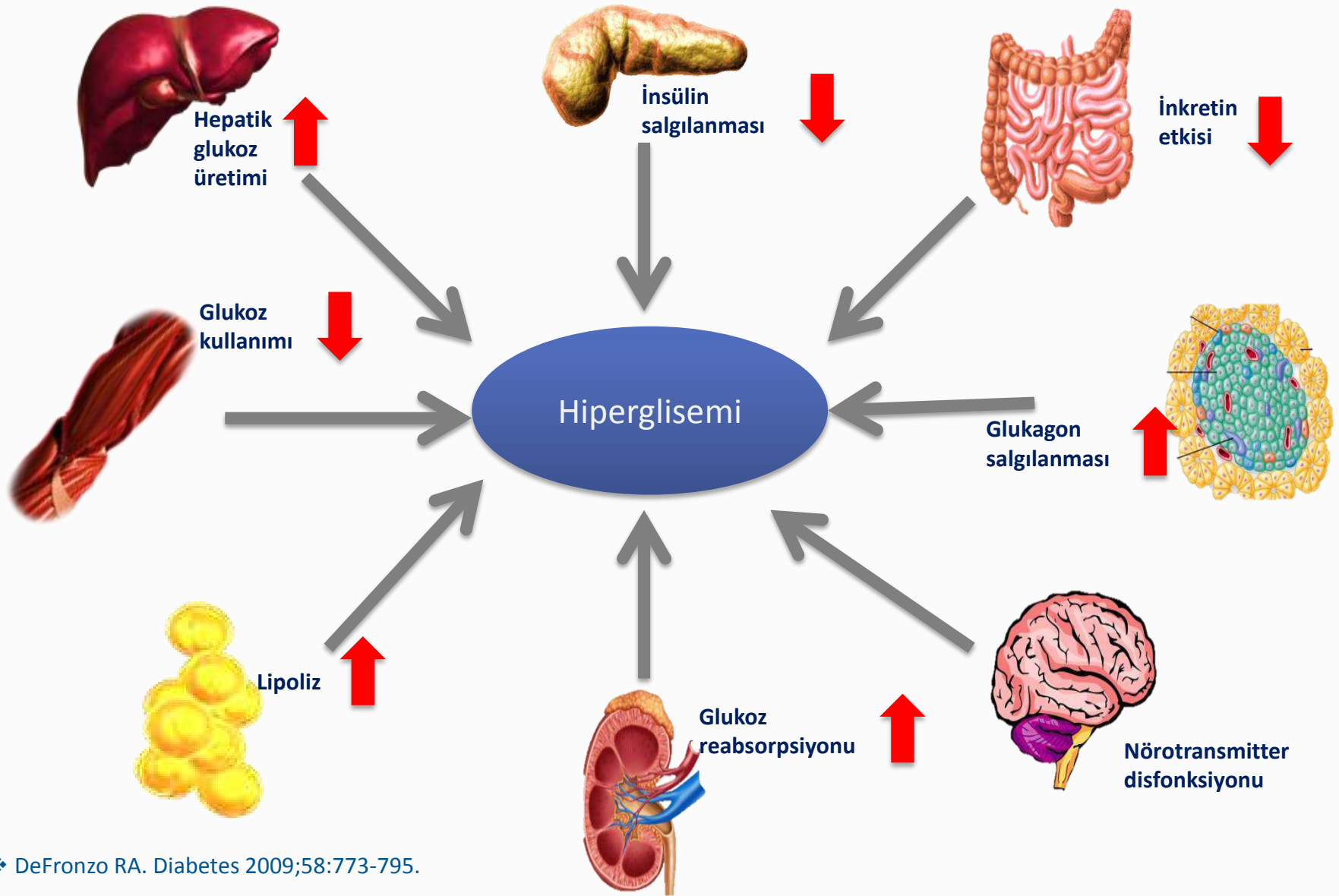
İNKRETİN MİMETİKLER

Prof. Dr. Engin GÜNEY

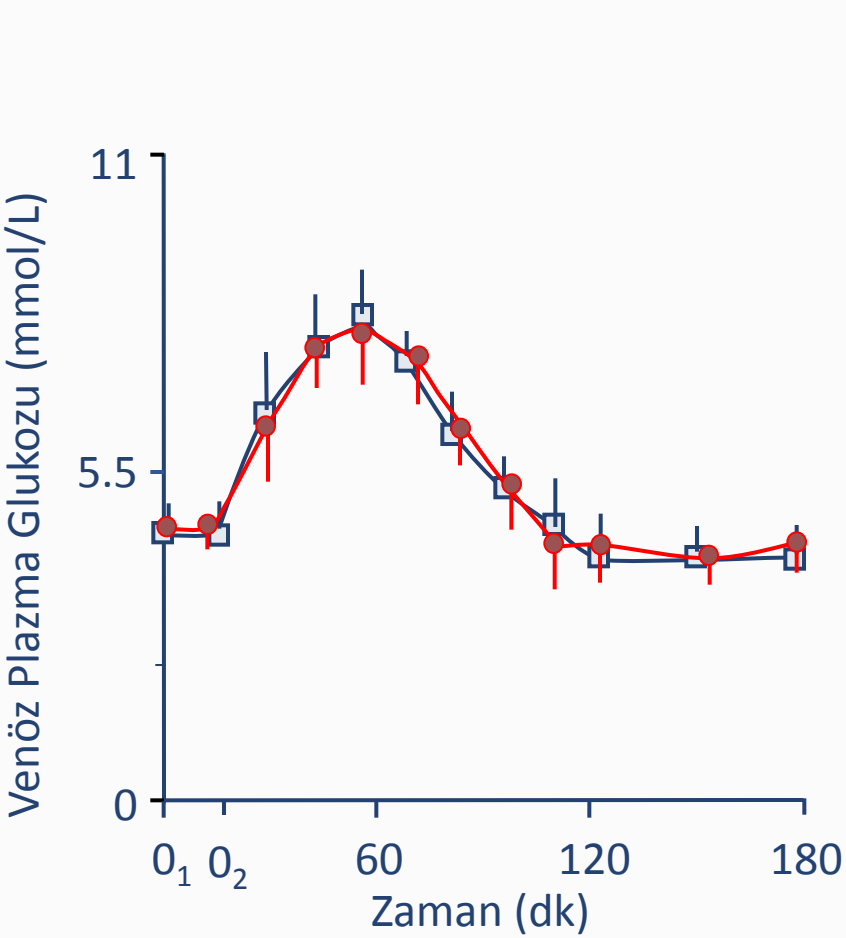
Adnan Menderes Üniversitesi Tıp Fakültesi
Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı

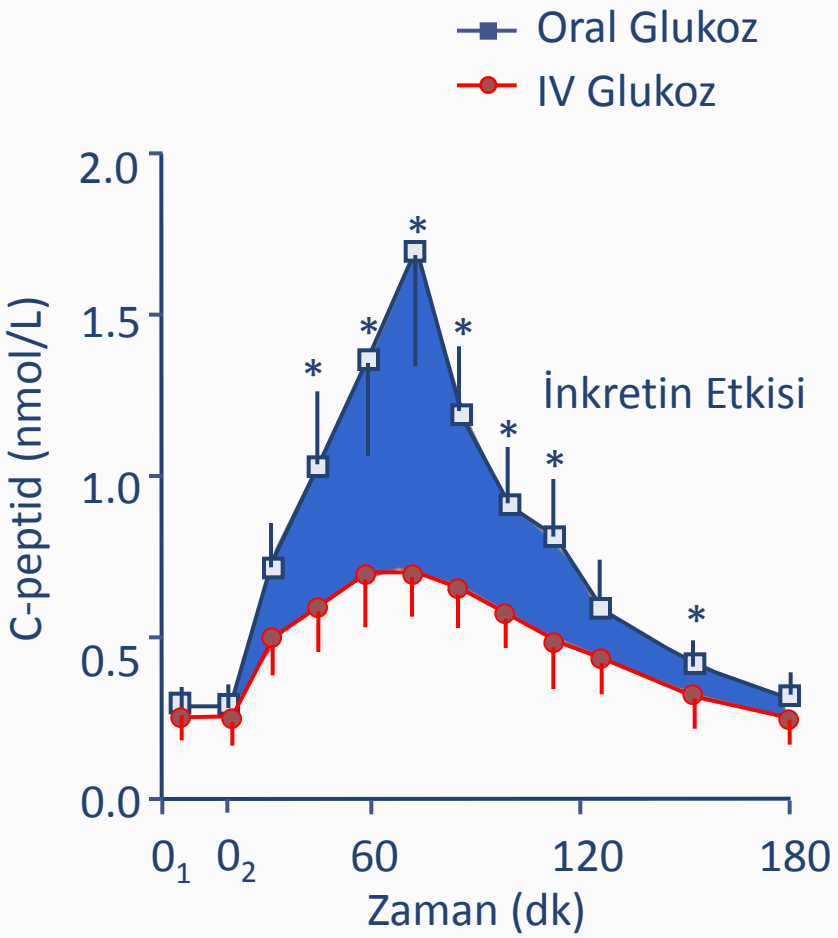
TİP 2 DİYABET PATOGENEZİ



❖ DeFronzo RA. Diabetes 2009;58:773-795.

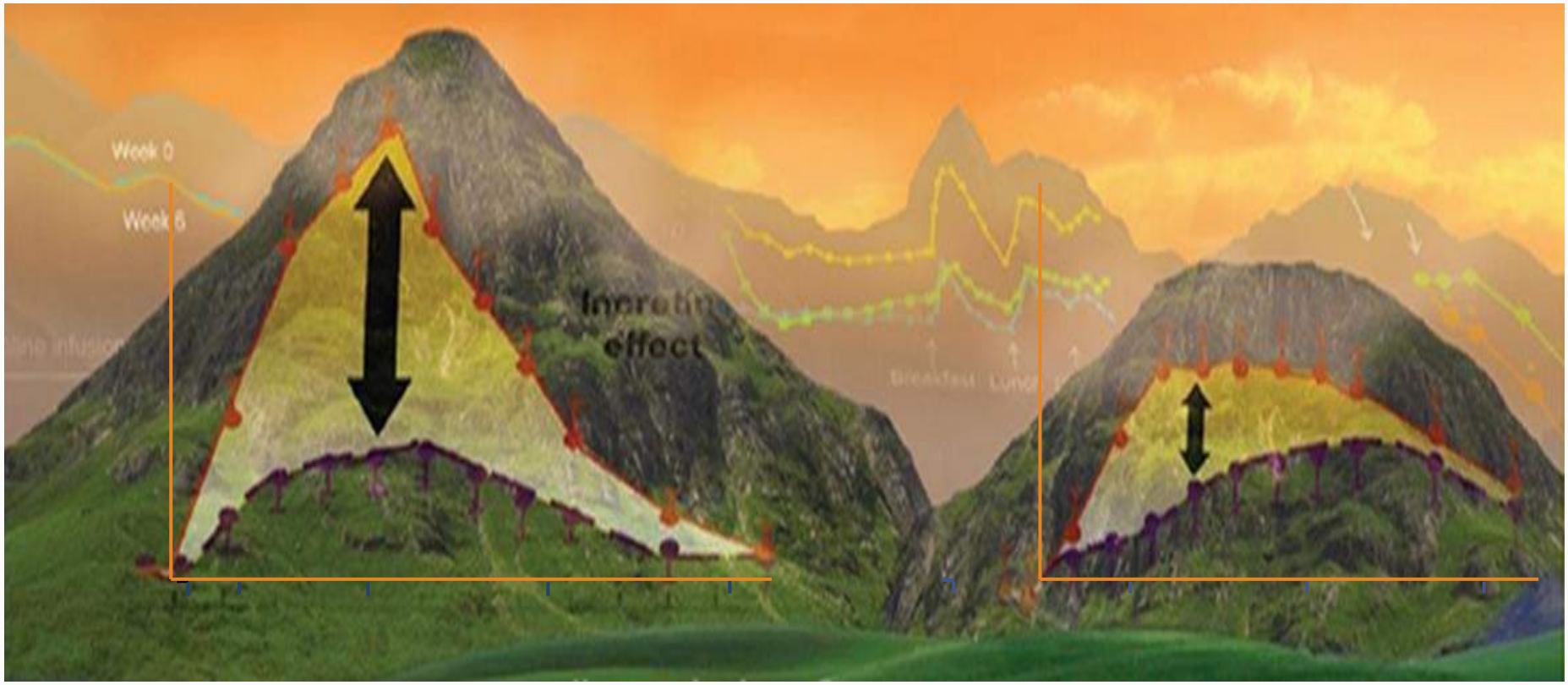
İNKRETİN ETKİSİ

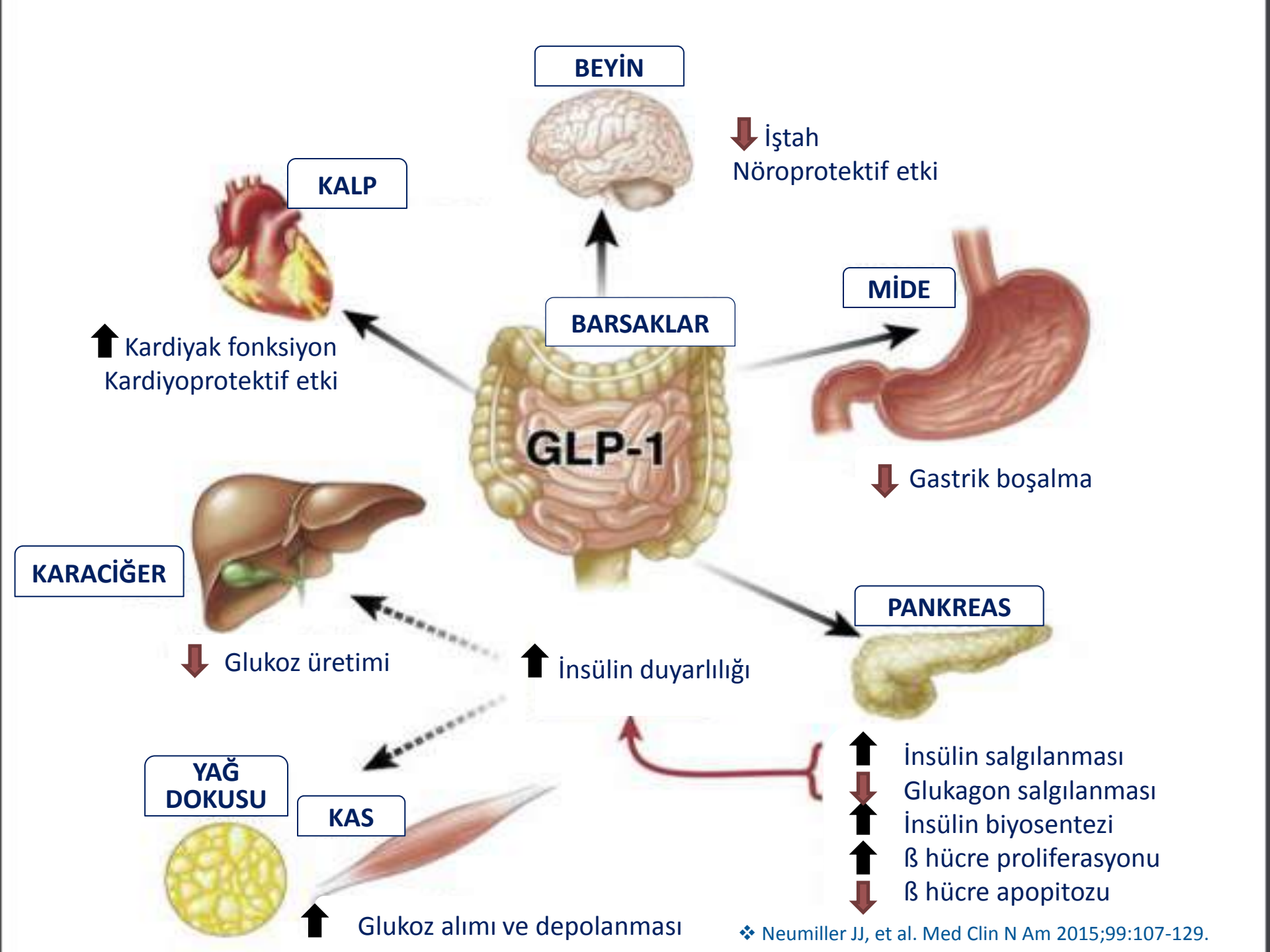




❖ Nauck MA et al. J Clin Endocrinol Metab 1986;63:492-498.

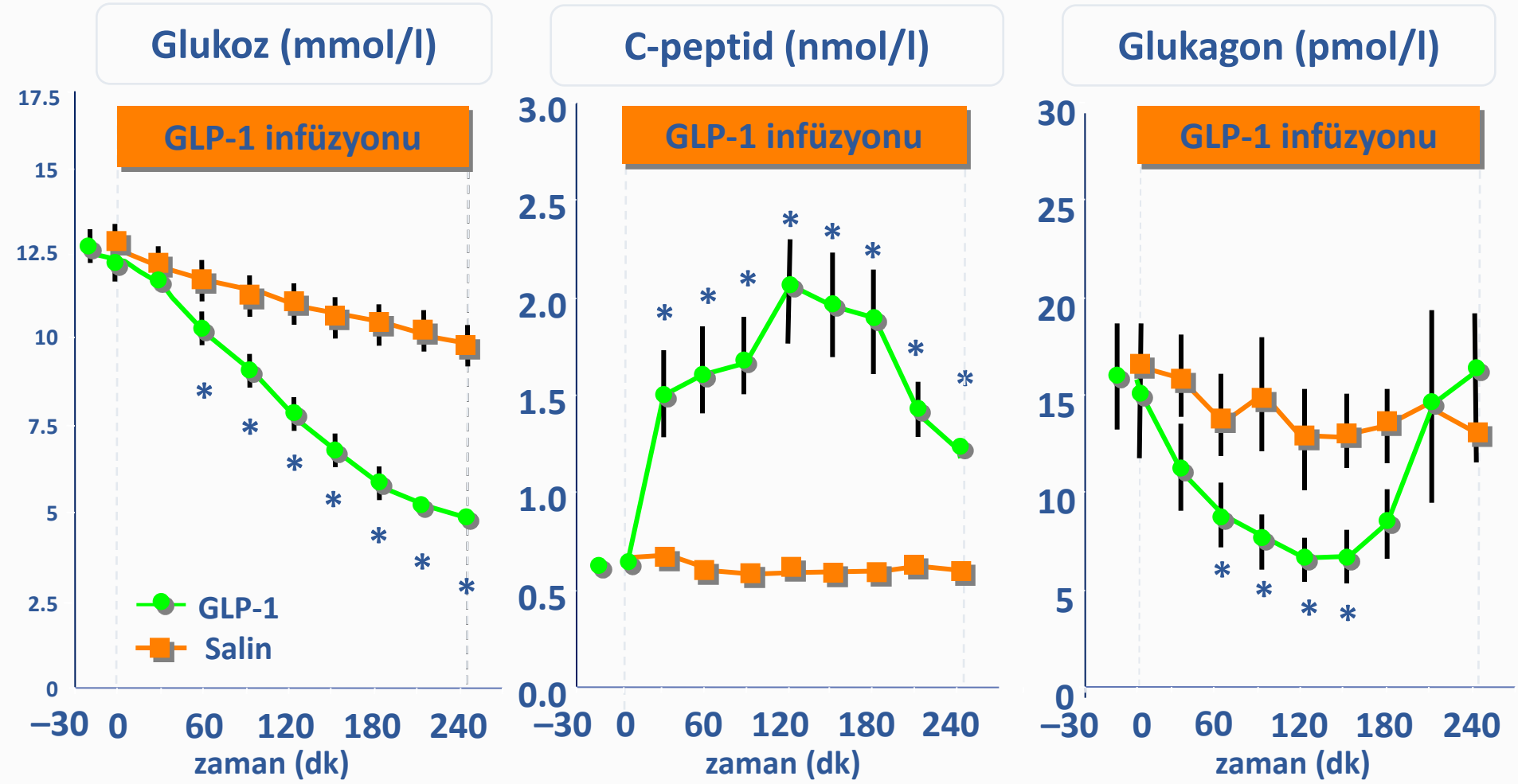
İNKRETİN ETKİSİ





❖ Neumiller JJ, et al. Med Clin N Am 2015;99:107-129.

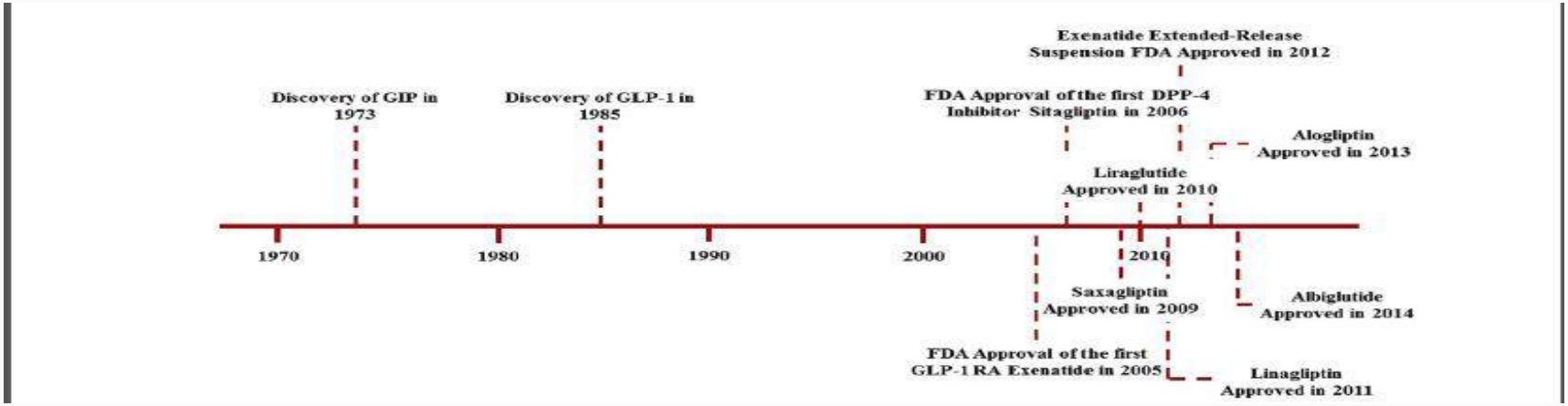
GLP-1



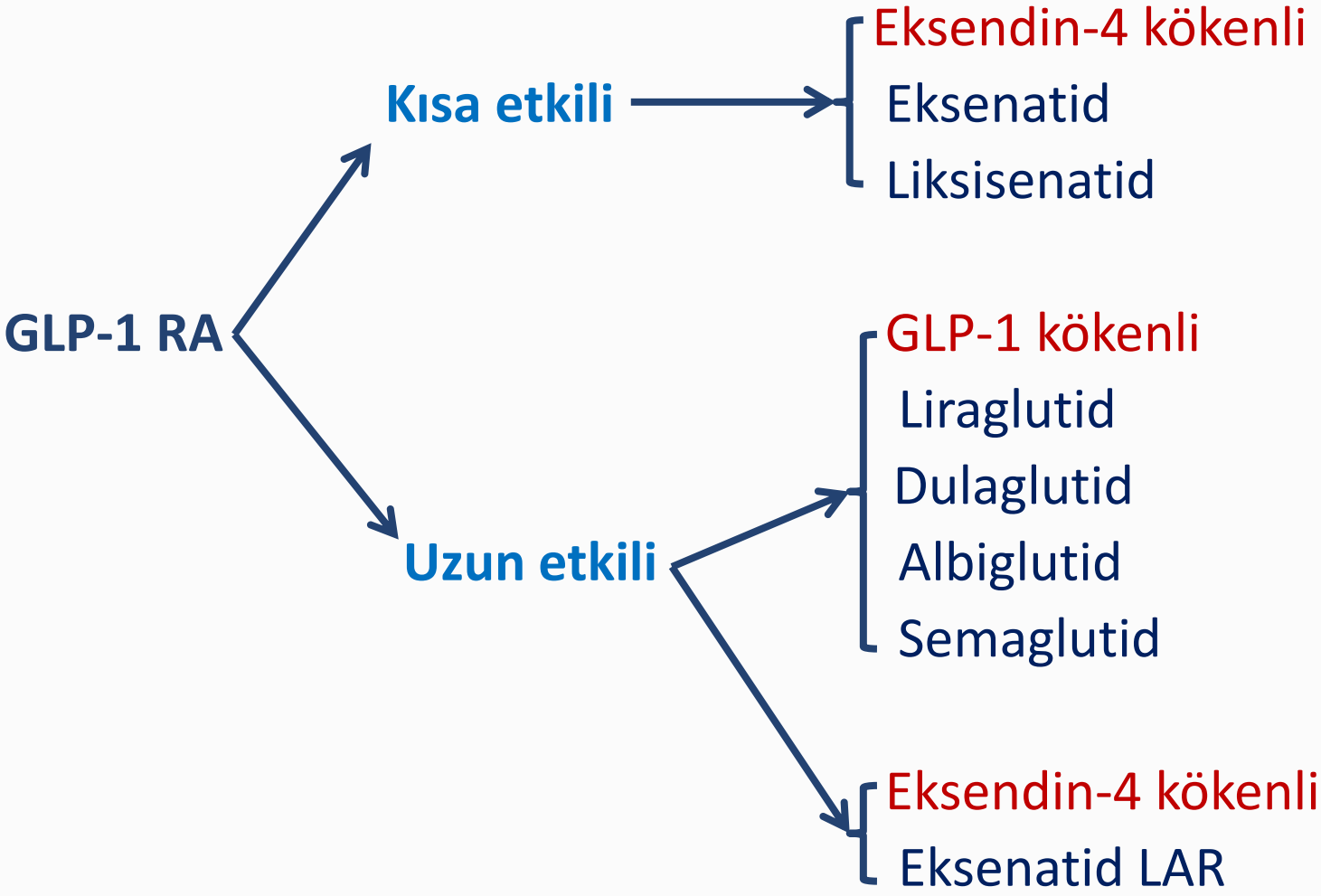
❖ Nauck et al. Diabetologia 1993;36:741-744.

GLP-1 ANALOGLARI

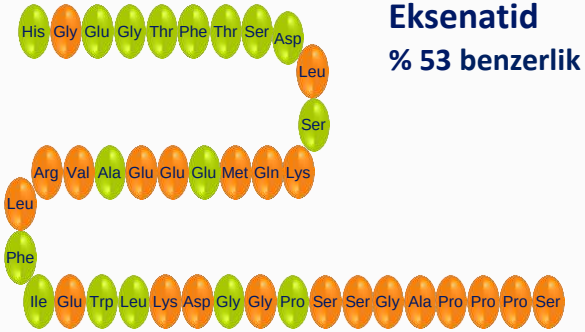
	EMA	FDA
Eksenatid	2006	2005
Liraglutid	2009	2012
Eksenatid LAR	2011	2012
Liksisenatid	2013	2016
Albiglutid	2014	2014
Dulaglutid	2014	2014
Semaglutid		



GLP-1 ANALOGLARI



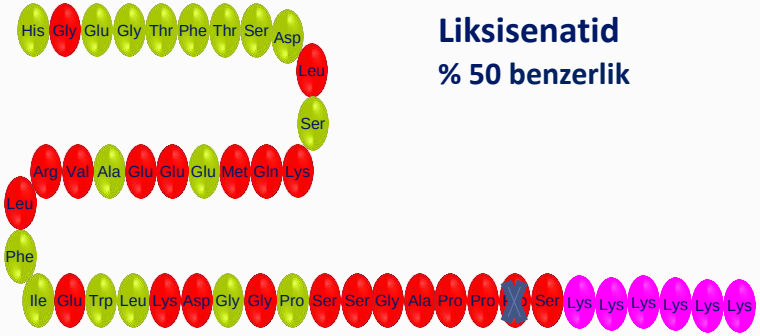
EKSENDİN-4 KÖKENLİ GLP-1 ANALOGLARI



Eksenatid

% 53 benzerlik

GLP-1

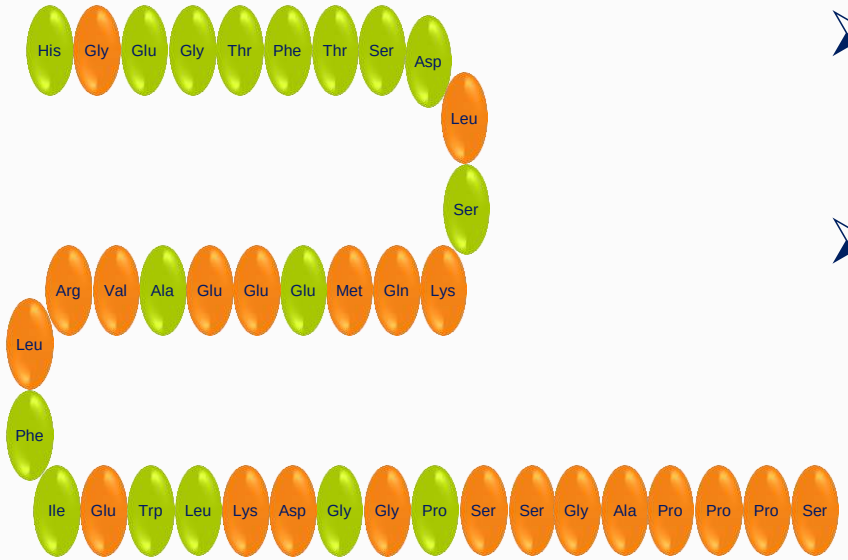


Liksisenatid

% 50 benzerlik

- Christensen et al. Drugs 2009;12:503–513.
- Ratner et al. Diabet Med 2010;27:1024–1032.

EKSENATİD

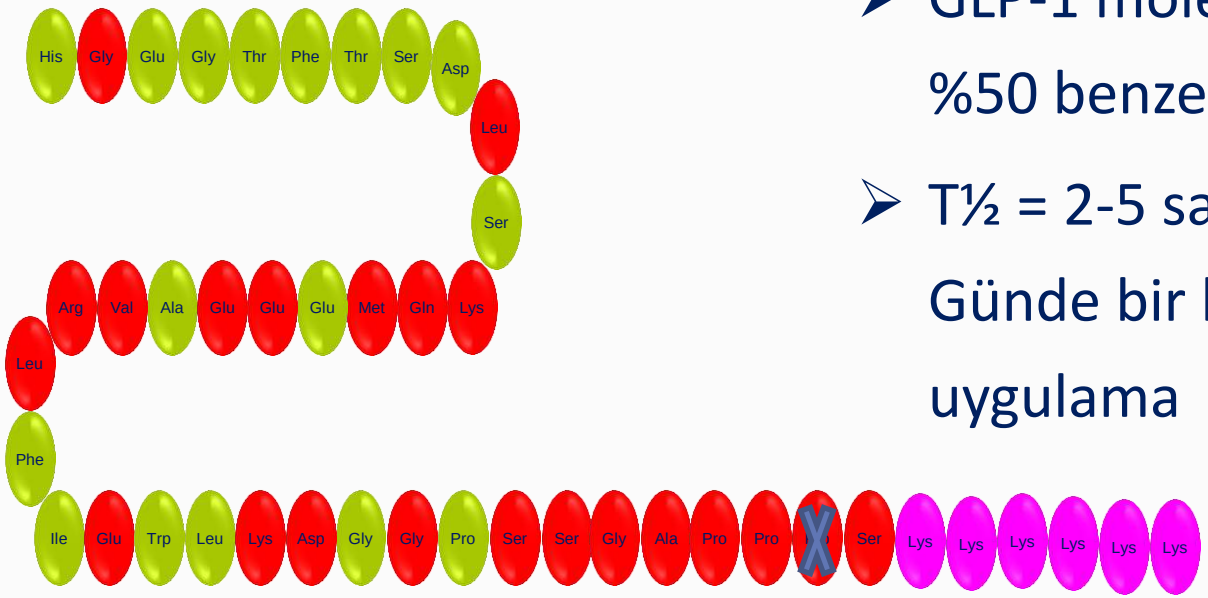


- GLP-1 molekülüne %53 benzerlik
- T½ = 2.4 saat Günde iki kez uygulama

- Eksenatid, eksendin-4 ile aynı amino asit sekansına sahip sentetik, 39 amino asitlik bir peptiddir.
- GLP-1 reseptörlerine bağlanır.
- Amino asid değişiklikleri nedeniyle DPP-4 tarafından inaktivasyona dirençlidir.

- Nielsen LL et al. Regulatory Peptides 2004;117:77-88.
- Fineman MS et al. Diabetes Care 2003;26:2370-2377.

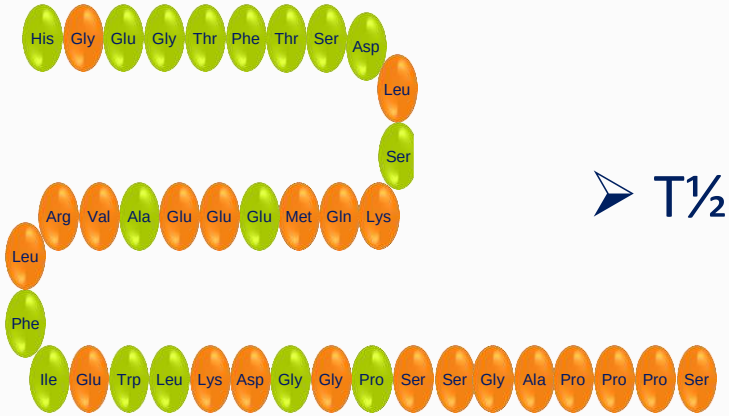
LİKSİSENATİD



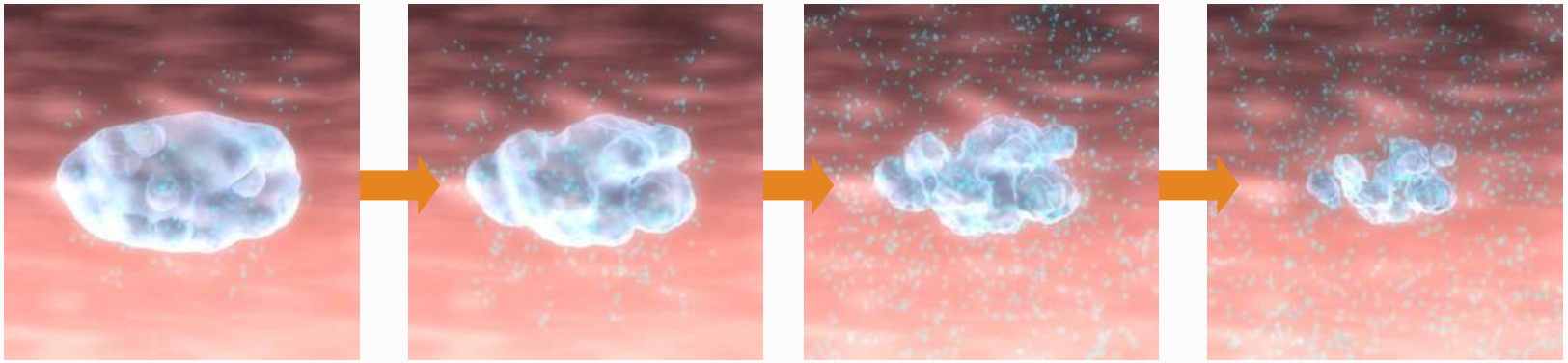
- GLP-1 molekülüne %50 benzerlik
- T½ = 2-5 saat
  Günde bir kez uygulama

- Amino asid değişiklikleri nedeniyle DPP-4 tarafından inaktivasyona dirençlidir.

EKSENATİD LAR



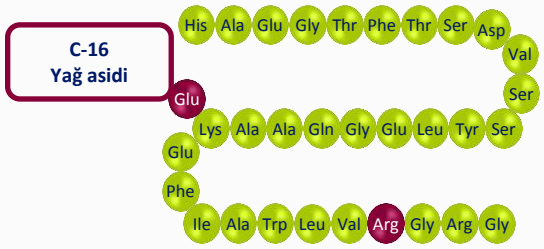
- T½ = 7-14 gün



- Biyolojik olarak parçalanabilir polimer mikrosferlerle birleşme subkutan dokudan salınımın uzamasını sağlar

- Fineman et al. Clin Pharmacokinet 2011;50:65-74.
- Meier JJ. Nat Rev Endocrinol 2012; 8:728-742.

GLP-1 KÖKENLİ GLP-1 ANALOGLARI



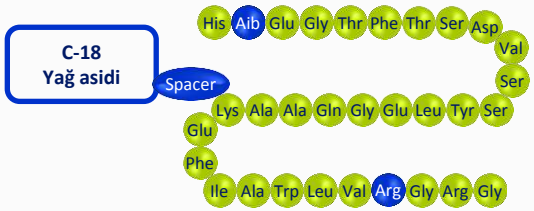
Liraglutid

% 97 benzerlik

GLP-1

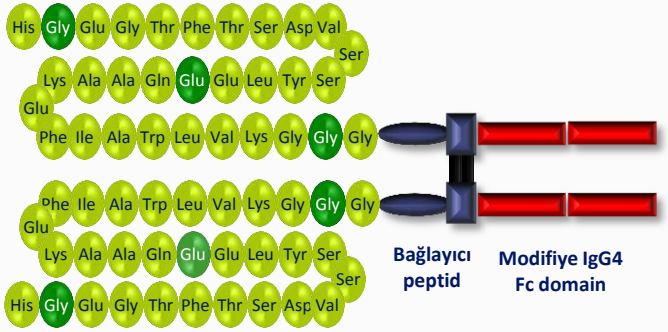
Albiglutid

% 95 benzerlik



Semaglutid

% 94 benzerlik



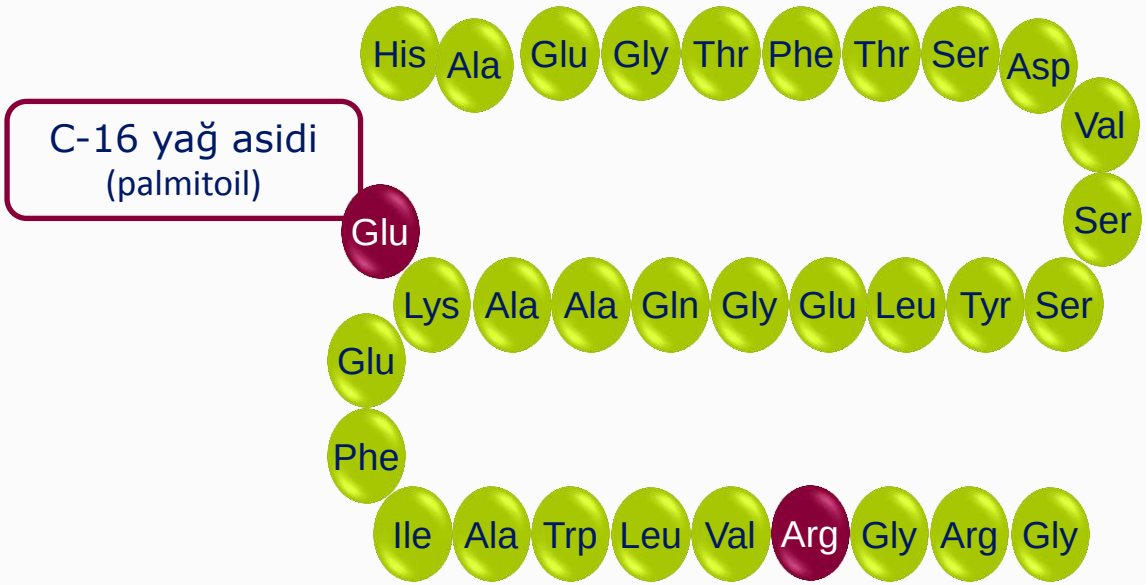
Dulaglutid

% 90 benzerlik

- Nauck MA et al. Diabetologia 2012;55(suppl1):S7.
- Lund A et al. Eur J Int Med 2014;25:407–414.

Fc: fragment crystallisable; IgG4: immunoglobulin G fraction 4

LİRAGLUTİD

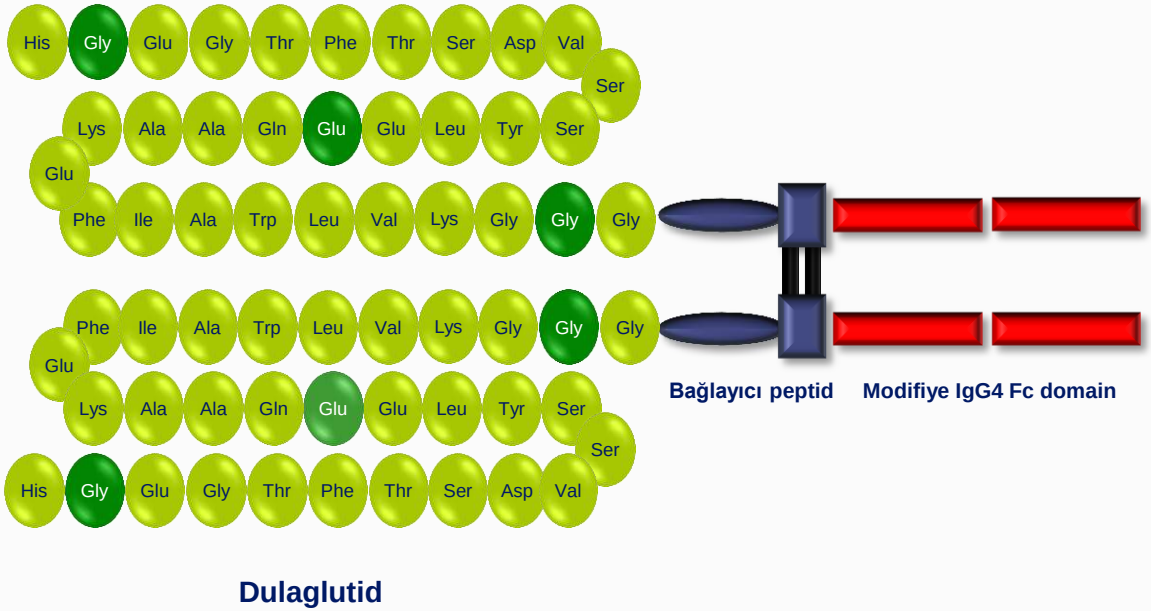


- GLP-1 molekülüne %97 benzerlik
- T½ = 13 saat
  Günde bir kez uygulama

- Yağ asidi yan zincirlerinin eklenmesi albüminin kovalent olmayan şekilde bağlanmasını sağlar

- Knudsen LB et al. J Med Chem 2000;43:1664–1669.
- Degn KB et al. Diabetes 2004;53:1187–1194.
- Meier JJ. Nat Rev Endocrinol 2012; 8:728-742.

DULAGLUTİD



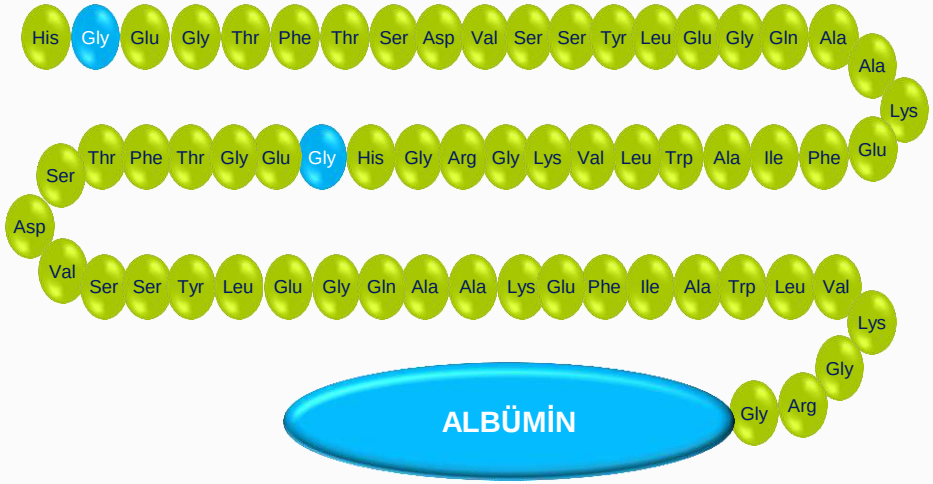
Dulaglutid

- GLP-1 molekülüne %94 benzerlik
- T½ = 90 saat

- IgG ile kovalent bağlanma renal eliminasyonu geciktirir

- Barrington et al. Diabetes Obes Metab 2011;13:434–438.
- Meier JJ. Nat Rev Endocrinol 2012;8:728-742.

ALBİGLUTİD



Albiglutid

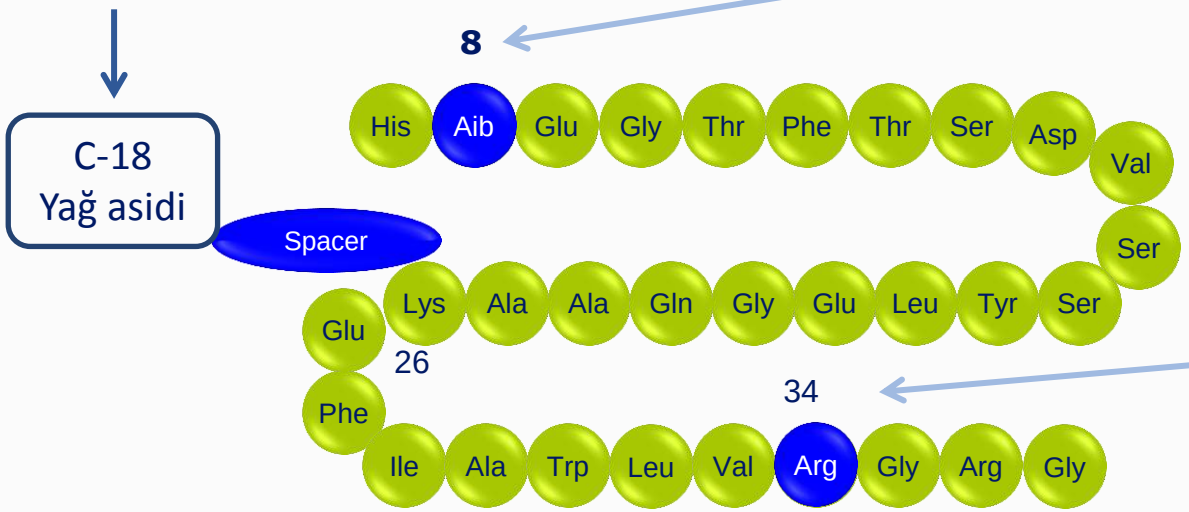
- GLP-1 molekülüne %94 benzerlik
- T½ = 6-7 gün

- Albümin ile kovalent bağlanma renal eliminasyonu geciktirir

- Bush et al. Diabetes Obes Metab 2009;11:498–505.
- Meier JJ. Nat Rev Endocrinol 2012; 8:728-742.

SEMAGLUTİD

C-18 yağ asidinin eklenmesi yıkımı yavaşlatır ve renal klirensi azaltır



Amino asid değişikliği DPP-4 tarafından yıkıma karşı korur

Amino asid değişikliği C-18 yağ asidinin yanlış yere bağlanmasını önler

➢ T½ = 155–184 saat (~7 gün)

❖ Kapitza C et al. J Clin Pharm 2015;55:497–504.

GLP-1 ANALOGLARI

Etken madde	Yarı ömür	T_{max}
Eksenatid	2.4 saat	2 saat
Liksisenatid	2–5 saat	1.25–2.25 saat
Liraglutid	13 saat	8–12 saat
Dulaglutid	90 saat (3.75 gün)	24–48 saat (1–2 gün)
Albiglutid	6–7 gün	3–5 gün
Semaglutid	155–184 saat (~7 gün)	24–36 saat (1–1.5 gün)
Eksenatide LAR	7–14 gün	6–7 hafta

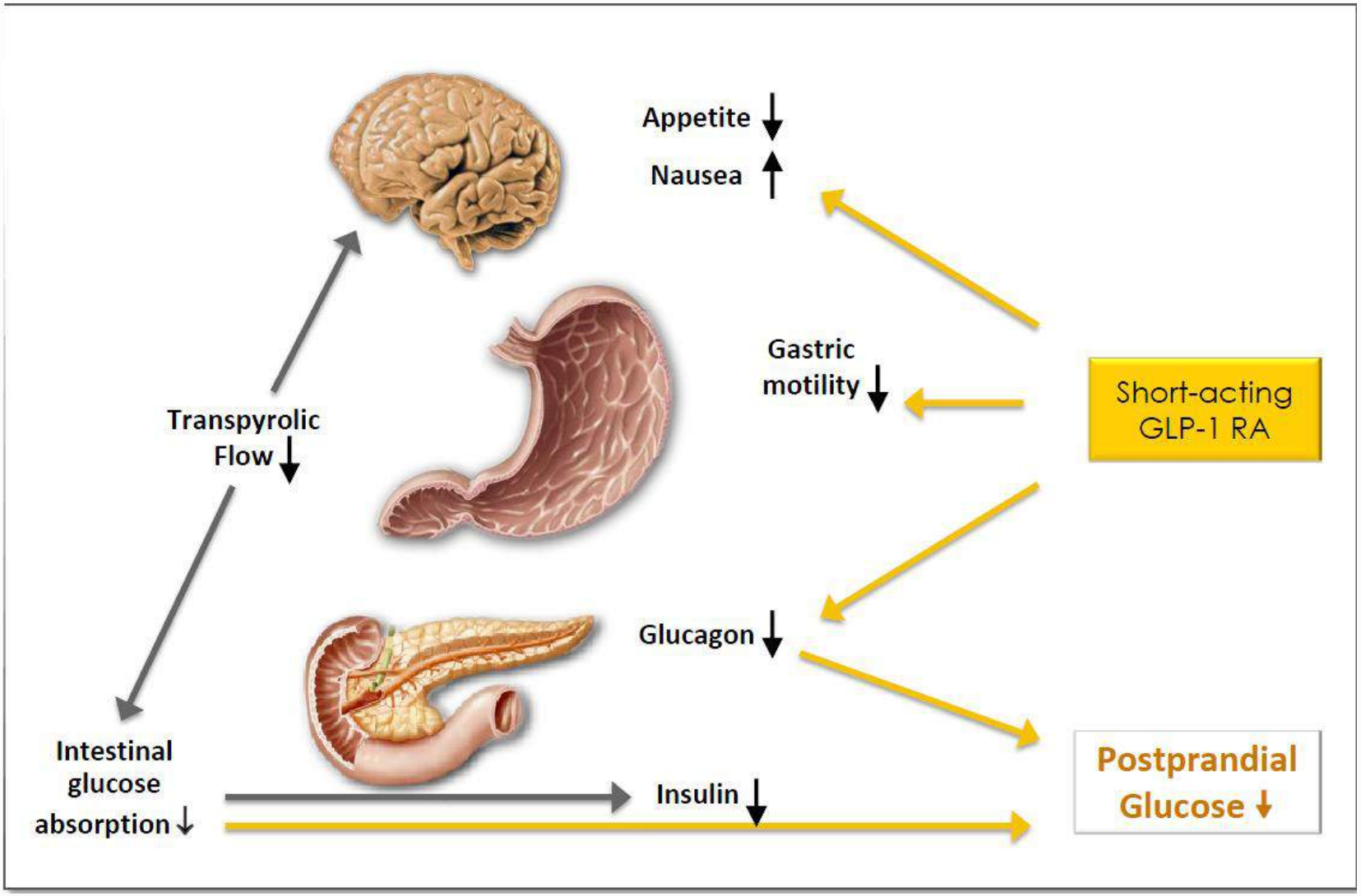
- Barrington et al. Diabetes Obes Metab 2011;13:434–438; Bush et al. Diabetes Obes Metab 2009;11:498–505.
- Matthews et al. J Clin Endo Metab 2008;93:4810–4817; Marbury T et al. Diabetes 2014;63(suppl 1):A260. Abst 1010-P.
- Kapitza C et al. J Clin Pharm 2015;55:497–504; Fineman et al. Clin Pharmacokinet 2011;50:65–74.

GLP-1 ANALOGLARI

	KISA ETKİLİ	UZUN ETKİLİ
Yarı ömür	2-5 saat	12 saat-günler
Açlık kan şekeri	Hafif azalma	Güçlü azalma
Postprandiyal kan şekeri	Güçlü azalma	Hafif azalma
Açlık insülin salgısı	Hafif uyarı	Güçlü uyarı
Postprandiyal insülin salgısı	Azalma	Hafif uyarı
Glukagon salgısı	Azalma	Azalma
Mide boşalma hızı	Uzama	Etki yok
Kan basıncı	Azalma	Azalma
Kalp hızı	0-2 atım/dk artış	2-5 atım/dk artış
Vücut ağırlığında azalma	1-5 kg	2-5 kg
Bulantı	%20-50 Yavaş düzelir (haftalar-aylar)	%20-40 Hızlı düzelir (4-8 hafta)

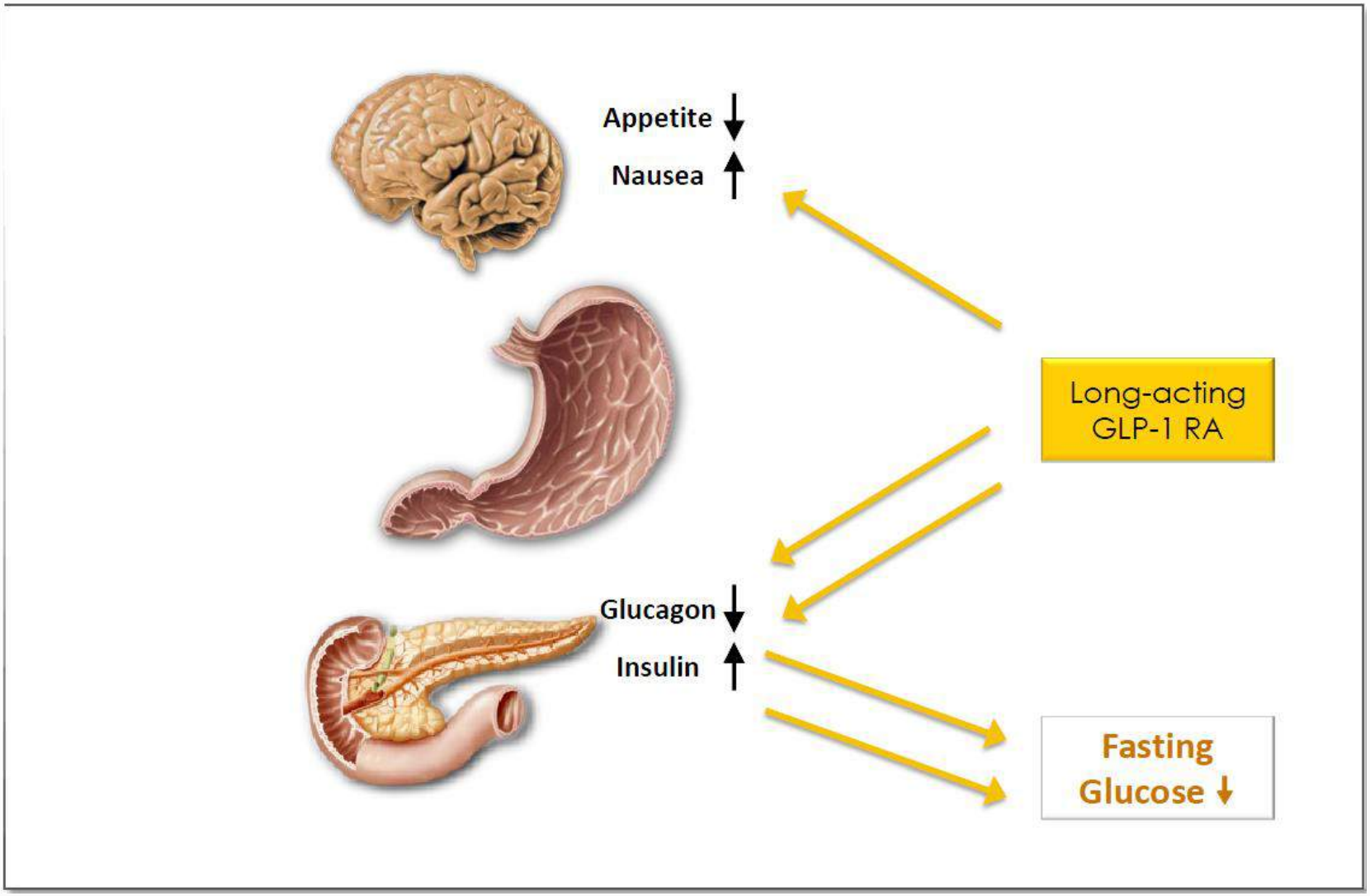
❖ Meier JJ. Nat Rev Endocrinol 2012; 8:728-742.

KISA ETKİLİ GLP-1 ANALOGLARI



❖ Meier JJ. Nat Rev Endocrinol 2012; 8:728-742.

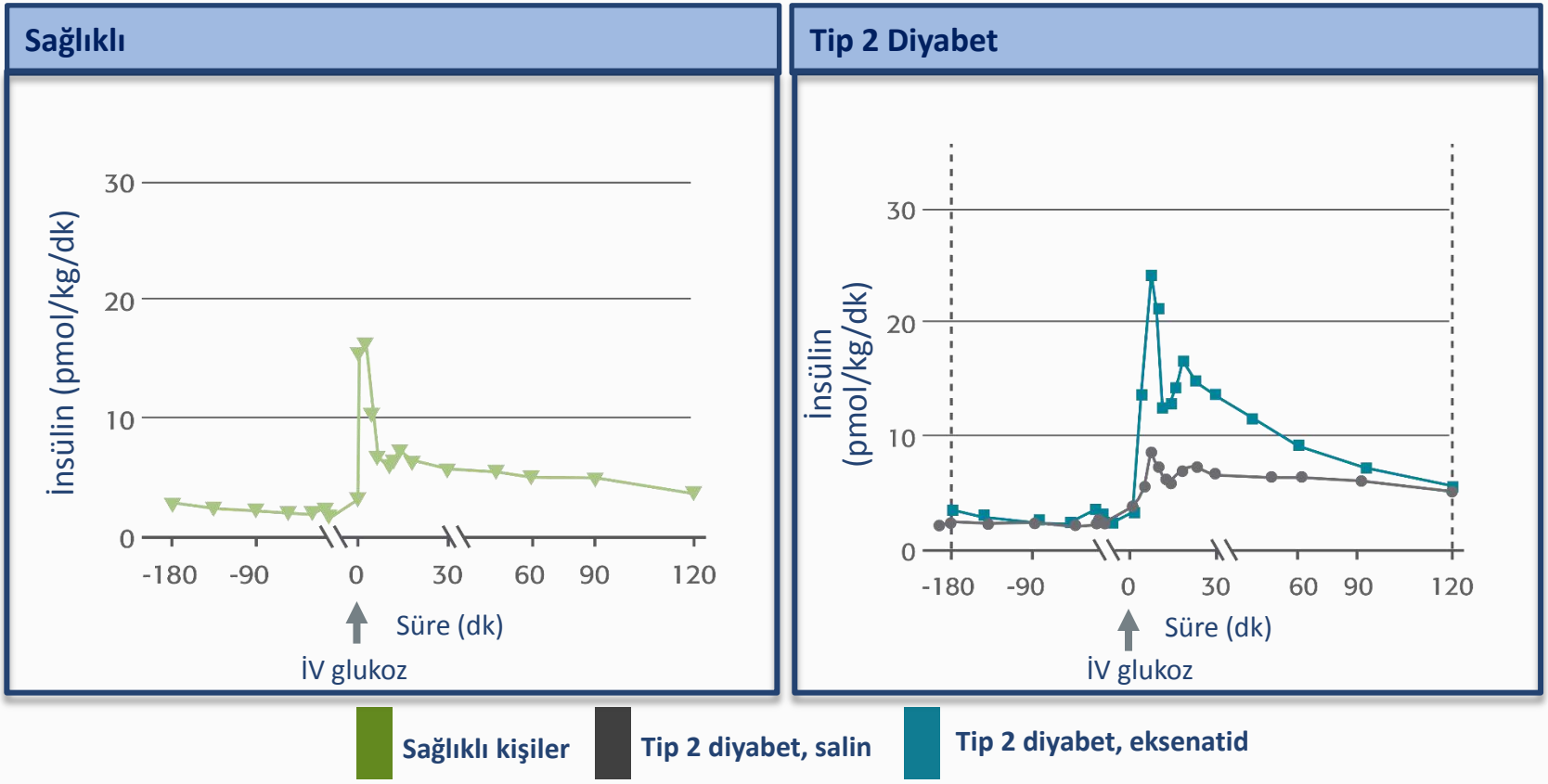
UZUN ETKİLİ GLP-1 ANALOGLARI



❖ Meier JJ. Nat Rev Endocrinol 2012; 8:728-742.

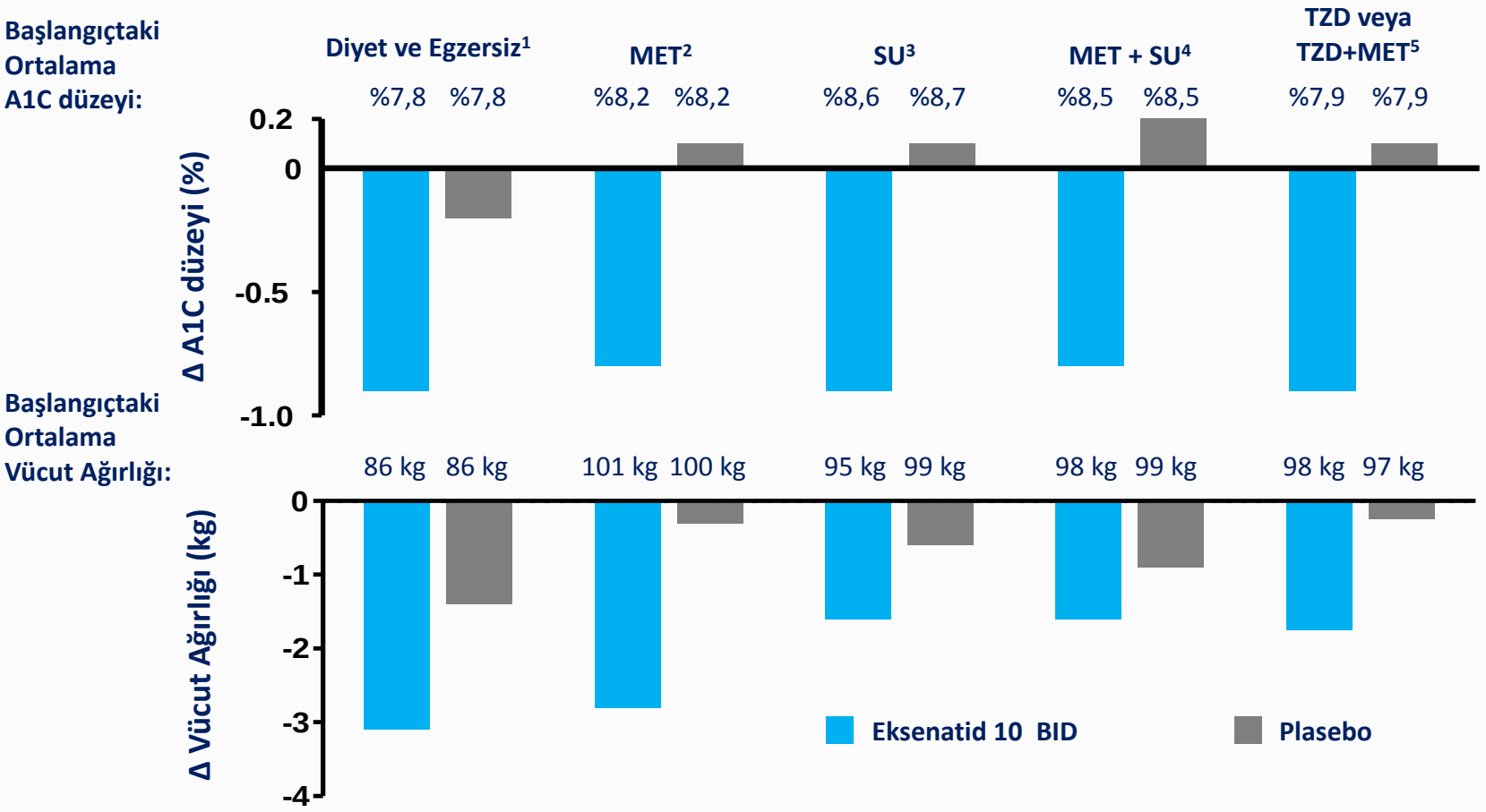
EKSENATİD

Tip 2 DM Hastalarında
Birinci Faz İnsülin Yanıtının Korunmasını Sağlamıştır



❖ Fehse F et al. J Clin Endocrinol Metab. 2005;90:5991-5997.

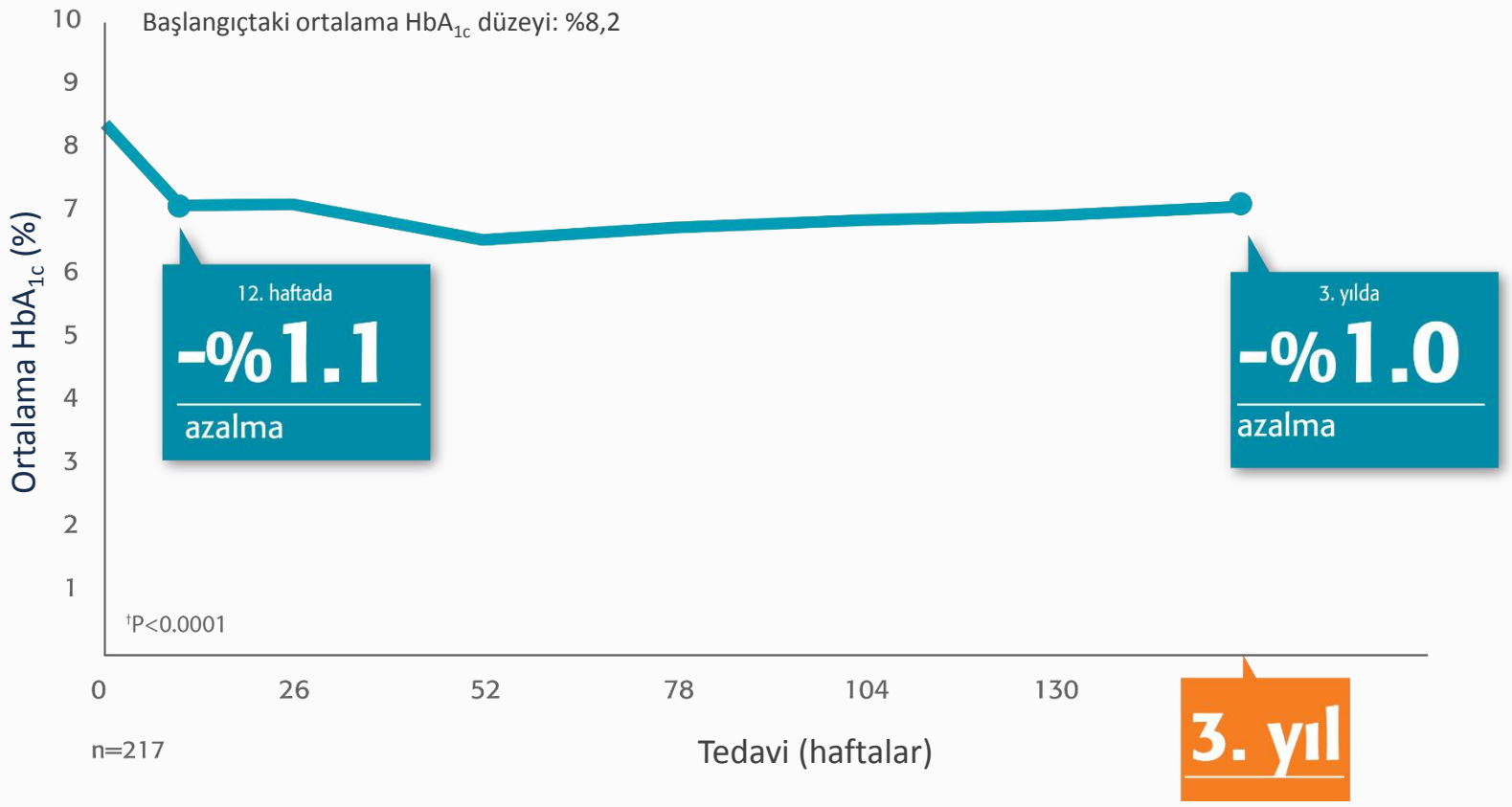
ETKİNLİK VE KİLO KAYBI



1. Moretto TJ et al. Clin Ther 2008;30:1448-1460.
2. DeFronzo RA et al. Diabetes Care 2005;28:1092-1100.
3. Buse JB et al. Diabetes Care 2004;27:2628-2635.
4. Kendall DM et al. Diabetes Care 2005;28:1083-1091.
5. Zinman B et al. Ann Intern Med 2007;146:477-485.

SÜRDÜRÜLEBİLİRLİK

HbA1c değişikliği (%)

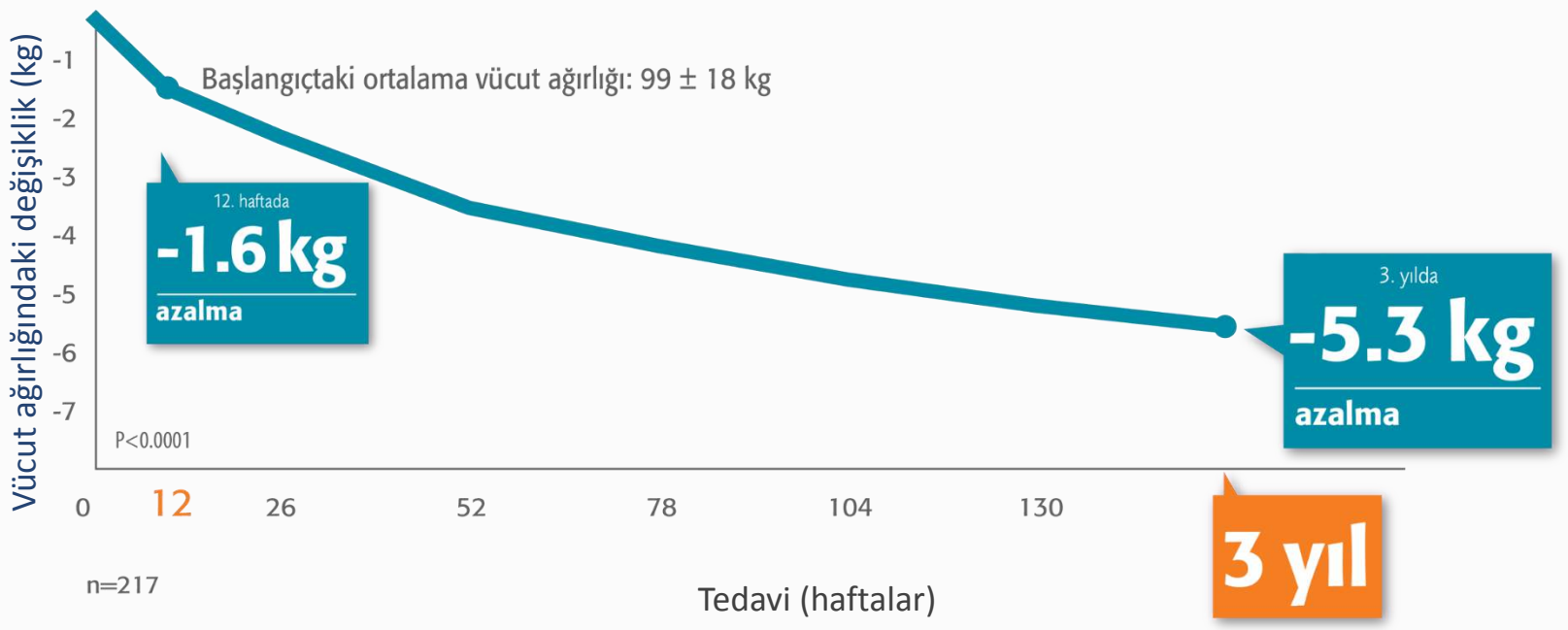


*527 hastadan 217'si çalışmanın 156 haftasını tamamlamış, bu hastaların %46'sı HbA_{1c} ≤%7 düzeyine ulaşmıştır.

❖ Klonoff DC et al. Curr Med Res Opin 2008;24:275-286.

SÜRDÜRÜLEBİLİRLİK

Vücut ağırlığı değişikliği (%)

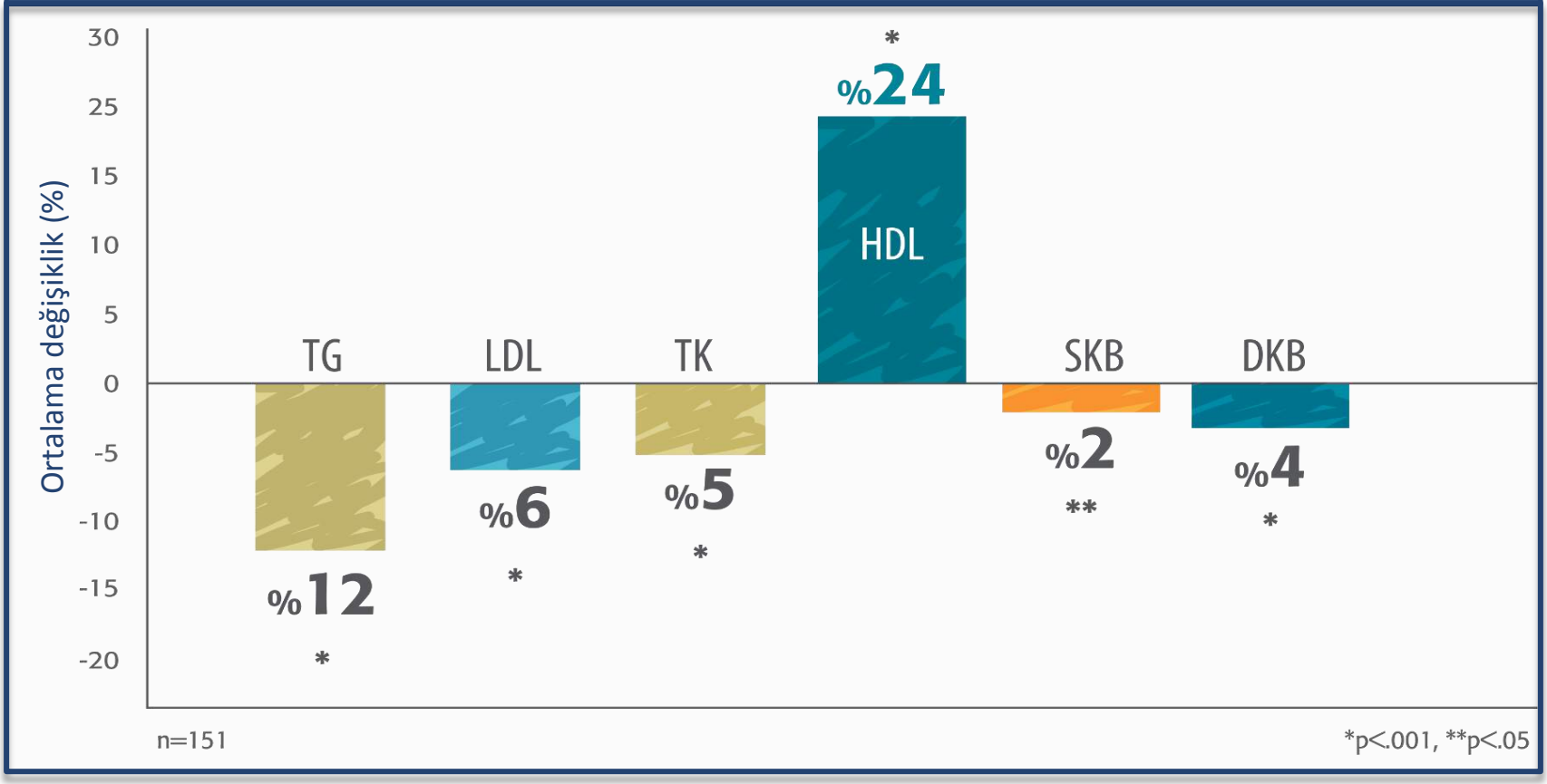


†527 gönüllüden 217'si çalışmanın 156 haftasını tamamlamış, bu hastaların %84'ünde vücut ağırlığı azalırken %50'si başlangıçtaki vücut ağırlığının en az %5'i oranında kilo kaybetmiştir.[1]

❖ Klonoff DC et al. Curr Med Res Opin 2008;24:275-286.

KARDİYOVASKÜLER RİSK FAKTÖRLERİ

Plasebo kontrollü, açık etiketli uzatma çalışmaları

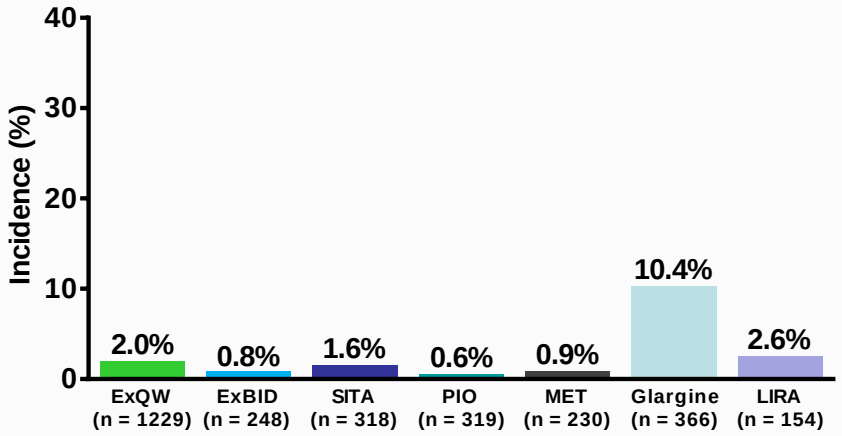


❖ Klonoff DC et al. Curr Med Res Opin 2008;24:275-286.

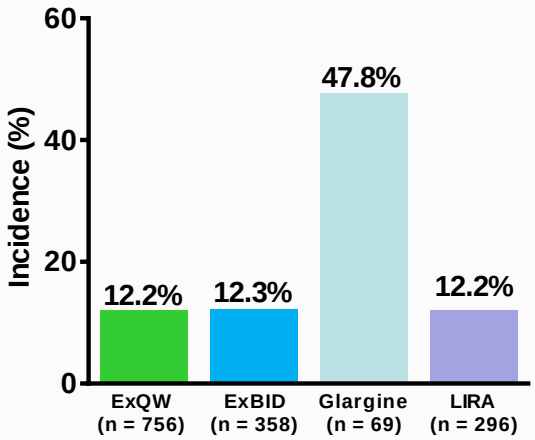
HİPOGLİSEMİ

Minör hipoglisemi insidansı

Eşzamanlı SU Kullanımı Olmadan İnsidans



Eşzamanlı SU Kullanımı ile Birlikte İnsidans

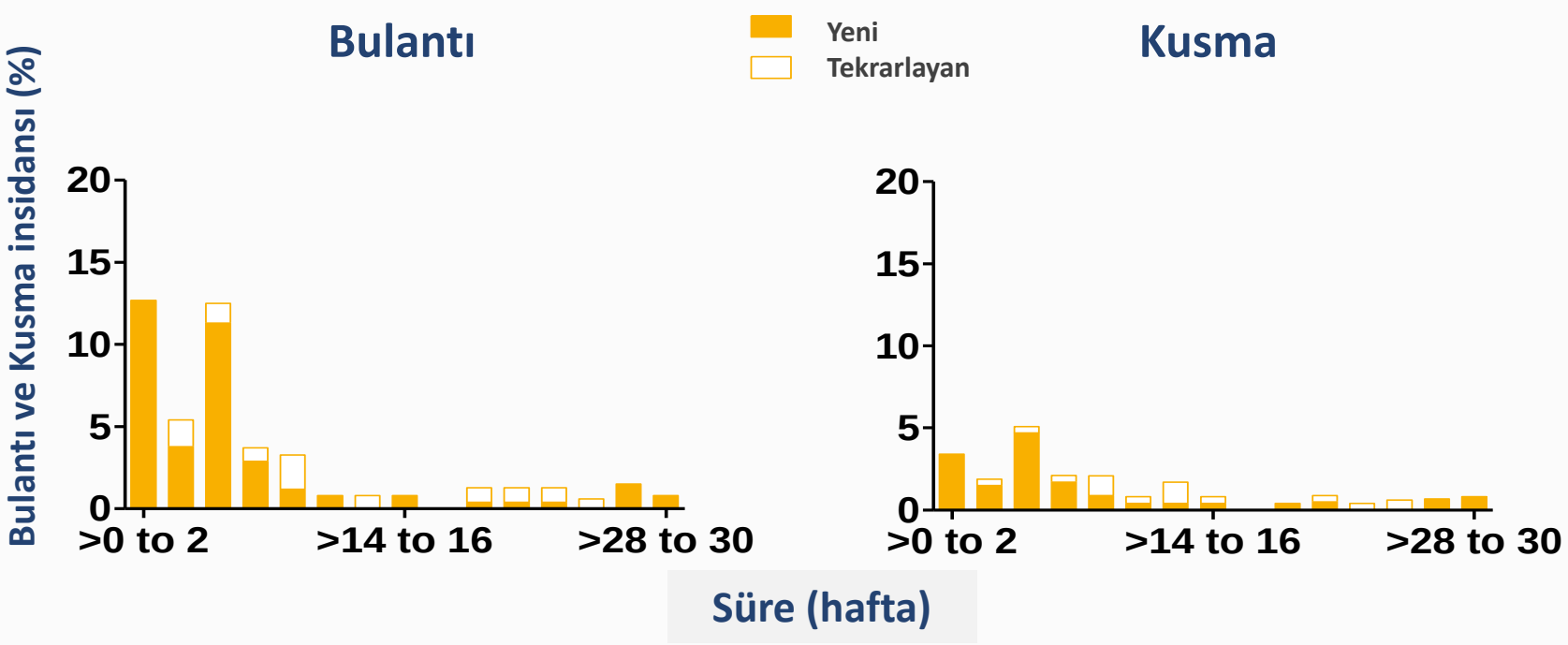


- **Majör hipoglisemi olayı olmamıştır.**
- **Eksenatid SU ile birlikte kullanıldığında hipoglisemi riskinin artmasına neden olur.**

❖ Buse JB et al. Lancet 2013;381:117-124.

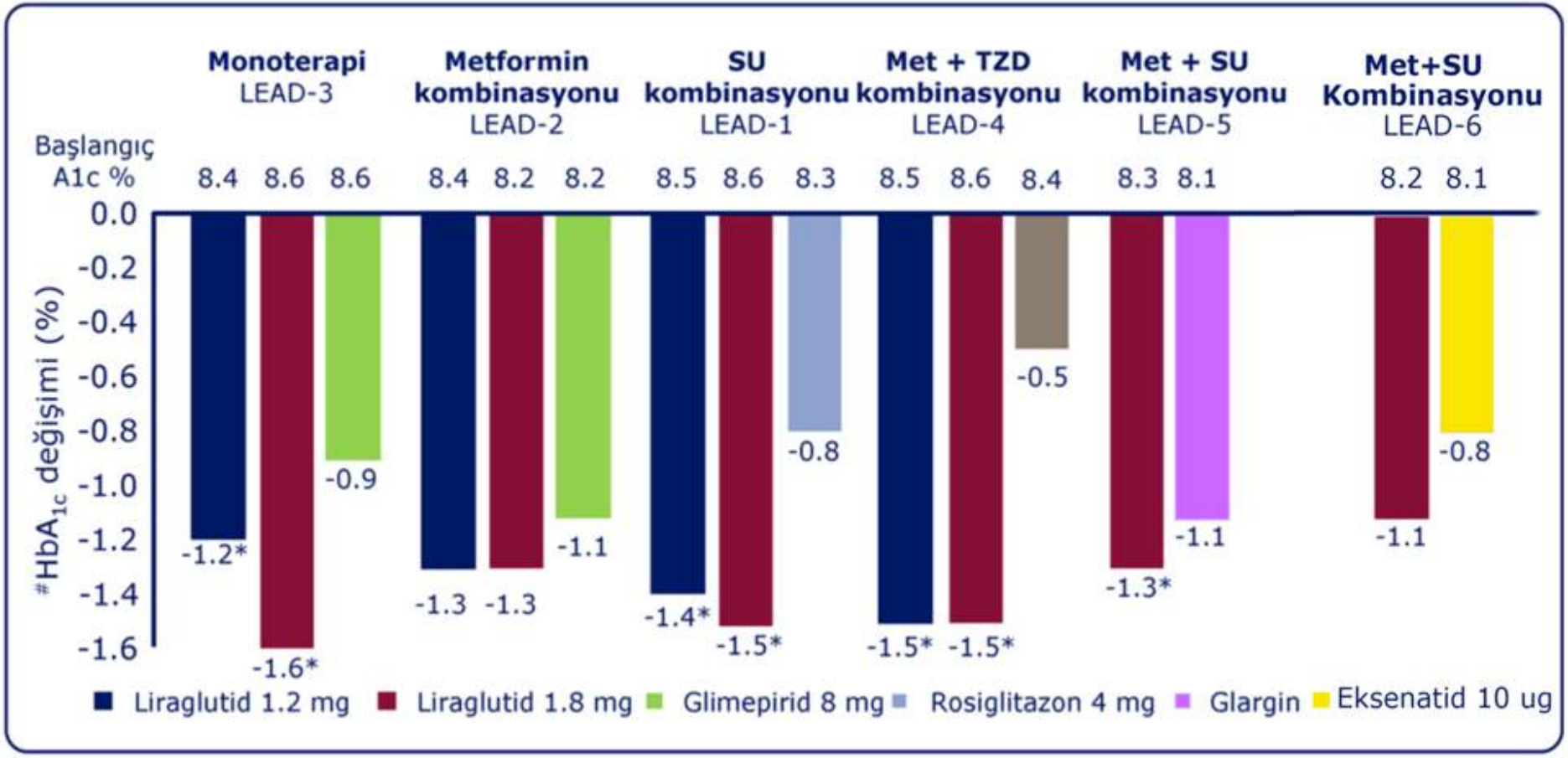
BULANTI

Bulantı ve Kusma insidansı (%)



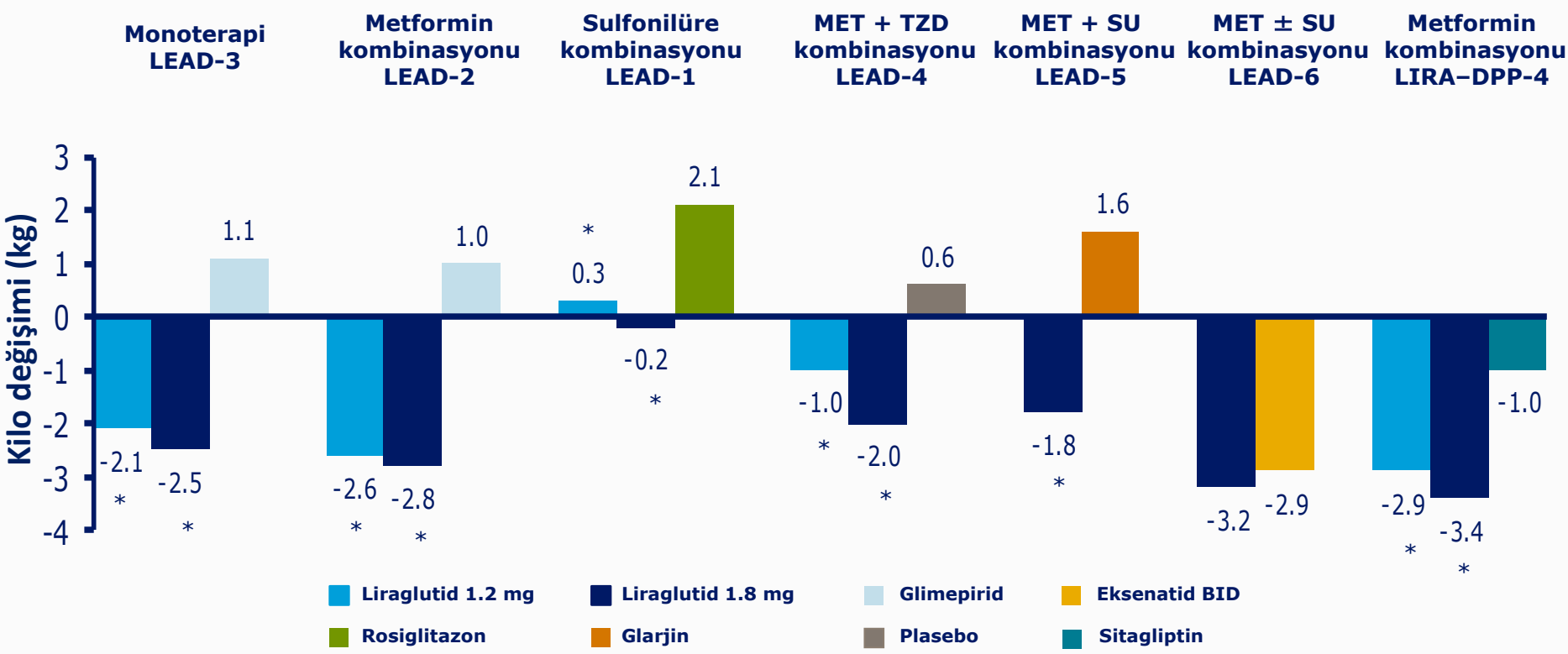
❖ Ridge T et al. Diabetes Obes Metab 2012;14:1097–1103.

LİRAGLUTİD



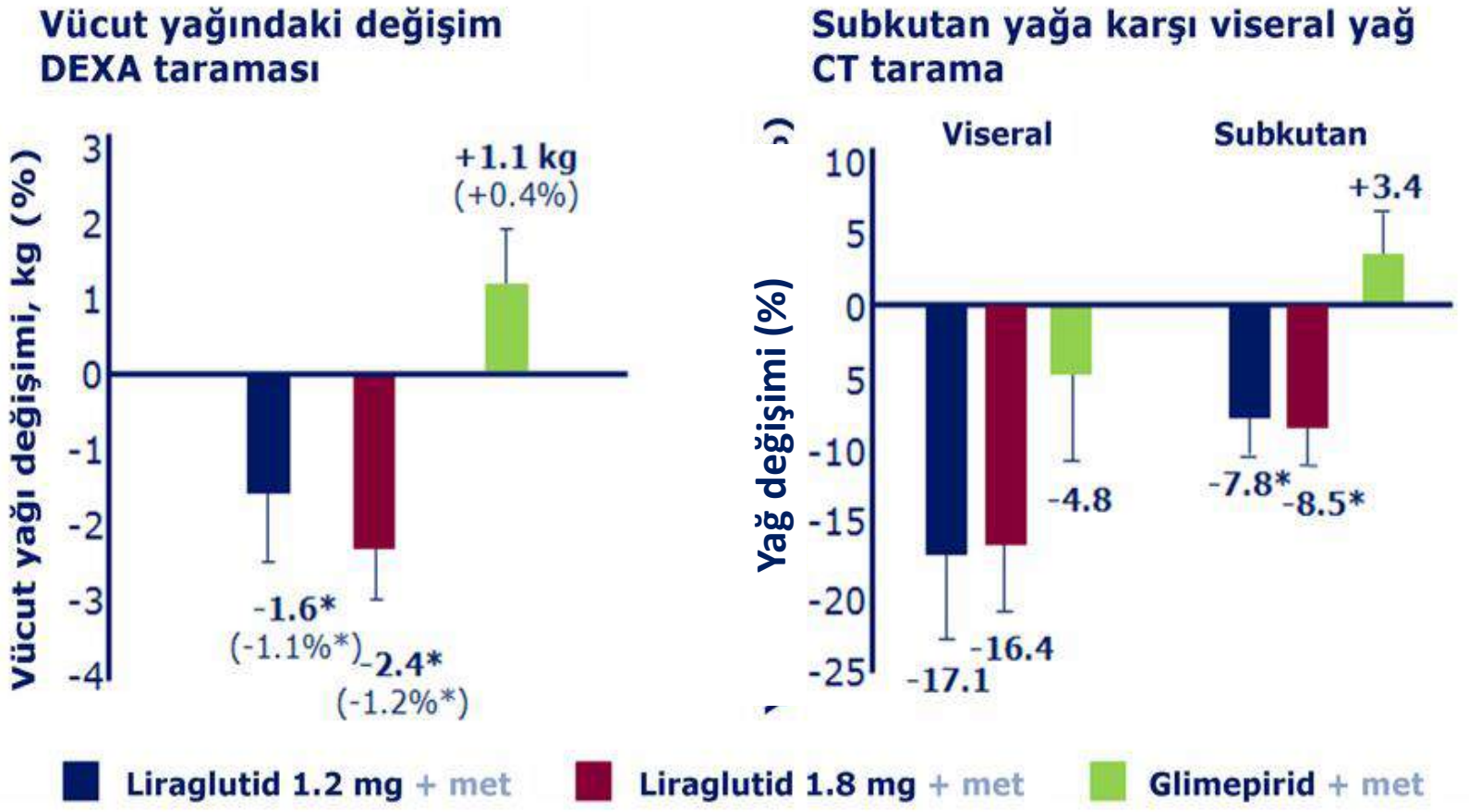
- Marre et al. Diabetic Medicine 2009;26;268–278 (LEAD-1); Nauck et al. Diabetes Care 2009;32;84–90 (LEAD-2).
- Garber et al. Lancet 2009;373:473–481 (LEAD-3); Zinman et al. Diabetes Care 2009; 32:1224-1230 (LEAD-4).
- Russell-Jones et al. Diabetes 2008;57(Suppl.1):A159 (LEAD-5); Buse et al. Lancet 2009;374, 9683 pp 39-47 (LEAD-6).

KİLO KAYBI



- Marre et al. Diabetic Medicine 2009;26;268–278 (LEAD-1); Nauck et al. Diabetes Care 2009;32;84–90 (LEAD-2).
- Garber et al. Lancet 2009;373:473–481 (LEAD-3); Zinman et al. Diabetes Care 2009; 32:1224-1230 (LEAD-4).
- Russell-Jones et al. Diabetes 2008;57(Suppl.1):A159 (LEAD-5); Buse et al. Lancet 2009;374, 9683 pp 39-47 (LEAD-6).
- Pratley RE et al. Lancet 2010;375:1447–1456 (LIRA-DPP-4).

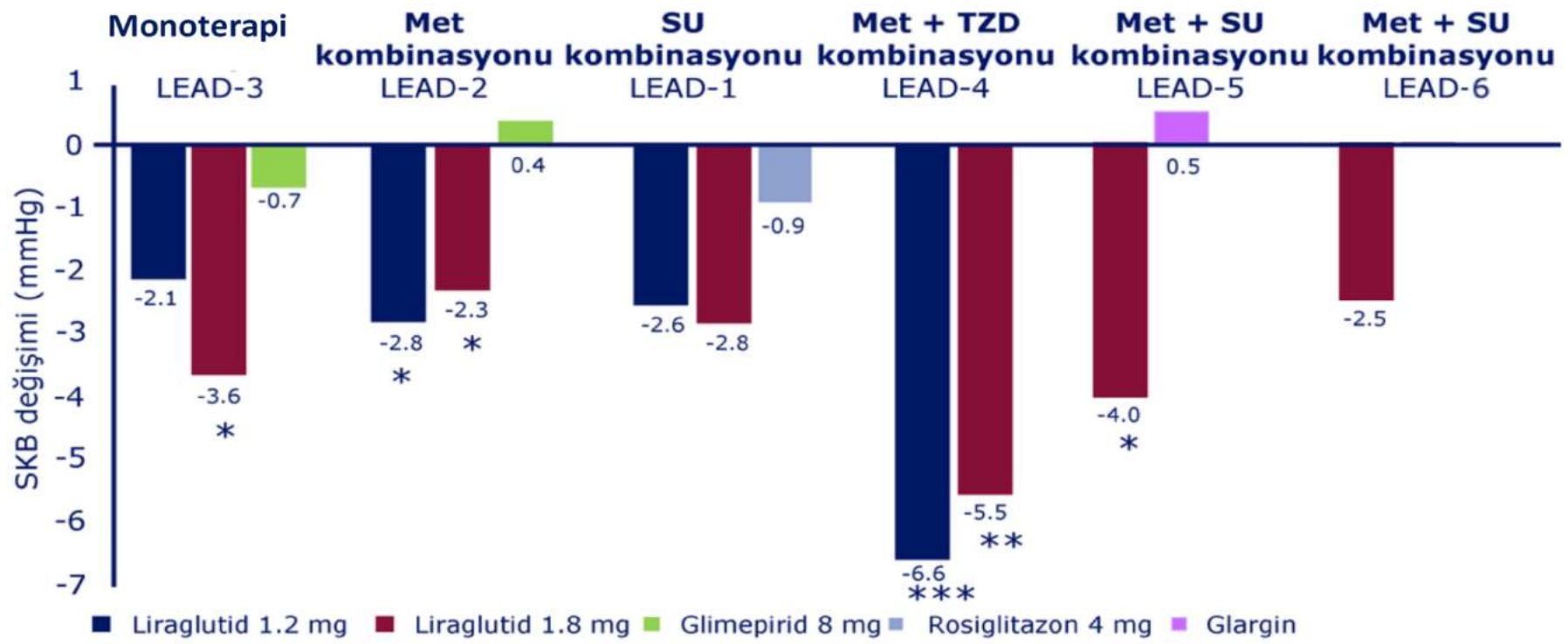
KİLO KAYBI



*Liraglutid ile kilo kaybının 2/3'ü yağ dokusundan olmuştur.

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

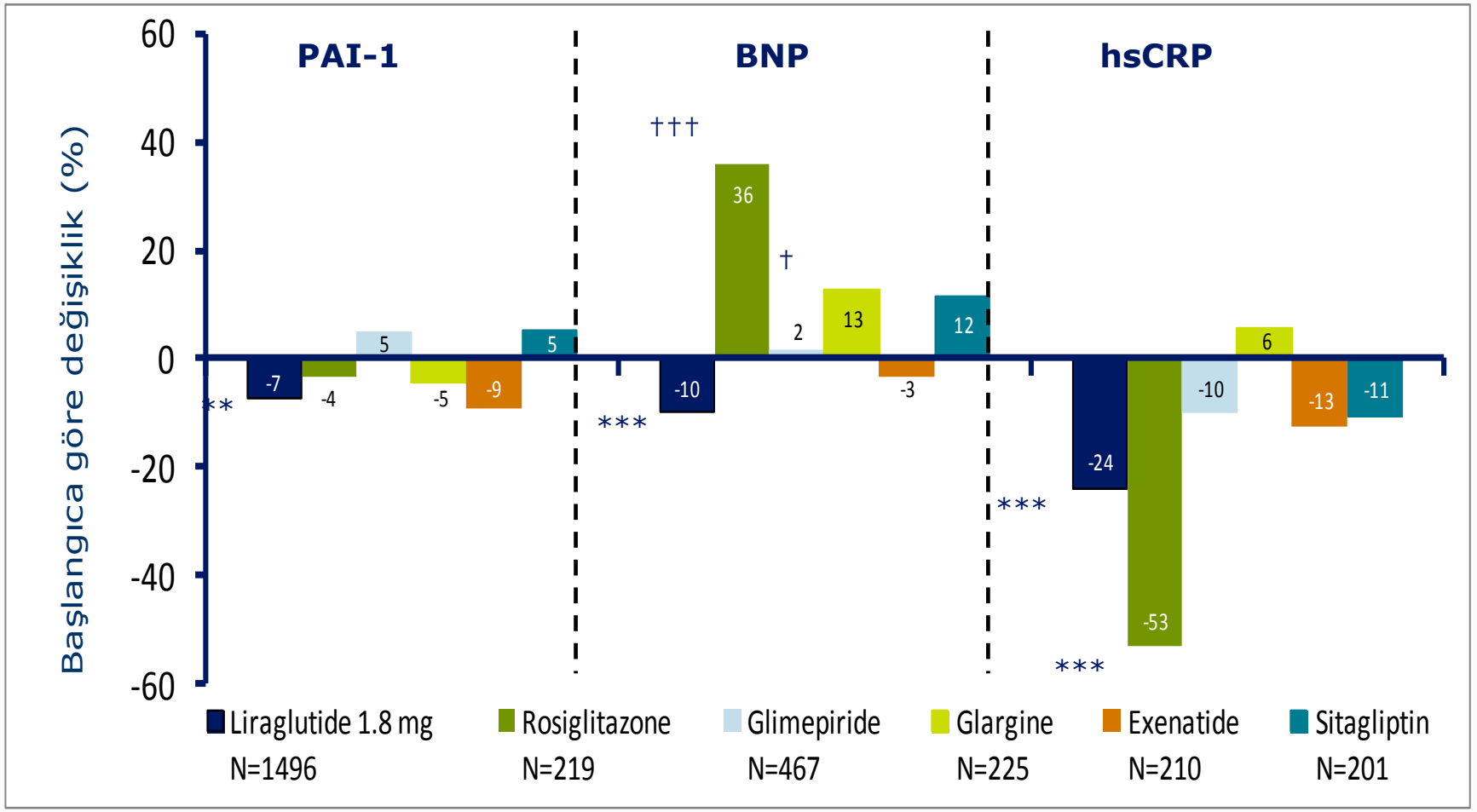
KAN BASINCI



***$p<0.0001$ **$p<0.001$ * Başlangıca karşı $p<0.05$
Veriler orijinal olarak Colagiuri *ve ark. Diabetes* 2008;57(Suppl. 1):A16'da sunulmuştur

- Marre et al. Diabetic Medicine 2009;26;268–278 (LEAD-1); Nauck et al. Diabetes Care 2009;32;84–90 (LEAD-2).
- Garber et al. Lancet 2009;373:473–481 (LEAD-3); Zinman et al. Diabetes Care 2009; 32:1224-1230 (LEAD-4).
- Russell-Jones et al. Diabetes 2008;57(Suppl.1):A159 (LEAD-5); Buse et al. Lancet 2009;374, 9683 pp 39-47 (LEAD-6).

KARDİYOVASKÜLER RİSK GÖSTERGELERİ



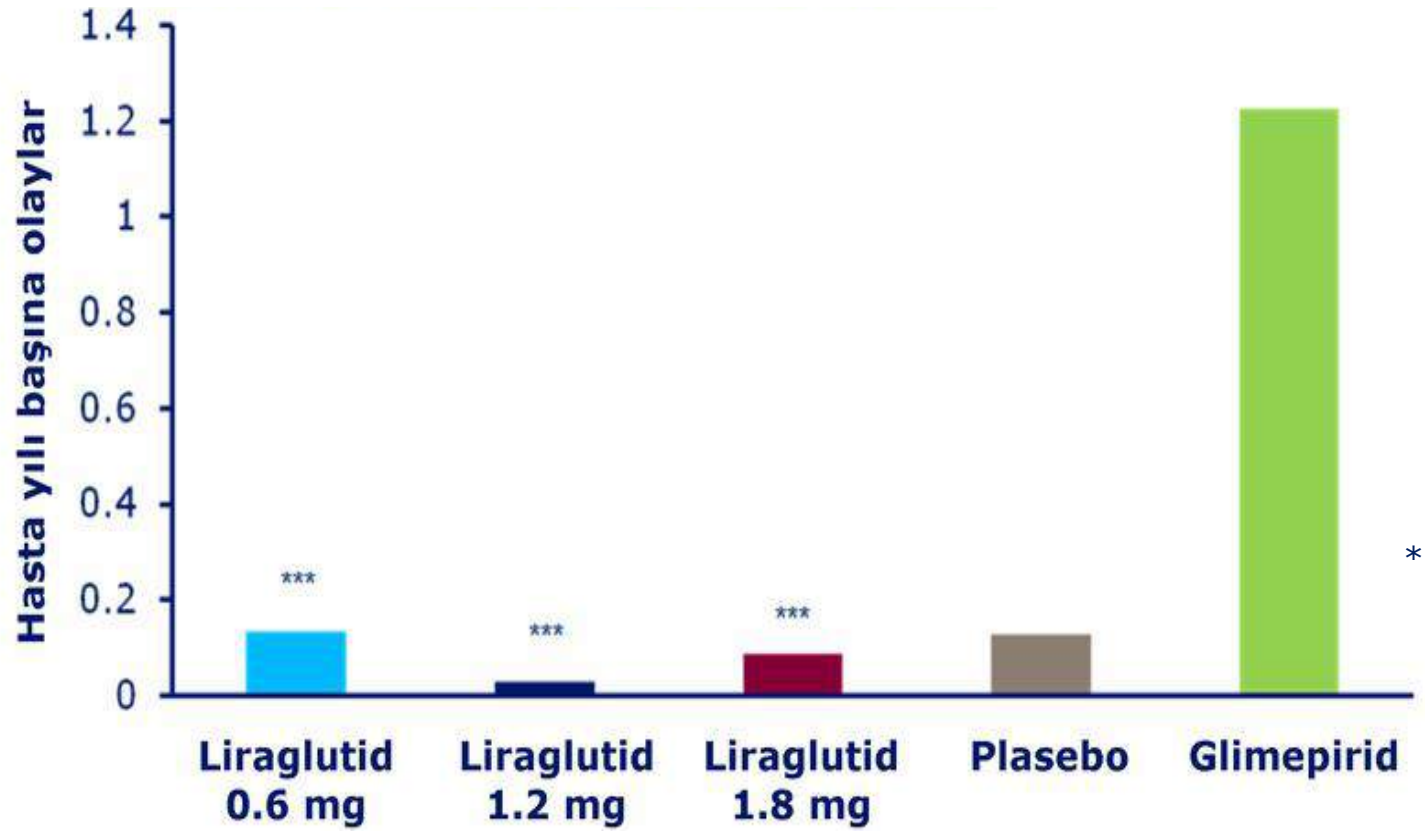
LEAD 1–6: meta-analysis

*p<0.05; **p<0.01; ***p<0.0001; all vs baseline; † is used instead of * to indicate a significant increase from baseline

BNP, brain natriuretic peptide; hsCRP, high-sensitivity C-reactive protein; PAI-1, plasminogen activator inhibitor-1

Fonseca VA et al. International Diabetes Federation 21st World Diabetes Congress, 4–8 December 2011.

HİPOGLİSEMİ



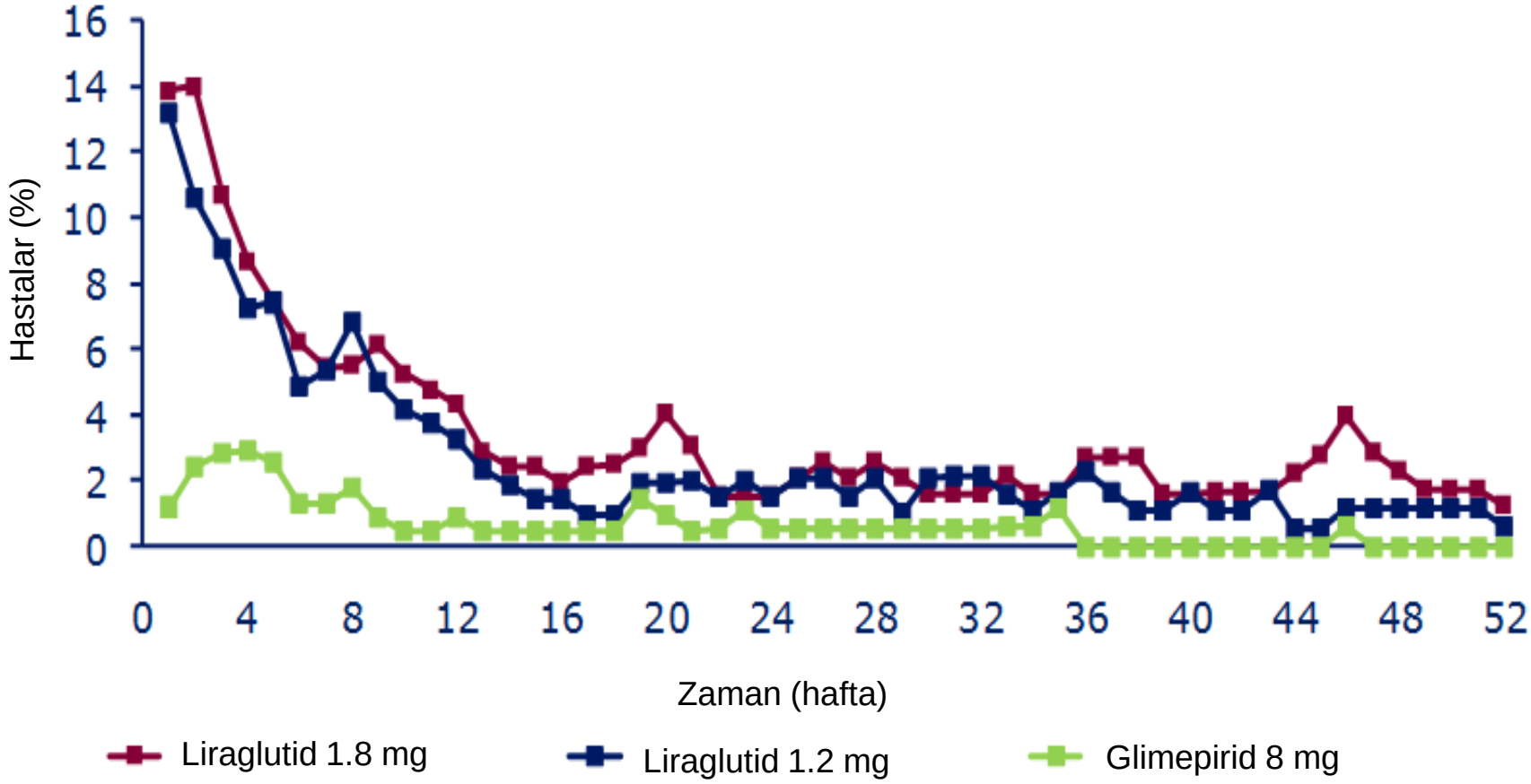
***p<0.0001

- Minör hipoglisemik olaylar plasebo düzeyindedir (LEAD-2)
- SU kombinasyonu ile küçük fakat artmış minör hipoglisemi riski! (LEAD-1)

❖ Marre M et al. Diabet Med 2009;26:268–278 (LEAD-1), Nauck M et al. Diabetes Care 2009;32:84–90 (LEAD-2).

BULANTI

Bulantısı olan hastaların hafta ve tedaviye göre oranı

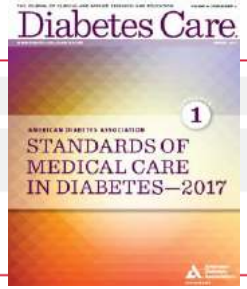


❖Garber et al. Lancet 2009;373:473–481 (LEAD-3).

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).



Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

2017 TEDAVİ KILAVUZU

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• Rare hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors • Associated with lower CVD event rate and mortality in patients with CVD (liraglutide LEADER) (30)	• Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
Amylin mimetics	• Pramlintide§	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs - Lispro - Aspart - Glulisine - Inhaled insulin • Short-acting - Human Regular • Intermediate-acting - Human NPH	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • Training requirements • Patient and provider reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	High#

❖ American Diabetes Association. Standards of Medical Care in Diabetes-2017. Diabetes Care 2017;40(Suppl.1):S64–S74.

KARDİYOVASKÜLER GÜVENLİK

Table 2—Available GLP-1 analogs

Drug	Dosing	Use in renal impairment	Cardiovascular outcome trials
Exenatide	10 μg b.i.d.	- CrCl 30–50 mL/min (caution when escalating dose) - CrCl <30 mL/min (avoid)	None
Exenatide QR	2 mg weekly	- CrCl 30–50 mL/min (caution) - CrCl 30 mL/min (avoid)	EXSCEL, *n* = 14,000: - June 2010–April 2018 - Inclusion criteria: HbA_{1c} ≥6.5 and ≤10.0%, age ≥18 years, and one of the following: *1*) Treatment with 0–3 oral antihyperglycemic agents and *2*) insulin therapy either alone or in combination with up to two oral agents - Primary outcome: time to first confirmed CV event in the primary composite of CV death, nonfatal MI, or nonfatal stroke
Liraglutide	1.2 mg OD 1.8 mg OD	- Mild–severe impairment - No dose adjustments (use with caution)	LEADER, *n* = 9,340: - August 2010–November 2015 - Inclusion criteria: ≥50 years old and concomitant CV, cerebrovascular, or peripheral vascular disease or chronic renal failure or chronic heart failure; ≥60 years old and other specified risk factors of vascular disease - HbA_{1c} ≥7%, age ≥50 years - Primary outcome: time from randomization to first occurrence of composite of CV death, nonfatal MI, or nonfatal stroke
Lixisenatide	10 μg OD 20 μg OD	- eGFR 30–50 mL/min · 1.73 m^2 (caution) - eGFR <30 mL/min · 1.73 m^2 (avoid)	ELIXA, *n* = 6,000: - June 2010–February 2015 - Median follow-up 2 years - Inclusion criteria: patients with spontaneous ACS admitted to acute care facility within 180 days after ACS and prior to screening - HbA_{1c} 5.5–11%, age ≥30 years - Primary outcome: composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA
Dulaglutide	0.75 mg weekly 1.5 mg weekly	- No dose adjustments - Caution during initiation and dose escalation	REWIND, *n* = 9,622: - July 2011–April 2019 - Inclusion criteria: ≥50 years old with established clinical vascular disease, ≥55 years and subclinical vascular disease, or ≥60 years and at least ≥2 CV risk factors - HbA_{1c} ≤9.5%, age ≥50 years - Primary outcome: time to first occurrence of CV death, nonfatal MI, or nonfatal stroke (composite CV outcome)
Albiglutide	30 mg weekly 50 mg weekly	- No dose adjustments - Caution during initiation and dose escalation	None

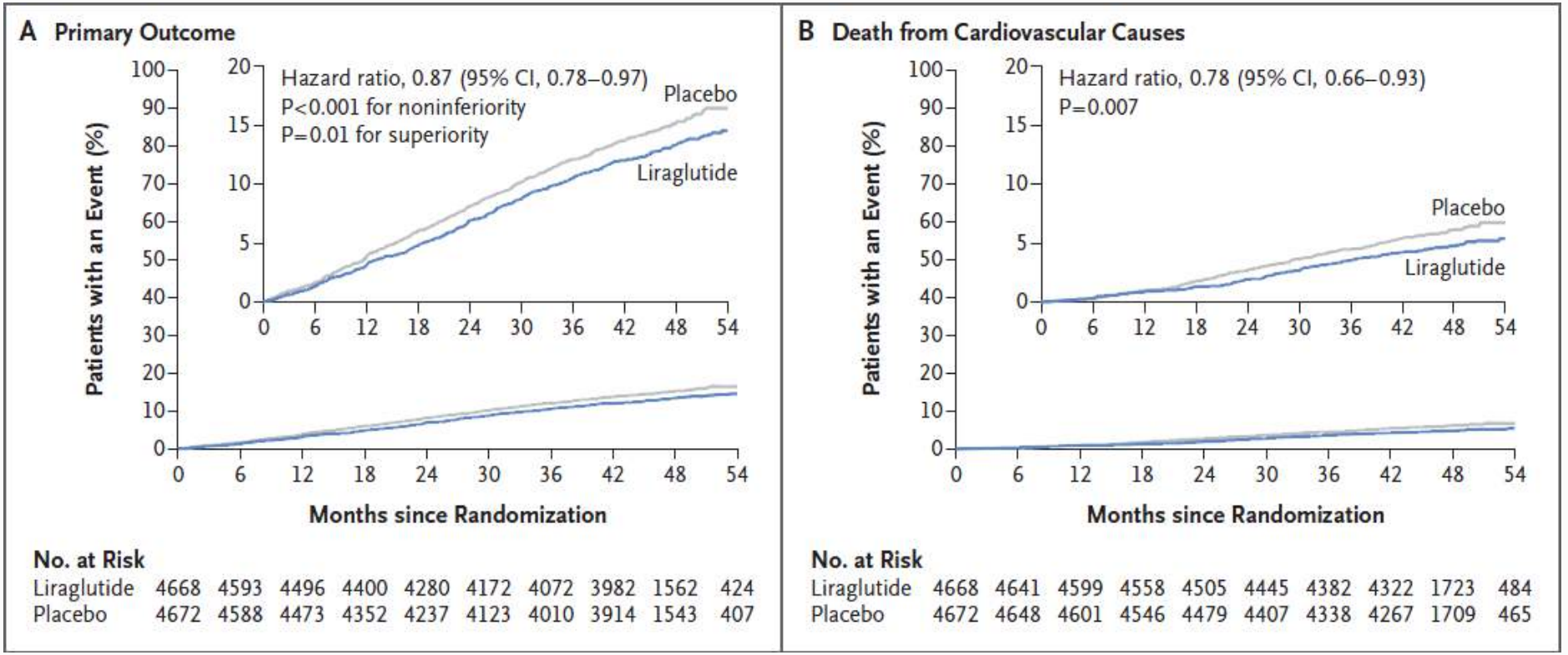
❖ Wilding JPH, Rajeev SP, DeFronzo RA. Diabetes Care 2016;39 Suppl 2:S154-64.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*



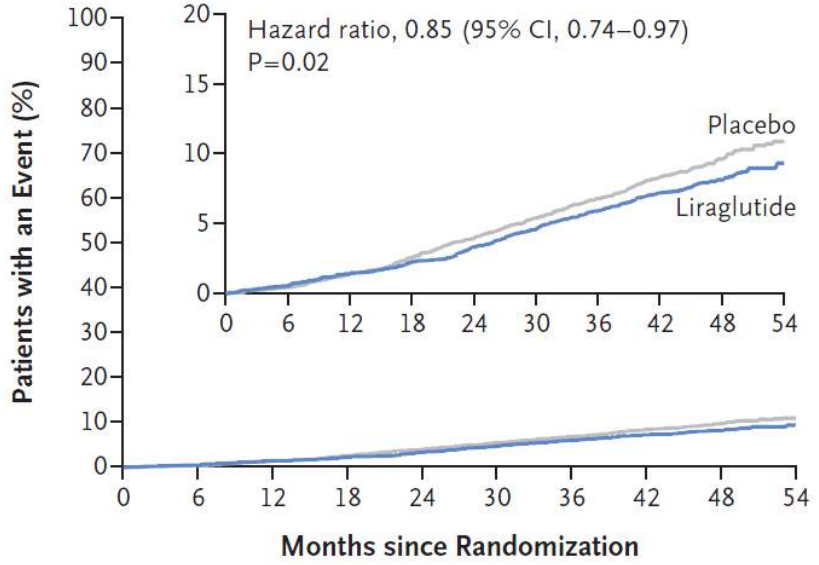
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

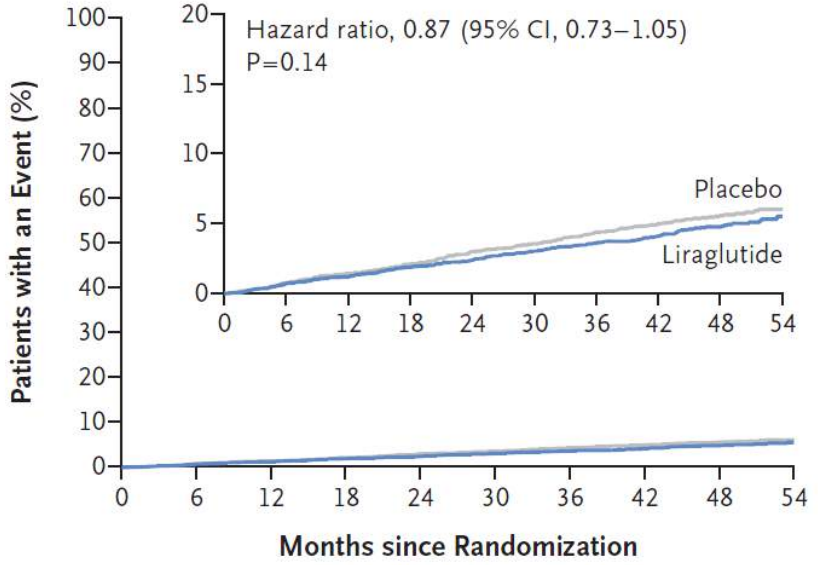
E **Death from Any Cause**



No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

F **Hospitalization for Heart Failure**



No. at Risk

Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Perspectives on cardiovascular effects of incretin-based drugs: From bedside to bench, return trip

Michaela Luconi [a,*], Giulia Cantini [a], Antonio Ceriello [b,c], Edoardo Mannucci [a,d,**]

[a] Department of Experimental and Clinical Biomedical Sciences, Endocrinology Unit, University of Florence, Florence, Italy
[b] Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS) and Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Barcelona, Spain
[c] IRCCS MultiMedica, Milan, Italy
[d] Diabetes Agency, Careggi Hospital, Florence, Italy

ARTICLE INFO

Article history:
Received 25 January 2017
Accepted 24 February 2017
Available online xxxx

Keywords:
Cardiovascular outcome trials
MACE
Heart failure
Glucagon-like peptide-1 receptor agonists
Dipeptidyl peptidase-4 inhibitors
Inflammatory chemokines

ABSTRACT

Recently, cardiovascular outcome trials with glucose-lowering drugs used in type 2 diabetes mellitus, namely glucagon-like peptide-1 receptor agonists (GLP-1RA), liraglutide and semaglutide, showed a reduction in cardiovascular events, which had not been observed in trials with other incretin-based drugs, such as lixisenatide or with dipeptidyl peptidase-4 inhibitors (DPP4i). Mechanisms underlying the observed cardiovascular differences between DPP4i and GLP1-RA, and across individual GLP1-RA are poorly understood. This review is aimed at collecting and summarizing available evidence from experimental and mechanistic studies on the action of GLP1-RA and DPP4i on the cardiovascular system, both deriving from clinical and pre-clinical sources. The results of cardiovascular outcome trials are interpreted on the basis of the experimental preclinical data available, paying particular attention to the heart failure results, and suggesting some novel intriguing hypotheses to explain some of the unexpected findings of cardioprotection of incretin-based drugs. In particular, we discuss the possible contribution to the incretin cardiovascular effects of a direct cardiac action of GLP-1 metabolites through GLP-1 receptor-independent pathways, and of DPP4 substrates other than GLP-1.

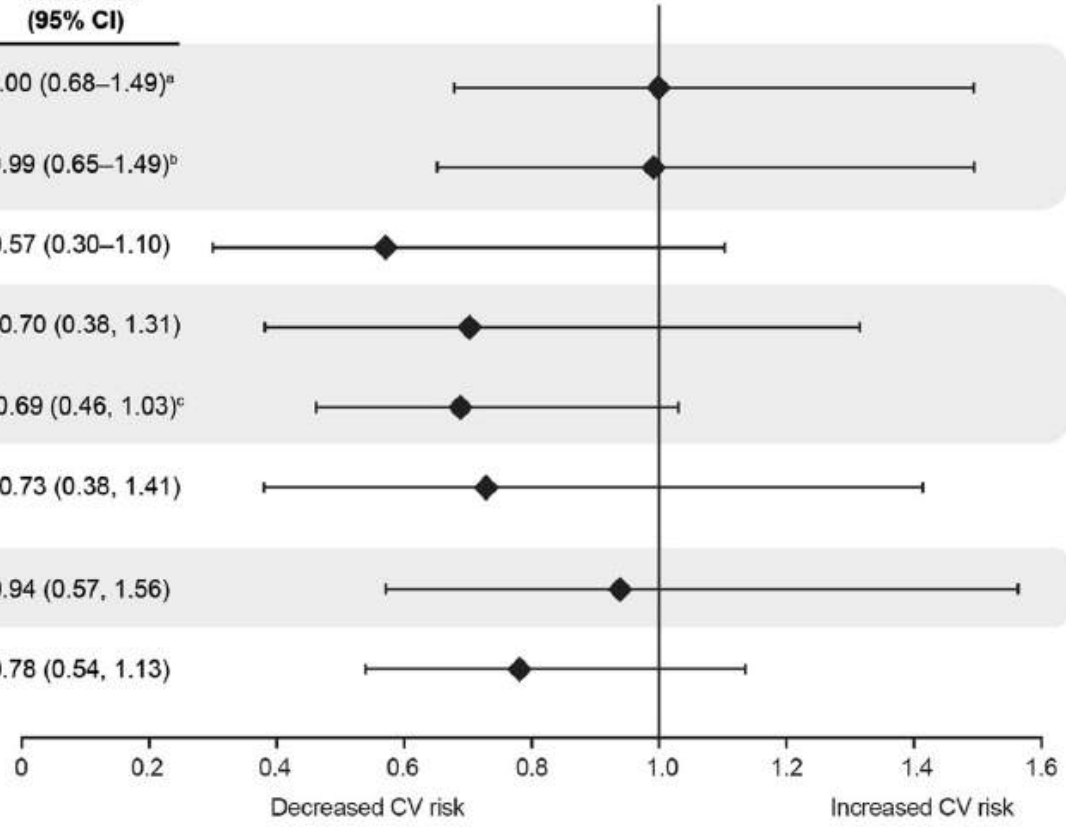
Adv Ther (2017) 34:1–40
DOI 10.1007/s12325-016-0432-4

REVIEW

Cardiovascular Safety of Incretin-Based Therapies in Type 2 Diabetes: Systematic Review of Integrated Analyses and Randomized Controlled Trials

Edoardo Mannucci · Matteo Monami

Drug [Reference]	Type of analysis	Primary statistical analysis	Number of patients	Risk ratio (95% CI)
Albiglutide [53]	Pooled analysis	Cox proportional hazards	5107	1.00 (0.68–1.49)[a] 0.99 (0.65–1.49)[b]
Dulaglutide [54]	Pooled analysis	Cox proportional hazards	6010	0.57 (0.30–1.10)
Exenatide twice daily [51]	Pooled analysis	Mantel–Haenszel RR	3945	0.70 (0.38, 1.31) 0.69 (0.46, 1.03)[c]
Liraglutide [50]	Pooled analysis	Incidence ratios estimated by Cochran–Mantel–Haenszel	6638	0.73 (0.38, 1.41)
Taspoglutide [52]	Pooled analysis	Peto fixed-effects OR	7056	0.94 (0.57, 1.56)
GLP-1 receptor agonists [12]	Meta-analysis	Mantel–Haenszel OR	12475	0.78 (0.54, 1.13)



Lorenz et al. Cardiovasc Diabetol (2017) 16:6
DOI 10.1186/s12933-016-0490-6

REVIEW Open Access

Differential effects of glucagon-like peptide-1 receptor agonists on heart rate

- Uzun etkili GLP-1 analoglarında daha belirgin ve daha uzun süreli olarak kalp hızında artış görülmektedir.
- Fizyolojik mekanizma tam olarak bilinmemekle birlikte, sino-atrial düğümdeki GLP-1 reseptörlerinin aktivasyonu ve/veya sempatik sinir sisteminin uyarılması ile ile ilişkili olduğu düşünülmektedir.
- Kan basıncı düşüşüne refleks bir yanıt olabilir.
- Kardiyovasküler risk artışına neden olmaz.

PANKREAS

Gastroenterology. 2011 July ; 141(1): 150–156. doi:10.1053/j.gastro.2011.02.018.

Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies

MICHAEL ELASHOFF, ALEKSEY V. MATVEYENKO, BELINDA GIER, ROBERT ELASHOFF, and **PETER C. BUTLER**
Larry L. Hillblom Islet Research Center at David Geffen School of Medicine and Department of Biomathematics, University of California, Los Angeles, California

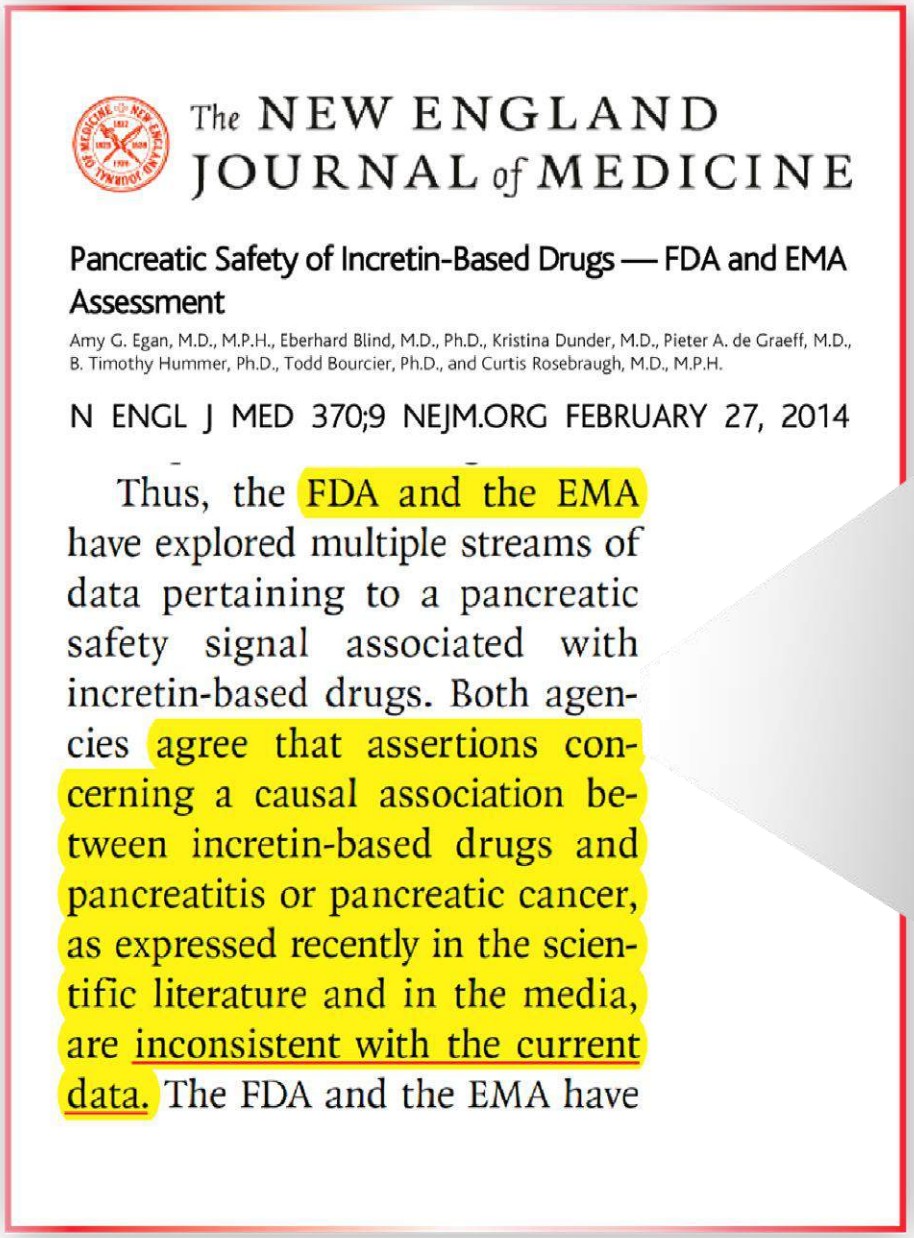
Abstract

BACKGROUND & AIMS—Glucagon-like peptide-1–based therapy is gaining widespread use for type 2 diabetes, although there are concerns about risks for pancreatitis and pancreatic and thyroid cancers. There are also concerns that dipeptidyl peptidase-4 inhibitors could cause cancer, given their effects on immune function.

METHODS—We examined the US Food and Drug Administration's database of reported adverse events for those associated with the dipeptidyl peptidase–4 inhibitor sitagliptin and the glucagon-like peptide-1 mimetic exenatide, from 2004–2009; data on adverse events associated with 4 other medications were compared as controls. The primary outcomes measures were rates of reported pancreatitis, pancreatic and thyroid cancer, and all cancers associated with sitagliptin or exenatide, compared with other therapies.

RESULTS—Use of sitagliptin or exenatide increased the odds ratio for reported pancreatitis 6-fold as compared with other therapies ($P < 2 \times 10^{-16}$). Pancreatic cancer was more commonly reported among patients who took sitagliptin or exenatide as compared with other therapies ($P < .008$, $P < 9 \times 10^{-5}$). All other cancers occurred similarly among patients who took sitagliptin compared with other therapies ($P = .20$).

CONCLUSIONS—These data are consistent with case reports and animal studies indicating an increased risk for pancreatitis with glucagon-like peptide-1–based therapy. The findings also raise caution about the potential long-term actions of these drugs to promote pancreatic cancer.



The NEW ENGLAND JOURNAL of MEDICINE

Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

Amy G. Egan, M.D., M.P.H., Eberhard Blind, M.D., Ph.D., Kristina Dunder, M.D., Pieter A. de Graeff, M.D., B. Timothy Hummer, Ph.D., Todd Bourcier, Ph.D., and Curtis Rosebraugh, M.D., M.P.H.

N ENGL J MED 370;9 NEJM.ORG FEBRUARY 27, 2014

Thus, the FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have

NEJM (Şubat 2014)
FDA ve EMA değerlendirmesine göre; inkretin-bazlı tedaviler ile pankreatit veya pankreatik kanser arasında nedensel bir ilişki olduğuna dair iddiaların tutarlı olmadığı belirtilmektedir.

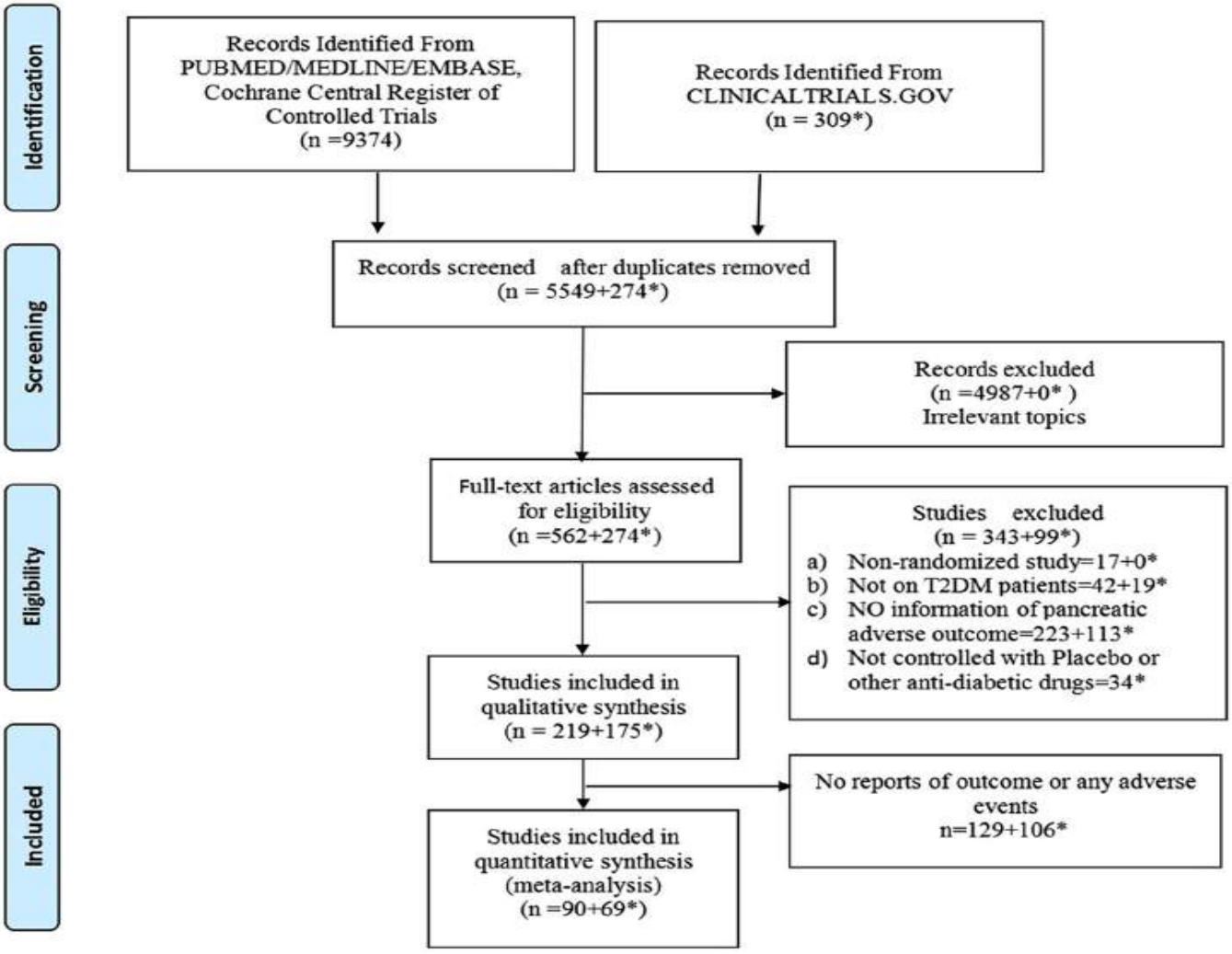
❖ Egan AG et al. New Engl J Med 2014 370:794-797.

Diabetes Ther (2016) 7:725–742
DOI 10.1007/s13300-016-0198-3

ORIGINAL RESEARCH

Incretin-Based Therapy and Risk of Pancreatic Cancer in Patients with Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Controlled Trials

Han Chen · Xiaoying Zhou · Tao Chen · Bingtuan Liu · Wujuan Jin · Huiyuan Gu · Tianyuan Hong · Guoxin Zhang



Diabetes Ther (2016) 7:725–742
DOI 10.1007/s13300-016-0198-3

ORIGINAL RESEARCH

Incretin-Based Therapy and Risk of Pancreatic Cancer in Patients with Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Controlled Trials

Han Chen · Xiaoying Zhou · Tao Chen · Bingtuan Liu · Wujuan Jin · Huiyuan Gu · Tianyuan Hong · Guoxin Zhang

Conclusion: This meta-analysis shows that incretin-based therapies are not associated with increase in the risk of pancreatic cancer. Interestingly, subgroup analyses suggested lower risk of pancreatic cancer in incretin groups than placebo in long-term studies (>104 weeks). Considering the inconsistent results among randomized trials and previous epidemiological investigations, more such studies should be conducted to clarify the existence or non-existence of this association.

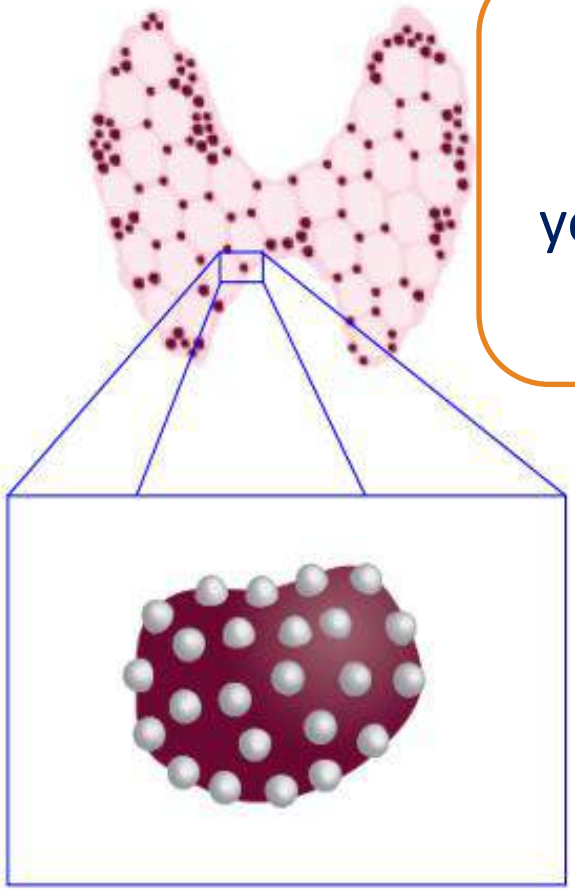
TİROİD

Endocrinology 151: 1473–1486, 2010

Glucagon-Like Peptide-1 Receptor Agonists Activate Rodent Thyroid C-Cells Causing Calcitonin Release and C-Cell Proliferation

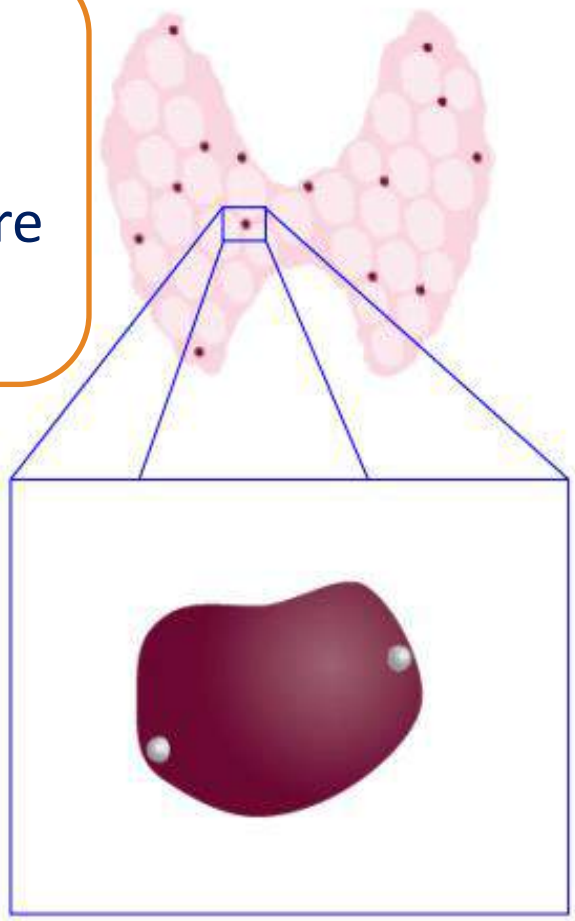
Lotte Bjerre Knudsen,* Lars Wichmann Madsen,* Søren Andersen, Kasper Almholt, Anne S. de Boer, Daniel J. Drucker, Carsten Gotfredsen, Frederikke Lihme Egerod, Anne Charlotte Hegelund, Helene Jacobsen, Sóren Dyring Jacobsen, Alan C. Moses, Anne-Marie Mølck, Henriette S. Nielsen, Jette Nowak, Helene Solberg, Tu D. L. Thi, and Milan Zdravkovic

Kemirgenler



Kemirgenlerin tiroidindeki C hücre yoğunluğu insanlara göre 45 kat daha fazladır

İnsanlar



The NEW ENGLAND JOURNAL of MEDICINE

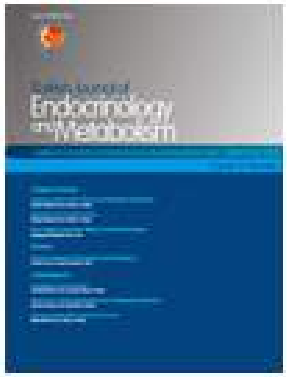
ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Adverse event leading to permanent discontinuation of trial regimen	Liraglutide (N=4668)	Placebo (N=4672)	
Any adverse event	444 (9.5)	339 (7.3)	<0.001
Serious adverse event	192 (4.1)	245 (5.2)	0.01
Severe adverse event	164 (3.5)	188 (4.0)	0.20
Nausea	77 (1.6)	18 (0.4)	<0.001
Vomiting	31 (0.7)	2 (<0.1)	<0.001
Diarrhea	27 (0.6)	5 (0.1)	<0.001
Increased lipase level‡	15 (0.3)	11 (0.2)	0.43
Abdominal pain	11 (0.2)	3 (0.1)	0.03
Decreased appetite	11 (0.2)	2 (<0.1)	0.01
Abdominal discomfort	10 (0.2)	0	0.002
Pancreatitis or neoplasm§			
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Medullary thyroid carcinoma	0	1 (<0.1)	0.32

BÖBREK



Exenatide-Induced Acute Renal Failure: A Case Report

Eksenatide İlişkili Akut Böbrek Yetmezliği: Olgu Sunumu

Mustafa Ünübol, Fatih Gencer*, Hakan Akdam**, Yavuz Yeniçerioğlu**, Harun Akar**, Engin Güney

Adnan Menderes University Medical Faculty, Division of Endocrinology and Metabolism, Aydın, Turkey
*Adnan Menderes University Medical Faculty, Department of Internal Medicine, Aydın, Turkey
**Adnan Menderes University Medical Faculty, Division of Nephrology, Aydın, Turkey

Abstract

Exenatide is a glucagon-like peptide-1 receptor agonist that is commonly used in the treatment of type II diabetes mellitus for its effects on the incretin system. The use of exenatide is also related to weight loss and it has reportedly been known to induce acute renal failure (ARF) according to clinical reports. We observed ARF and severe weight loss two months after beginning the treatment with exenatide in a 59-year-old female patient with type II diabetes mellitus. We present this case in which ARF was considered to be a rare adverse effect of exenatide use. In conclusion, renal functions should be closely monitored, especially in patients prescribed nephrotoxic agents and for those with a high risk of nephropathy and dehydration due to their treatment with exenatide. The usage of this drug should also be carefully planned in these patients. *Turk Jem 2013; 17: 68-70*

Key words: Exenatide, acute renal failure, obesity, diabetes

Özet

Eksenatide, inkretin sistem üzerine etkileriyle Tip 2 DM tedavisinde sık kullanılan bir ajan olup glucagon benzeri peptid-1 (GLP-1) reseptörü agonistidir. Eksenatide kullanımı kilo kaybı ile ilişkilidir ve akut böbrek yetmezliğine (ABY) neden olduğu klinik raporlar şeklinde bildirilmiştir. Elli dokuz yaşında Tip 2 DM tanılı bayan hastada eksenatide tedavisinden 2 ay sonra ciddi kilo kaybı ve ABY gözlemledik. Biz, eksenatide kullanımı sonrası gelişen nadir bir advers olay olarak ABY gelişmesi nedeniyle olguyu sunduk. Sonuç olarak, nefrotoksik ajan kullanan, nefropati riski yüksek olan ve dehidratasyon riski oluşturabileceği öngörülen hastalarda eksenatide'nin dikkatli kullanılması ve bu hastalarda böbrek fonksiyonlarının yakın takip edilmesi gerektiğini vurgulamak istemekteyiz. *Turk Jem 2013; 17: 68-70*

Anahtar kelimeler: Eksenatide, akut böbrek yetmezliği, obezite, diyabet

Safety and Efficacy of Incretin-Based Therapies in Patients With Type 2 Diabetes Mellitus and CKD: A Systematic Review and Meta-analysis

Patricia M. Howse, BSc,[1] Lyudmila N. Chibrikova, PhD,[2] Laurie K. Twells, PhD,[1,2] Brendan J. Barrett, MD, MSc, FRCPC,[1] and John-Michael Gamble, PhD[2]

Background: The pharmacokinetics and pharmacodynamics of antidiabetic therapies for patients with type 2 diabetes are often altered in the context of chronic kidney disease (CKD).

Study Design: Systematic review and meta-analysis.

Setting & Population: Patients with type 2 diabetes and CKD.

Selection Criteria for Studies: 2 reviewers independently screened studies identified through bibliographic databases (Cochrane Library, PubMed, Embase, International Pharmaceutical Abstracts), clinical trial registries, and references from pertinent articles and clinical practice guidelines. Eligible studies included randomized controlled trials evaluating incretin-based therapy in adults with type 2 diabetes and estimated glomerular filtration rates < 60 mL/min/1.73 m^2.

Interventions: Incretin-based therapies (dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists) compared to placebo or active antidiabetic therapies.

Outcomes: Changes in glycated hemoglobin (HbA_{1c}), hypoglycemia, mortality, change in fasting plasma glucose, cardiovascular events, and end-stage renal disease.

Results: Of 1,619 nonduplicate records screened, 13 studies were included. Compared to placebo, incretin-based therapies significantly reduced HbA_{1c} levels (n = 9; weighted mean difference, −0.64; 95% CI, −0.79 to −0.48; I^2 = 43%); however, compared with active comparators, they did not (n = 4; weighted mean difference, −0.07; 95% CI, −0.25 to 0.12; I^2 = 38%). Incretin-based therapies significantly increased the risk for hypoglycemia compared to placebo (n = 7; relative risk [RR], 1.38; 95% CI, 1.01-1.89; I^2 = 0%) but no effect was observed versus active comparators (n = 4; RR, 0.24; 95% CI, 0.03-1.94; I^2 = 52%). Limited evidence exists for all-cause mortality (placebo: n = 7 [RR, 1.21; 95% CI, 0.64-2.29; I^2 = 0%]; active comparators: n = 3 [RR, 0.70; 95% CI, 0.32-1.54; I^2 = 0%]).

Limitations: Variation among interventions, small number of studies, heterogeneity between studies, and high risk for attrition bias in 7 of the selected studies.

Conclusions: In patients with moderate or severe CKD, incretin-based therapies are effective in reducing HbA_{1c} levels. Hypoglycemic events are rare, and wide CIs for the association preclude any definitive conclusions. Likewise, wide CIs were observed for mortality, cardiovascular events, and end-stage renal disease.

Am J Kidney Dis. 68(5):733-742.


DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

review article

Diabetes, Obesity and Metabolism 18: 317–332, 2016.

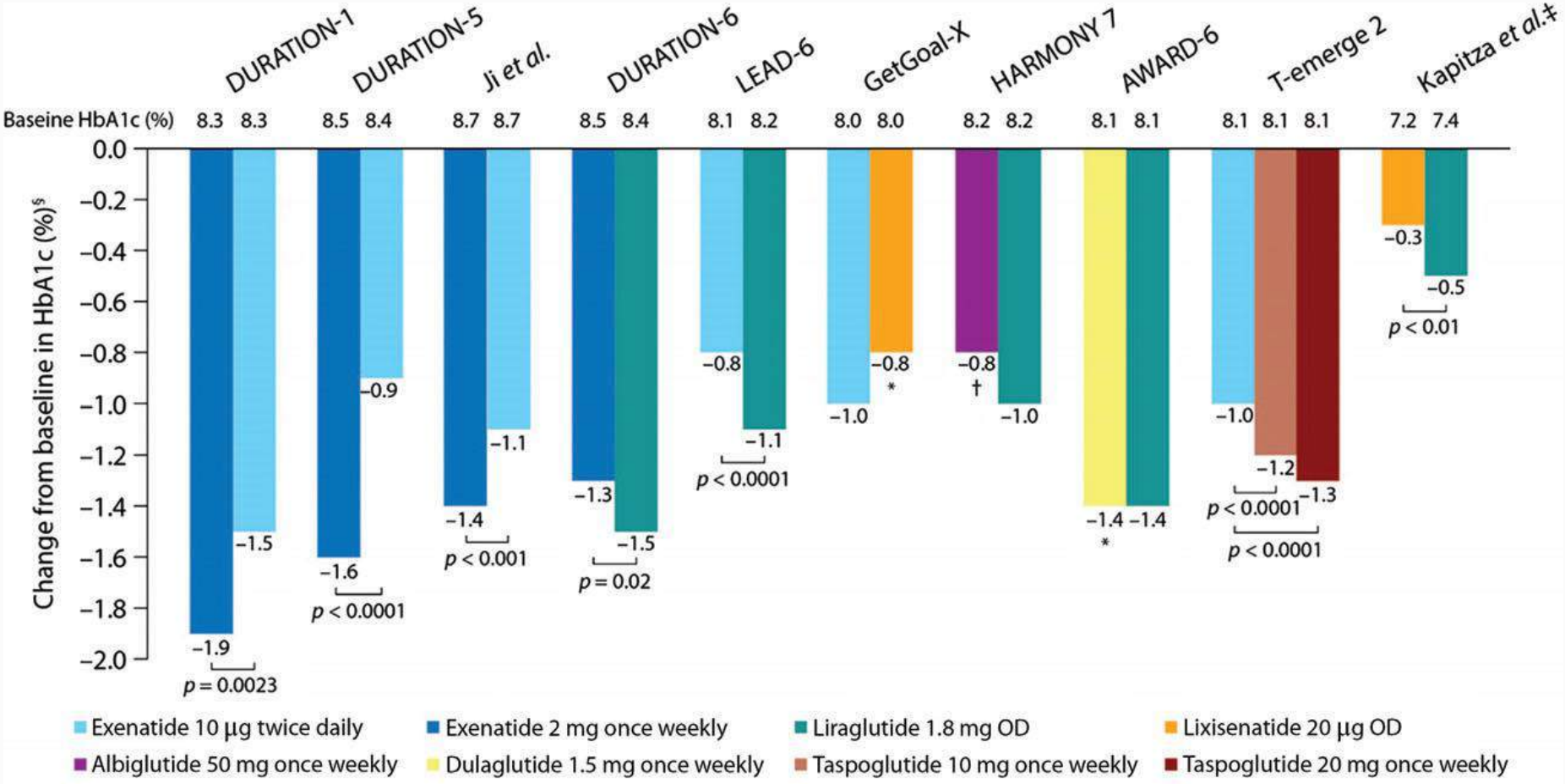
Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists

Sten Madsbad

Department of Endocrinology, Hvidovre Hospital, University of Copenhagen, Hvidovre, Denmark

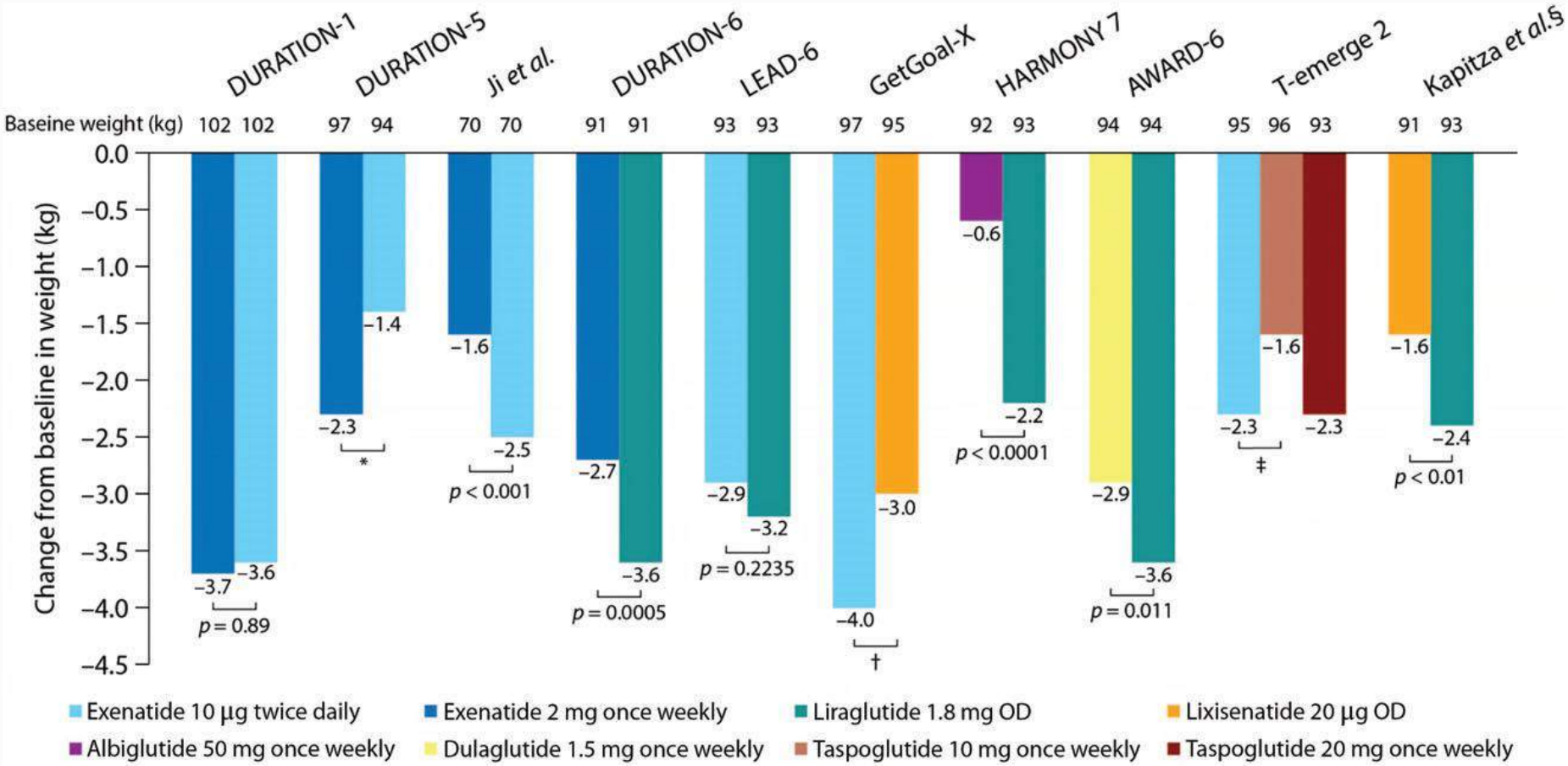
- GLP-1 analogları, etki sürelerinde farklılık yanı sıra GLP-1 reseptörüne de değişik derecelerde affinite gösterir.
- Bu da GLP-1 analoglarının A1C ve kilo üzerine etkileri ile birlikte tolerabilite profilleri ve immunojenik özelliklerindeki farklılıklarda rol oynar.

A1C



❖ Madsbad S. Diabetes, Obesity and Metabolism 2016;18:317–332.

KİLO



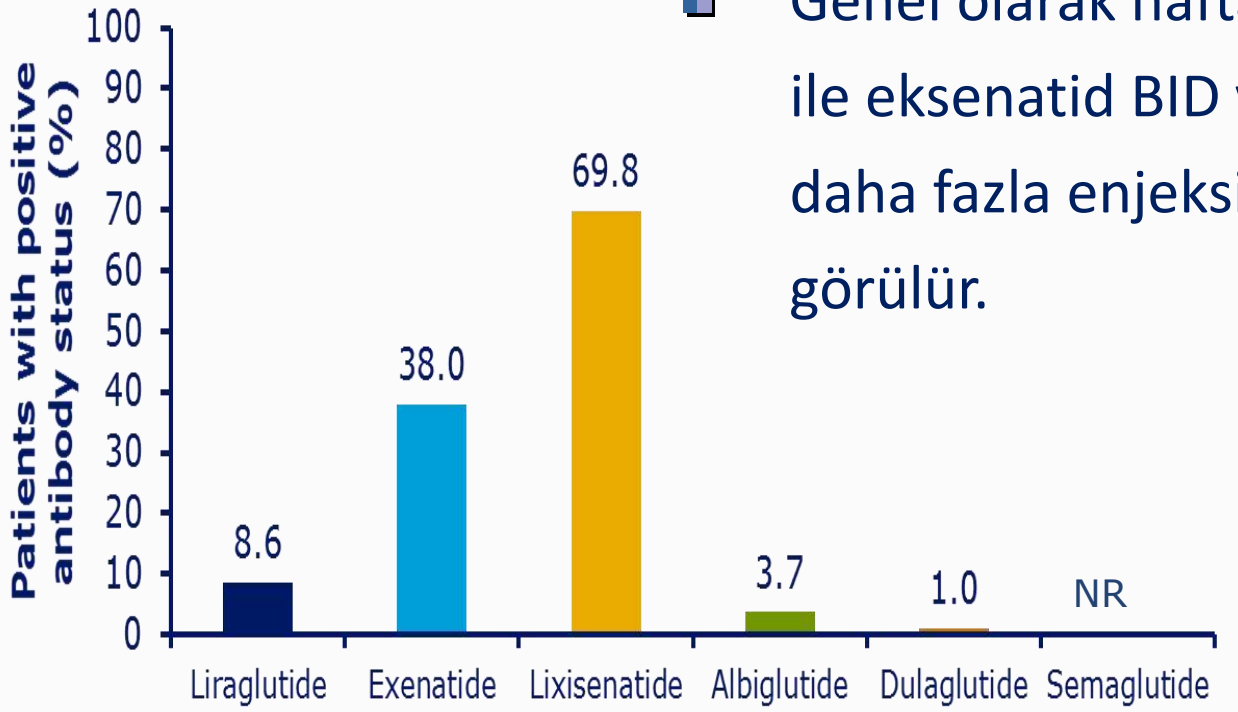
❖ Madsbad S. Diabetes, Obesity and Metabolism 2016;18:317–332.

KAN BASINCI

- GLP-1 analogları, sistolik kan basıncında istatistiksel olarak anlamlı azalma sağlamaktadır.
- Diastolik kan basıncında da hafif azalma görülür ama azalma istatistiksel olarak anlamlı düzeye ulaşmamaktadır.
- Karşılaştırmalı çalışmalarda farklı GLP-1 analoglarının kan basıncı üzerine etkileri arasında anlamlı fark bulunmamıştır.

İMMUNOJENİSİTE

- Antikorların etkinlik ve yan etkilerle çok az ilişkili olduğu saptanmıştır.
- Genel olarak haftalık formülasyonlar ile eksenatid BID ve liraglutide göre daha fazla enjeksiyon yeri reaksiyonu görülür.

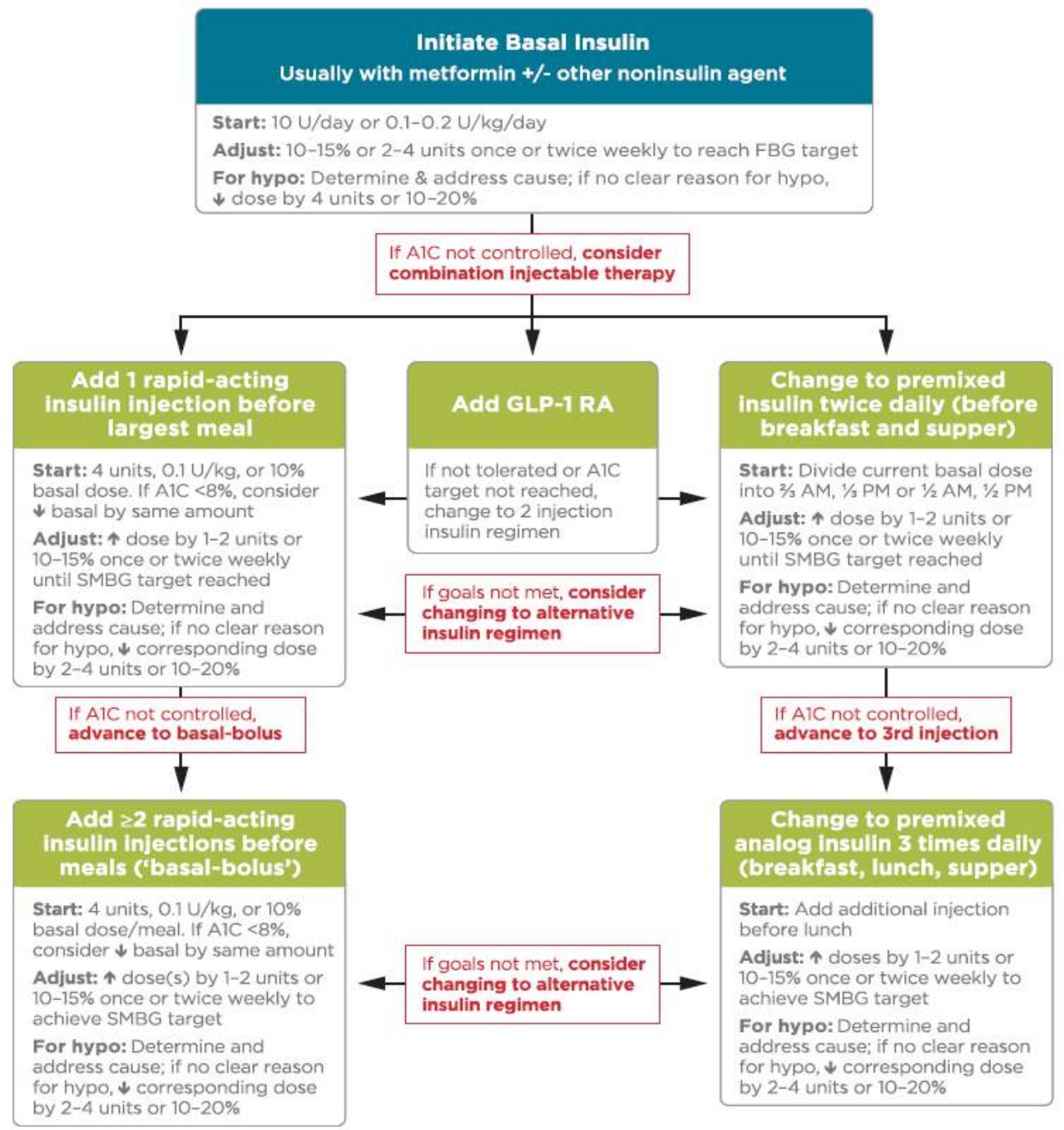


- Pratley RE et al. Lancet Diabetes Endocrinol 2014;2:289–297; Dungan KM et al. Lancet 2014;384:1349–1357.
- Madsbad S. Diabetes, Obesity and Metabolism 2016;18:317–332.

TOLERABİLİTE

- Albiglutid A1C düzeylerini diğer GLP-1 analoglarına göre daha az (<%1) düşürür.
- Karşılaştırıldığı diğer GLP-1 analoglarına göre daha az gastrointestinal yan etkiler gösterir.
- Her ilacın kendine özgü etkinlik ve tolerabilite profillerinin daha iyi anlaşılması, bireysel tedavi planlamasında hangi hastaya hangi GLP-1 analoğunun daha uygun olduğunu belirlemek için önemlidir.

❖ Rendell MS. Expert Opin Biol Ther 2016;16:1557-1569.

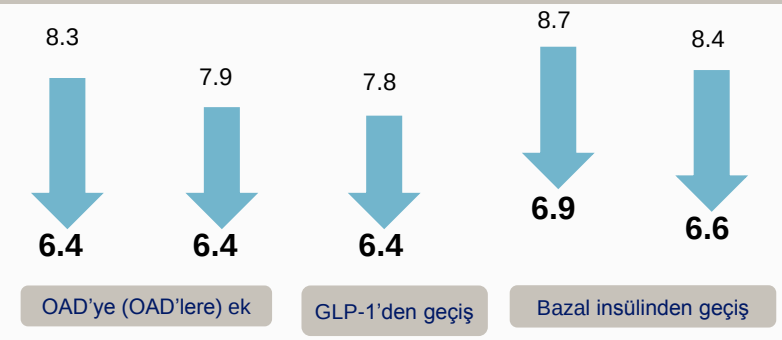


❖ American Diabetes Association. Standards of Medical Care in Diabetes-2017. Diabetes Care 2017;40(Suppl.1):S64–S74.

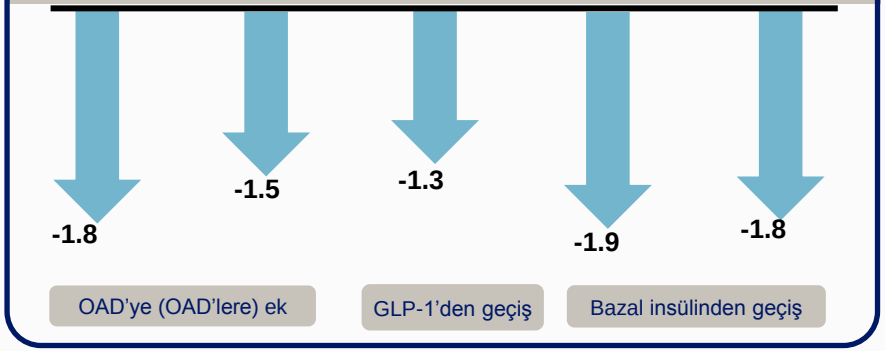
IDEGLIRA

Kritik klinik bulguların özeti

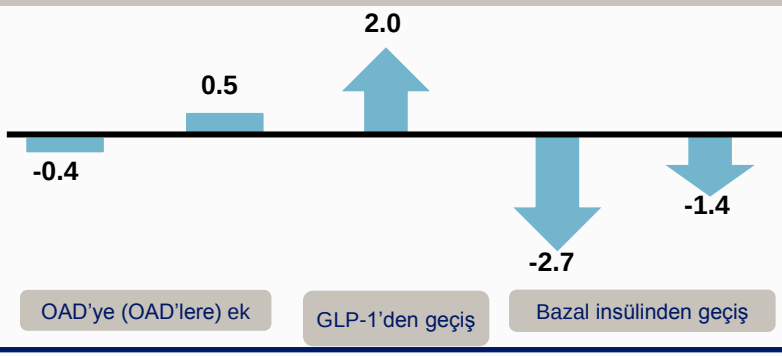
Çalışma sonu HbA_{1c} (%)



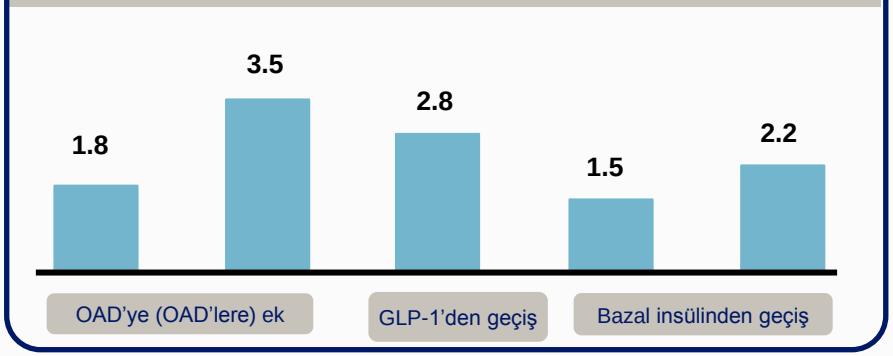
HbA_{1c}'deki değişim (%)



Vücut ağırlığındaki değişim (kg)



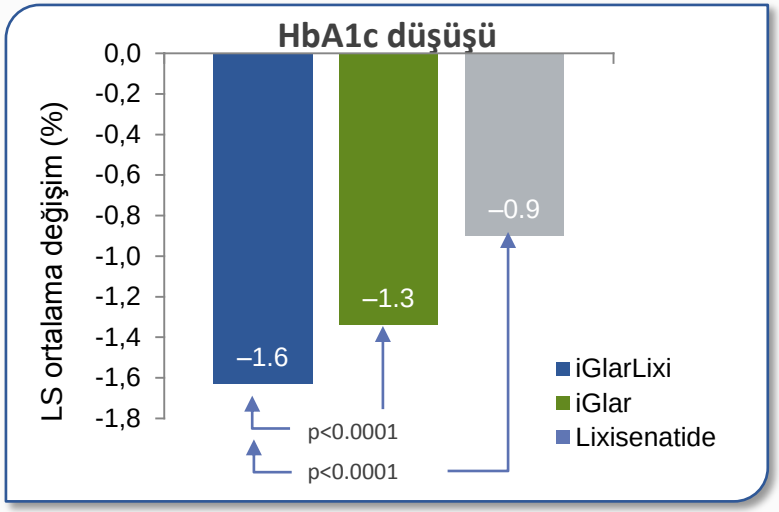
Hipoglisemi (olay/gönüllü-yıl)

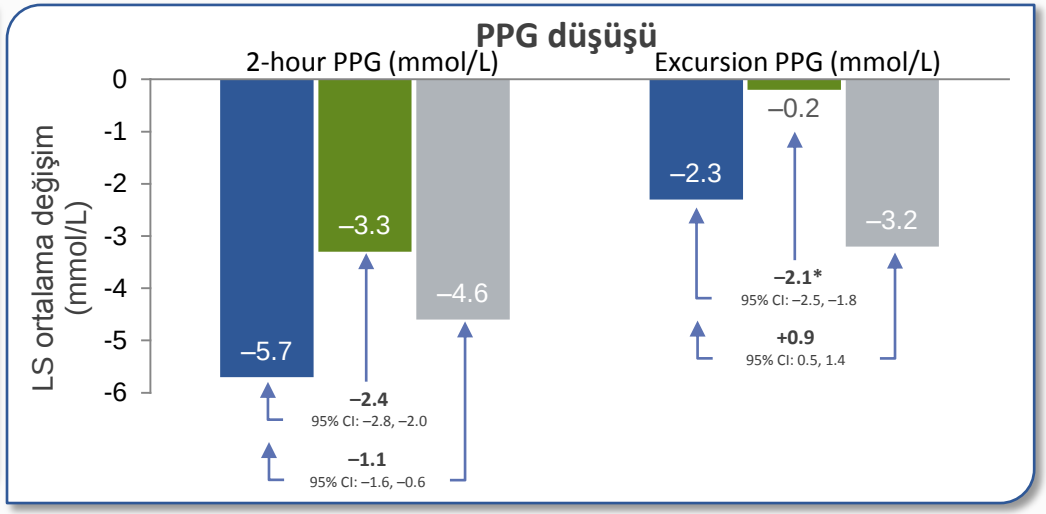


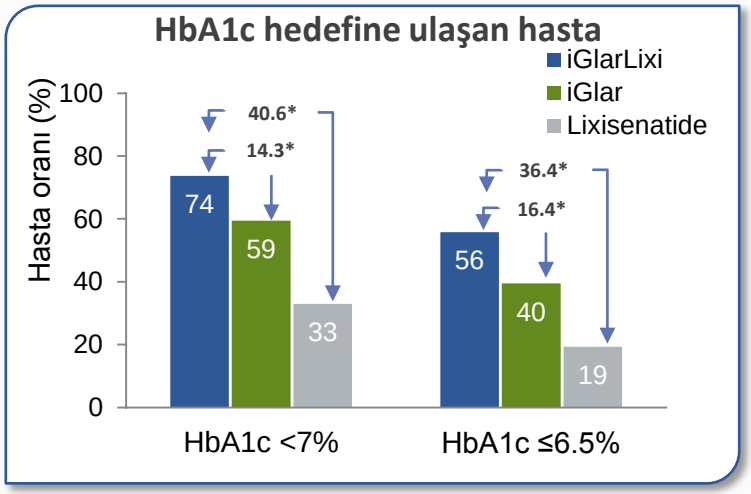
Buse et al. Diabetes Care 2014;37:2926–2933; Buse et al. Diabetes 2015; 64 (Suppl.1): A43-A44; abstract 166-OR; Linjawi et al. Diabetes 2015; 64 (Suppl.1): A255; abstract 1002-P; Rodbard et al. Diabetes 2015; 64 (Suppl.1): A255-A256; abstract 1003-P.

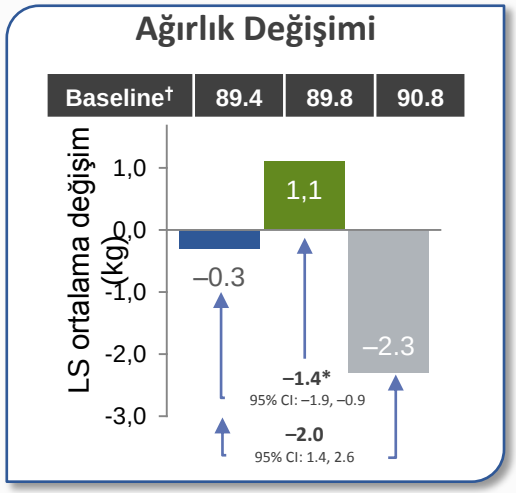
IGLARLIXI

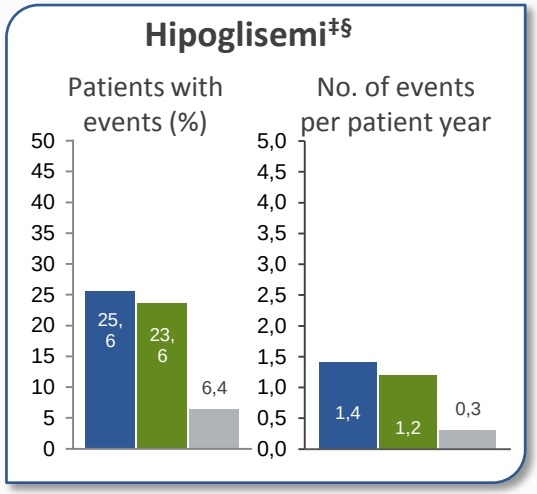
LixiLan-O: Temel Sonuçlar











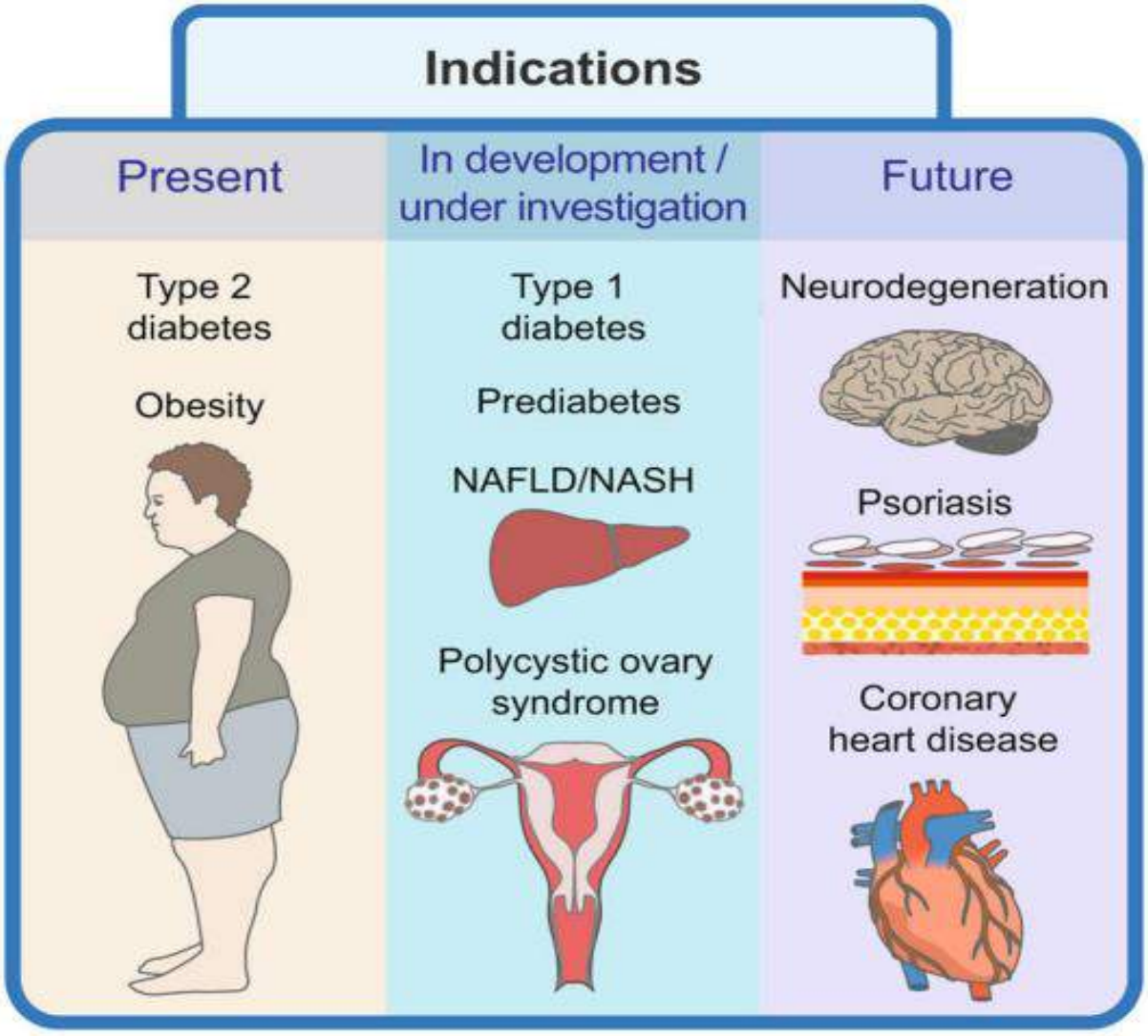
❖ Rosenstock J et al. Diabetes Care 2016;39:2026-2035.

Diabetologia (2015) 58:1745–1750
DOI 10.1007/s00125-015-3608-6

COMMENTARY

Incretin-based therapies: where will we be 50 years from now?

Juris J. Meier[1] · **Michael A. Nauck**[1]

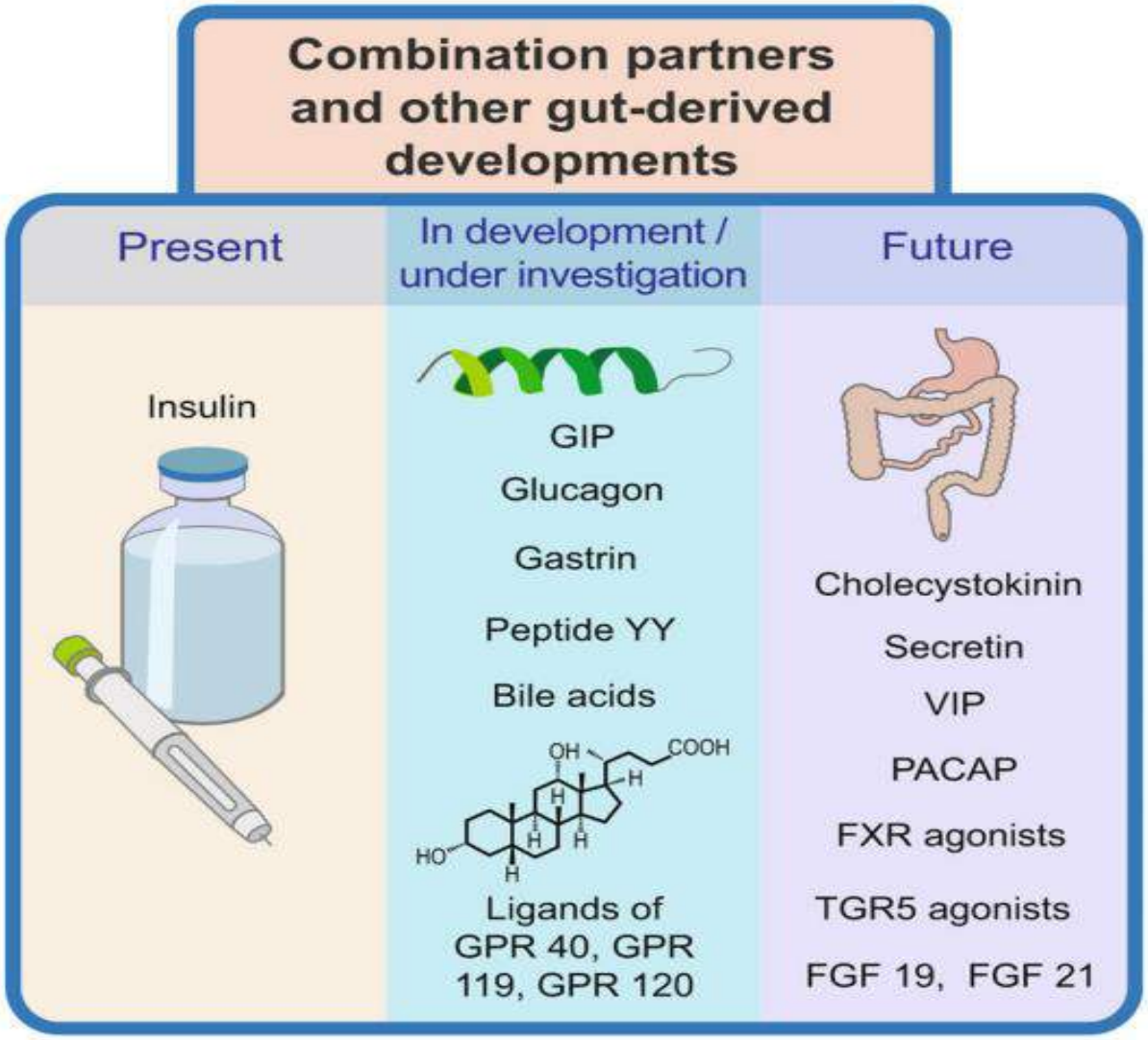


Diabetologia (2015) 58:1745–1750
DOI 10.1007/s00125-015-3608-6

COMMENTARY

Incretin-based therapies: where will we be 50 years from now?

Juris J. Meier[1] · **Michael A. Nauck**[1]

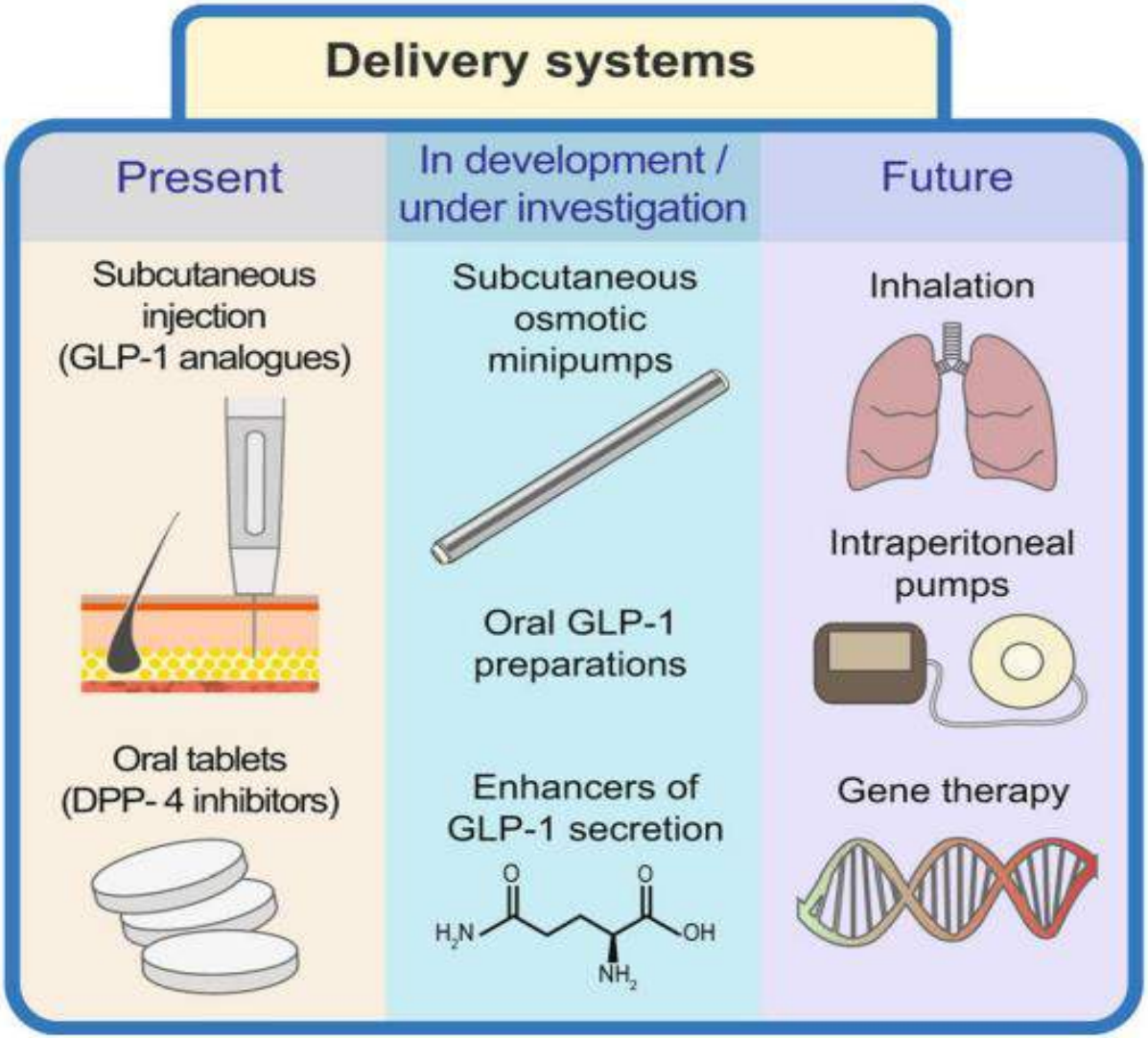


Diabetologia (2015) 58:1745–1750
DOI 10.1007/s00125-015-3608-6

COMMENTARY

Incretin-based therapies: where will we be 50 years from now?

Juris J. Meier[1] · **Michael A. Nauck**[1]



TEŞEKKÜRLER