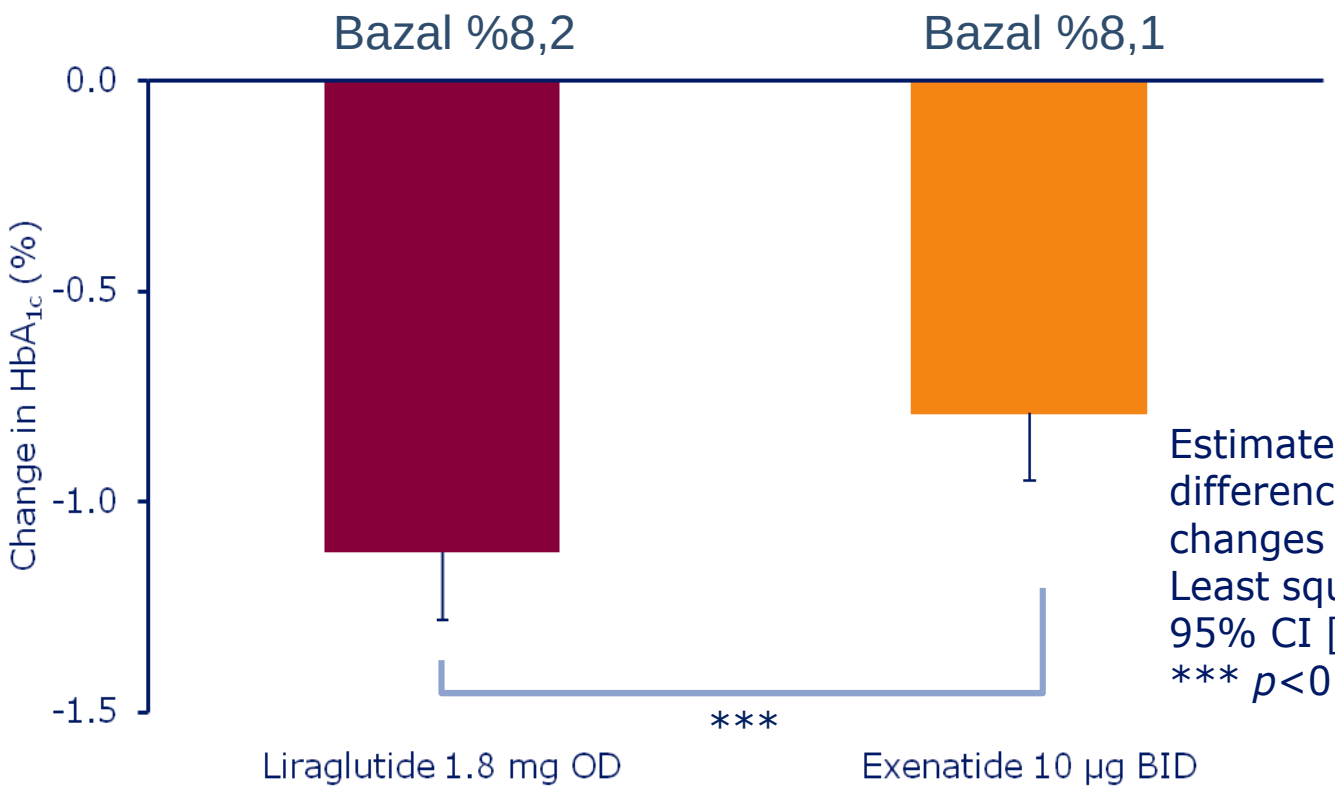
Hastaların ¼'ü liraglutide ile ortalama 7.7 kg kaybeder



0–Q1: mean weight change for the 25% of subjects who had the largest weight loss
Q1–Q2: mean weight change for the 25–50% weight loss quartile
Q2–Q3: mean weight change for the 50–75% weight loss quartile
Q3–Q4: mean weight change for the 75–100% weight loss quartile, that is, the 25% who had the smallest weight loss

Nauck *et al. Diabetes Care* 2009;32;84–90 (LEAD-2)

Liraglutide vs Exenatide: A_{1c} Düşüşü

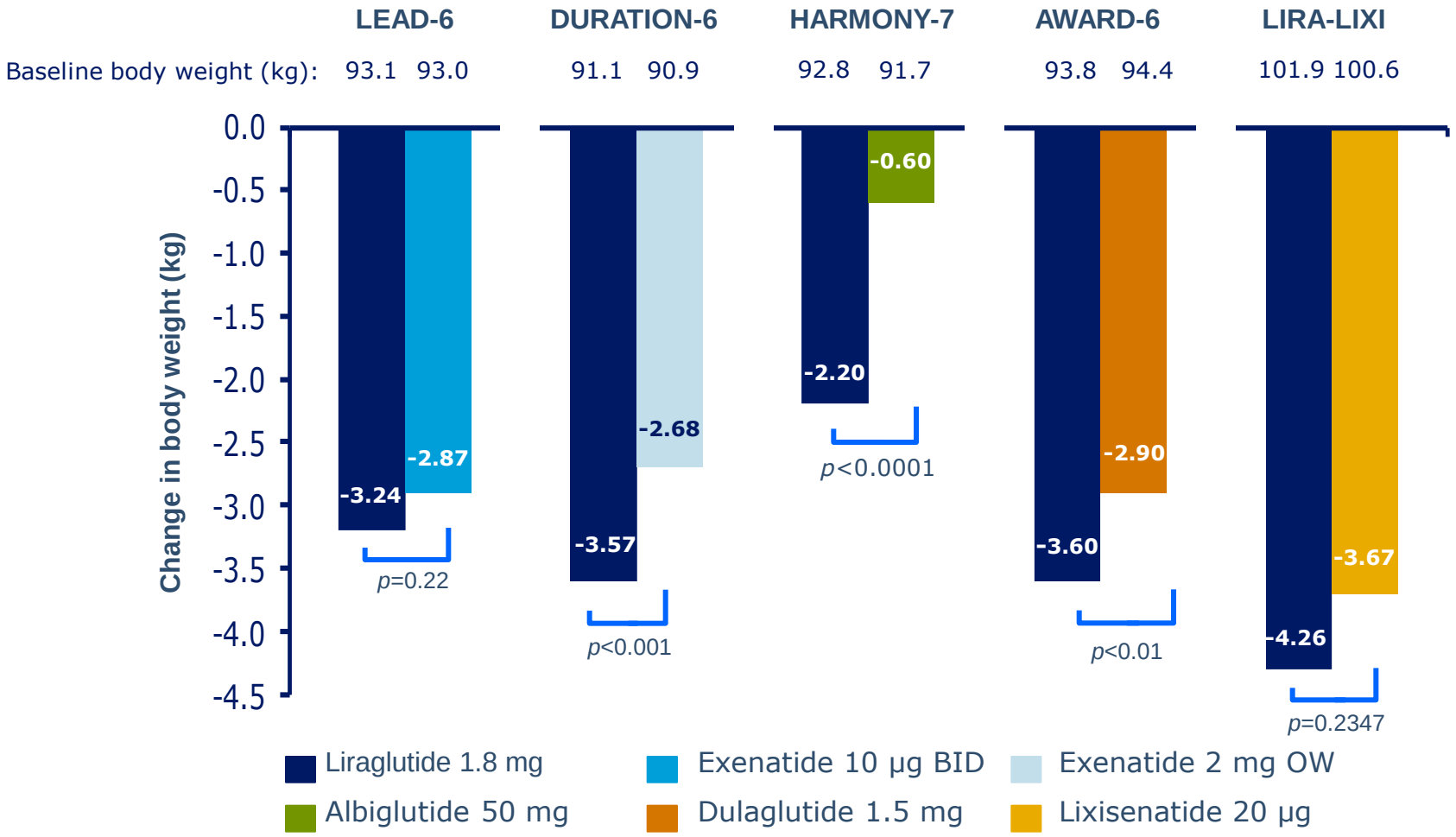


Estimated treatment difference for changes from baseline
Least square mean: −0.33
95% CI [−0.47; −0.18]
*** $p<0.0001$

Mean (2SE)

Buse *et al. Lancet* 2009; DOI:10.1016/S0140-6736(09)60659-0 (LEAD-6)

GLP-1RA karşılaştırma çalışmaları: Kilo değişimi



BID, twice a day; GLP-1RA, glucagon-like peptide-1 receptor agonist

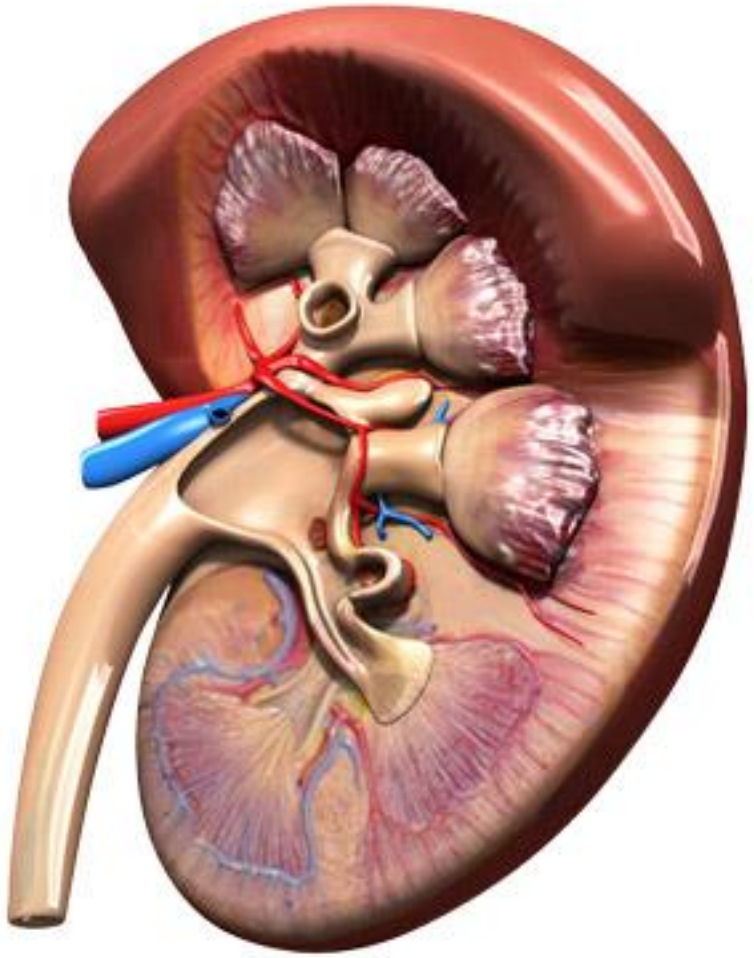
Buse JB et al. *Lancet* 2009;374:39–47 (LEAD-6); Buse JB et al. *Lancet* 2013;381:117–124 (DURATION-6); Pratley RE et al. *Lancet Diabetes Endocrinol* 2014;2:289–297 (Harmony-7); Dungan KM et al. *Lancet* 2014;384(9951):1349–1357 (AWARD-6); Nauck MA et al. EASD 2015 Annual Meeting. Oral presentation #75 (LIRA-LIXI)

Exenatide LAR

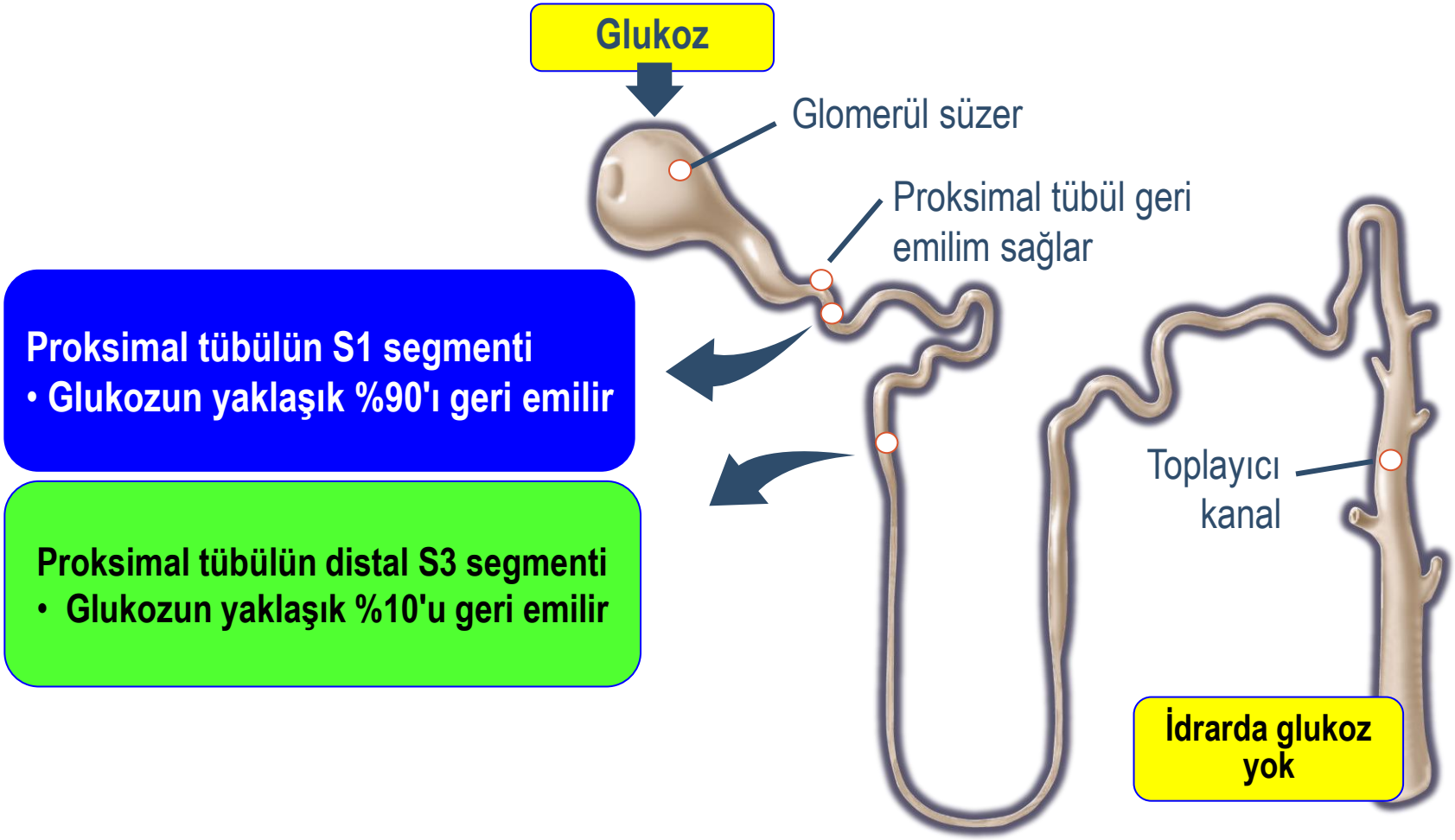
- DURATİON-5 çalışması

- Günde 2 kez verilen Exenatide göre
  - AKŞ, A1c ↓
  - Kilo kaybı ↑
- Yan etki açısından Exenatid ile benzer

SGLT2-inhibitörleri



Böbrekte Glukozun Geri Emilmesi



1.Silverman M, Turner RJ. In: Windhager EE, ed. *Handbook of Physiology, Vol. II*. New York, NY: Oxford University Press; 1992:2017-2038.
2.Bakris GL, et al. *Kidney Int*. 2009;75(12):1272-1277.

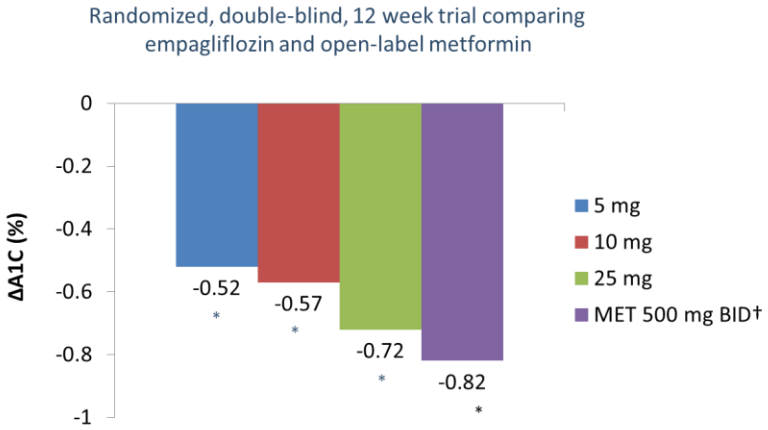
SGLT2 Inhibitörlerinin Farmakokinetik Özellikleri

	Dapagliflozin [16, 17, 34]	Canagliflozin [21, 35]	Empagliflozin [22, 36]	Ipragliflozin [25]	Luseogliflozin [67]	Tofogliflozin [27, 64, 65]
Trade name	Forxiga (Europe) Farxiga (USA)	Invokana (Europe and USA)	Jardiance (Europe and USA)	Suglat (Japan)	Lusefi (Japan)	Apleway, Deberza (Japan)
Tablets (mg)	5, 10	100, 300	10, 25	25, 50	2.5, 5	20
Oral bioavailability (%)	78	≈65	>60 %	NA	NA	97.5
Food effect	Not clinically relevant	Not clinically relevant	Not clinically relevant	NA	Not clinically relevant	NA
t_{max} (h)	1–2	1–2	1	1–2	1–2	0.75
Volume of distribution (L)	118	119	74	NA	39	50
Plasma protein binding (%)	91	98	86	NA	NA	83
$t_{½}$ (h)	12.2	11–13	12.4	10–13	10–12	6.8
Hepatic metabolism	Extensive glucuronidation to inactive conjugates (primarily dapagliflozin 3-0 glucuronide)	Extensively metabolized by O-glucuronidation to two major inactive metabolites (M5 and M7)	Extensively metabolized by glucuronidation, and to a lesser extent, oxidation to six inactive metabolites	Extensively metabolized by glucuronidation to two major inactive metabolites (M2 and M4)	NA	Metabolism predominantly oxidative with minor glucuronide conjugates
Urinary elimination	<2 % eliminated as unchanged drug in urine (primarily inactive metabolites)	<1 % eliminated as unchanged drug in urine	28.6 % excreted unchanged in urine	≤1 % eliminated as unchanged drug in urine (primarily inactive metabolites)	NA	About 76 % of the dose excreted in urine mainly as metabolites (mean portion of 16.1 % as the unchanged parent drug)

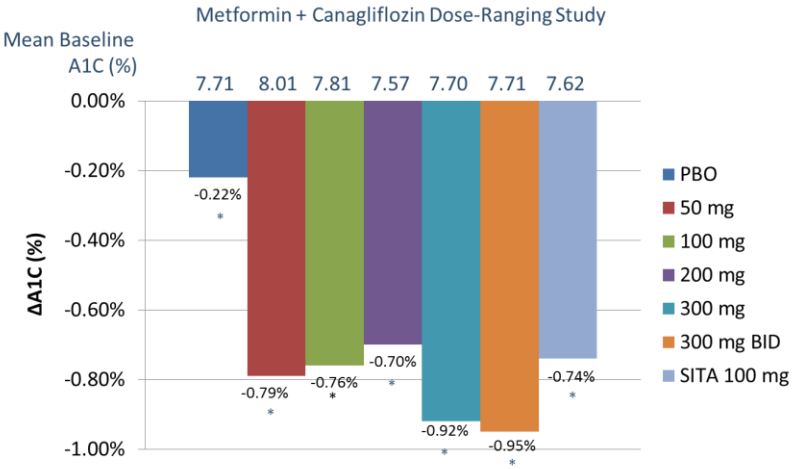
Scheen AJ. Clin Pharmacokinet (2015) 54:691–708

Etkin A1c kontrolü

Empagliflozin

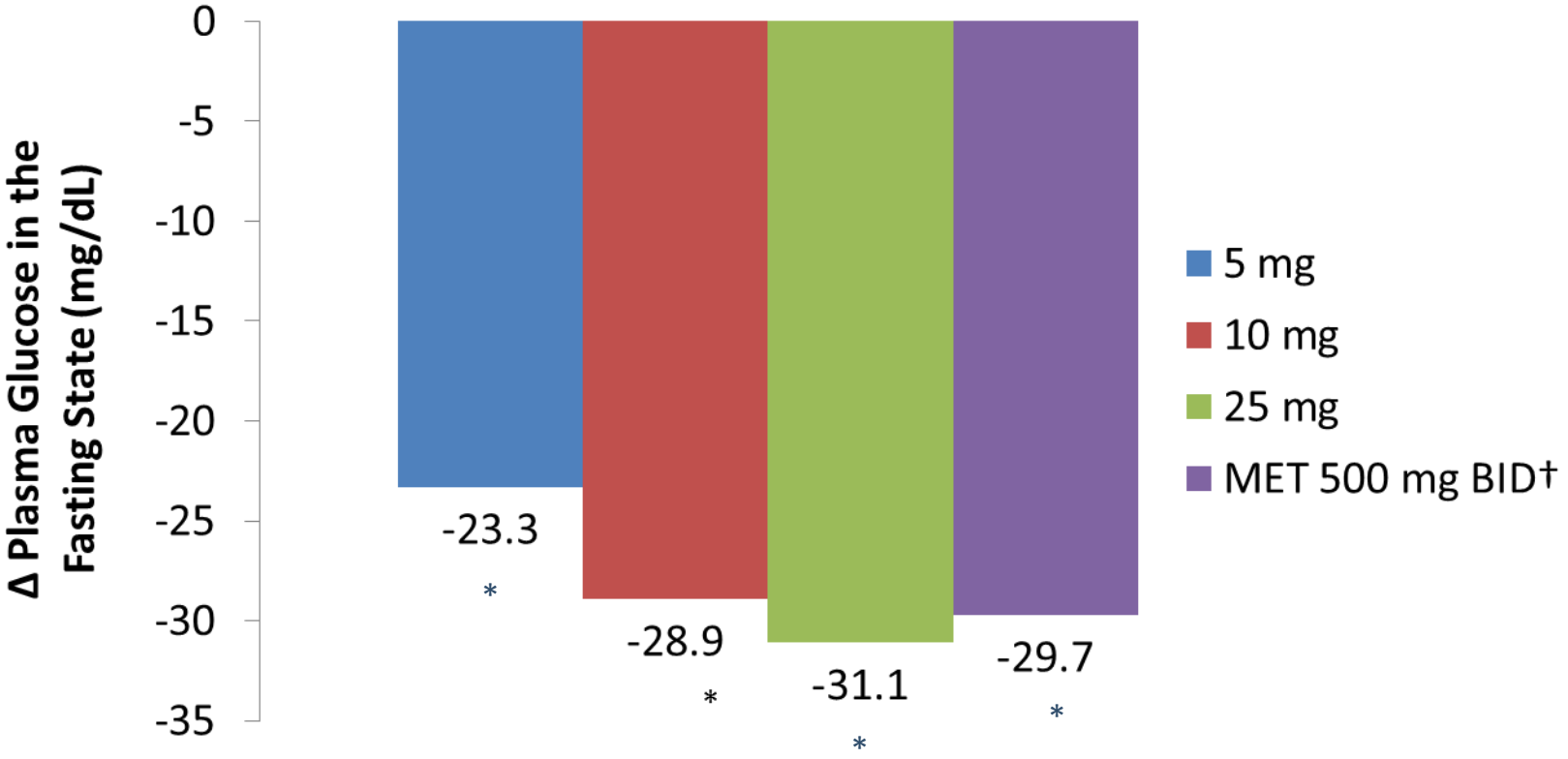


Canagliflozin



AKŞ etkisi belirgindir

Randomized, double-blind, 12 week trial comparing empagliflozin and open-label metformin

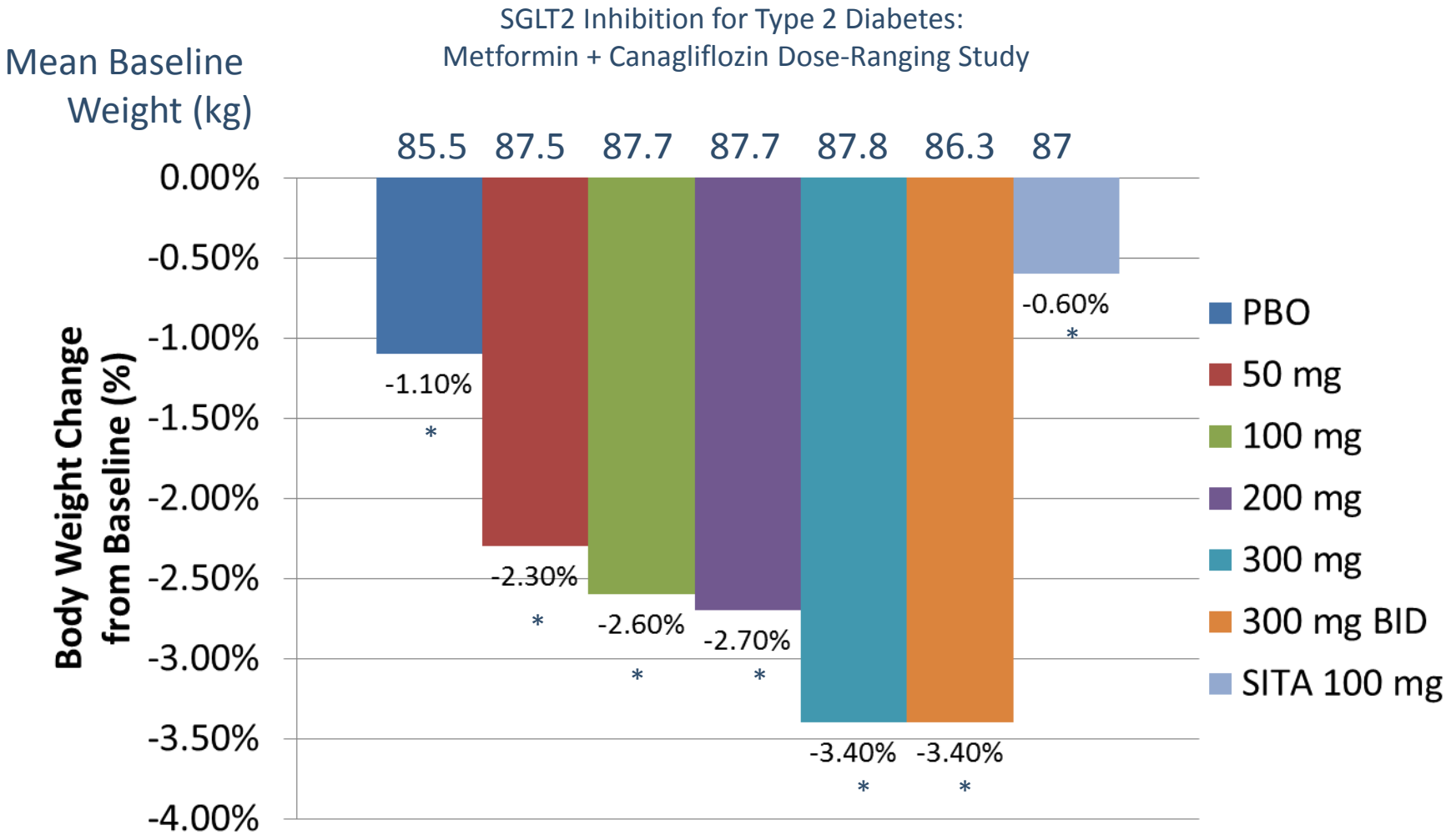


*P<.001 vs. placebo

†500 mg BID for four weeks, then 1000 mg BID or the maximum tolerate dose

Ferrannini E, et al. Abstract 877. EASD 2010.

Kilo kaybı yaratırlar



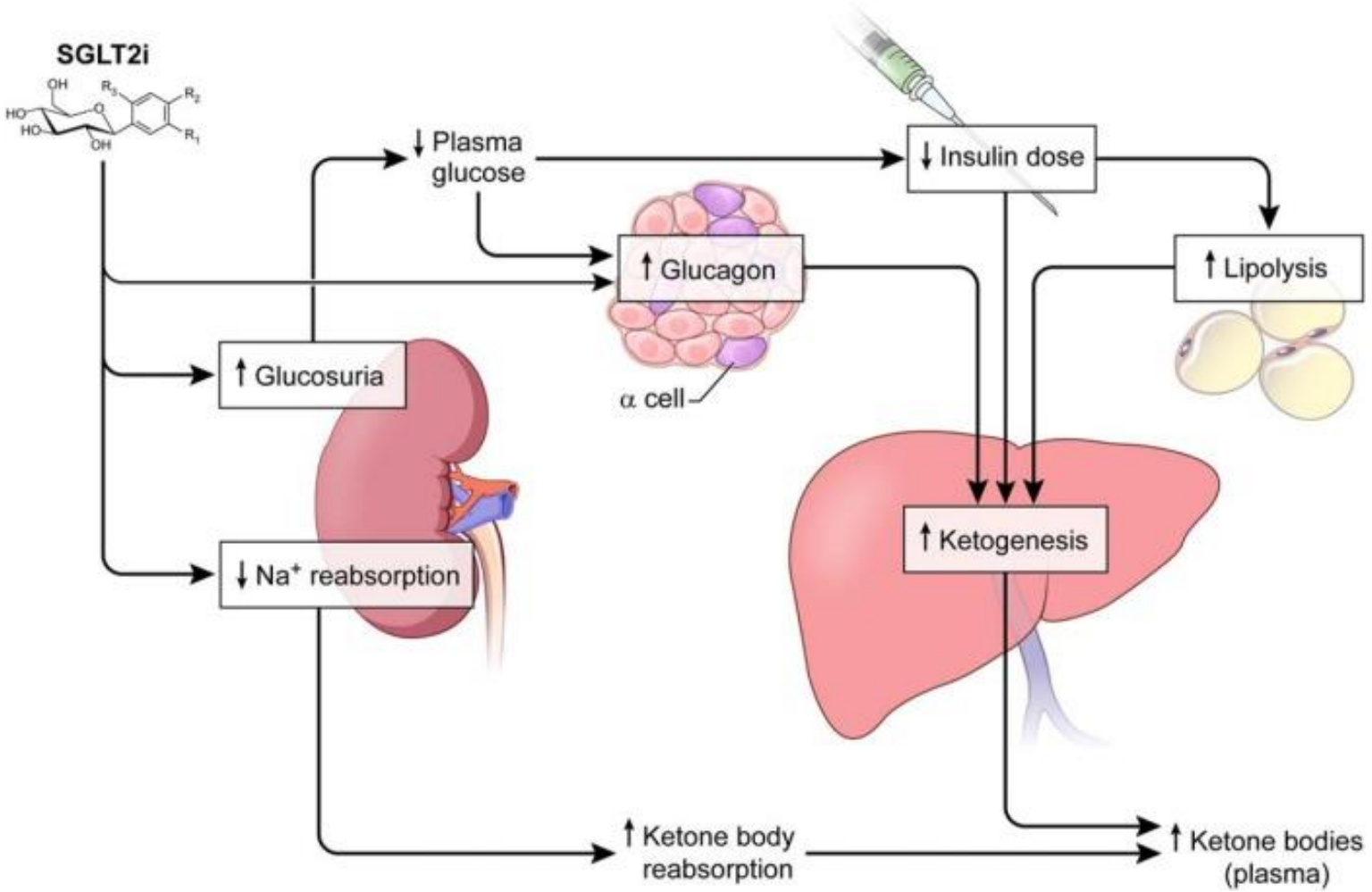
Rosenstock J, et al. Abstract 77-OR. ADA 2010.

*P<.001 vs. placebo calculated using LS means

SGLT2 İnhibititörleri

- Avantajları
  - İnsülinden bağımsız etki
  - Kilo kaybı(75g idrar glukoz kaybı = 300kcal/gün)
  - Düşük hipoglisemi riski
  - Kan basıncı düşüşü
- Dikkat
  - Poliüri
  - Elektrolit bozukluğu
  - Bakteriyel idrar yolu infeksiyonları
  - Fungal genital infeksiyonlar
  - Malignite?

Normoglisemik Ketoasidoz



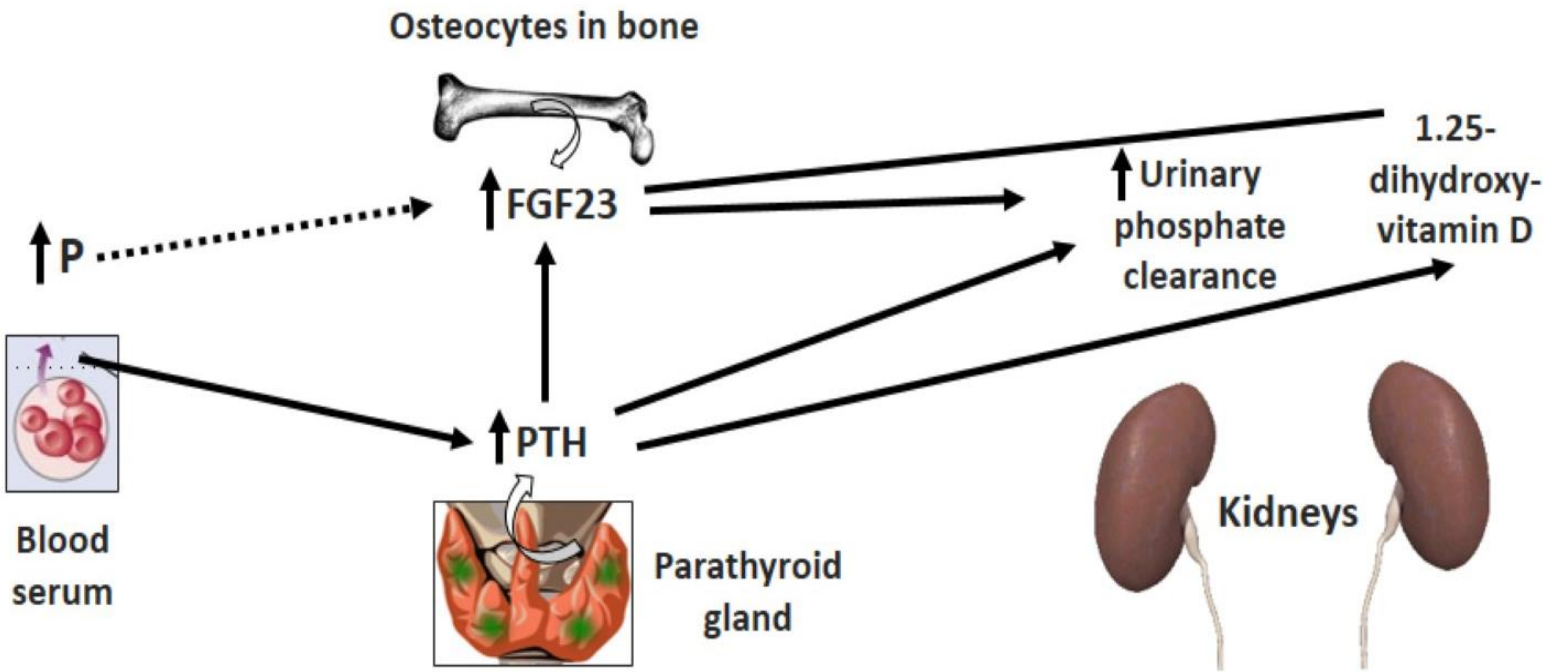
Mart 2013-Mayıs 2015 Toplam 73 vaka, 44 T2 DM, 16 Tip 1, 13 Tip rapor edilmemiş

J Clin Endocrinol Metab. 2015 Aug; 100(8): 2849–2852.

Normoglisemik Ketoasidoz - Risk faktörleri

- Beta-hücre fonksiyonu rezervinin düşük olması (örn. Tip 2 diyabet hastalarında düşük C-peptit düzeyleri, erişkinlerde görülen latent otoimmün hastalık (LADA) ya da pankreatit öyküsü olan hastalar),
- Kısıtlı gıda alımına ya da şiddetli dehidratasyona yol açan hastalıklar,
- Hipoinsülinemi,
- Akut tıbbi hastalık nedeniyle insülin ihtiyacının artması,
- Cerrahi,
- Alkol suistimali

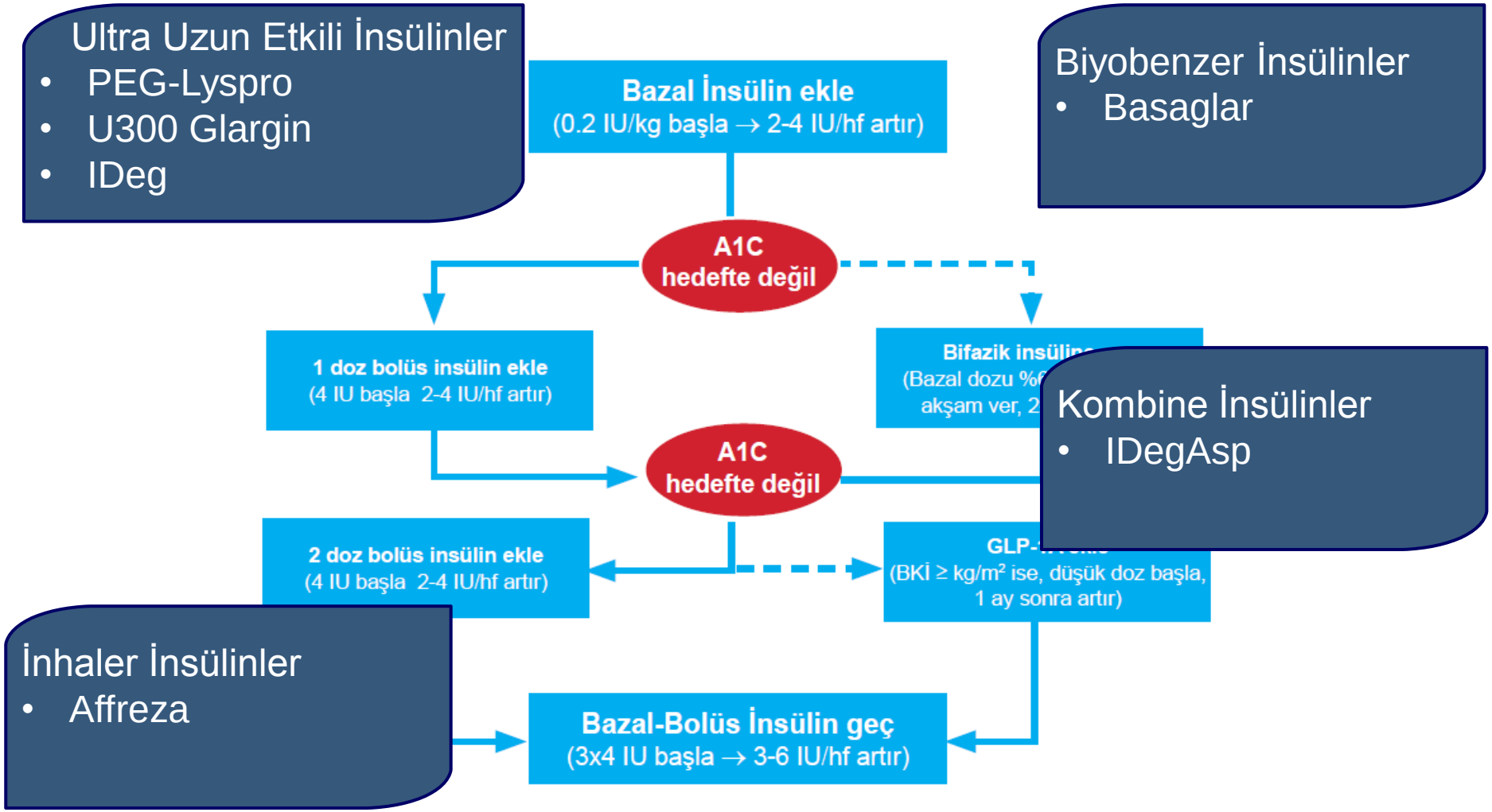
SGLT2 Kemik Kırık İlişkisi



Taylor et al. Lancet Diabetes endocrinol 2015;3:8-10

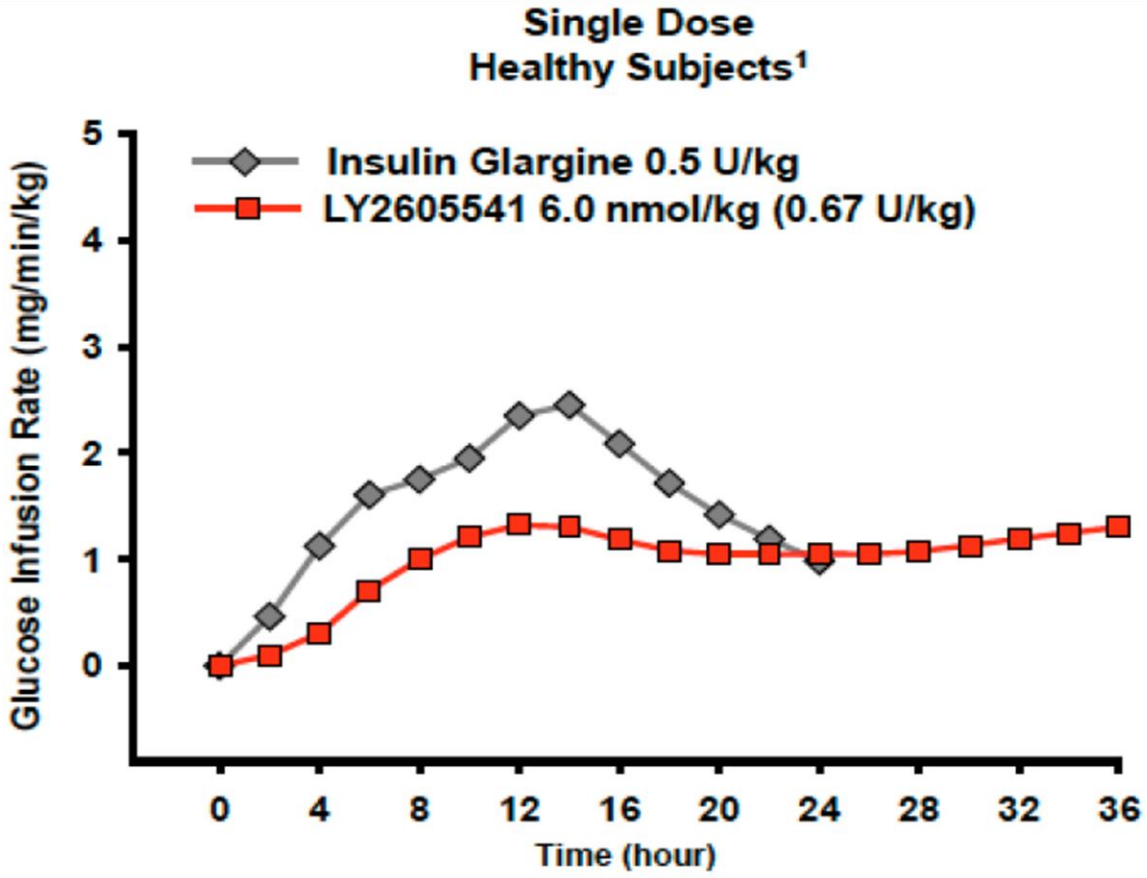
Yeni İnsülinler

Tip 2 Diyabette İnsülin Tedavisi



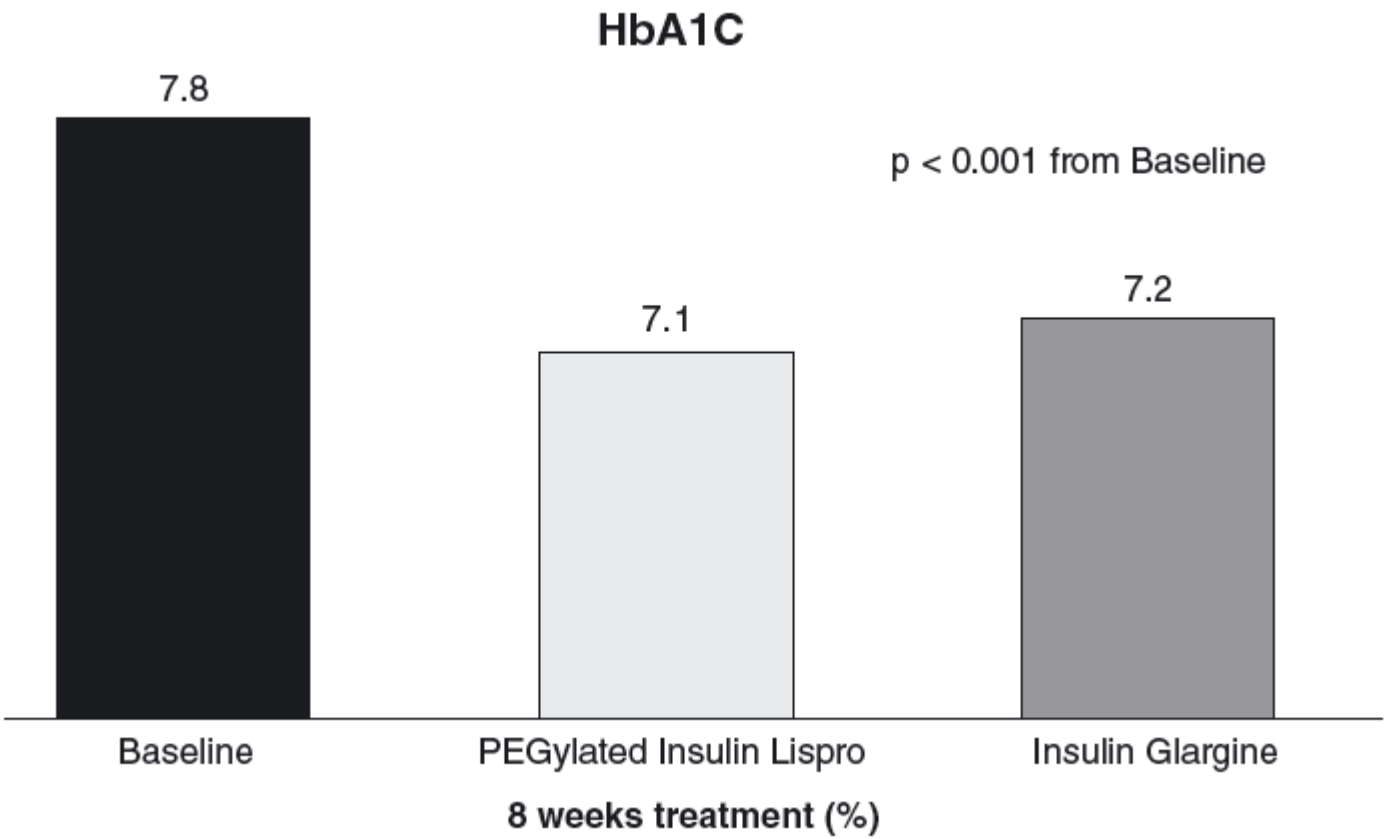
Ultra Uzun Etkili İnsülinler

PEG-Lyspro tek doz farmakodinamik



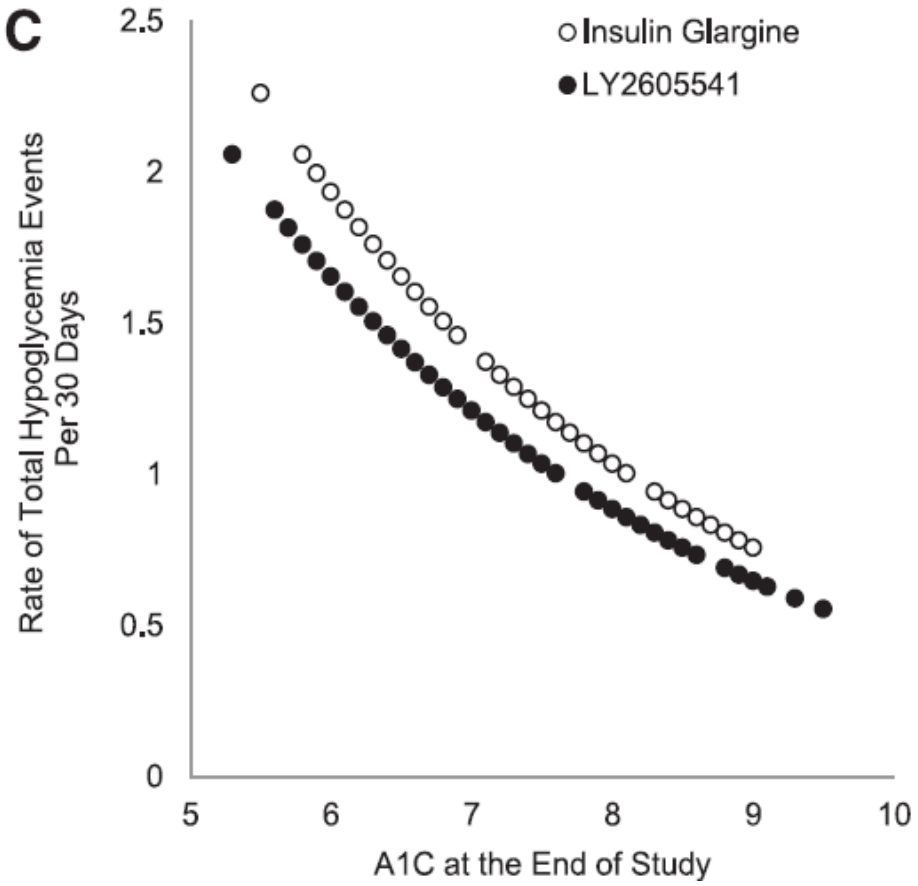
Sinha et al. ADA 2012 Poster 106-P

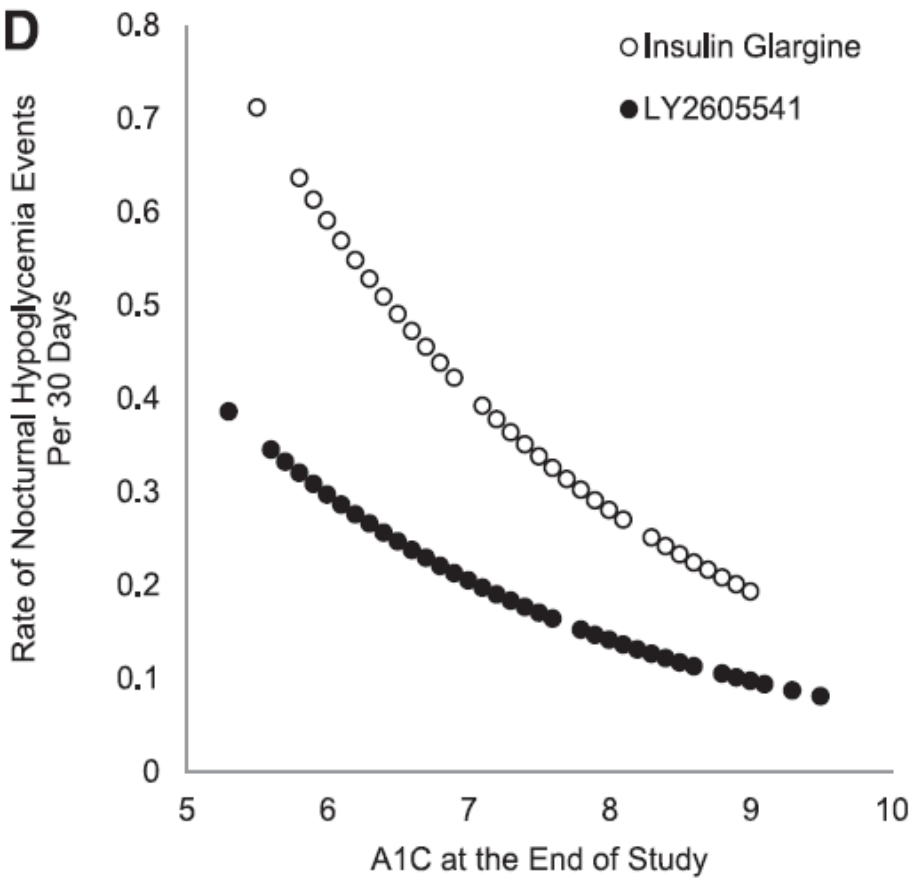
Tip 1 diyabetli hastalarda glisemik kontrol



Diabetes, Obesity and Metabolism 15 No (Suppl.1) 2013, 695-706,2013

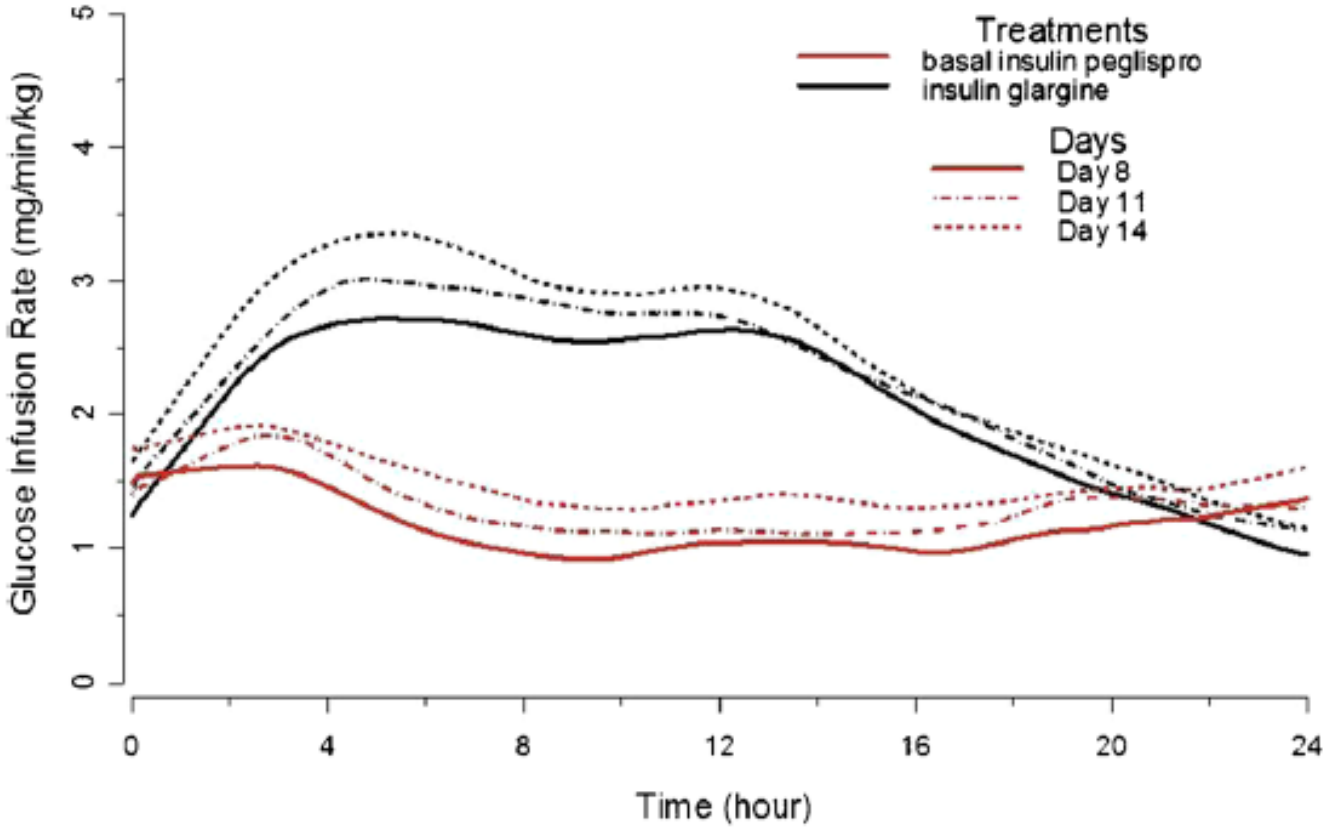
Hipoglisemi



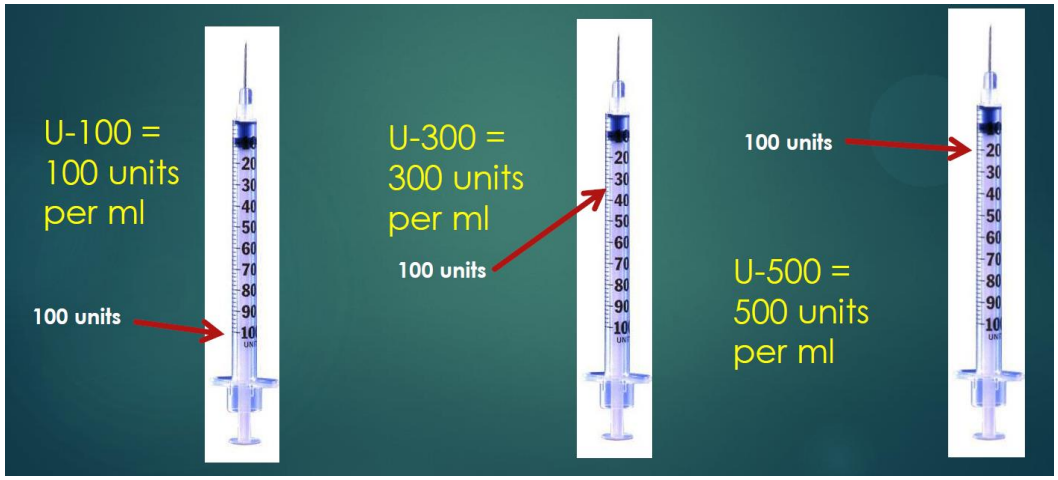


Bergenstal RM, Rosenstock J, Arakaki RF, et al. Diabetes Care 35:2140–2147, 2012

Reduced intra-subject variability of basal insulin peglispro (BIL) compared to insulin glargine (GL) in patients with type 1 diabetes mellitus



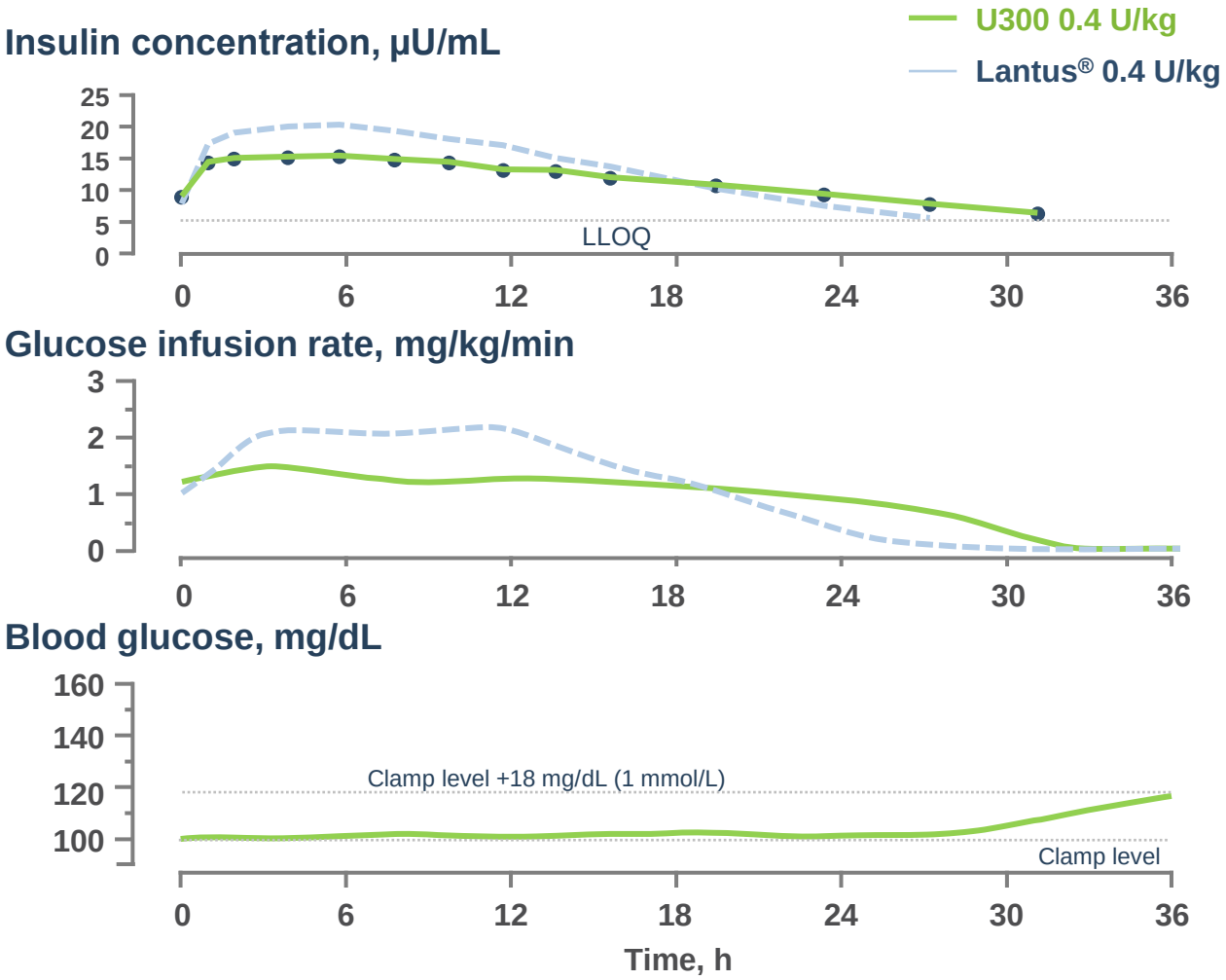
Glargine U 300



farmakokinezi
ve
farmakodinami
} değişir.

Etki süresi ↑

U300 ile daha dengeli ve uzamış etki profili vs Glargine Tip 1 DM'da 8 günlük düzenli tedavi



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

Glargine U 300

Bazal insülin dozu ≥ 42 U/gün

Tip 1 diyabette[1] ; Glarjinle kıyaslanmış. U 300' ün etkisi 36. saatte devam etmiş.

Tip 2 diyabette bazal insülin olarak glarjine göre kıyaslanmış.

a) Bazal + bolus [2]

b) Bazal + OAD[3]

Sonuçlar:

→Etkinlik glarjinle (100 U/mL) aynı

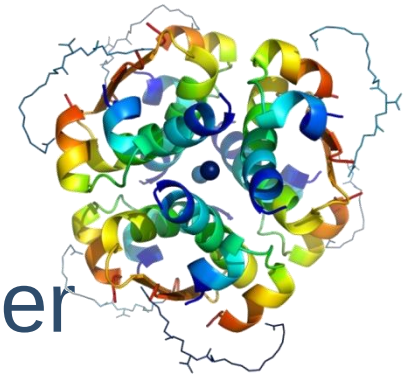
→Nokturnal hipoglisemi az (1,2,3)

→Nokturnal ve tüm gün hipoglisemi az (3)

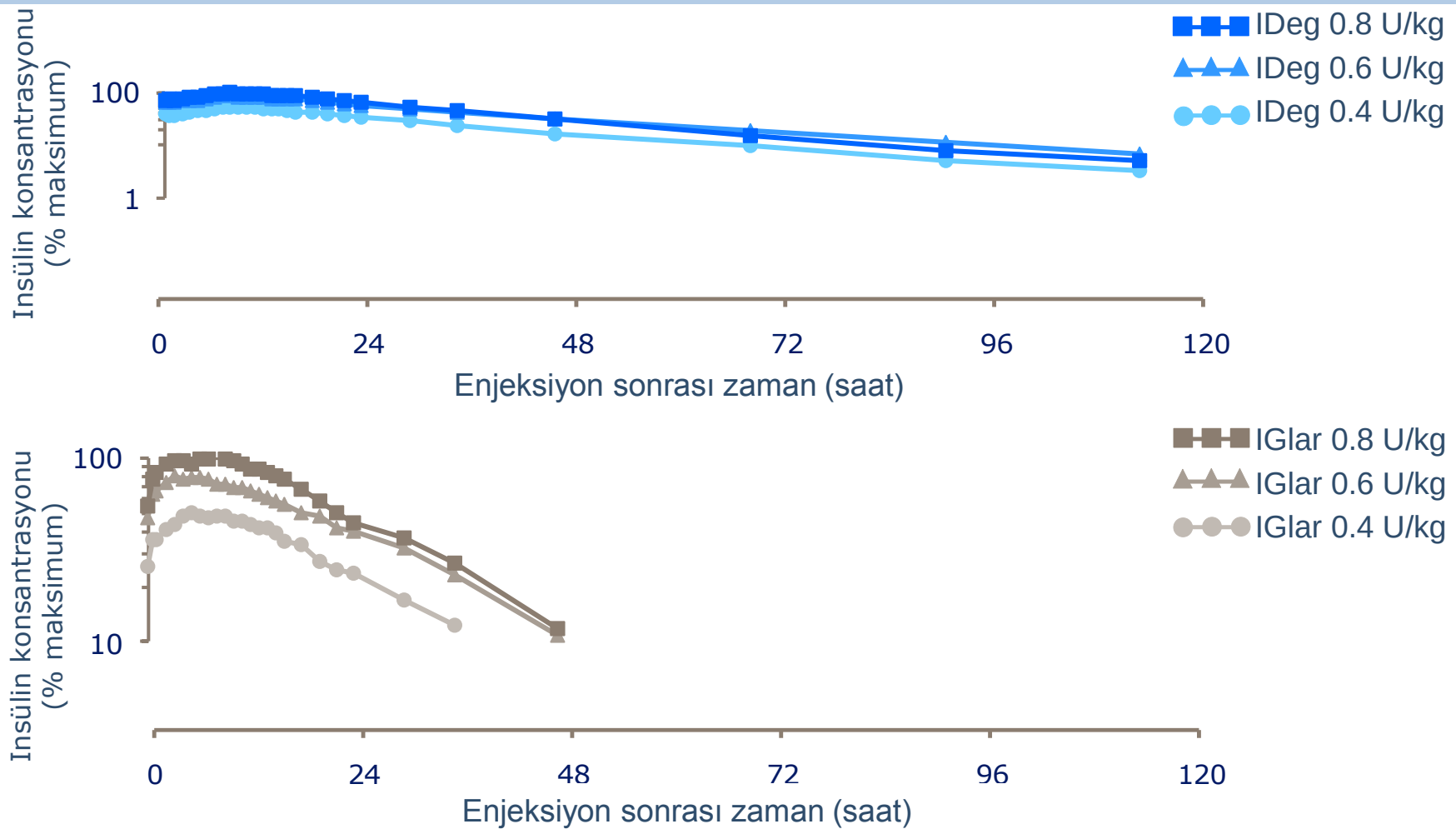
1 Diabetologia 2013; 56 (Suppl1):415
2 EDITION1 Diabetes Care 2014;37:2755-2762
3 EDITION2 Diabetes Care 2014;37:3235-3243

İnsülin degludec

- İnsulin degludec'in farklı etki mekanizması:
  - Enjeksiyon sonrası multi-hekzamer oluşumu
  - Yavaş ve stabil monomer salınımı

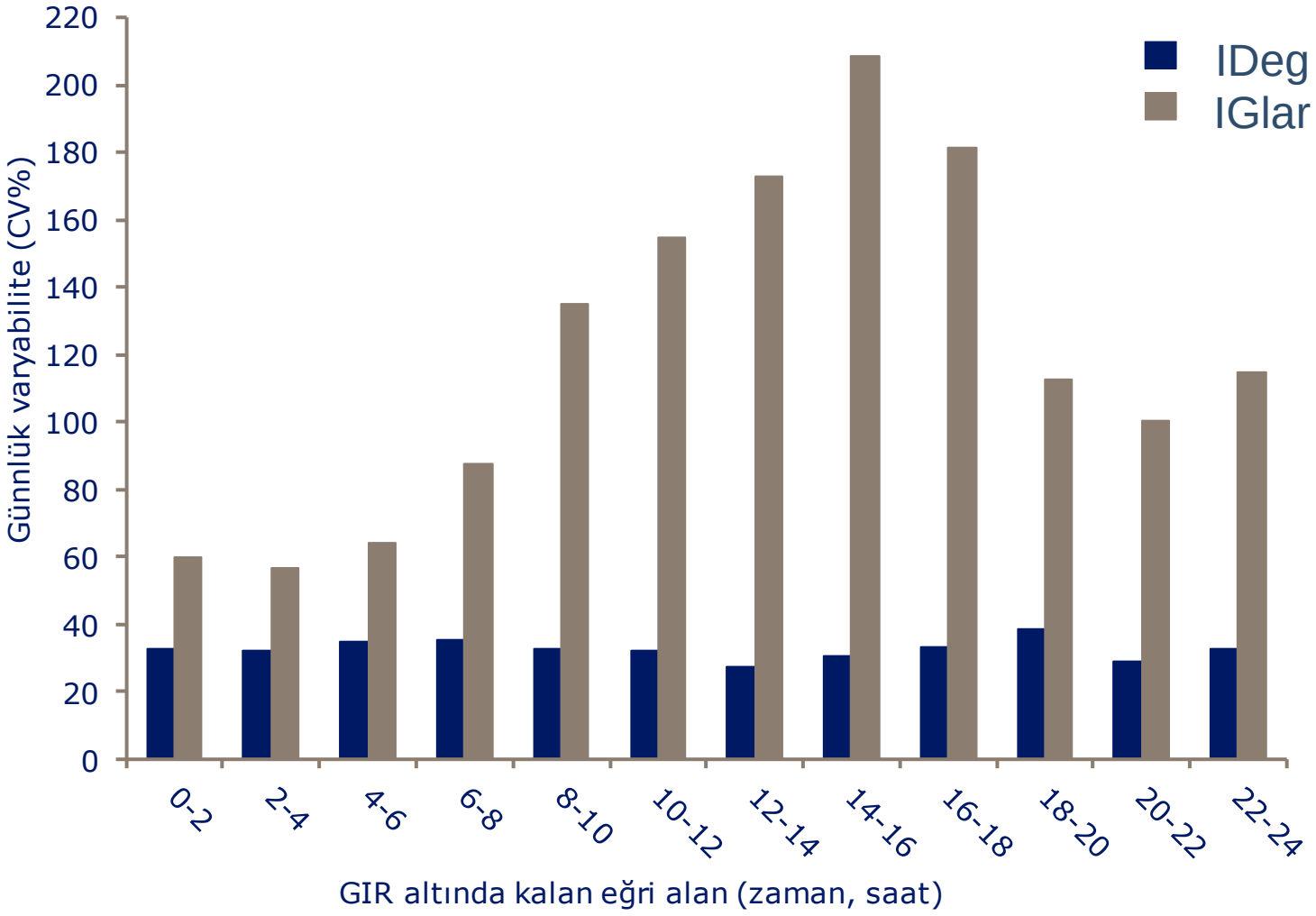


IDeg serumda 120 saatten fazlaca bir süre izlenebilir – bu etki süresi anlamlı şekilde IGlar'den uzundur



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

IDeg 24 saatlik dozlama sürecinde IGlar oranla çok daha düşük değişkenliğe sahiptir



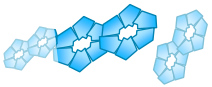
Heise *et al. Diabetes Obesity Met*ab 2012;14(9):859-864.

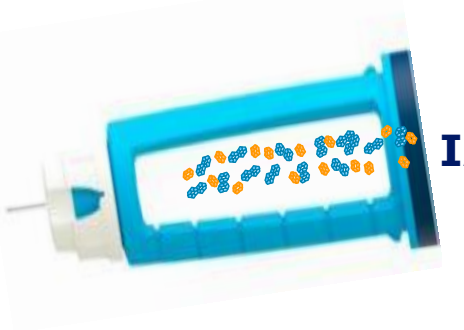
IDegAsp

İnsulin degludec ve insulin aspart koformülasyonu

Formulation

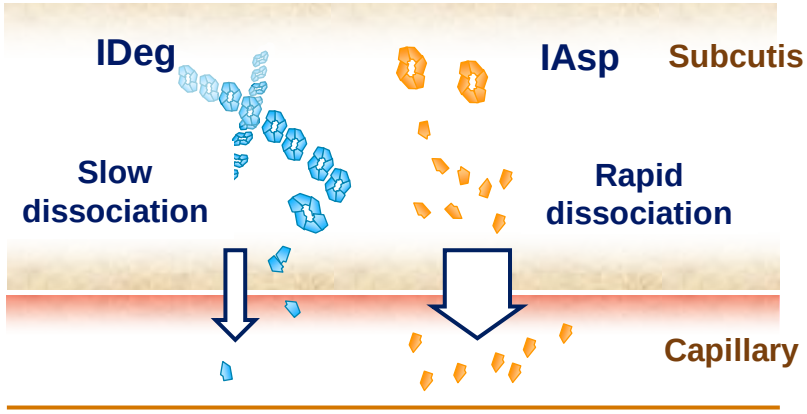
IDeg di-hexamers (70%)

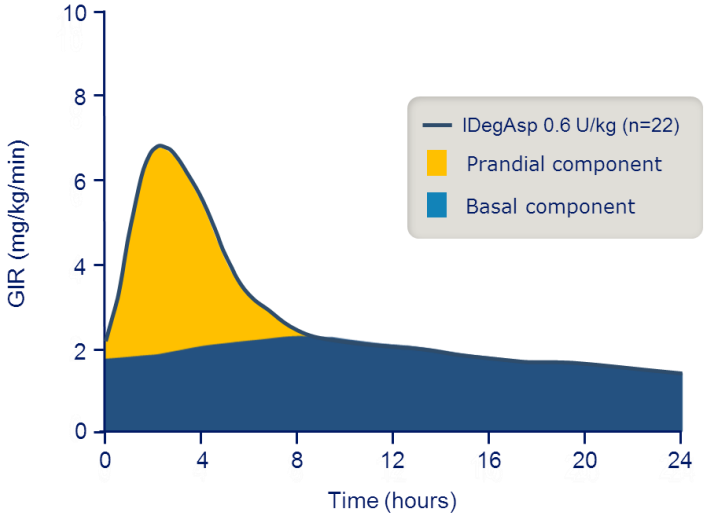




IAsp hexamers (30%)

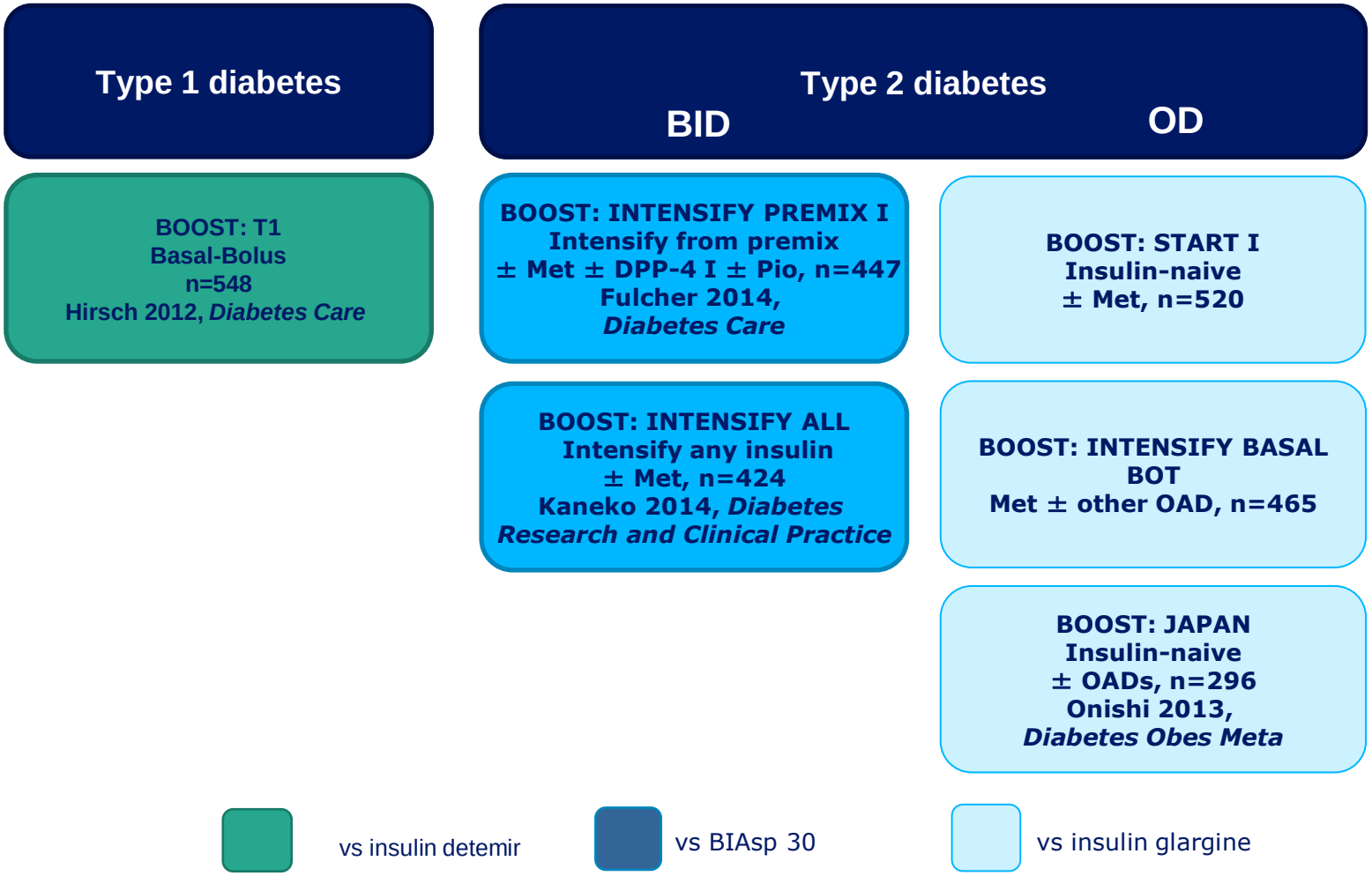
In subcutaneous depot





Havelund et al. ADA 2013 Poster 945-P

IDegAsp phase 3a study programme (BOOST)



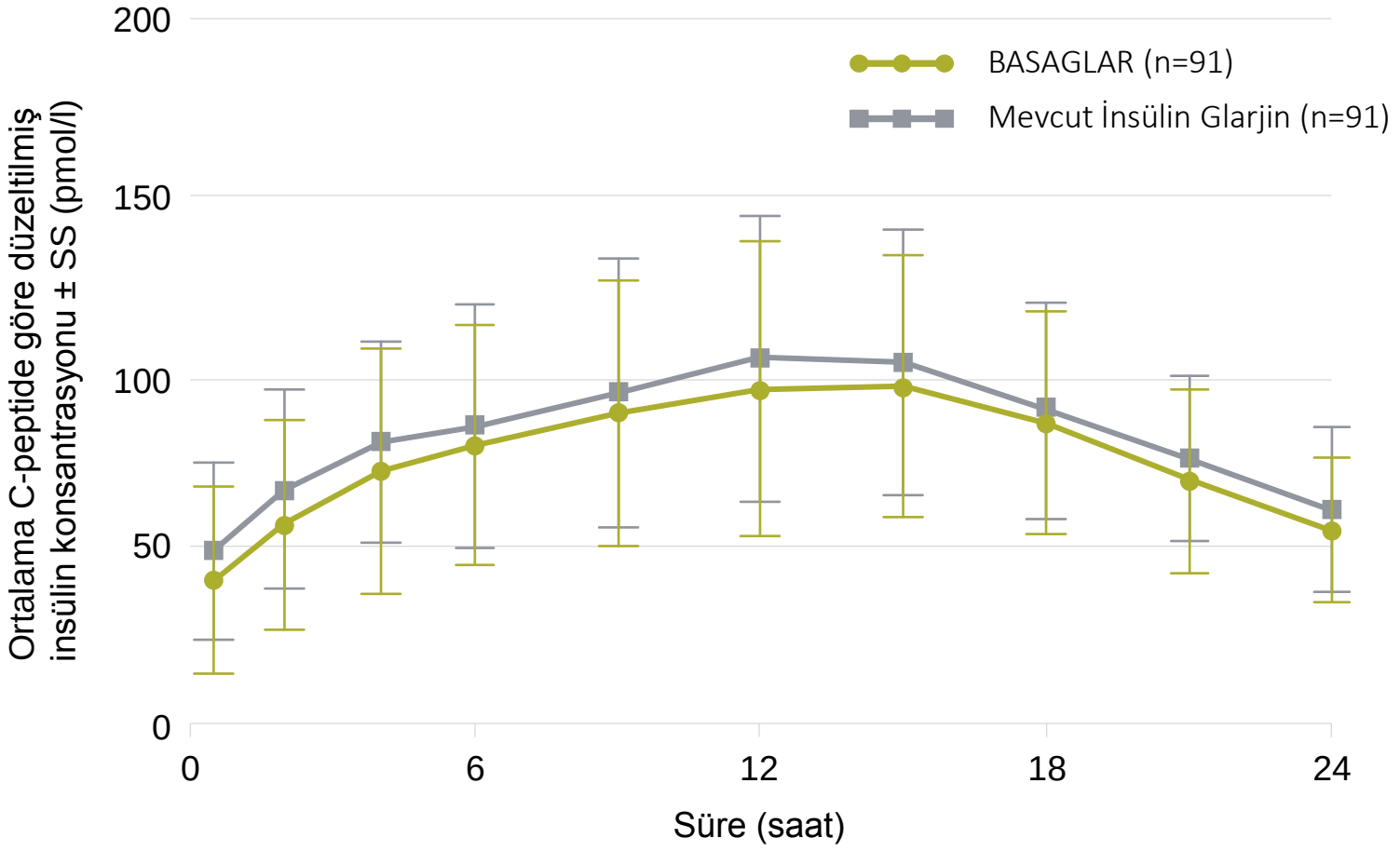
M DPP-4 I, DPP-4 inhibitors; met, metformin; pio, pioglitazones

IDegAsp

- Karşılaştırma ilaçları ile benzer veya daha iyi A1c kontrolü
- Daha iyi tokluk kan glukozu
- Daha düşük hipoglisemi
- Yaşam kalite ölçeklerinde iyileşme

Biyobenzer İnsülinler

BASAGLAR'ın farmakokinetik (FK) profili

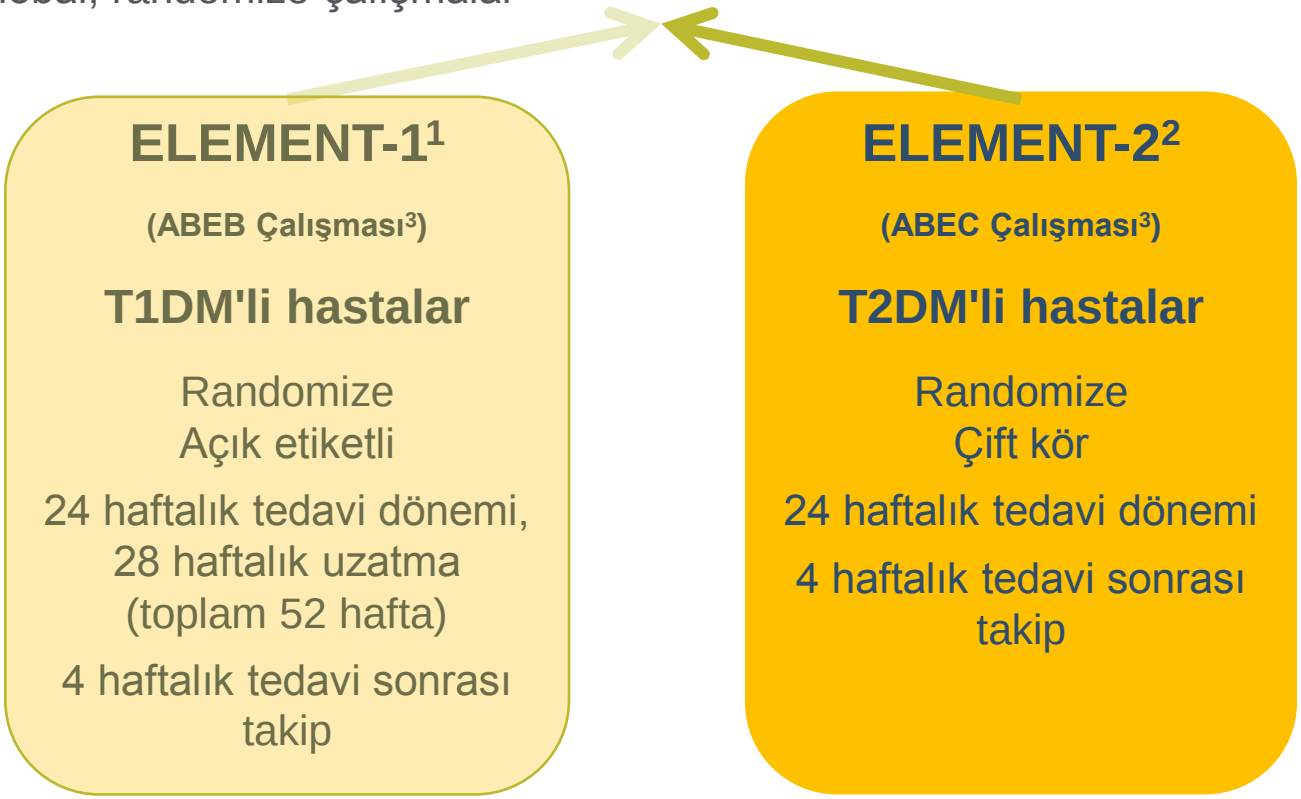


Sağlıklı bireylerin yer aldığı ABEO (faz 1) çalışması[1]
SS, standart sapma

1. Linnebjerg et al. *Diabetes Care* 2015;38(12):2226–33

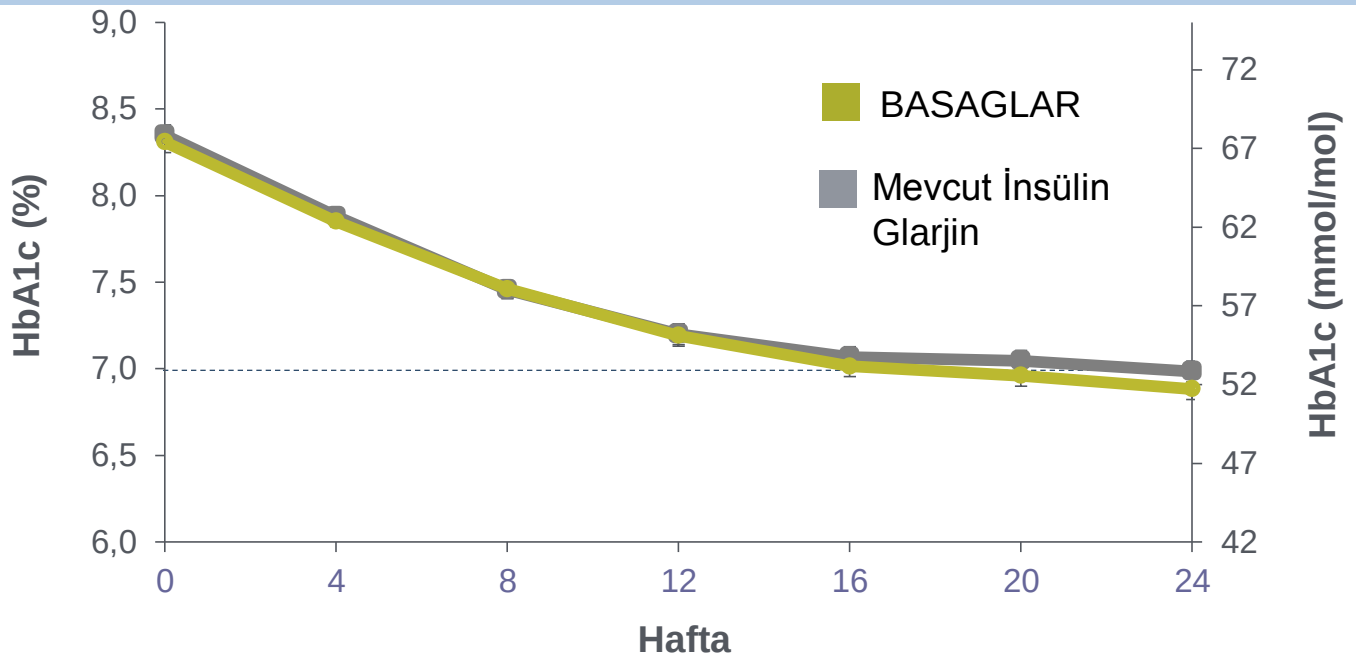
Faz 3 Çalışmaları

Başlangıçtan 24. haftaya kadar görülen HbA1c değişikliği bakımından BASAGLAR ile Mevcut Glarjin arasındaki benzer etkililiğin ortaya konmasına ve T1DM veya T2DM'li hastalarda etkililik ve ilaçla ilgili güvenlilik bakımından önemli farkların saptanmasına yönelik global, randomize çalışmalar



1. Blevins TC et al. *Diabetes Obes Metab* 2015;17:726-33
2. Rosenstock J et al. *Diabetes Obes Metab* 2015;17:734-41
3. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf

ELEMENT-2: 24 haftada HbA1c düzeyleri



		Mevcut İnsülin Glarjin N=380[a]	BASAGLAR N=376[a]	p-value
HbA1c, %	**Başlangıç**	8.31 ± 1.06	8.34 ± 1.09	NS
LSM ± SE	**Sonlanım LOCF**	6.99 ± 0.06	7.04 ± 0.06	NS

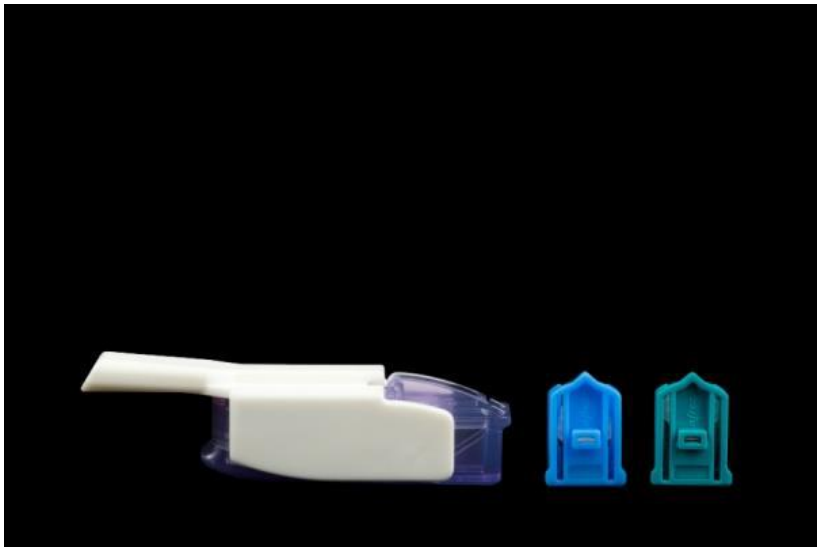
Data are LSM ± SE; [a]Full Analysis Set, N numbers reflect maximum sample size

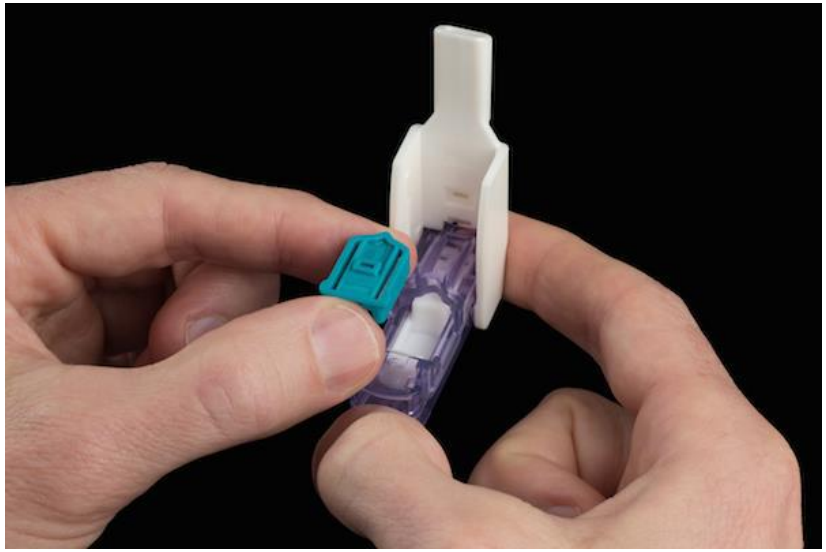
Rosenstock J et al. *Diabetes Obes Metab* 2015;17:734-41

- BASAGLAR, T1DM[1] veya T2DM[2] hastalarında 24 haftada[1,2] ve 52 haftada[1] iyi tolere edilmiştir.
  - İmmünojenitede anlamlı fark yoktur (allerjik reaksiyonlar, insülin antikorları)[1,2]
  - Benzer AE, hipoglisemi oranları ve VA değişimleri [1,2]
- BASAGLAR ve Orjinal İnsülin Glarjin arasında, insülin naiv ve daha önce insülin kullanmış T2DM hastalarında benzer güvenlik verileri saptanmıştır[2]

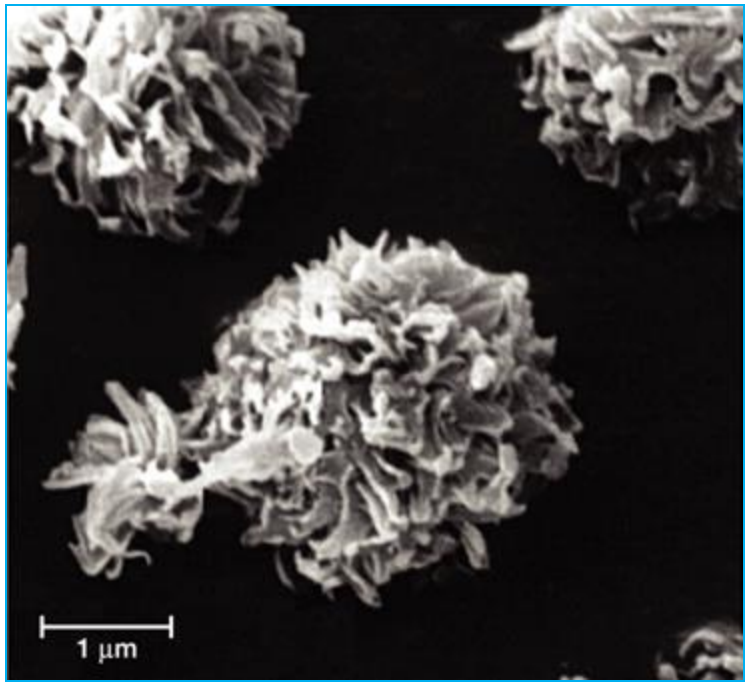
1. Blevins TC et al. *Diabetes Obes Metab* 2015;17:726-33
2. Rosenstock J et al. *Diabetes Obes Metab* 2015;17:734-41

İnhale insülin



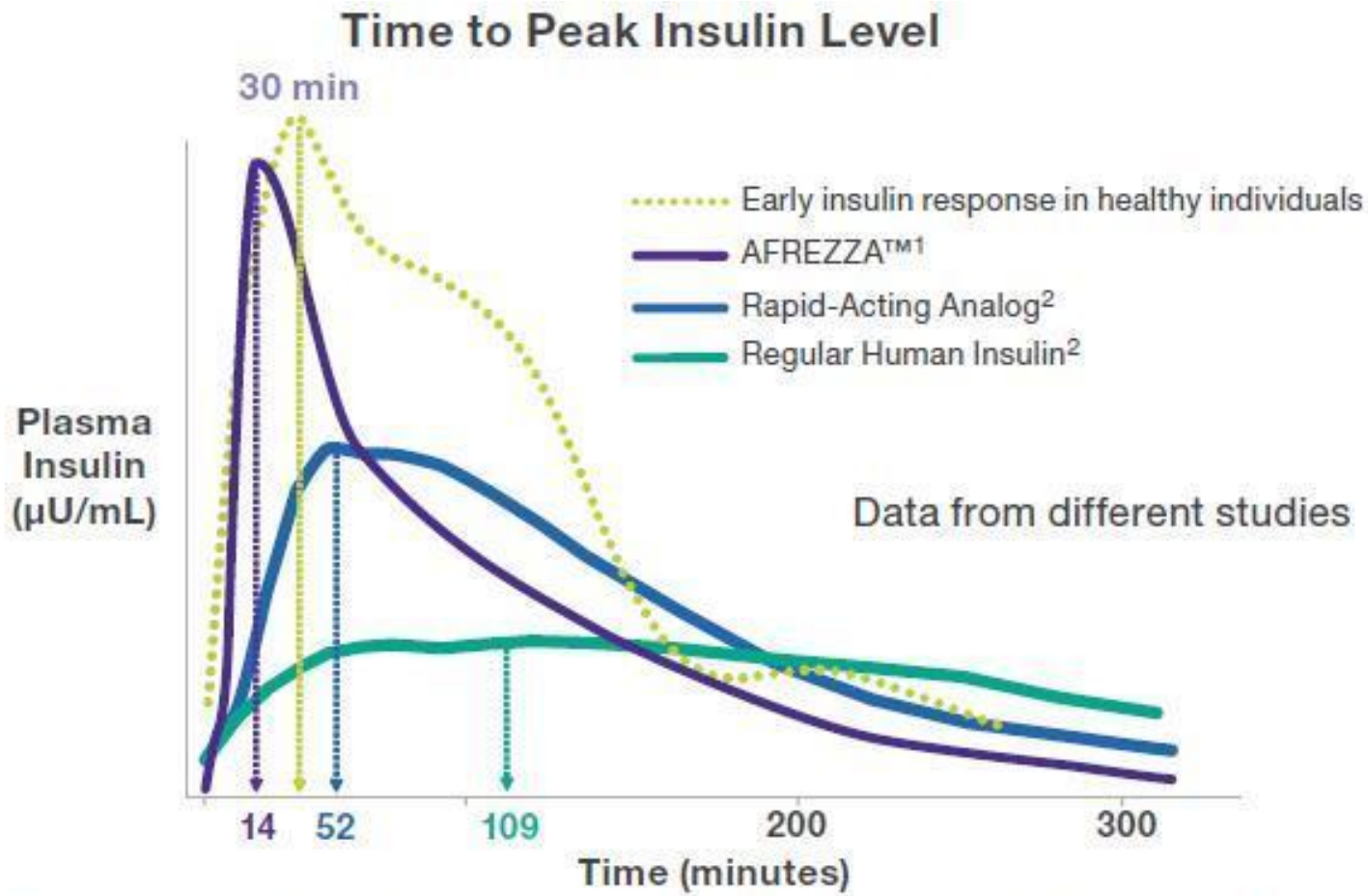


Afrezza (Technosphere insulin)



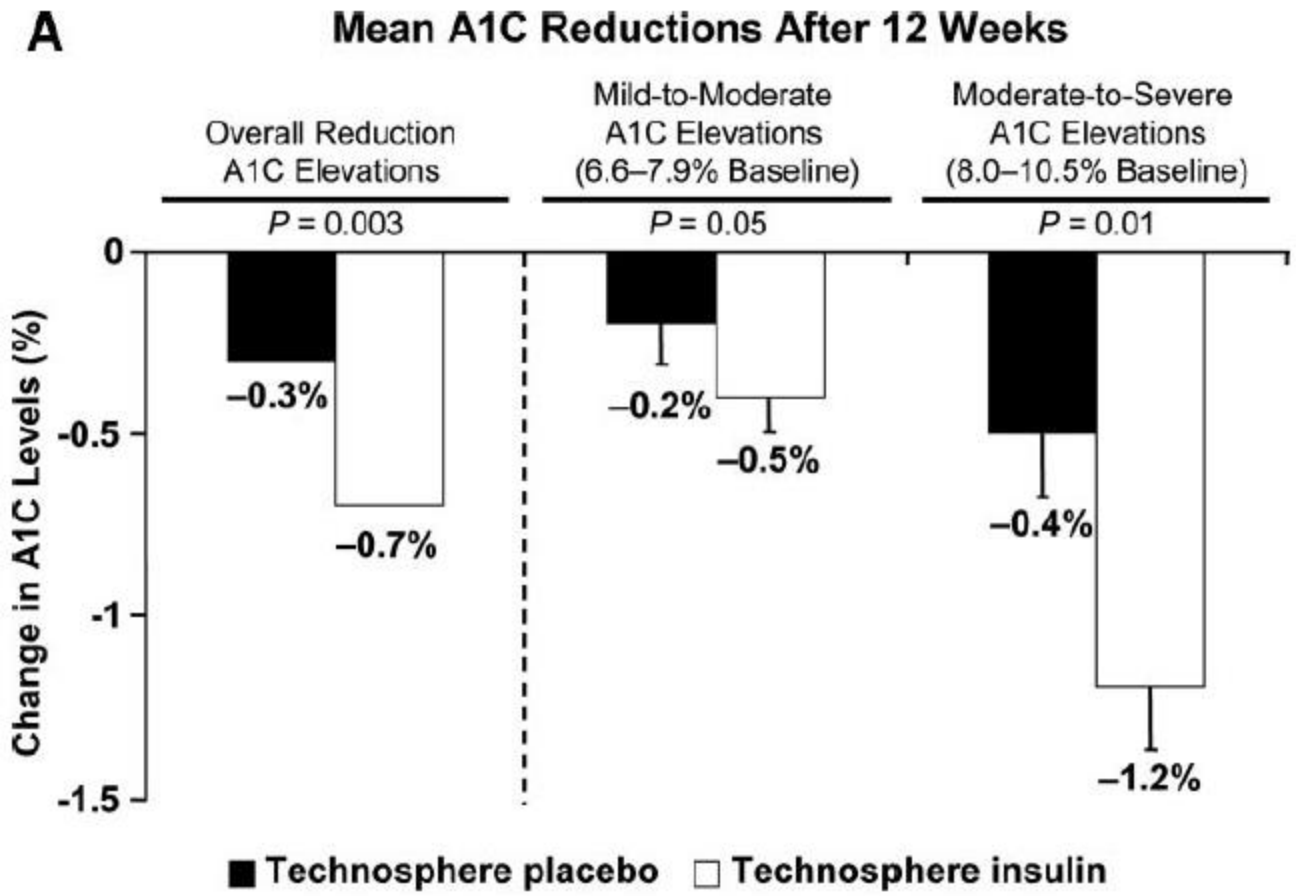
Technosphere insulin particles

Technosphere insulin



1. Non-diabetic obese subjects after 100 g oral glucose. Adapted from Kipnis D. *Ann Intern Med*. 1968;69:891-900.
2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudaliar SR et al. *Diabetes Care*. 1999;22:1501-1506.

Efficacy and Safety of Technosphere Inhaled Insulin Compared With Technosphere Powder Placebo in Insulin-Naive Type 2 Diabetes Suboptimally Controlled With Oral Agents



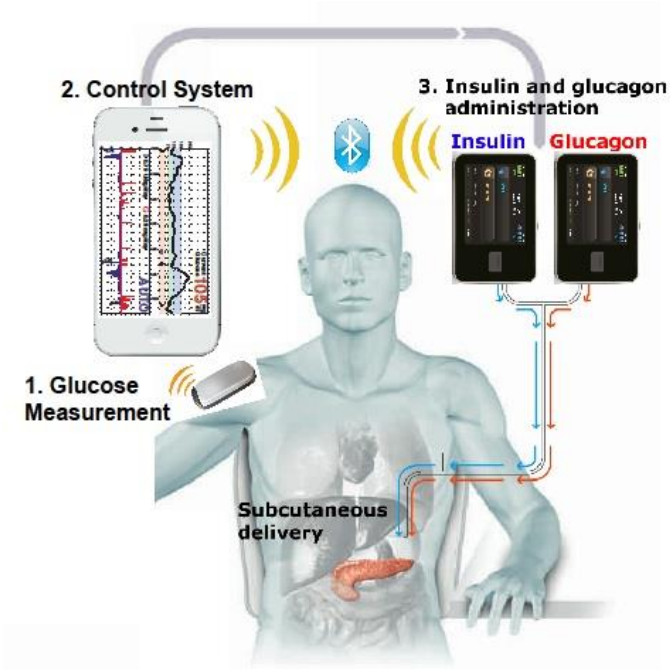
Diabetes Care 31:2177–2182, 2008

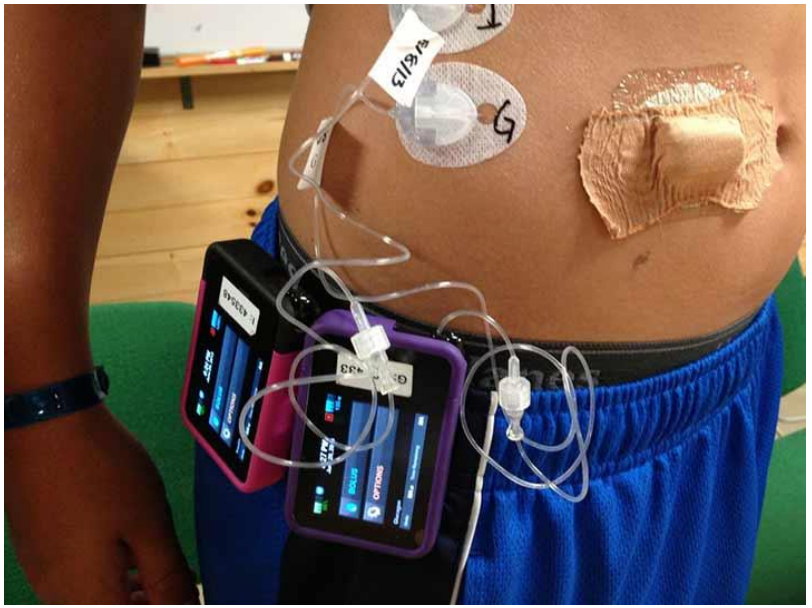
İnhale insülin

- Sigara içenlerde ve akciğer hastalığı olanlarda kontrendike
- Tedavi başlangıcında, başladıktan 6 ay sonra ve yıllık FEV1 ölçümü (FEV-1 > 80% olanlar Afrezza kullanabilir)
- Maliyet $237/4 ünitelik doz/90adet (360 ünite)

Biyonik Pankreas

Biyonik Pankreas



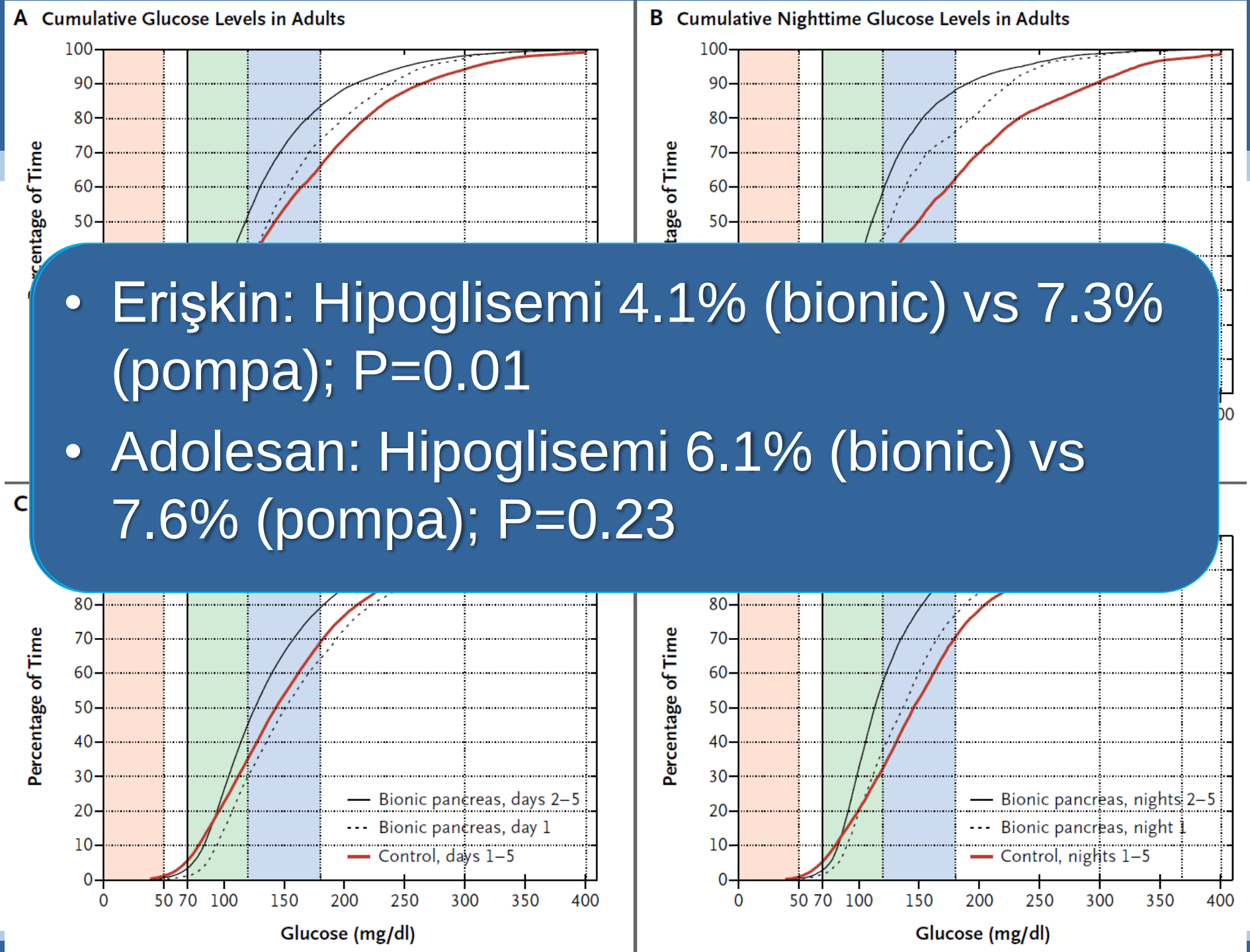


Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes

Steven J. Russell, M.D., Ph.D., Firas H. El-Khatib, Ph.D., Manasi Sinha, M.D., M.P.H., Kendra L. Magyar, M.S.N., N.P., Katherine McKeon, M.Eng., Laura G. Goergen, B.S.N., R.N., Courtney Balliro, B.S.N, R.N., Mallory A. Hillard, B.S., David M. Nathan, M.D., and Edward R. Damiano, Ph.D.

- 5 günlük ayaktan takipli 20 erişkin 32 adolesan tip 1 DMli hasta
- Bionic pancreas vs konvansiyonel insülin pompası

N ENGL J MED 371;4 NEJM.ORG JULY 24, 2014



- Erişkin: Hipoglisemi 4.1% (bionic) vs 7.3% (pompa); P=0.01
- Adolesan: Hipoglisemi 6.1% (bionic) vs 7.6% (pompa); P=0.23

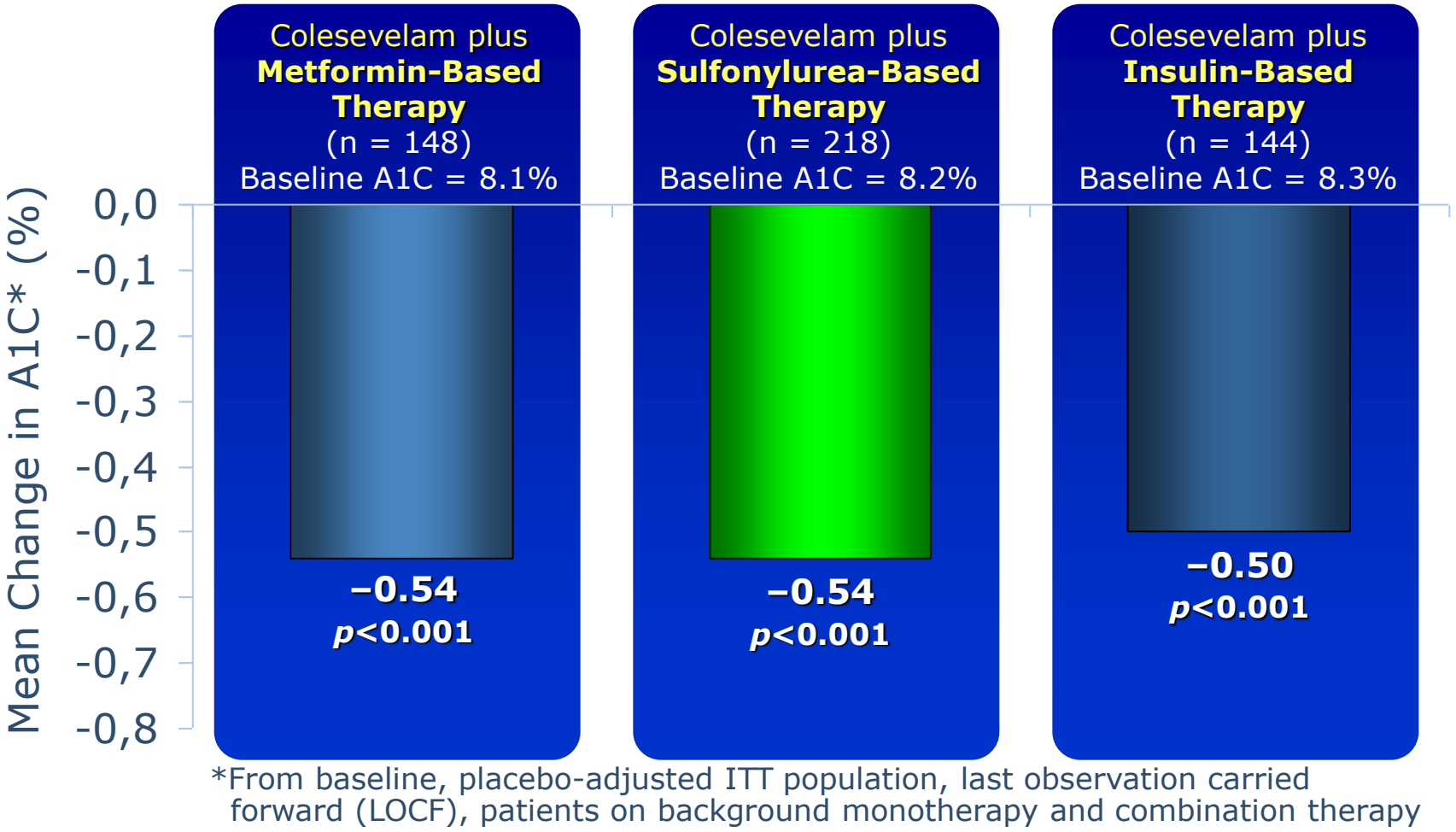
Diğer Ajanlar

Safra Asidi Bağlayıcı Reçineler Colesevelam

- Hiperlipidemisi olan hastalarda kan şekeri düşüşü ile keşfedilmiş.
- Diyet ile kontrol edilemeyen hafif diyabetli olgularda endikedir.
- FDA tarafından onaylı EMA onayı yok
- Glikoz düşürücü mekanizma ??
- Karaciğerde FARNESOİD reseptörler uyarılması ile glukoneogenez baskılanır ?
- Hipoglisemi riskini artırmıyorlar

www.thelancet.com Vol 378,2011

Colesevelam A1C'yi %0,5 Düşürür



*From baseline, placebo-adjusted ITT population, last observation carried forward (LOCF), patients on background monotherapy and combination therapy

Bays HE et al. *Arch Intern Med.* 2008;168:1975-1983 | Fonseca VA et al. *Diabetes Care.* 2008;31:1479-1484 | Goldberg RB et al. *Arch Intern Med.* 2008;168:1531-1540.

Dopamin Agonisti- Bromokriptin

- Diyabetin sirkadyen ritmi vardır
- Glukoz intoleransi sabah saatlerinde belirgindir
- Bu ritim dopamin tarafından kontrol edilmektedir

Meier AH et al. *Diabetes Reviews.* 1996;4:464-487.

Bromocriptine QR

- 2009 FDA onayı almış, EMA onayı yok
- Monoterapi ve kombine tedavi
- En ciddi yan etkisi hipotansiyon
- Psikotik hastalığı olanlarda dikkatli olunmalı
- CV açıdan veriler yetersiz

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

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

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

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

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

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

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

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

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

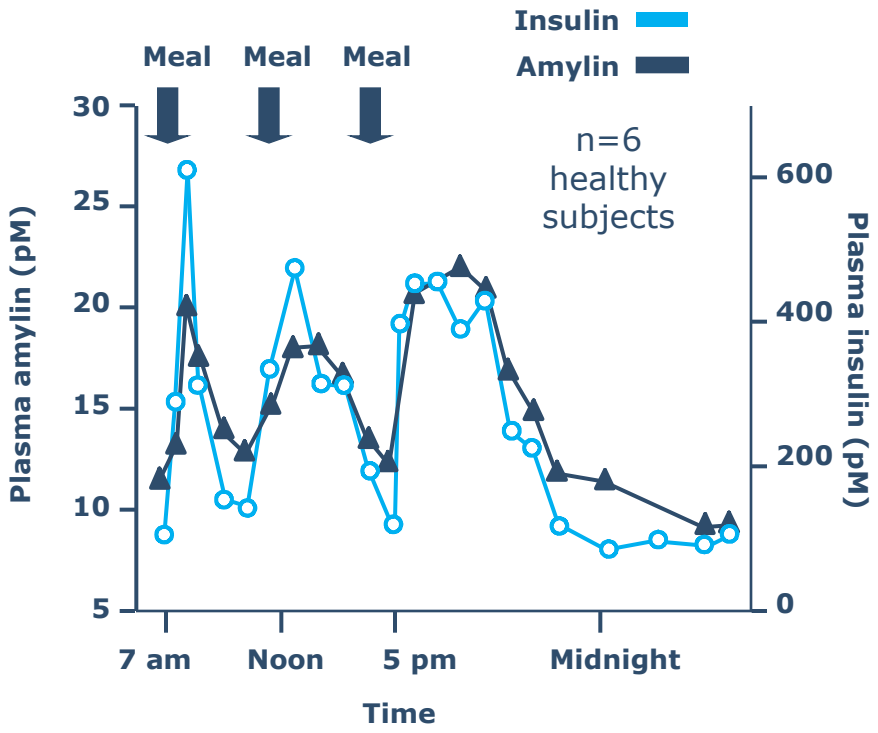
LEGEND

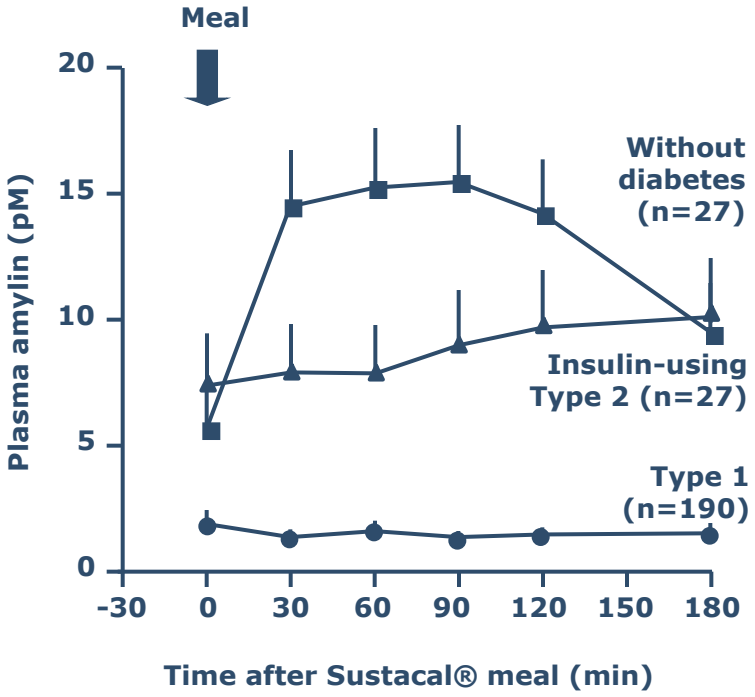
- ✓ Few adverse events and/or possible benefits
- ! Use with caution

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

PROGRESSION OF DISEASE

Amylin: insülin ile birlikte kosekrete edilir ve diyabette eksiktir.





Kruger D et al. *Diabetes Educ.* 1999; 25:389-397

Pramlintide

- Tip 1 diyabette insülin tedavisine ek olarak
- Optimal tedaviye rağmen kan şekeri regülasyonu bozuk olan Tip 2 diyabetik hastalarda

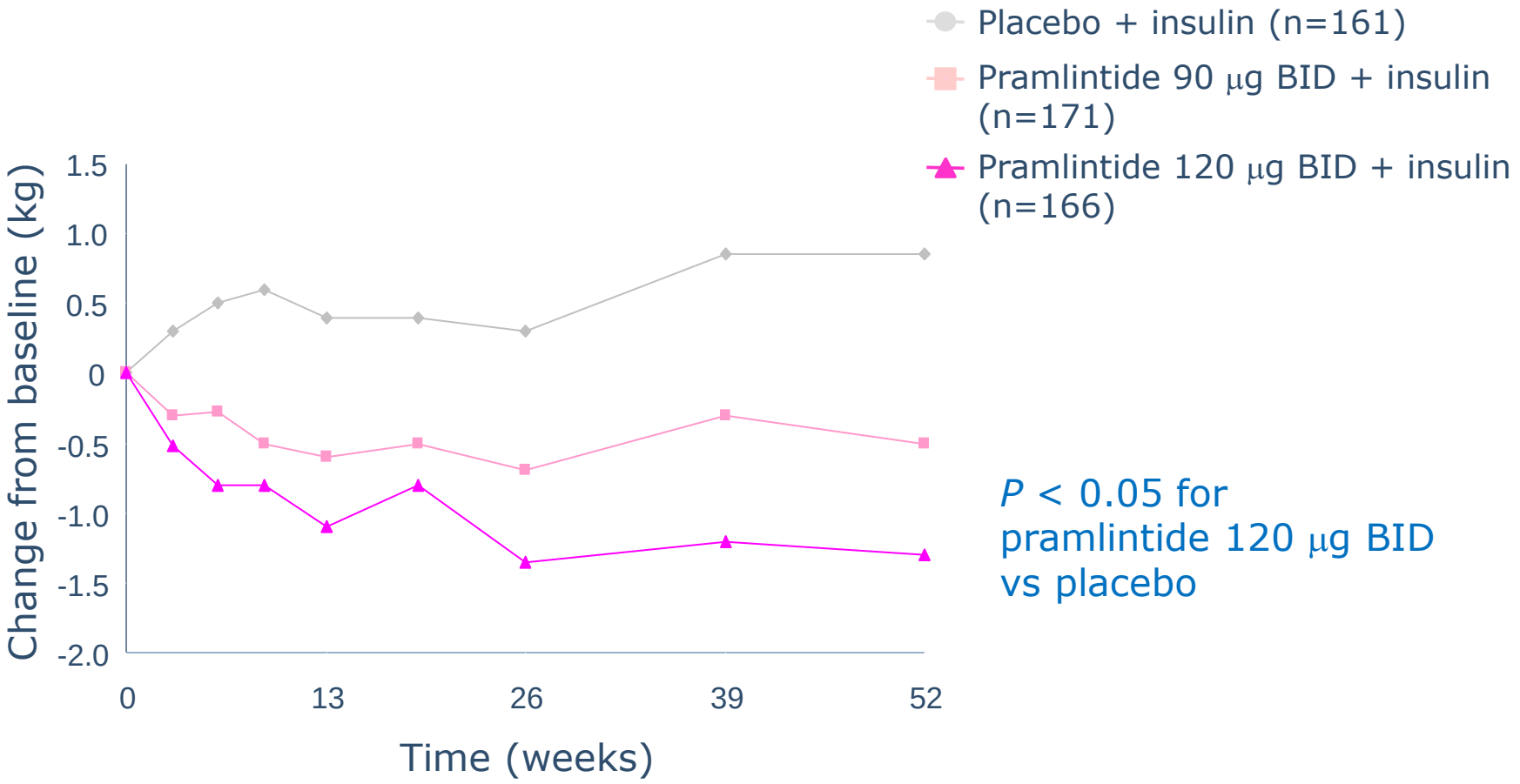
- Glukagon sekresyonu
- Enerji alımı
- Gastrik motilite

azalmakta → TKŞ düşüşü

Pramlintide

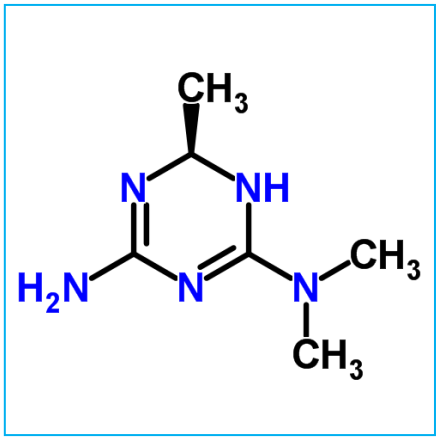
- Pramlintide'in en uygun enjeksiyon zamanı ise hemen yemek öncesidir
- Tüm insülin tipleri ile uygulanabilir (bazal/miks)
- İnsülin dozunu %20-50 azaltır
- 15-60 mcg/gün uygulanır
- En sık yan etkisi gastrik motiliteyi yavaşlattığı için bulantı ve kusmadır

Pramlintide Tip 2 DM'li hastalarda kilo kaybı sağlar



P < 0.05 for pramlintide 120 μg BID vs placebo

Imeglimin



- Mitokondride oksidatif fosforilasyonu bloke eder
- Hepatik glukoneogenezi inhibe eder
- Kas glukoz uptake artırır
- Glukoza cevaben insülin salgısını artırır

Imeglimin

Table 1 Summary of clinical study evidence

References	Imeglimin dose	Comparator	Results	*P* value
Fouqueray et al. [15]	1500 mg BID + sitagliptin	Placebo + sitagliptin	Change in A1c from baseline at 12 weeks (−0.6 vs. +0.12 %)	<0.001
			Change in FPG from baseline at 12 weeks (−16.75 vs. −1.98 mg/dl)	0.014
Fouqueray et al. [14]	1500 mg BID + metformin	Placebo + metformin	Change in A1c from baseline at 12 weeks (−0.65 vs. −0.21 %)	<0.001
			Change in FPG from baseline at 12 weeks (−0.91 mg/dl vs. +0.36 mg/dl)	<0.001
			Change from baseline in proinsulin/insulin ratio at week 12 (−7.5 vs. +11.81)	<0.007
Pirags et al. [11]	2000 mg once daily	Metformin 850 mg twice daily	Change in baseline of AUC plasma glucose at 4 weeks (−10 vs. 30 %)	<0.0001, <0.0004
	1000 mg twice daily		Change in baseline of AUC plasma glucose at 4 weeks (−33 vs. 30 %)	<0.0305, <0.0004
	500 mg twice daily	Metformin 850 mg twice daily or placebo	AUC glucose at week 8 (72,661 vs. 58,054 or 78,174 mg/dl)	Not provided
			FPG at week 8 (172 vs. 144.7 or 182 mg/dl)	
			A1c at week 8 (7.58 vs. 6.97 or 7.52 %)	
	1500 mg twice daily		AUC glucose at week 8 (63,293 vs. 58,054 or 78,174 mg/dl)	
			FPG at week 8 (154 vs. 144.7 or 182 mg/dl)	
			A1c at week 8 (7.17 vs. 6.97 or 7.52 %)	

AUC area under the curve, *A1c* hemoglobin A1c, *BID* twice a day, *FPG* fasting plasma glucose

Araştırmaları devam eden ilaçlar

- Uzun etkili GLP-1 reseptör agonistleri
- Sodium/glucose cotransporter (SGLT)–1 and –2 inhibitörleri
- Dual (α/ɣ) ve pan (α/ɣ/β) PPAR agonistleri
- 11β-Hydroxysteroid dehydrogenase (HSD)–1 inhibitörleri
- Fruktoz 1,6-bisfosfataz inhibitörleri
- Glukokinaz aktivatörleri
- G protein–eşleşmiş reseptör (GPR)–40 ve –119 agonistleri
- Protein tirozin fosfataz (PTB)–1b inhibitörleri
- Karnitin palmitoyltransferaz (CPT)–1 inhibitörleri
- Acetyl CoA karboksilaz (ACC)–1 ve–2 inhibitörleri
- Glukagon reseptör antagonistleri
- Salisilat türevleri
- İmmunomodulatör ilaçlar
- Yeni insülinler