Kısa ve Uzun Etkili İnkretin Tedavilerinin Güvenilirlikleri

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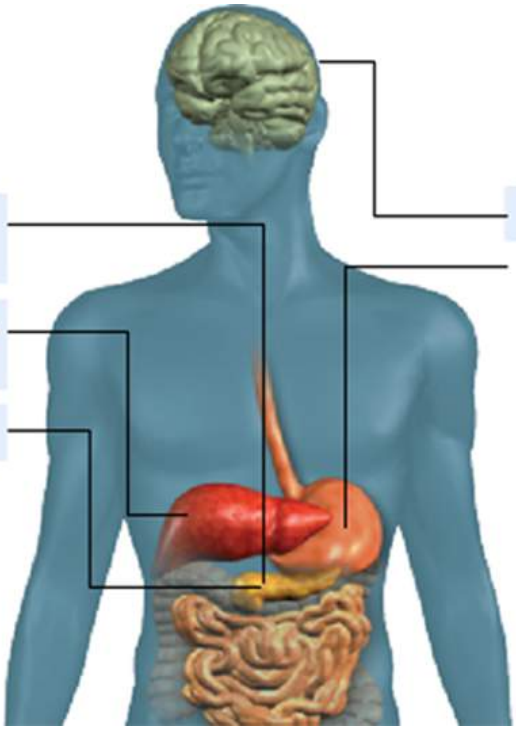
Endokrinoloji Bilim Dalı

GLP-1 analogları, metabolik etkiler

Pankreatik etkiler

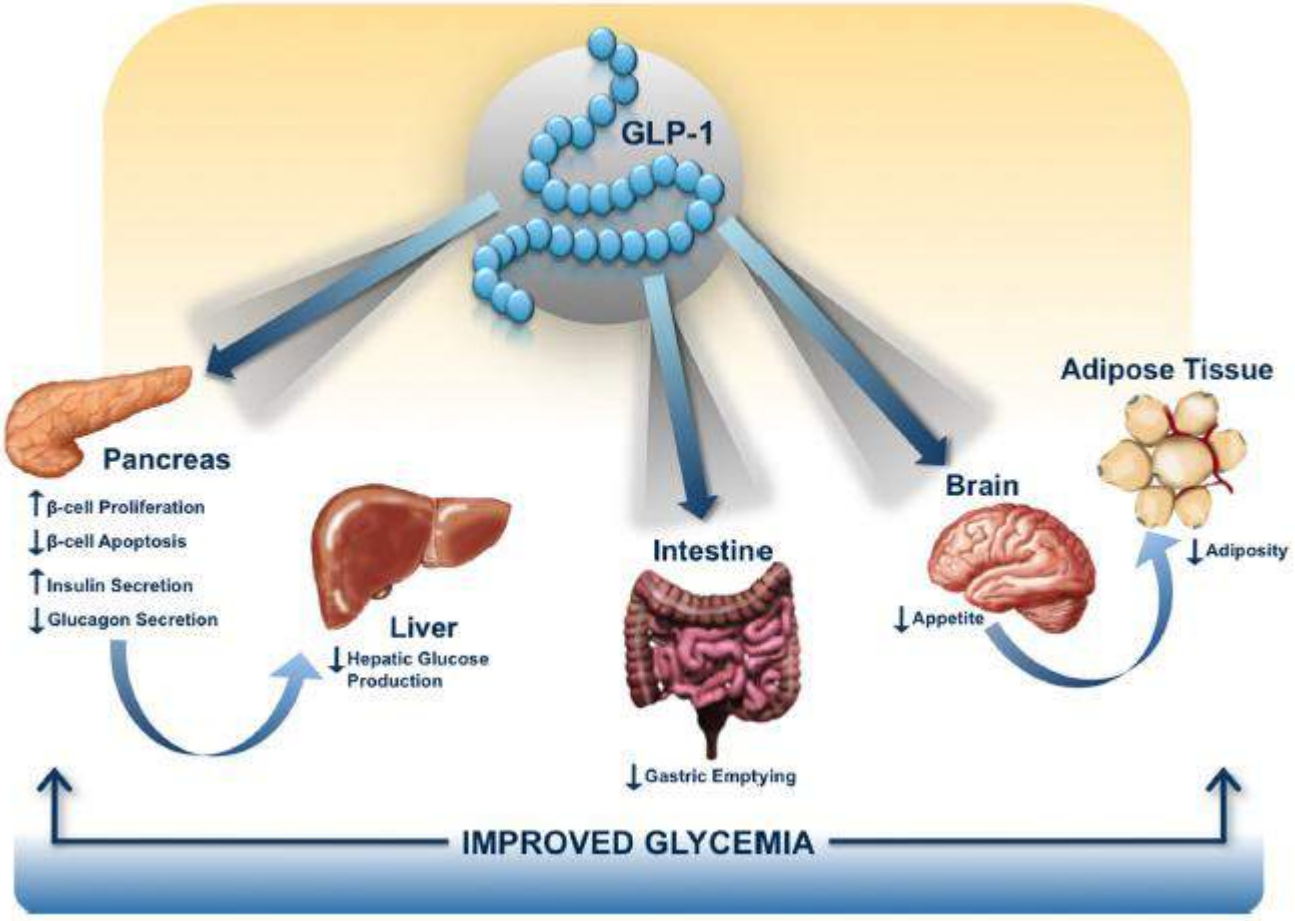
- İnsülin salgısını glikoza bağlı şekilde artırır.
- Glukagon salgısını baskılayarak hepatik glikoz üretimini azaltır.
- Birinci faz insülin yanıtını korur.



Pankreas dışı etkiler

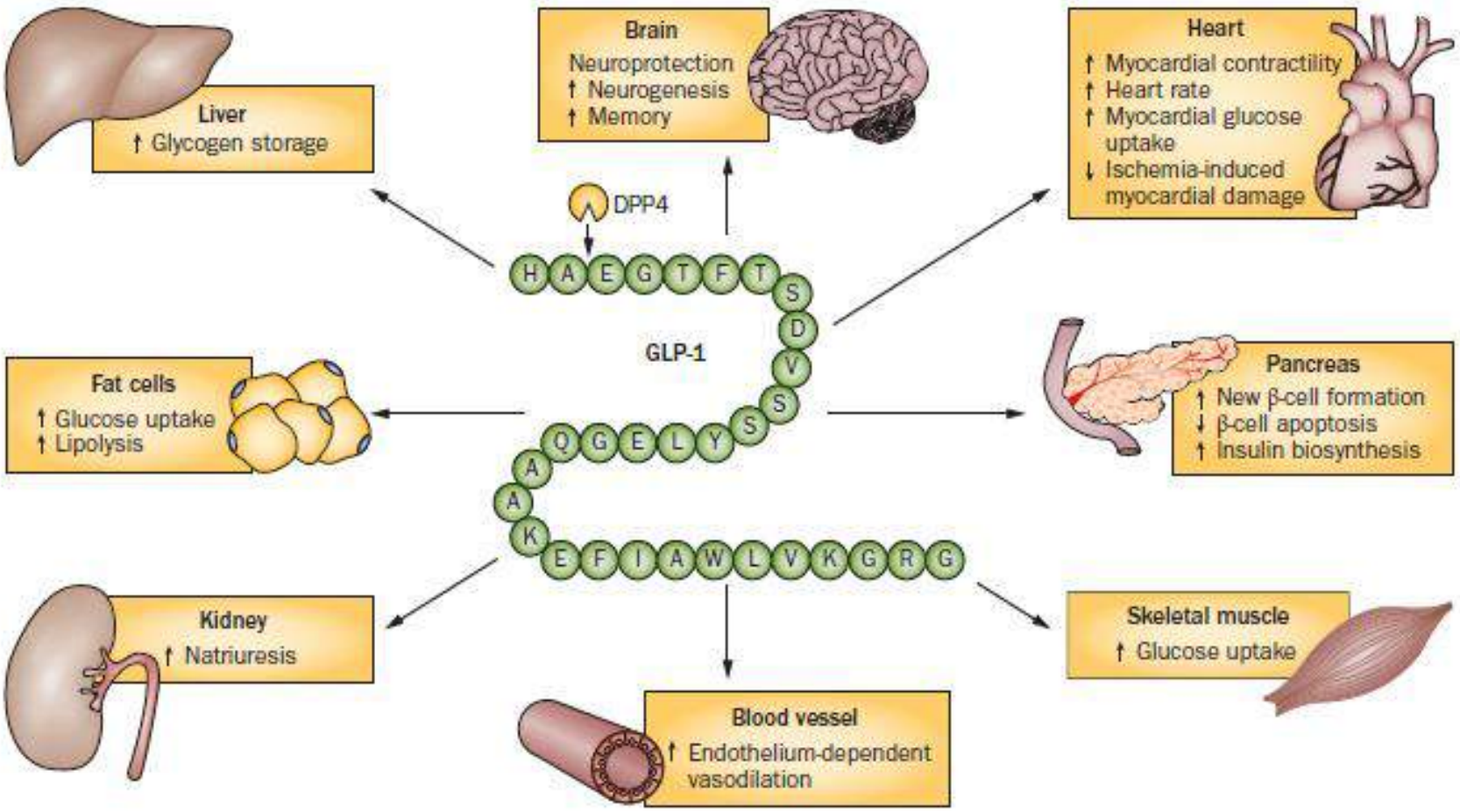
- Gastrik boşalmayı geciktirir.
- Doygunluk hissini artırır ve yiyecek alımını azaltır.

GLP-1 analogları: Etki mekanizması



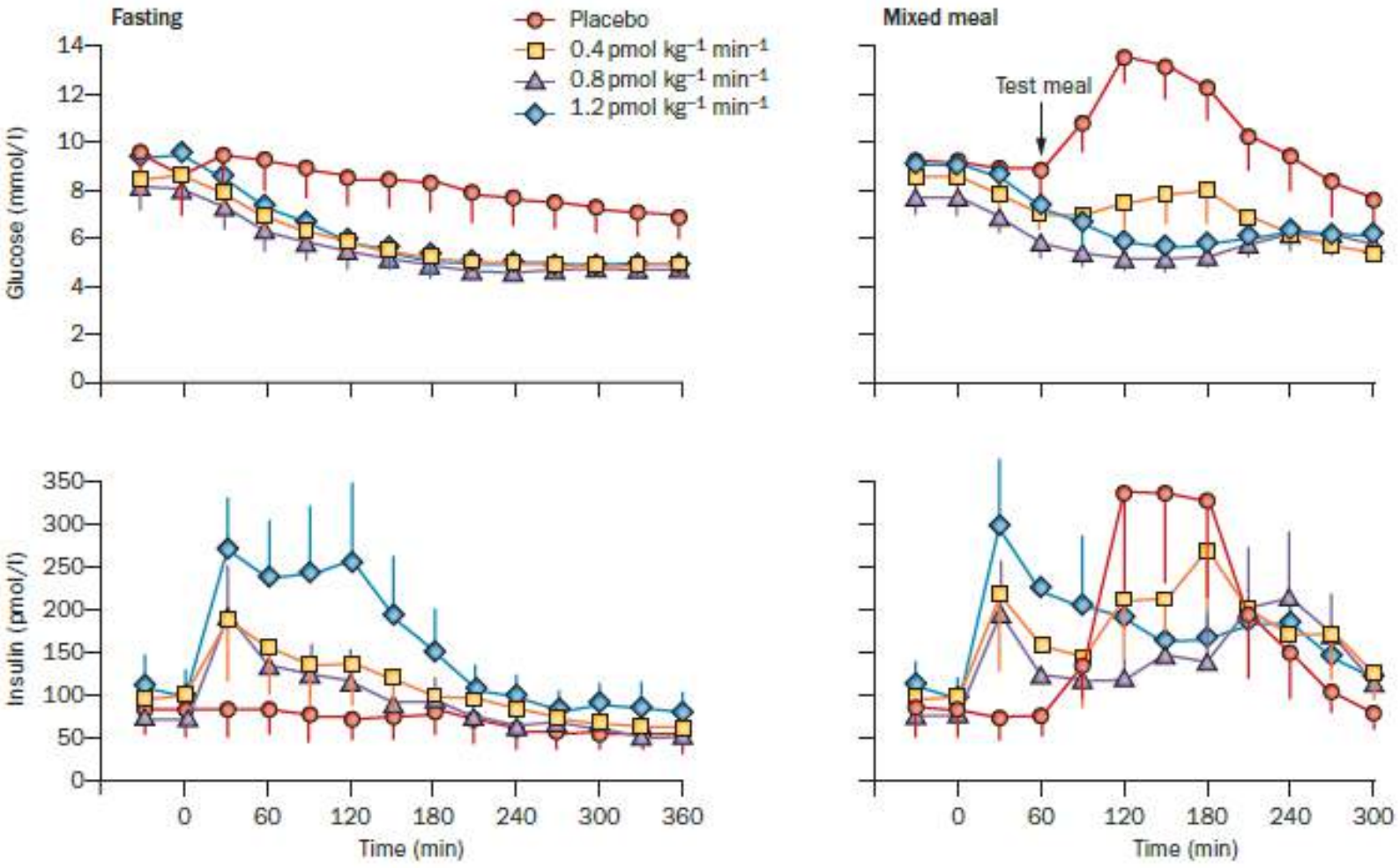
Endocrine Reviews, April 2012, 33(2):187–215

GLP-1: Sistemler üzerindeki etkileri



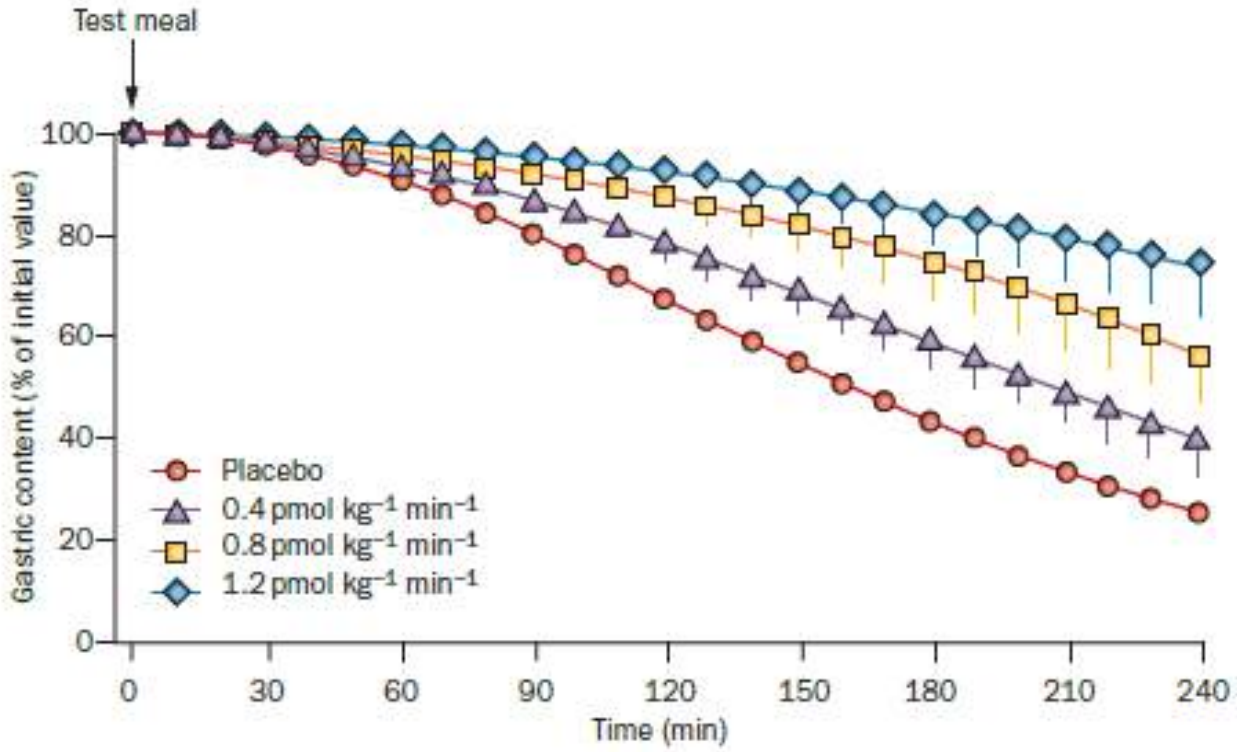
Meier, J. J. *Nat. Rev. Endocrinol.* **8**, 728–742 (2012)

GLP-1 infüzyonu: Metabolik etkiler



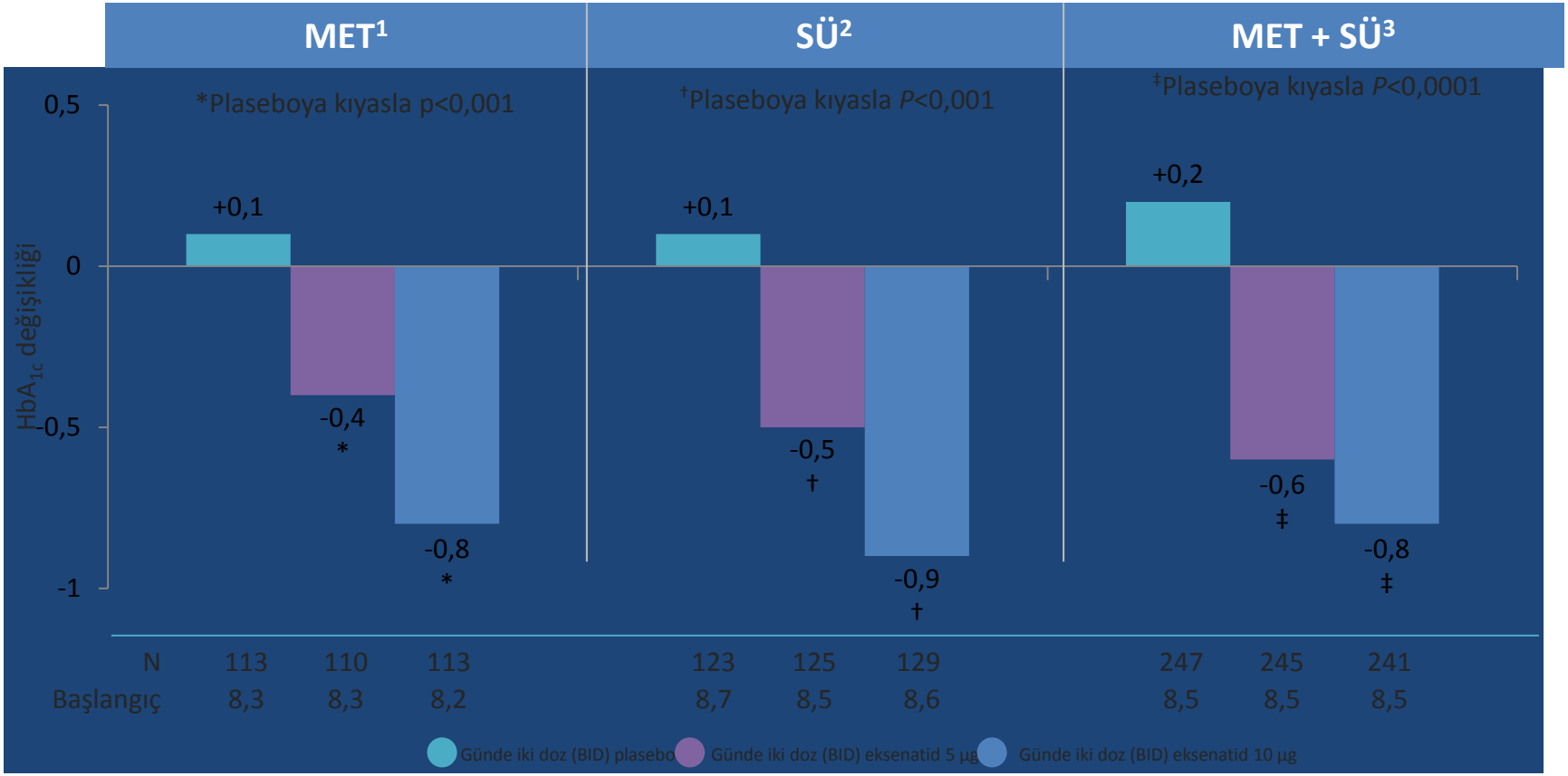
Meier, J. J. *Nat. Rev. Endocrinol.* **8**, 728–742 (2012)

GLP-1 infüzyonu: Gastrik boşalma zamanı



Meier, J. J. *et al. J. Clin. Endocrinol.* **88**, 2716–2725 (2003).

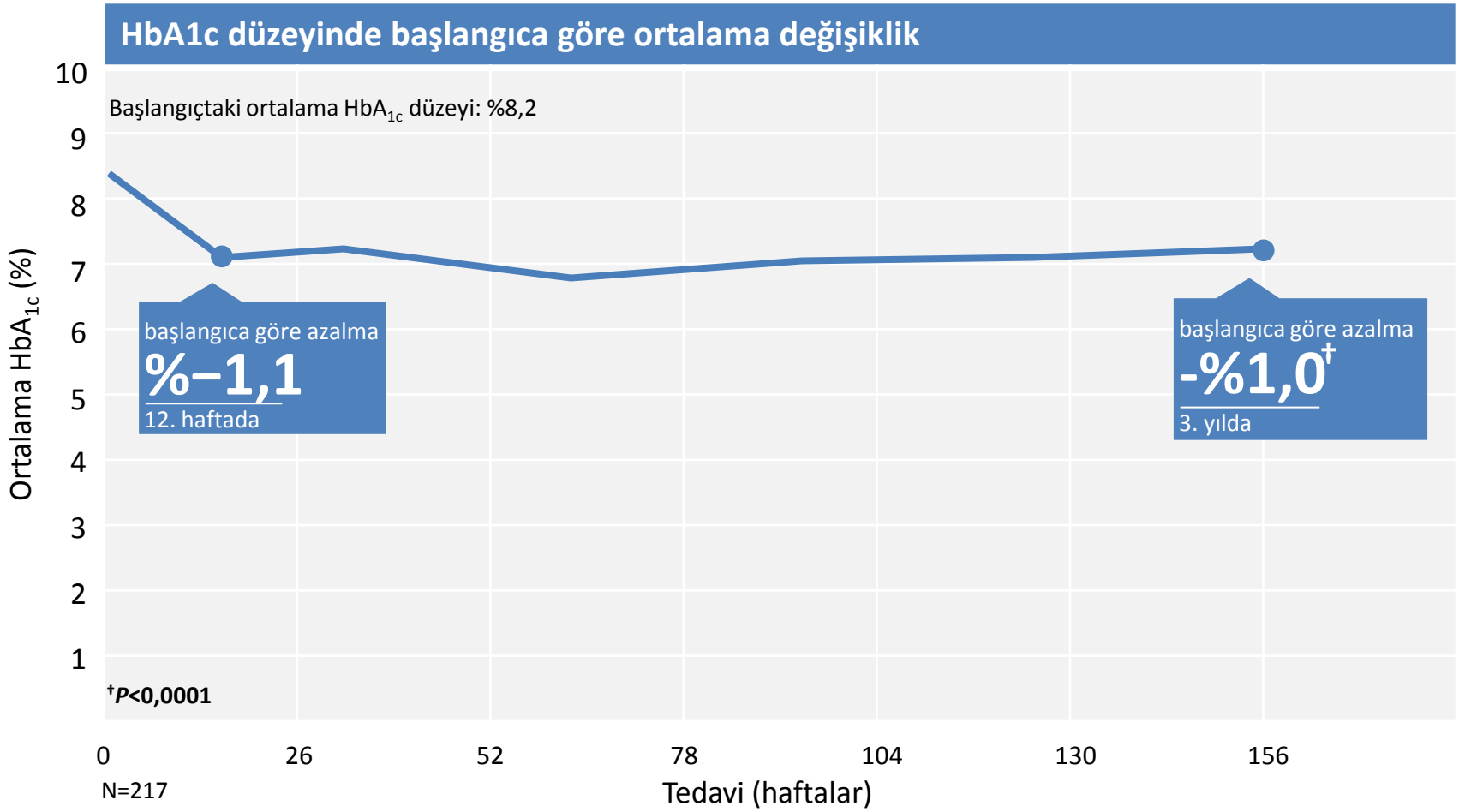
Efektif kan şekeri kontrolü



30 haftalık veriler; ortalama (SE).

1. DeFronzo RA et al. *Diabetes Care.* 2005;28:1092-1100. 2. Buse JB et al. *Diabetes Care.* 2004;27:2628-2635. 3. Kendall DM et al. *Diabetes Care.* 2005;28:1083-1091.

Uzun süreli efektif kan şekeri kontrolü

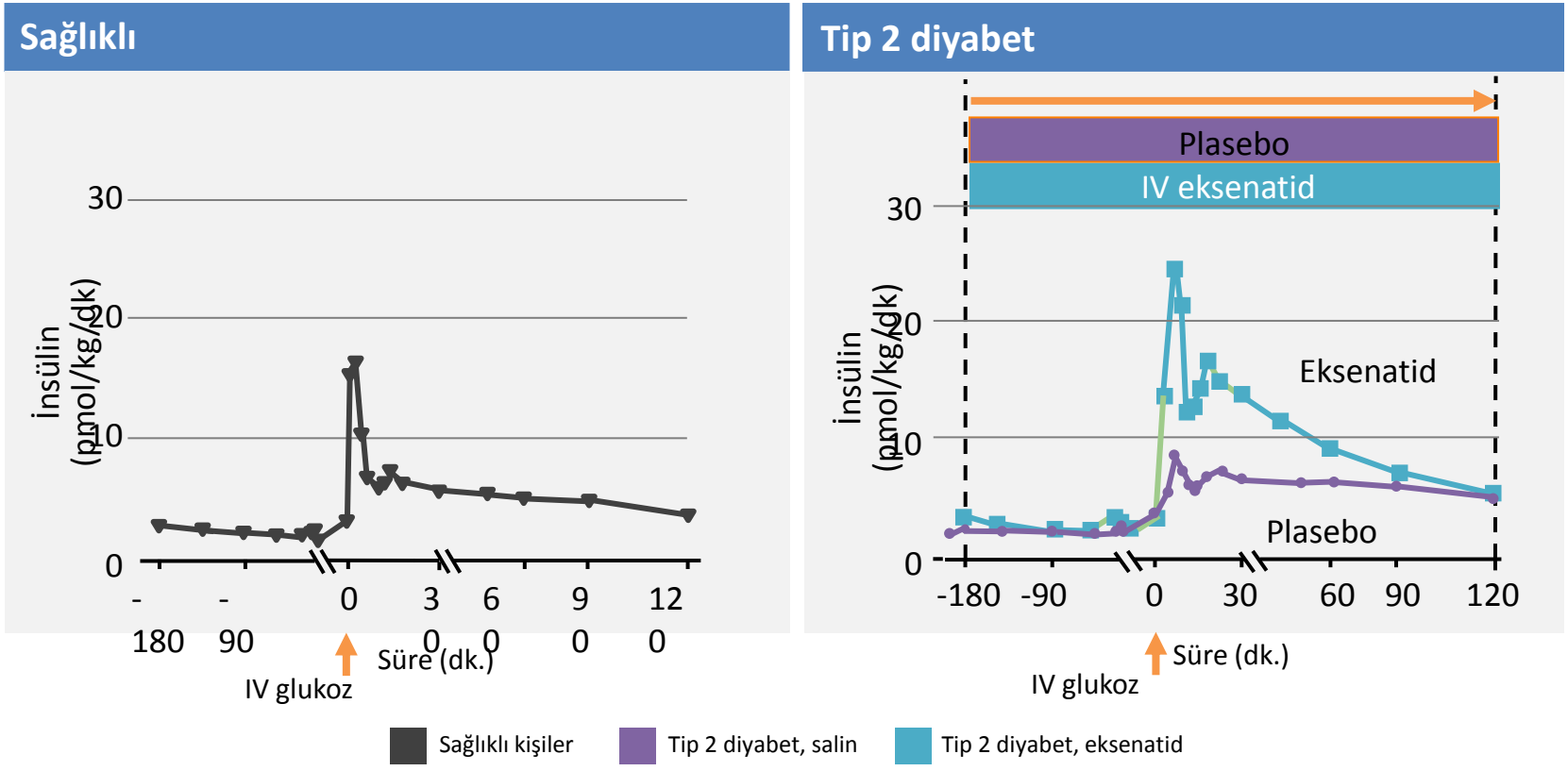


*527 hastadan 217'si çalışmanın 156 haftasını tamamlamış, bu hastaların %46'sı HbA_{1c} ≤%7 düzeyine ulaşmıştır.

Uyarlandığı kaynak: Klonoff DC, et al. *Curr Med Res Opin.* 2008;24:275-286.

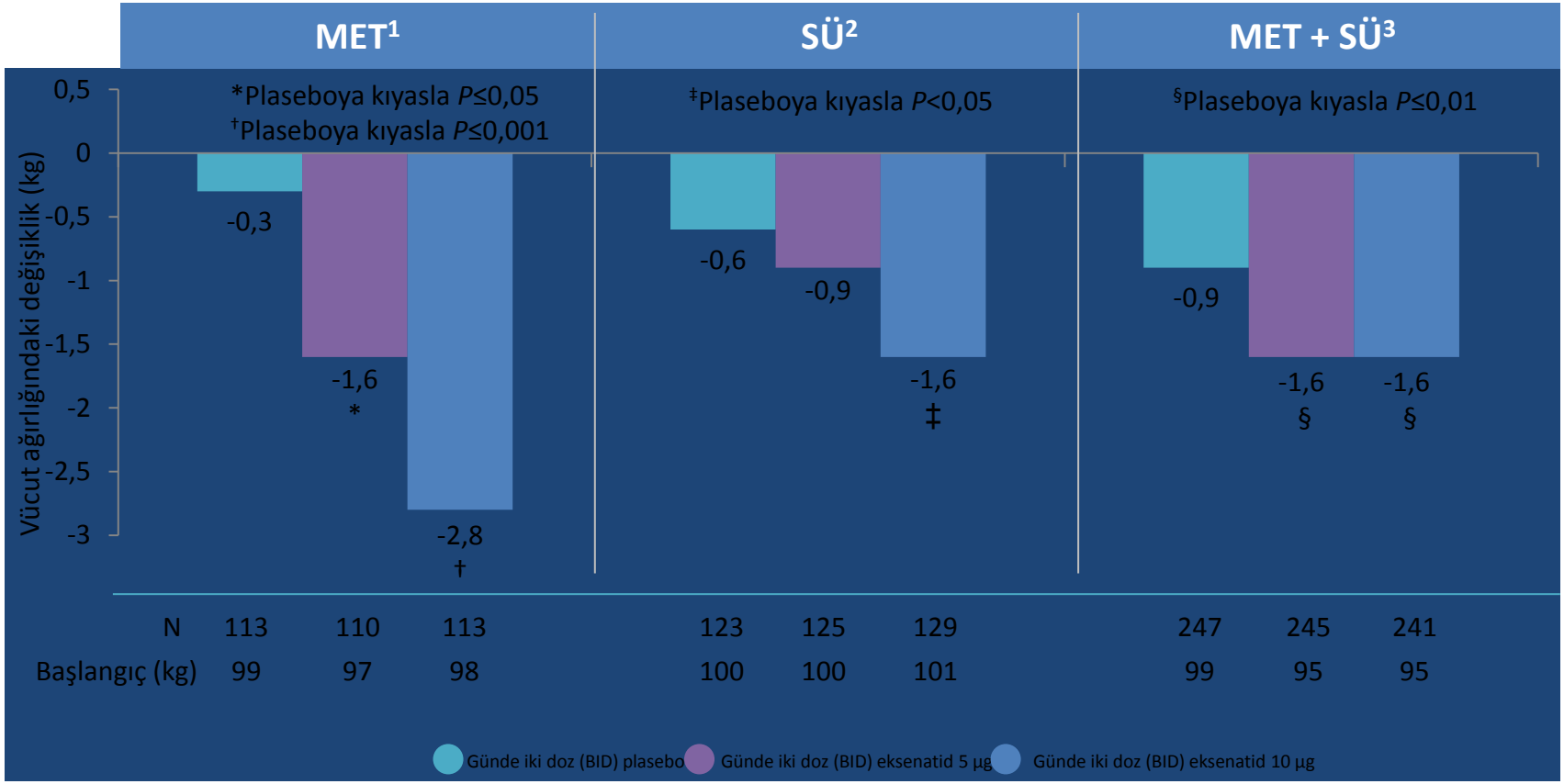
Korunmuş birinci faz insülin yanıtı

- Tip 2 diyabet hastalarında tipik olarak birinci faz insülin yanıtı gelişmez ve bu beta hücrelerinde fonksiyon bozukluğunun erken dönemdeki bir göstergesidir.



İV infüzyon, eksenatid için onaylı bir uygulama yolu değildir. Değerlendirilebilen; Sağlıklı n=12; Tip 2 diyabet n=13; ortalama (SE).
Uyarlandığı kaynak: Fehse F et al. *J Clin Endocrinol Metab.* 2005;90:5991-5997.

Vücut ağırlığı üzerinde olumlu etki



***Eksenatid obezitenin kontrol altına alınmasında endike değildir ve vücut ağırlığındaki değişiklik klinik çalışmaların sekonder sonlanım noktalarından biri olmuştur.**

Dönüştürülmüş veriler; ortalama (SE).

1. DeFronzo RA et al. *Diabetes Care.* 2005;28:1092-1100. 2. Buse JB et al. *Diabetes Care.* 2004;27:2628-2635. 3. Kendall DM et al. *Diabetes Care.* 2005;28:1083-1091.

İnkretin bazlı tedaviler
GLP-1 analogları

Uluslararası markette bulunan inkretin bazlı tedaviler

Drug	Incretin-Based Mechanism	Approval Date	
		FDA	EMA
Exenatide	GLP1 agonist	April 28, 2005	November 20, 2006
Sitagliptin	DPP4 inhibitor	October 16, 2006	March 21, 2007
Vildagliptin	DPP4 inhibitor	(Not approved by the FDA)	September 26, 2007
Saxagliptin	DPP4 inhibitor	July 31, 2009	October 1, 2009
Liraglutide	GLP1 agonist	January 25, 2010	June 30, 2009
Linagliptin	DPP4 inhibitor	May 2, 2011	August 24, 2011
Exenatide extended-release	GLP1 agonist	January 27, 2012	June 17, 2011
Alogliptin	DPP4 inhibitor	January 25, 2013	September 19, 2013
Lixisenatide	GLP1 agonist	(Not approved by the FDA)	February 1, 2013

N ENGL J MED 370;9

Kısa etkili GLP-1 analogları

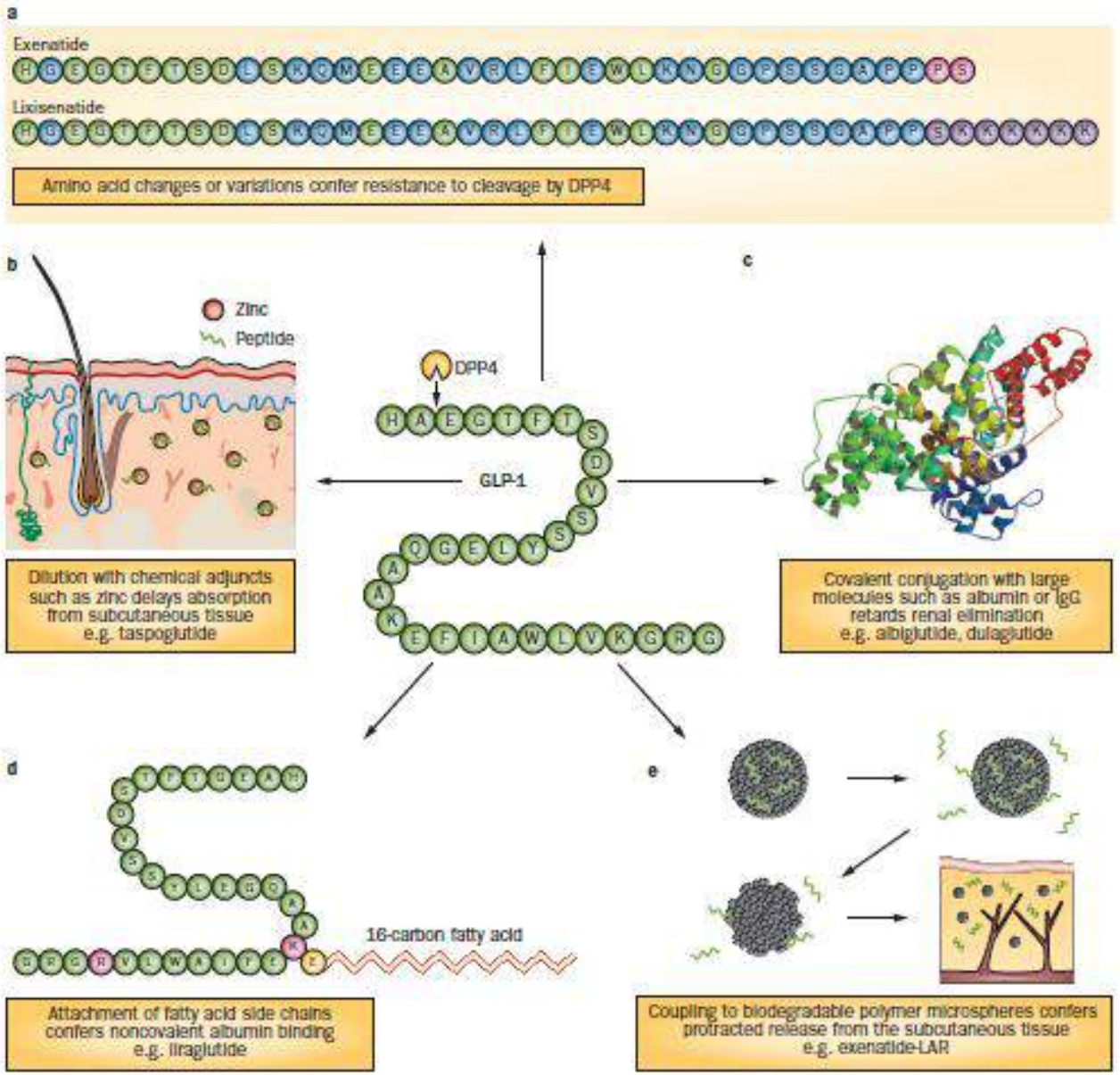
Exenatide

Lixisenatide

Uzun etkili GLP-1 analogları

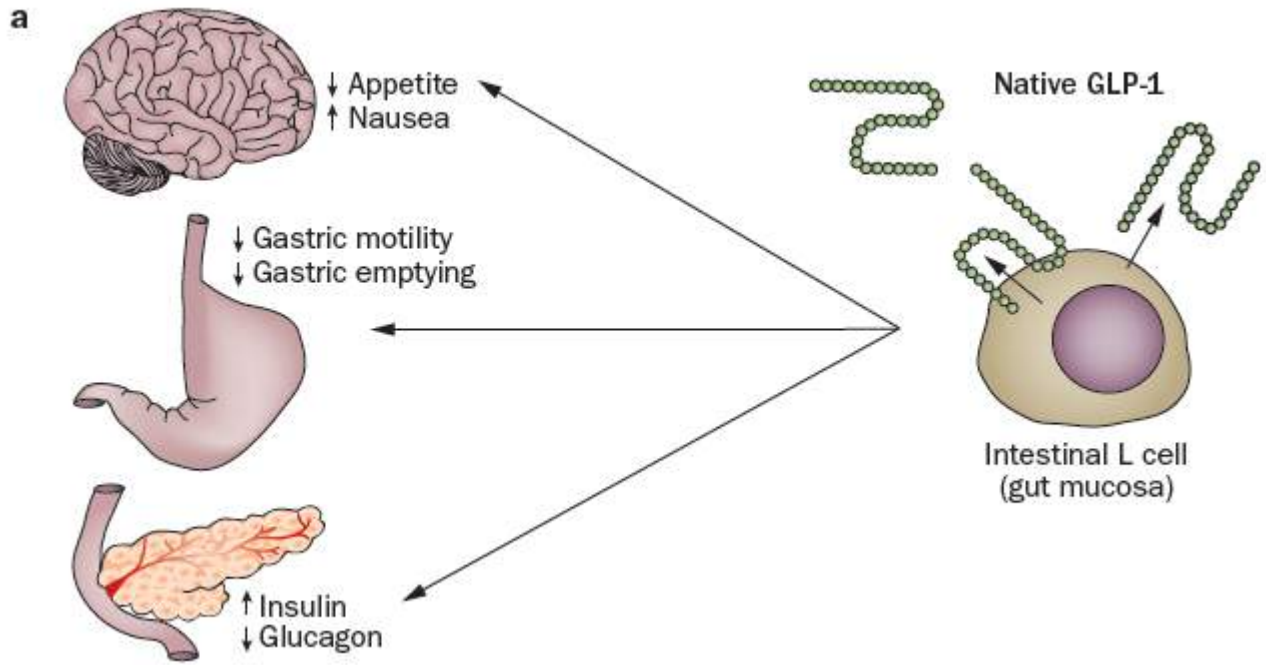
Albiglutide
Dulaglutide
Exenatide-LAR
Liraglutide

Uzun etkili GLP-1 analoğu geliştirme stratejileri



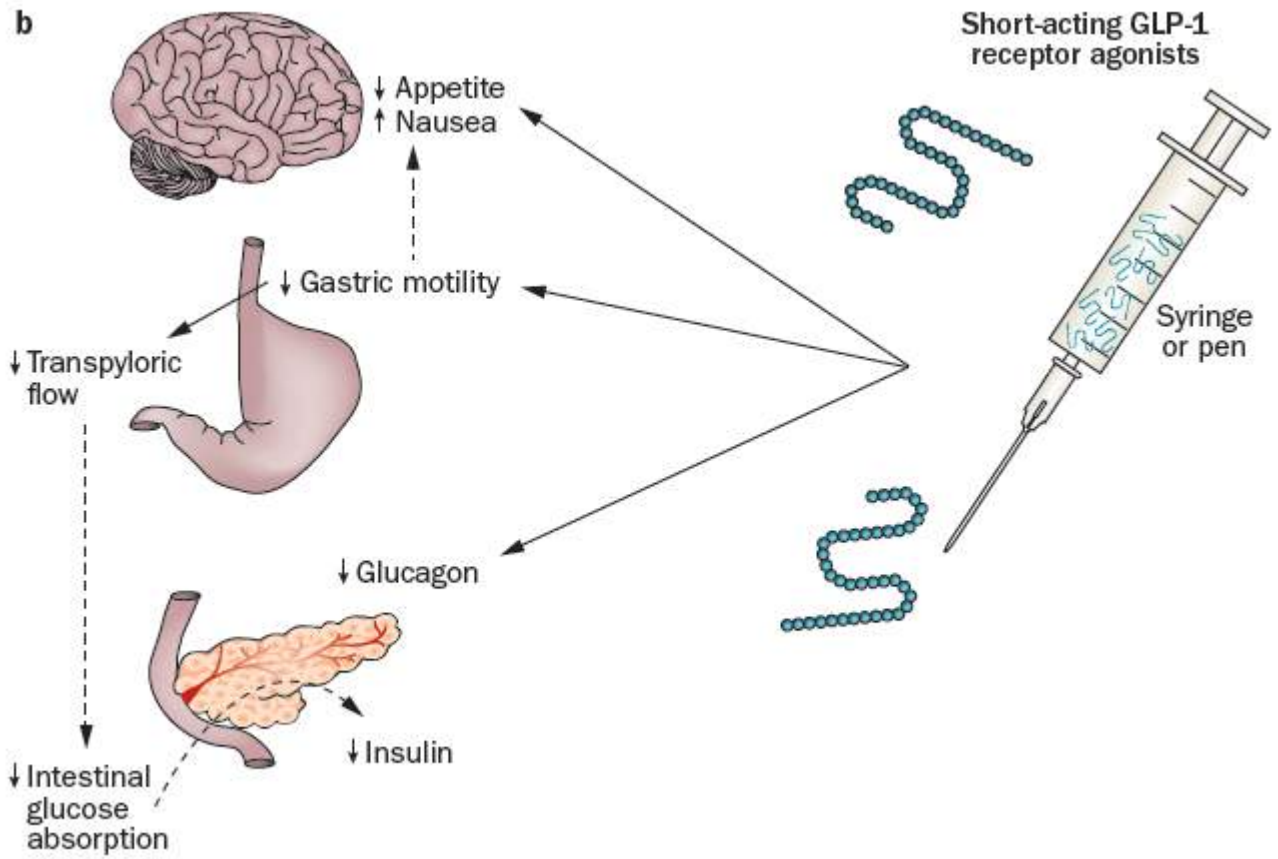
Meier, J. J. *Nat. Rev. Endocrinol.* **8**, 728–742 (2012)

Doğal GLP-1 Etkisi



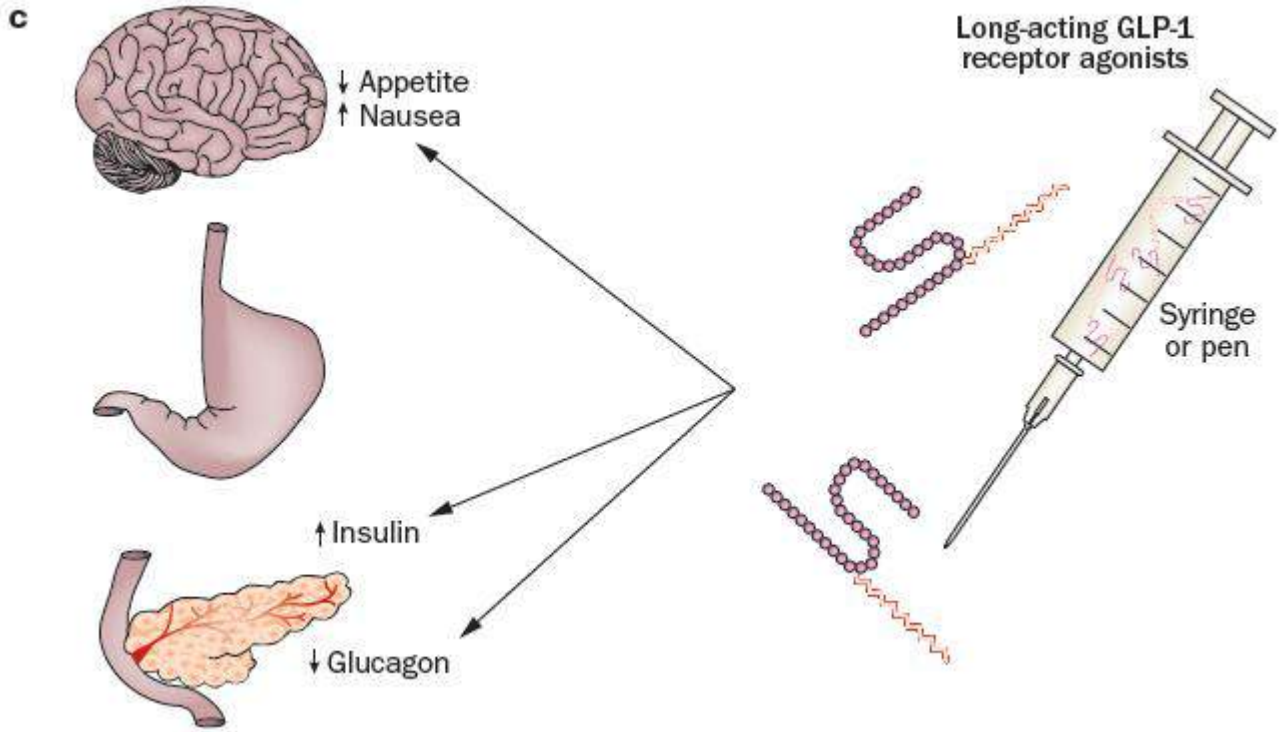
J. Meier, Nature Reviews Endocrinol, 2012

Kısa Etkili GLP-1 Agonisti Etkisi



J. Meier, Nature Reviews Endocrinol, 2012

Uzun Etkili GLP-1 Agonisti Etkisi



J. Meier, Nature Reviews Endocrinol, 2012

Kısa vs Uzun Etkili GLP-1 Agonisti Etkisi

	Kısa etkili	Uzun etkili
Yarı ömür	2-5 saat	> 12 saat
Açlık KŞ	Hafif düzeyde	Güçlü
Postprandial KŞ	Güçlü	Hafif düzeyde
Açlık insülin sekresyonu	Hafif düzeyde	Güçlü
Postprandial insülin sekresyonu	Azalma	Güçlü
Glukagon sekresyonu	Azalma	Azalma
Mide boşalma zamanı	Uzar	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 Daha hızlı düzelir (4-8 hafta)

J. Meier, Nature Reviews Endocrinol, 2012

İnkretin bazlı tedaviler

Efektif kan şekeri kontrolü

Düşük kan şekeri varlığında insülin stimulasyonuna neden olmaması

Kg alımı etkisi olmaması

Sistolik kan basıncında düşme

Beta hücre üzerinde koruyucu etkinlik

Hipotetik olarak olumlu kardiyovasküler etkinlik

GIS yan etkileri

Pankreatit

Pankreatik kanser ?

C-hücre hiperplazisi ?

Tiroid kanseri ?

Diğer kanserler ?

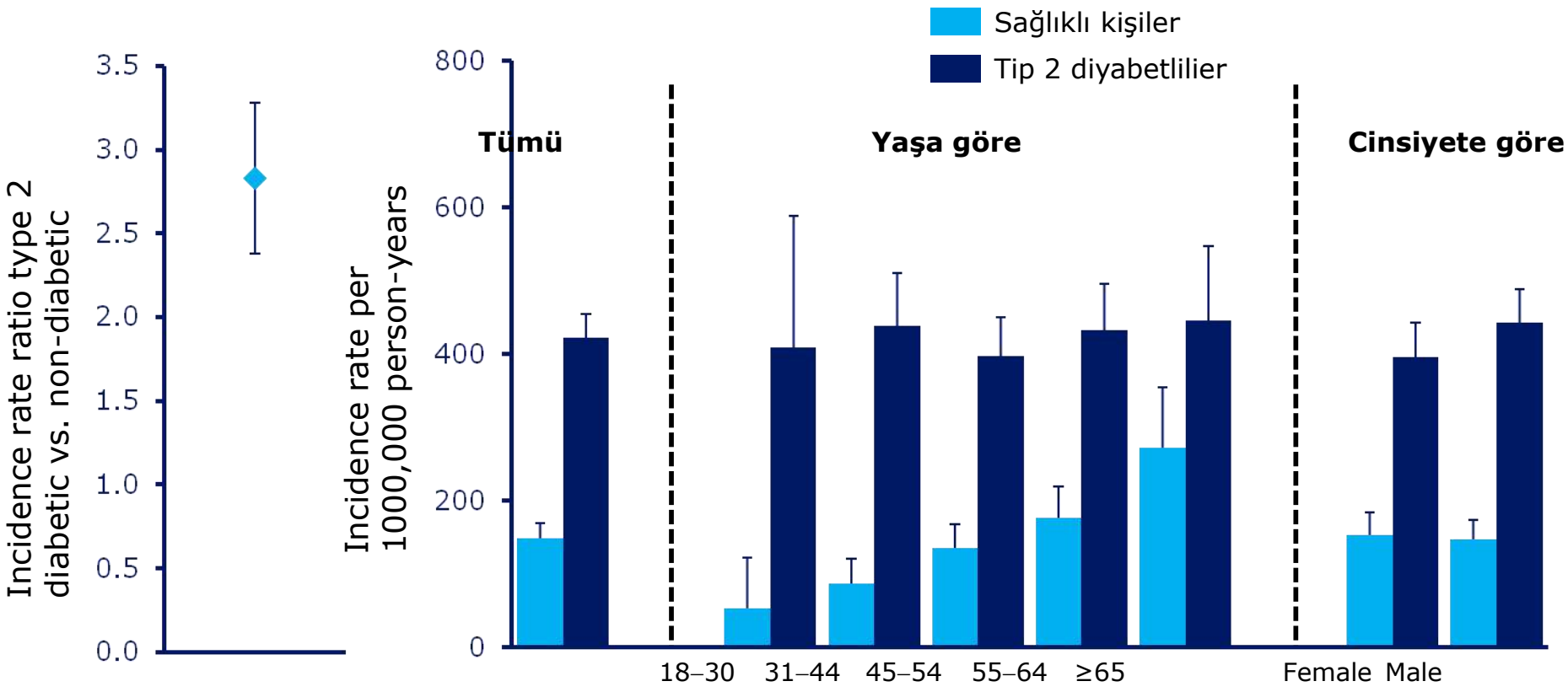
Kardiyovasküler güvenlik

Güvenirlilik

Pankreatit
Pankreas kanseri
Tiroid C hücre hiperplazisi
Tiroid kanseri
Diğer kanserler
Kardiyovasküler etkiler
Diğer advers etkiler

Pankreas

Akut pankreatit insidansı:
Tip 2 diyabet vs diyabet olmayan hastalar



Noel et al. *Diabetes Care* 2009;32:834-8

Pankreatit sıklığı ve risk faktörleri

Genel popülasyonda pankreatit sıklığı

- Avrupa: 1000 sağlıklı kişide yılda[1] 0.04–0.5 vaka
- ABD:1000 kişide yılda 0.5–0.8 hastane yatışı
- ABD: 1000 sağlıklı kişide yılda 1.5 vaka[2]

Diğer pankreatit risk faktörleri

- Obezite, alkol, hipertrigliseridemi ve safra kesesi taşı pankreatiti oluşumunu arttıran risk faktörleridir.[3,4]

Tip 2 diyabet hastalarında pankreatit insidansı

- Tip 2 diyabet hastalarında pankreatit riski genel popülasyondan 2.8 kat daha fazladır. population[2]

1. Yadav *et al*. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006;33(4):323–30.
2. Noel *et al*. Increased risk of acute pancreatitis observed in patients with type 2 diabetes. *Diabetes Care* 2009;32(5):834–8.
3. Linares *et al.* Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. *Pancreas* 2008;37(1):13–2.
4. Martinez *et al*. Is obesity a risk factor in acute pancreatitis? A meta-analysis. *Pancreatology* 2004;4:42–8.

Pankreatit

- Ekim 2007'de FDA exenatide ile tedavi edilen 30 hastada akut pankreatit varlığını bildirdi.

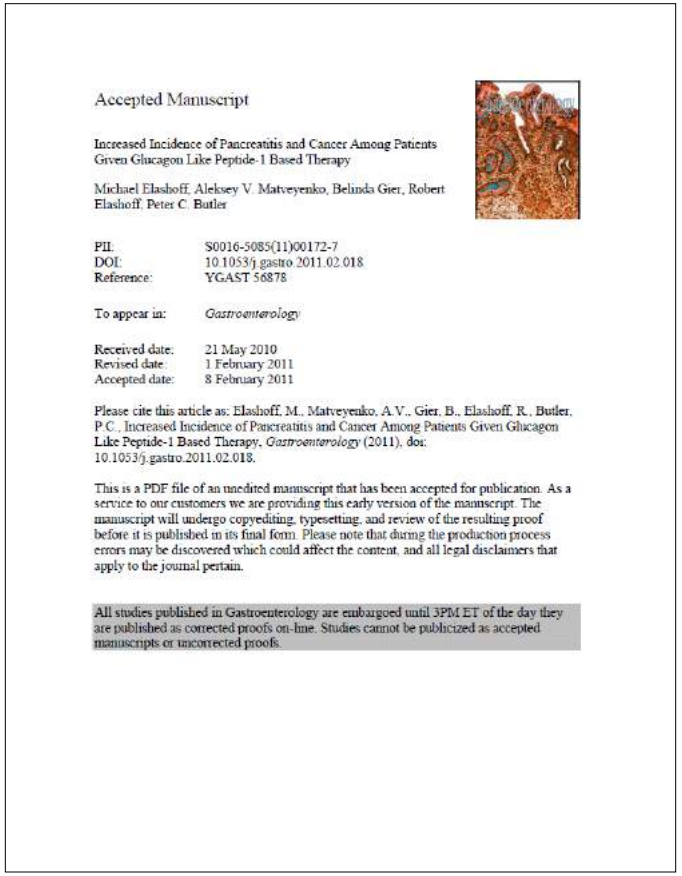
- Bunlardan yalnızca birinde pankreatit predispozisyonu yaratan bir neden vardı. 21'ini yatırmak gerekti, 5 tanesinde ciddi sorunlar gelişti ancak hemoraji ve nekroz gözlenmedi.

- Vakaların % 73'ünde ilaç kesilince semptomlar geriledi.

Butler ve arkadaşlarının yayını : inkretin bazlı tedavilerle ilgili güvenlik verileri

- Şubat 2011 – online yayın
- Mart 2011 – editörler tarafından geri çekilmesi
- Nisan 2011- EASD'nin yayın hakkındaki yorumunun yayınlanması

Mayıs 2011- Makalenin tekrar yayını



Accepted Manuscript

Increased Incidence of Pancreatitis and Cancer Among Patients Given Glucagon Like Peptide-1 Based Therapy

Michael Elashoff, Aleksey V. Matveyenko, Belinda Gier, Robert Elashoff, Peter C. Butler

PII: S0016-5085(11)00172-7
DOI: 10.1053/j.gastro.2011.02.018
Reference: YGAST 56878

To appear in: *Gastroenterology*

Received date: 21 May 2010
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Accepted date: 8 February 2011

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All studies published in Gastroenterology are embargoed until 3PM ET of the day they are published as corrected proofs on-line. Studies cannot be publicized as accepted manuscripts or uncorrected proofs.

Butler & Elashoff yayınının anlattıkları

- Elashoff ve arkadaşları yayınlarını Yan Etki Raporlama Sistemi-Adverse Event Reporting System (AERS) sistemine rapor edilen yan etki bildirimlerini veri olarak kullanarak hazırlamışlardır. Raporlarda
- a) pankreatit
- b) tiroid kanseri
- c) pankreas kanseri
- d) tüm kanserler

  sitagliptin ve eksenatid kullanımı ile ilişkilendirilmiştir.

Veri kaynağı: Yan etki raporlama sistemi (AERS)

- The Adverse Event Reporting System (AERS) Amerikan ilaç idaresinin (FDA) tüm ilaçlar ve biyolojik ürünlerin piyasaya verilmesinde sonra post marketing güvenlik verilerinin kaydedildiği komputerize bir sistemdir.
- FDA bu sistemi yeni yan etki bildirimlerini ve tıbbi kullanım hatalarını gözlemlemek için kullanır.
- Bu yan etki raporlamaları gönüllülük esasına dayanır ve herkes tarafından gerçekleştirilebilir.
- FDA bu bildirimleri direk olarak sağlık çalışanlarından (doktor , eczacı, hemşire vb.) veya tüketicilerden (hasta, hasta yakını, avukat ve diğerleri) alır.

FDA -AERS resmi web sitesinden alıntılanmıştır.

- AERS verileri kısıtlıdır. Öncelikle bildirilen yan etkinin ürünle bağlantısı mutlak değildir.
- FDA bu bildirimlerde neden- sonuç ilişkisinin kanıtlanmasını talep etmez.
- Raporlar olayı değerlendirecek detayları içermezler.
- **Bu ve başka diğer nedenlerden dolayı bu veriler yan etki insidansı hesaplamasında kullanılamazlar.**
- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm

FDA yan etki bildirimi veri tabanı analizi

2004-2009 yılları arasında yapılmış olan yan etki bildirimlerinin analizi sonucunda;

Exenatide kullanımı pankreatit riskini diğer tedavilere kıyasla 6 kat arttırmaktadır.

Pankreas kanseri exenatide kullanan hastalarda daha sık bildirilmiştir.

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.

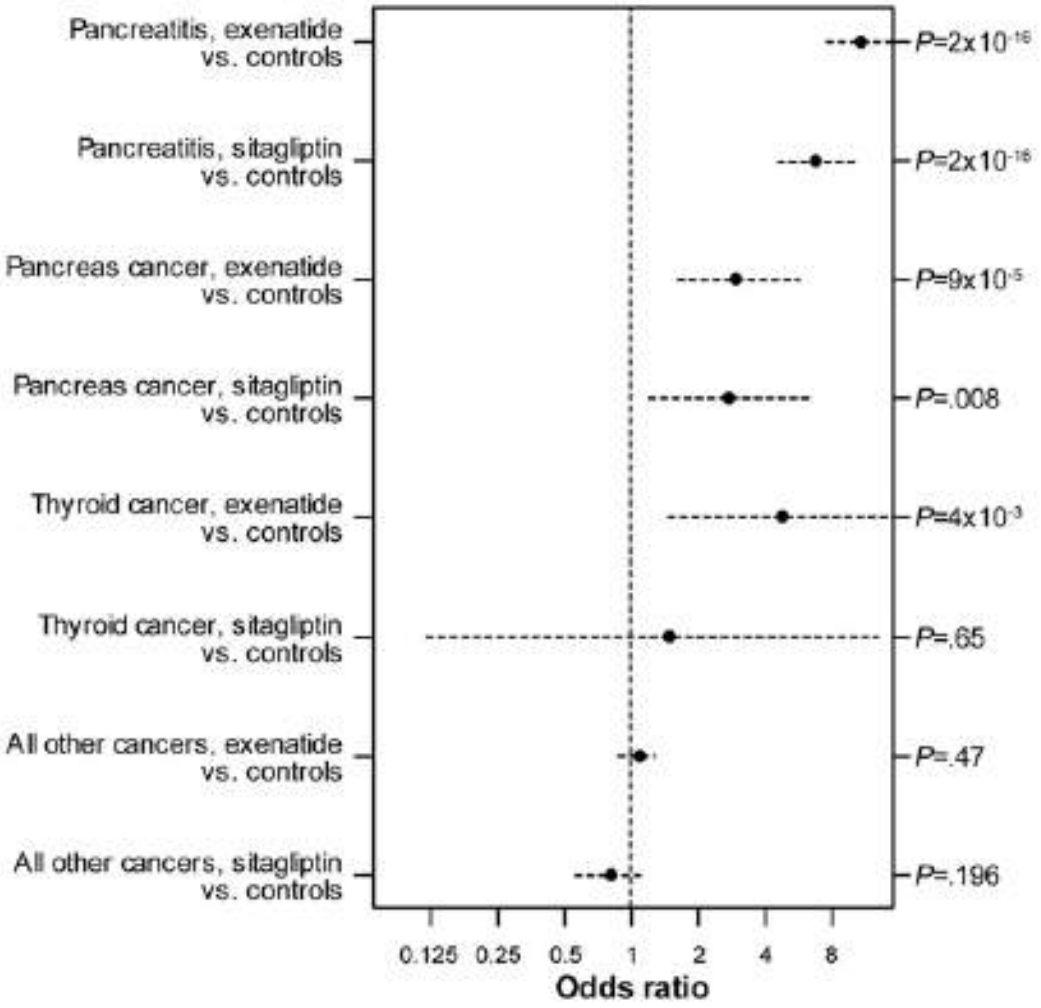
GASTROENTEROLOGY 2011;141:150–156

FDA yan etki bildirimi veri tabanı analizi

PANCREATITIS				
Drug	Pancreatitis events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	971	1433	10.68	2×10^{-16}
Sitagliptin	131	306	6.74	2×10^{-16}
Controls	43	678	—	—
PANCREATITIS (2006 AND PRIOR)				
Drug	Pancreatitis events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	152	748	2.57	8×10^{-7}
Sitagliptin	2	15	1.69	.37
Controls	32	405	—	—
PANCREAS CANCER				
Drug	Pancreas cancer events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	81	1433	2.95	9×10^{-5}
Sitagliptin	16	306	2.72	.008
Controls	13	678	—	—
THYROID CANCER				
Drug	Thyroid cancer events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	30	1433	4.73	4×10^{-3}
Sitagliptin	2	306	1.48	.65
Controls	3	678	—	—
ALL OTHER CANCERS				
Drug	All cancer events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	375	1433	1.08	.47
Sitagliptin	59	306	0.8	.2
Controls	164	678	—	—

GASTROENTEROLOGY 2011;141:150–156

FDA yan etki bildirimi veri tabanı analizi



GASTROENTEROLOGY 2011;141:150–156

Analiz hakkındaki eleştiriler

Sistematik bir analiz değil
- Dahil etme/dahil etmeme kriterleri belli değil
- Metodoloji net değil

Diyabette artmış pankreatit ve kanser riski +
- Diğer karıştırıcı faktörler istatistiğe katılmamış
- Eşlik eden diğer hastalıklar irdelenmemiş

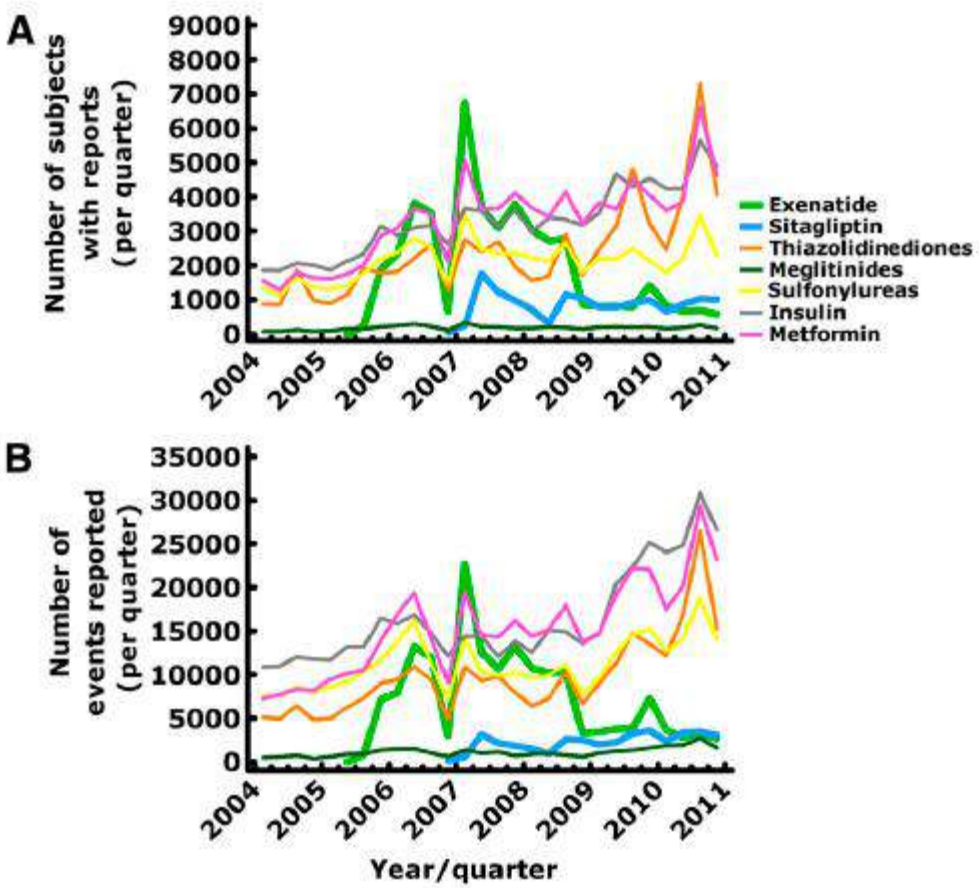
Kanser riskinde artışı destekleyen rasyonel kanıtlar sunmuyor

Odds oranlarının spontan raporların ortak analizi doğrultusunda sunulması doğru değil

Fayda/risk analizi yapılmamış

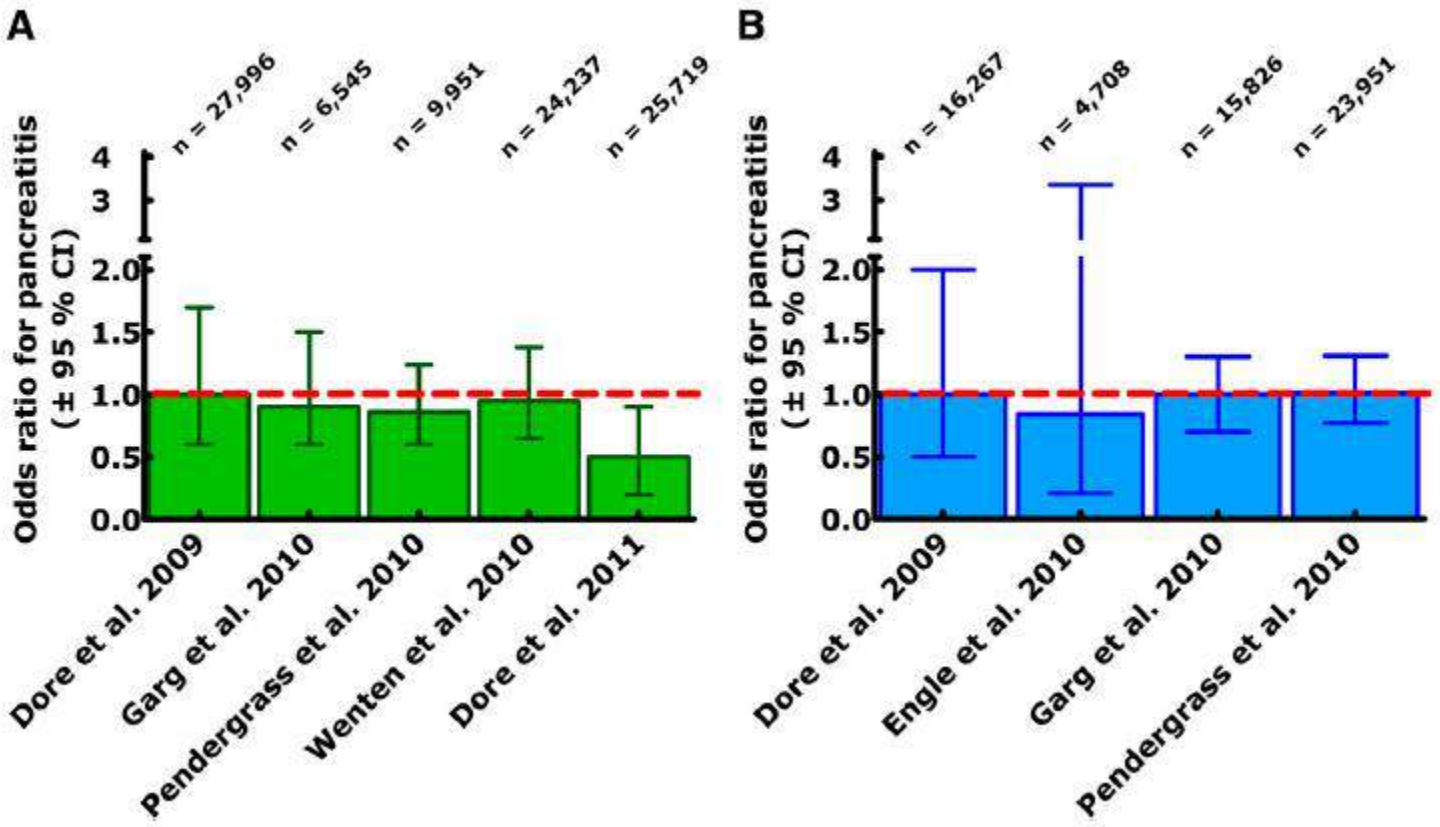
Üretici firma verileri değerlendirilmemiş

Tip2 DM'de İnkretin tabanlı Tedavi Alan Hastalarda Advers Olay Raporları



Nauck, Friedrich, Diabetes Care , 2013

Tip2 DM'de İnkretin tabanlı Tedavi Alan Hastalarda Pankreatit



Exenatide

Sitagliptin

Nauck, Friedrich, Diabetes Care , 2013

FDA yan etki bildirim raporlarına göre GLP-1 analogları

Exenatide and sitagliptin vs. controls (04Q1 to 12Q2)

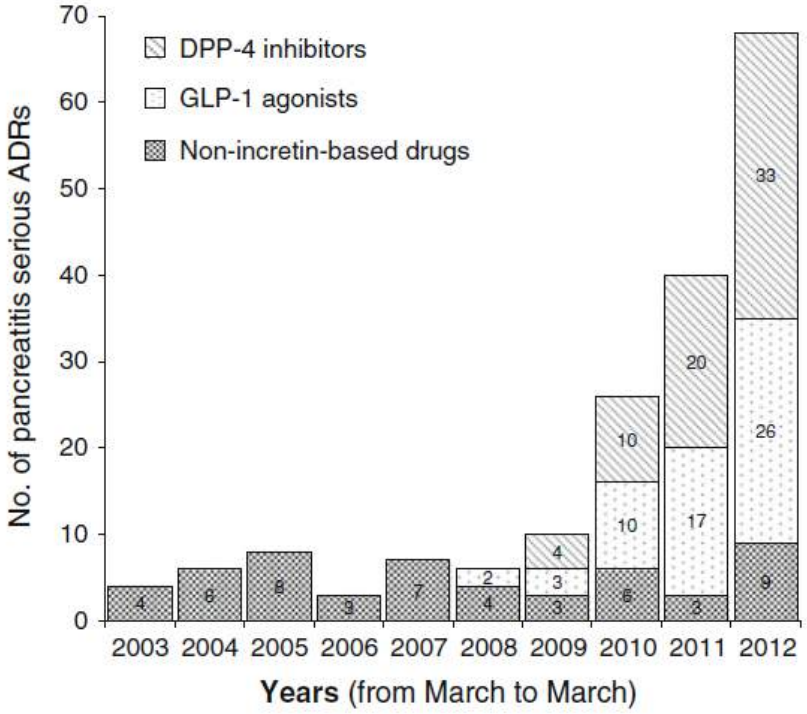
Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Exenatide	2,327	1,660	19.17	(16.41–22.50)	<2.2e-16
Sitagliptin	718	411	23.89	(19.76–28.93)	<2.2e-16
Controls	207	2,832			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Exenatide	258	1,660	2.99	(2.41–3.73)	<2.2e-16
Sitagliptin	81	411	3.80	(2.80–5.11)	<2.2e-16
Controls	147	2,832			
Drug	Thyroid cancer events	Control events	OR	95% CI	*P* value
Exenatide	74	1,660	3.94	(2.56–6.20)	1.67e-11
Sitagliptin	5	411	1.08	(0.33–2.81)	0.80
Controls	32	2,832			

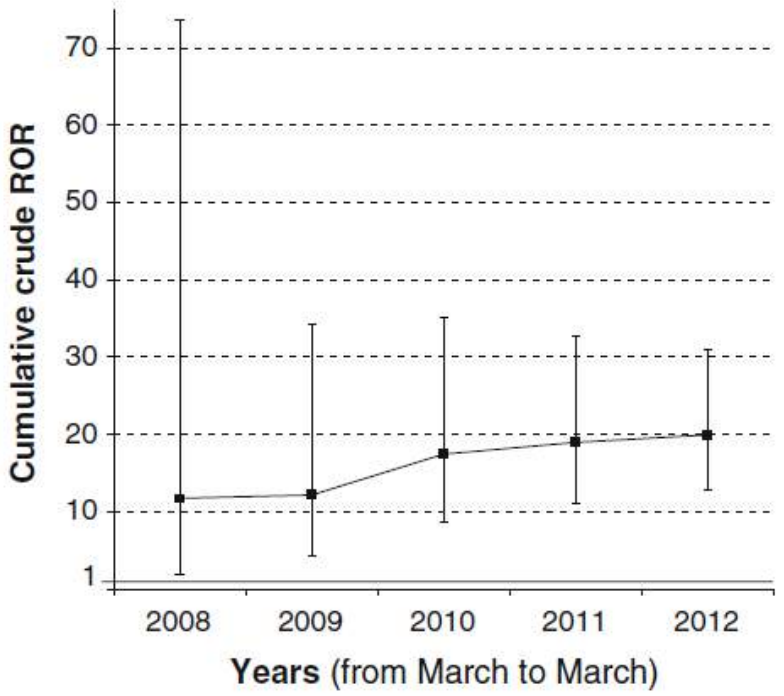
Liraglutide vs. controls (10Q2 to 12Q2)

Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Liraglutide	888	259	56.81	(43.52–74.71)	<2.2e-16
Controls	84	1,393			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Liraglutide	63	259	5.64	(3.80–8.38)	<2.2e-16
Controls	60	1,393			
Drug	Thyroid cancer events	Control events	OR	95% CI	*P* value
Liraglutide	57	259	17.99	(10.12–33.56)	<2.2e-16
Controls	17	1,393			

Butler et al. Diabetes Care, 2013

İnkretin bazlı tedaviler: Pankreatit, Fransız veri sistemi





Faillie et al. Acta Diabetol, 2013

İnkretin bazlı tedaviler: Pankreatit, Fransız veri sistemi

Drug or pharmacological class	Cases of pancreatitis ($N = 147$)	Non-cases ($N = 2{,}962$)	Adjusted ROR[a]	95 % CI		p value
All incretin-based drugs	122	568	15.62	9.81	24.87	<0.0001
All GLP-1 agonists	58	150	29.36	16.02	53.81	<0.0001
Exenatide	19	52	28.29	12.84	62.34	<0.0001
Liraglutide	39	99	30.36	15.36	60.01	<0.0001
All DPP-4 inhibitors	67	421	12.08	7.30	20.00	<0.0001
Sitagliptin	53	315	12.36	7.29	20.97	<0.0001
Vildagliptin	9	87	7.43	3.14	17.58	<0.0001
Saxagliptin	5	23	15.09	4.32	52.72	<0.0001
Metformin	84	1,841	0.86	0.59	1.26	0.438
Sulfonylureas/glinides	53	1,381	1.24	0.83	1.85	0.295
Acarbose	2	137	0.41	0.09	1.89	0.255
Thiazolidinediones	2	235	0.31	0.07	1.32	0.114
Insulin	14	356	0.84	0.45	1.57	0.587

Faillie et al. Acta Diabetol, 2013

Eksenatid veya sitagliptin tedavisinde gerçek yaşam koşullarında pankreatit prevalansı

	Vaka sayısı	Hasta sayısı	Mutlak risk (%)	Relatif risk	95% CI
İlaç çifti 1					
- Eksenatide	37	27,996	0.13	1.0	0.6–1.7
- Metformin/gliburid	36	27,983	0.13	1.0	Ref
İlaç çifti 2					
- Sitagliptin	19	16,267	0.12	1.0	0.5–2.0
- Metformin/gliburid	19	16,281	0.12	1.0	Ref

Eksenatid veya sitagliptin kullanan hastalarla metformin veya gliburid kullanan hastaların primer akut pankreatit tanısı ile hastane yatışı olan hastalarda mutlak ve rölatif risk oranları, Ingenix Research Datamart, 6/1/2005–6/30/2008

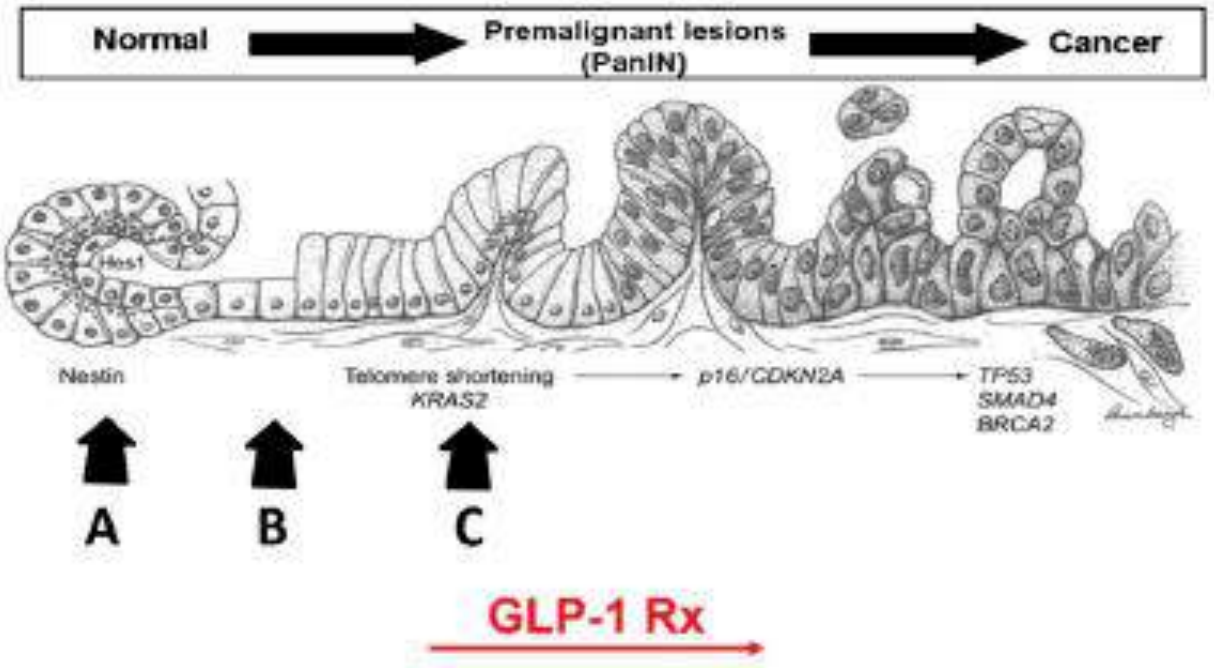
Dore. *Curr Med Res Opin* 2009;25:1019–27.

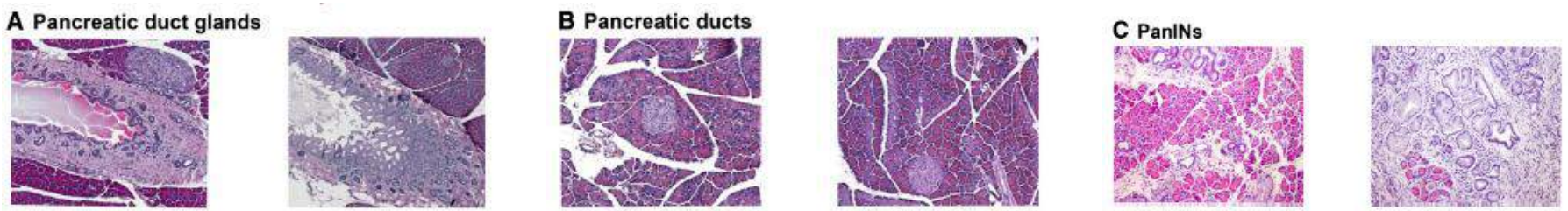
GLP-1 bazlı tedavilerin ekzokrin pankreas etkileri: Hayvan çalışmaları

Reference	Species/age	Treatment/day duration#	Pancreas weight	Pancreas enzymes	Histology	Replication/ method
Perfetti et al., 2000 (5)	Wistar rat 22 months	GLP-1 1.5 pmol/kg · min, 5 days	↑	→	NR	↑ Ducts and acinar cells PCNA
Koehler et al., 2009 (6)	Mice 9–12 weeks	Exenatide 48 nmol/kg, 4 wks	↑	→	NR	NR
	Mice 9–12 weeks	Liraglutide 75 μg/kg, 1 wk	↑	→	NR	NR
Matveyenko et al., 2009 (7)	HIP rats 2 months	Sitagliptin 200 mg/kg, 12 weeks	↑	NR	Pancreatitis (1/8) and acinar to ductal metaplasia (3/16)	↑ Ducts, Ki67
Nachnani et al., 2010 (12)	Rats 8 weeks	Exenatide 10 μg/kg, 11 weeks	NR	↑ Amylase	Exocrine inflammation	NR
Tatarkiewicz et al., 2010 (11)	Mice 10 weeks	Exenatide 7.2 nmol/kg, 4 weeks	→	→	No pancreatitis	→ Ducts Ki67
Vrang et al., 2012 (9)	ZDF rats 7 weeks	Exenatide 0.25 mg/kg, 13 weeks	→	↑ Amylase	1/12 death pancreatic necrosis; focal acinar hyperplasia;	→ Ducts Ki67*
		Liraglutide 1.0 mg/kg, 13 weeks	→	→	3/12 death by overdose, unexplained; increased ductal proliferation and acinar to ductal metaplasia	→ Ducts Ki67*
Nyborg et al., 2012 (13)	Cynomolgus monkeys age NR	Liraglutide 5 mg/kg, 87 weeks	NR	NR	Normal	NR
	Rats age NR	Liraglutide 1 mg/kg 26 weeks	NR	NR	Normal	NR
	Mice age NR	Liraglutide 3 mg/kg, 104 weeks	NR	NR	Normal	NR
Gier et al., 2012 (8)	Rats 10 weeks	Exenatide 10 μg/kg, 12 weeks	↑	→	PDG hyperplasia;	↑ PDG and ducts Ki67
	Pdx-1 Kras mice 6 weeks	Exenatide 5 nmol/kg, 12 weeks	↑	↑ Lipase	chronic pancreatitis and advanced PanINs	↑ Ducts Ki67
Tatarkiewicz et al., 2012 (10)	ZDF rats 8 wks	Exenatide 250 μg/kg, 12 weeks	→	↑ Amylase	Normal	→ Ducts Ki67*

Butler et al. Diabetes Care, 2013

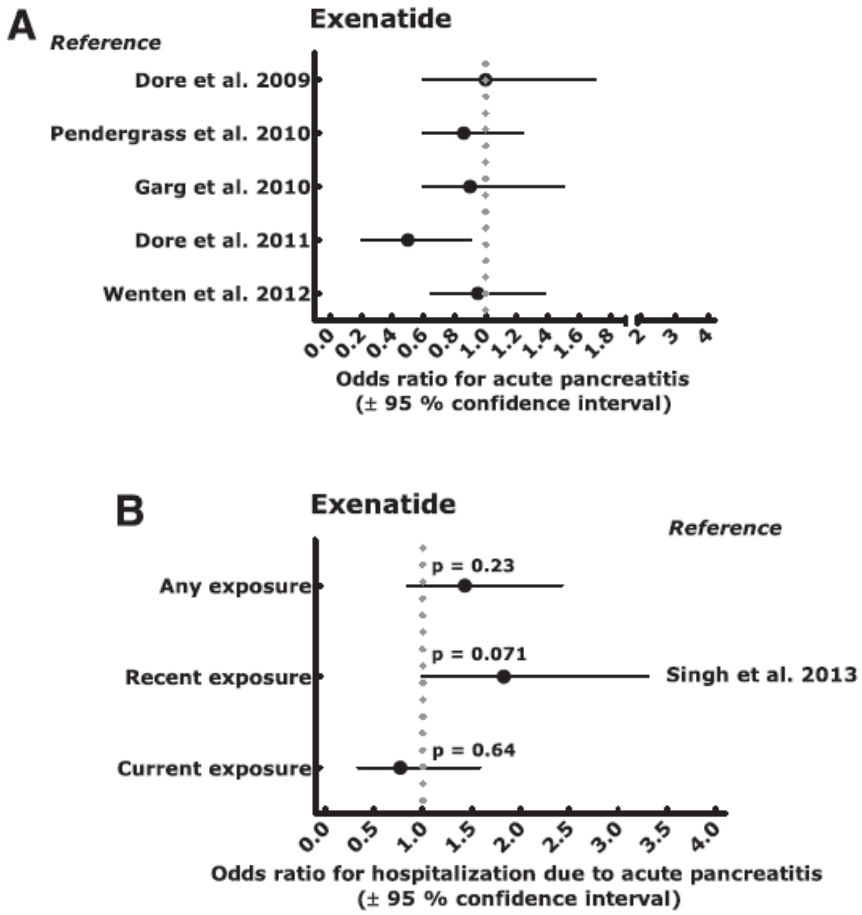
Hayvan çalışmalarında pankreas kanseri gelişimi ile ilişkili süreçler





Butler et al. Diabetes Care, 2013

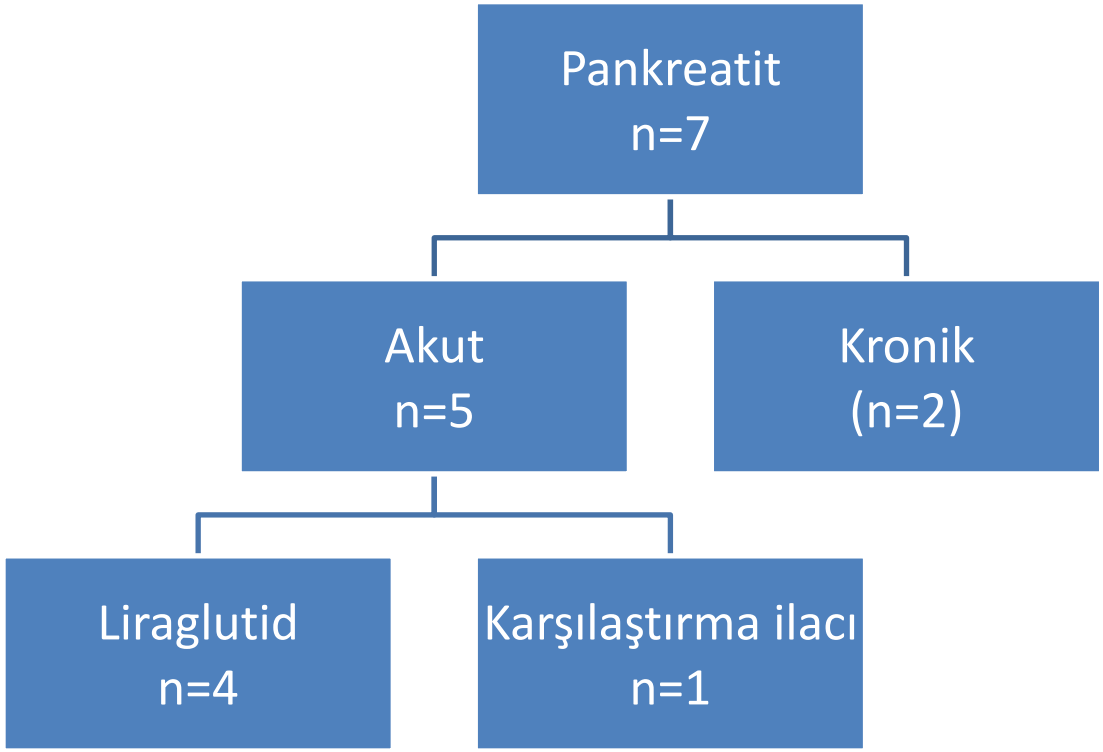
Exenatide ve pankreatit



Thus, while the benefits—expected or proven—from using incretin-based medications seem to be substantial and address risks central to patients with type 2 diabetes, the potential harms and risks typically refer to rare events and are discussed in a controversial manner, e.g., without certainty regarding a potential role of incretin-based medications to cause substantial harm. Obviously more needs to be learned regarding the open questions, but based on today's available knowledge, incretin-based medications can be considered effective and safe. Safety concerns related to the exocrine pancreas and the thyroid are not substantiated enough. Such considerations should not currently influence our treatment decisions regarding the potential prescription of GLP-1 receptor agonists or DPP-4 inhibitors within a treatment regimen for type 2 diabetes.

Nauck M, Diabetes Care, 2013

LEAD çalışmalarıdaki pankreatit vakaları



Aynı özellikteki (tip 2 diyabet) popülasyonda beklenen pankreatit vaka sayıları:

Liraglutid: 13 **Karşılaştırma ilacı: 4**

NN2211: FDA 120 day safety update

THE ENDOCRINE SOCIETY

8401 CONNECTICUT AVENUE, SUITE 900 ■ CHEVY CHASE, MARYLAND ■ 20815-5817 ■ TELEPHONE 301-941-0200 ■ FAX 301-941-0259 ■

Society Joins Call for Review of Incretin-based Therapy for Diabetes Mellitus
June 18, 2013

We urge all manufacturers of incretin-based therapy to make the data from these studies on rates of pancreatitis and pancreatic cancer transparent and available to an independent group of scientists for analysis as it becomes available. We support the American Diabetes Association's offer to coordinate that effort.

We discourage patients from stopping medications on their own without consulting their health care provider, since this can lead to higher levels of blood glucose that may cause serious short-term health problems and, if prolonged, could increase the risk of long term diabetes-related complications.

Tiroid

FDA yan etki bildirim raporlarına göre GLP-1 analogları

Exenatide and sitagliptin vs. controls (04Q1 to 12Q2)

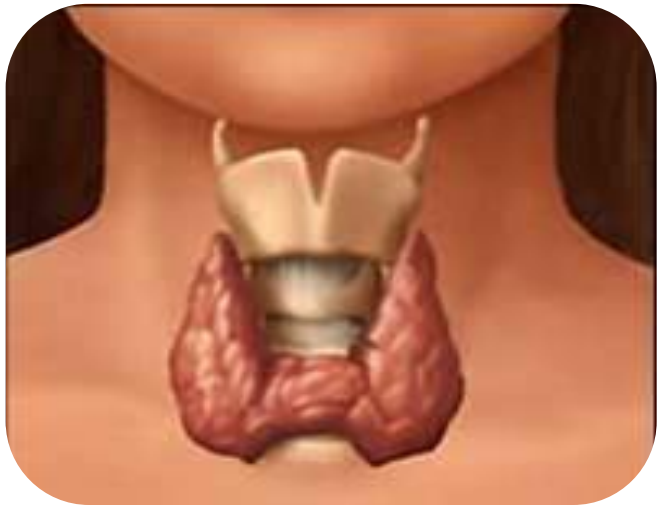
Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Exenatide	2,327	1,660	19.17	(16.41–22.50)	<2.2e-16
Sitagliptin	718	411	23.89	(19.76–28.93)	<2.2e-16
Controls	207	2,832			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Exenatide	258	1,660	2.99	(2.41–3.73)	<2.2e-16
Sitagliptin	81	411	3.80	(2.80–5.11)	<2.2e-16
Controls	147	2,832			
Drug	Thyroid cancer events	Control events	OR	95% CI	*P* value
Exenatide	74	1,660	3.94	(2.56–6.20)	1.67e-11
Sitagliptin	5	411	1.08	(0.33–2.81)	0.80
Controls	32	2,832			

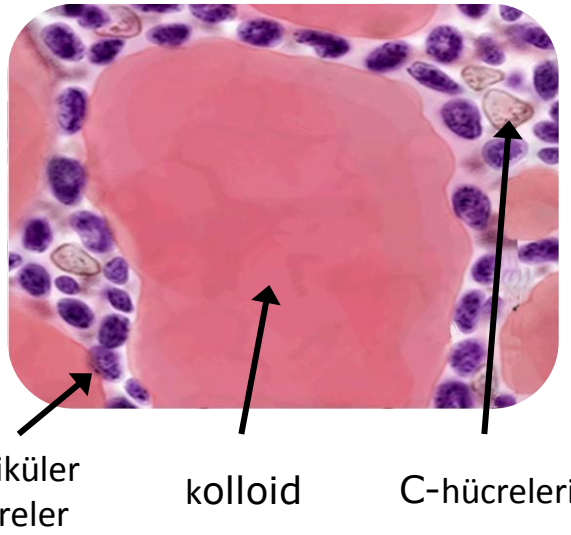
Liraglutide vs. controls (10Q2 to 12Q2)

Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Liraglutide	888	259	56.81	(43.52–74.71)	<2.2e-16
Controls	84	1,393			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Liraglutide	63	259	5.64	(3.80–8.38)	<2.2e-16
Controls	60	1,393			
Drug	Thyroid cancer events	Control events	OR	95% CI	*P* value
Liraglutide	57	259	17.99	(10.12–33.56)	<2.2e-16
Controls	17	1,393			

Butler et al. Diabetes Care, 2013

Tiroid bezi

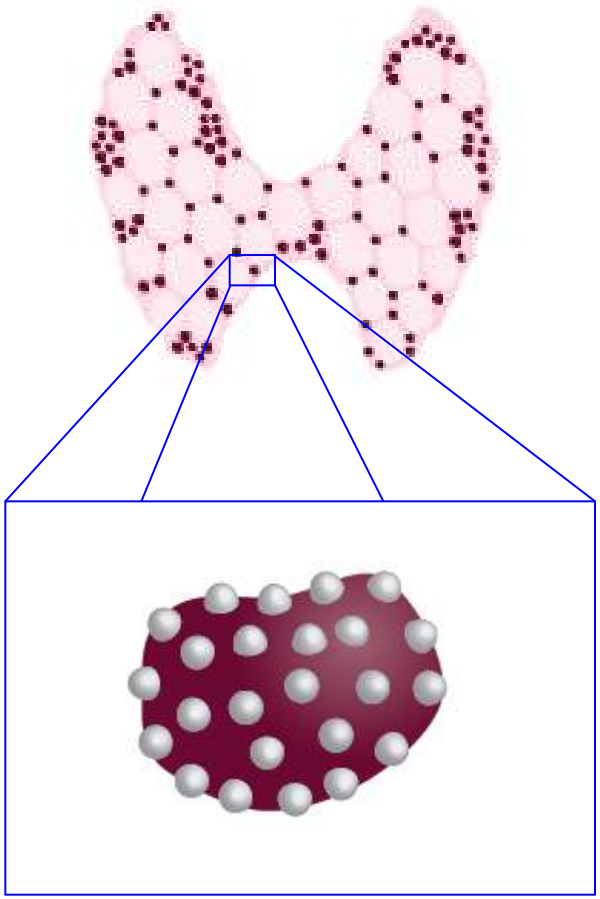




- Tiroid bezi metabolik işlevlerin birçoğunu düzenleyen tiroid hormonlarını salgılamaktan sorumludur
- Tiroid aynı zamanda kalsitonin üreten C-hücrelerini de içerir.
- Kalsitonin kalsiyum seviyelerini denetlemekten sorumludur
- C-hücreli kanser tiroid kanserlerinin nadir görülen bir şeklidir.

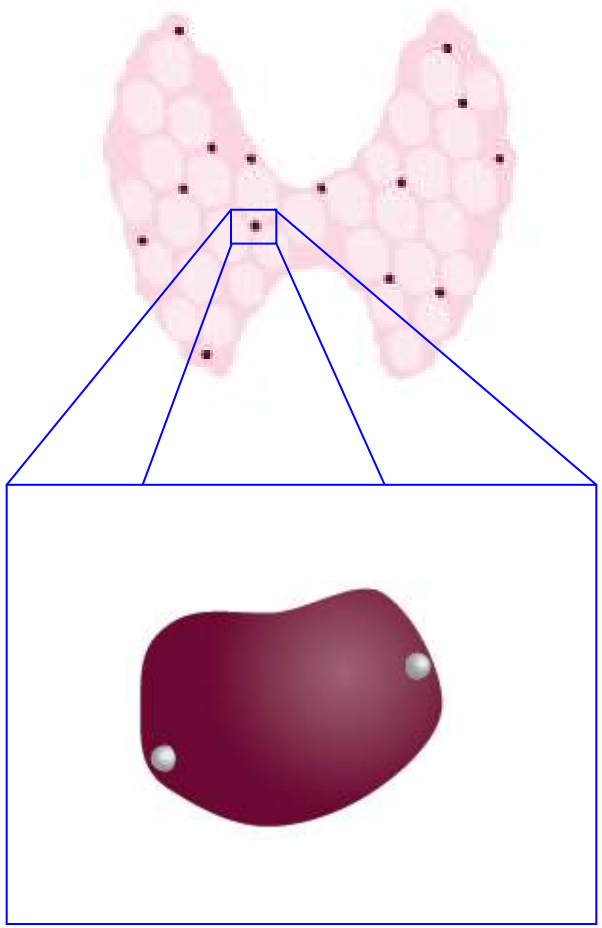
Fare ve İnsan Tiroidi

Kemirgenler



Kemirgen hücrelerindeki c-hücreleri primatlardan daha bol miktardadır. Kemirgenlerdeki c-hücre yoğunluğu insanlara göre 45 kat daha yüksektir.

İnsanlar



Maymun çalışmalarında C-hücrelerinde büyüme izlenmemiştir.

- 87 haftalık çalışmada yüksek Liraglutid dozları primatlarda C-hücresi hiperplazisini stimüle etmemiştir.

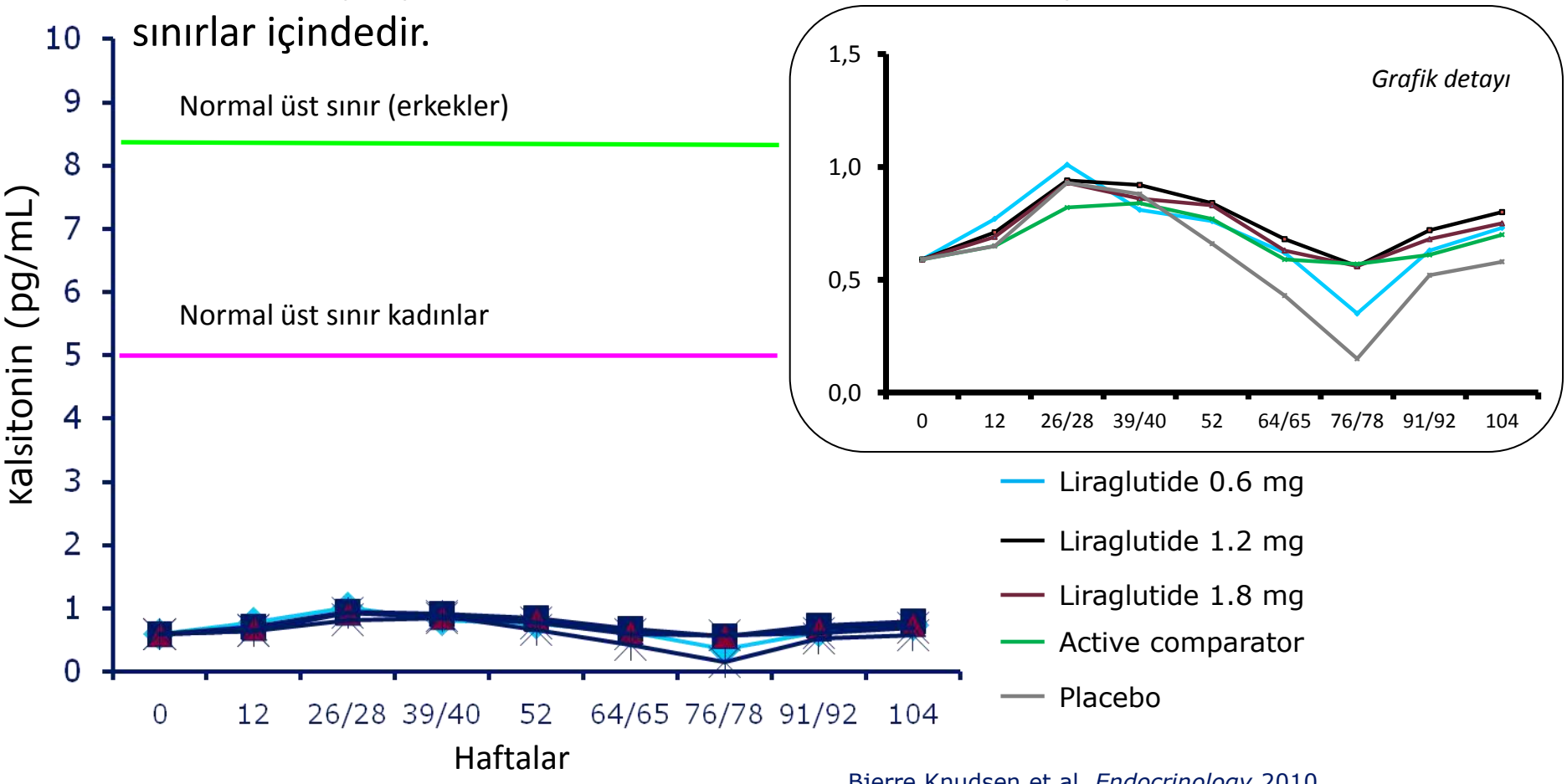
Maymunlar

Doz (mg/kg)	0	0.2	5.0
İnsan maruziyet katları	N/A	8	64
C-hücresi hiperplazi insidansı	Yok	Yok	Yok

Bjerre Knudsen et al. *Endocrinology* 2010; DOI: 10.1210/en.2009-1272

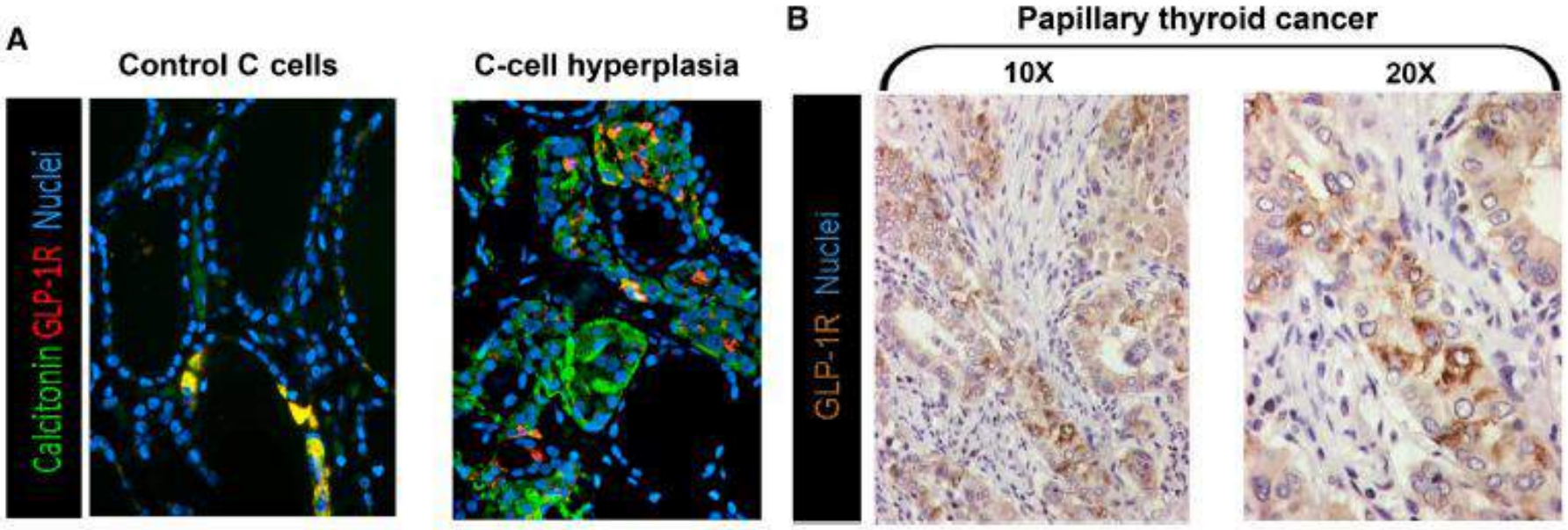
LEAD Çalışmalarında Kalsitonin düzeyleri

- Çalışma sırasında değişkenlikler karşılaştırıldığında (plasebo eğrisine bakınız) karşılaştırılan moleküller arasındaki farklar çok azdır ve normal sınırlar içindedir.



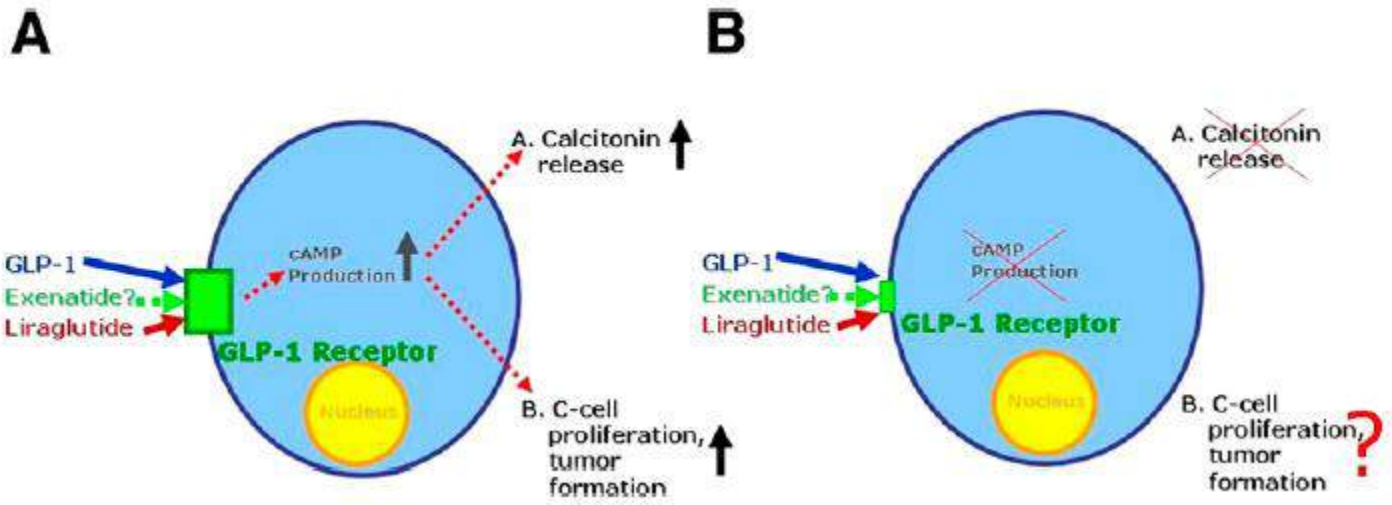
Bjerre Knudsen et al. *Endocrinology* 2010
Parks & Rosenbraugh. *NEJM* 2010
LEAD2 and LEAD3

İnsan tiroid kanser ve C hücre hiperplazi dokularında GLP-1 ekspresyonu



Gier et al.. JCEM, 2012

Tiroid C Hücreleri ve GLP-1 Reseptörleri Uyarı Yanıtları



Rodent

İnsan

Nauck, Friedrich, Diabetes Care , 2013

FDA raporu

Perspective

Weighing Risks and Benefits of Liraglutide — The FDA's Review of a New Antidiabetic Therapy

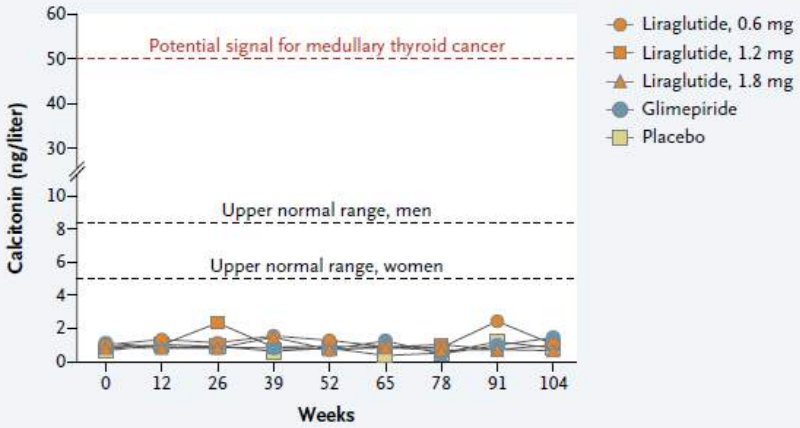
Mary Parks, M.D., and Curtis Rosebraugh, M.D., M.P.H.

Type 2 diabetes mellitus affects approximately 24 million people in the United States, is the leading cause of kidney failure and blindness, and is associated with a doubling to quadrupling of the risk of death from cardiovascular causes. Furthermore, the prevalence of type 2 diabetes is expected to increase because of the obesity epidemic. Although many antidiabetic therapies have been approved by the Food and Drug Administration (FDA), new therapies are needed to achieve glycemic goals, because beta-cell function declines over time in patients with diabetes.

On January 25, 2010, the FDA approved liraglutide, a glucagon-like-peptide-1 (GLP-1) receptor agonist that can be taken once daily to improve glycemic control in adults with type 2 diabetes. We granted the approval on the basis of careful consideration of the drug's benefits, weighed against several complex safety-related concerns.

In clinical trials, when used in addition to other antidiabetic therapies, liraglutide resulted in reductions in the mean glycated hemoglobin concentration of 0.8 to 1.4 percentage points as compared with placebo. When compared as monotherapy with a sulfonylurea, liraglutide was associated with a lower risk of hypoglycemia. Other potential benefits include greater weight loss than that achieved with some active controls and the absence of a need to adjust the dose for patients with renal impairment.

On the other hand, there are potentially serious safety concerns. First, data from studies in

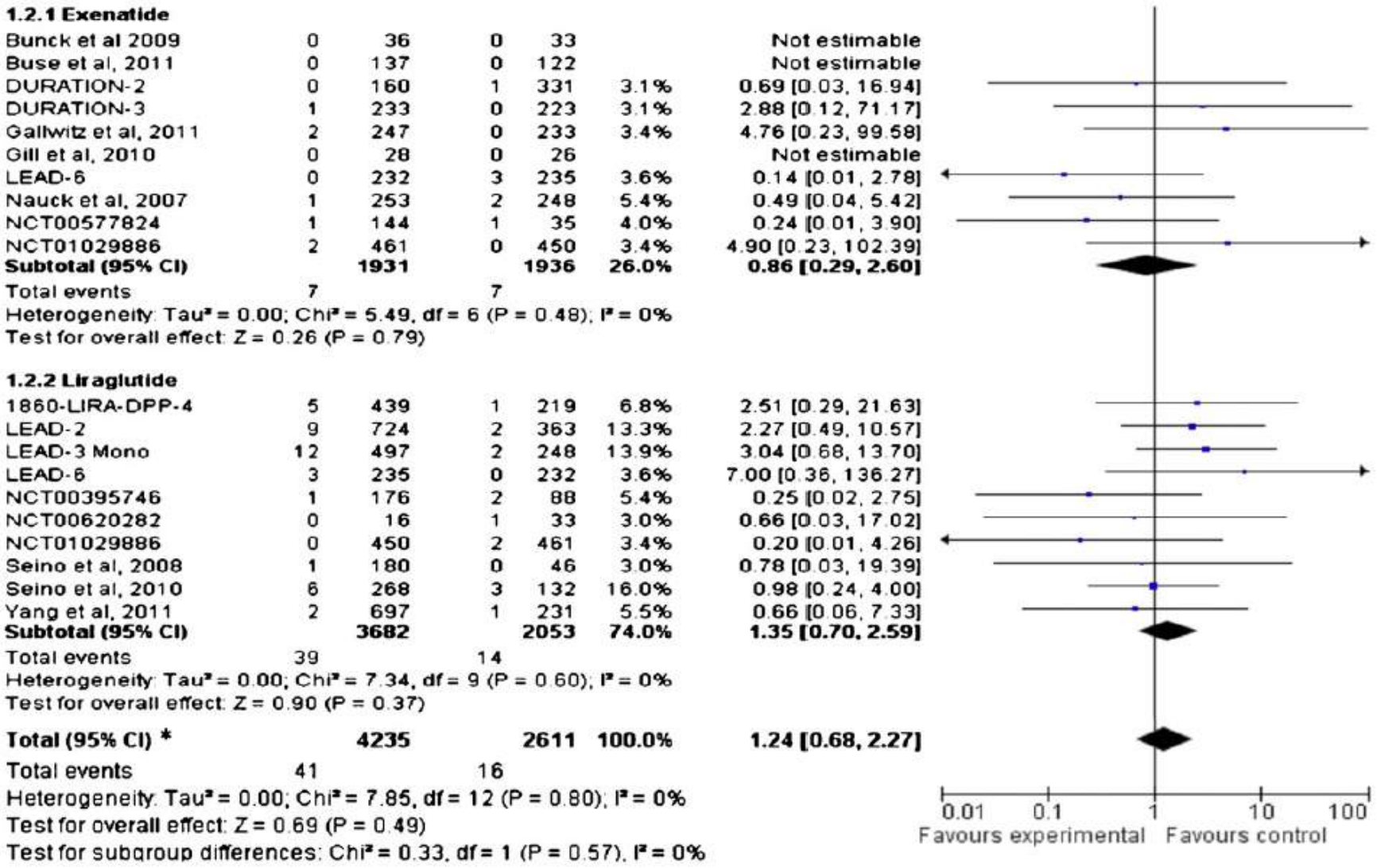


”FDA rodentlerde karsinoma insidansının **insanlar için düşük risk olarak değerlendirildiğini** bildirmekte**.** Rodentlerde bildirilmiş olan risk insanlarda beklenen ilaca maruziyetden çok daha yüksek oranda maruziyetle ortaya çıkmaktadır”

Parks & Rosebraugh. *NEJM* 2010; DOI: 10.1056/NEJMp1001578
Available at: http://content.nejm.org/cgi/content/short/NEJMp1001578?resourcetype=HWCIT

Diğer kanserler

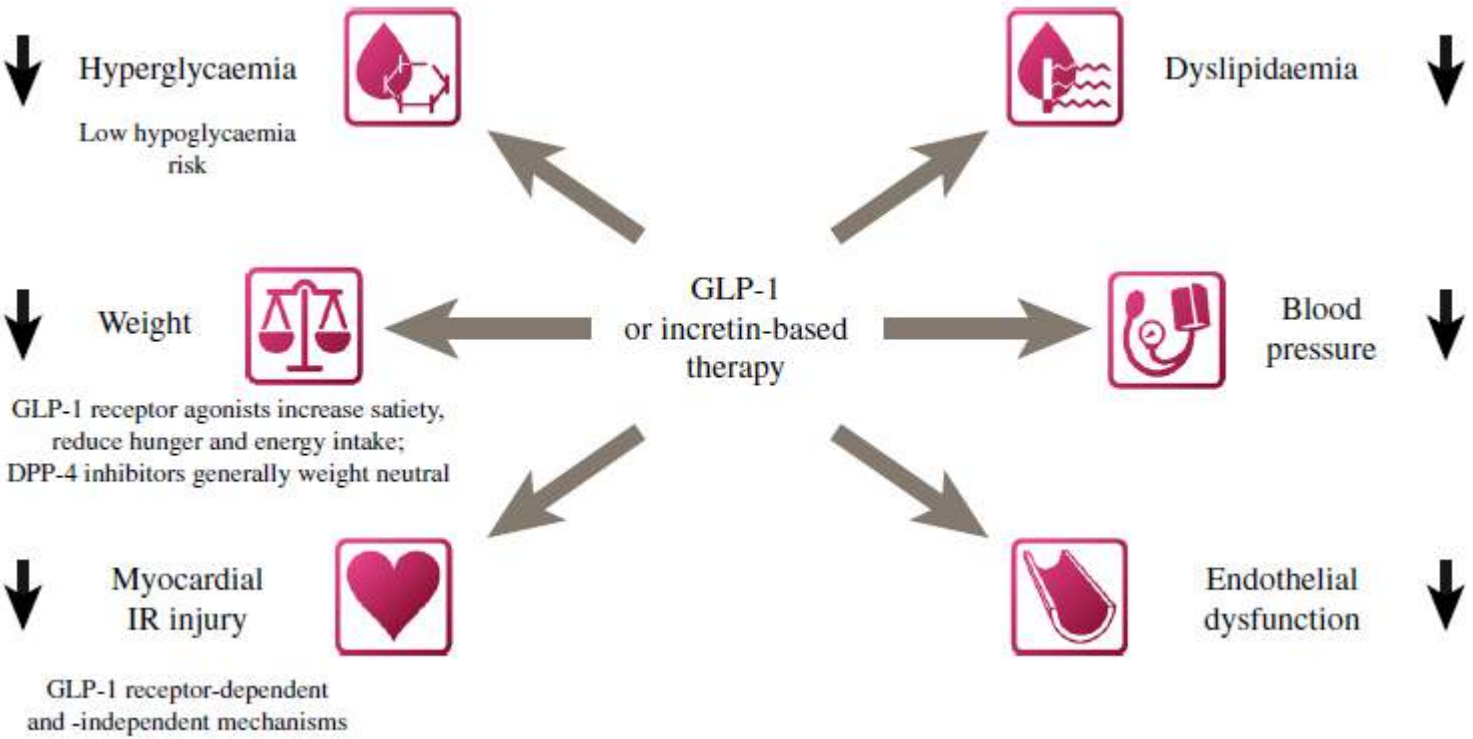
GLP-1 analogları: Tüm kanserler, metanaliz



1.2.1 Exenatide						
Bunck et al 2009	0	36	0	33		Not estimable
Buse et al, 2011	0	137	0	122		Not estimable
DURATION-2	0	160	1	331	3.1%	0.69 [0.03, 16.94]
DURATION-3	1	233	0	223	3.1%	2.88 [0.12, 71.17]
Gallwitz et al, 2011	2	247	0	233	3.4%	4.76 [0.23, 99.58]
Gill et al, 2010	0	28	0	26		Not estimable
LEAD-6	0	232	3	235	3.6%	0.14 [0.01, 2.78]
Nauck et al, 2007	1	253	2	248	5.4%	0.49 [0.04, 5.42]
NCT00577824	1	144	1	35	4.0%	0.24 [0.01, 3.90]
NCT01029886	2	461	0	450	3.4%	4.90 [0.23, 102.39]
Subtotal (95% CI)		**1931**		**1936**	**26.0%**	**0.86 [0.29, 2.60]**
Total events	7		7			
Heterogeneity: Tau² = 0.00; Chi² = 5.49, df = 6 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.79)						
1.2.2 Liraglutide						
1860-LIRA-DPP-4	5	439	1	219	6.8%	2.51 [0.29, 21.63]
LEAD-2	9	724	2	363	13.3%	2.27 [0.49, 10.57]
LEAD-3 Mono	12	497	2	248	13.9%	3.04 [0.68, 13.70]
LEAD-6	3	235	0	232	3.6%	7.00 [0.36, 136.27]
NCT00395746	1	176	2	88	5.4%	0.25 [0.02, 2.75]
NCT00620282	0	16	1	33	3.0%	0.66 [0.03, 17.02]
NCT01029886	0	450	2	461	3.4%	0.20 [0.01, 4.26]
Seino et al, 2008	1	180	0	46	3.0%	0.78 [0.03, 19.39]
Seino et al, 2010	6	268	3	132	16.0%	0.98 [0.24, 4.00]
Yang et al, 2011	2	697	1	231	5.5%	0.66 [0.06, 7.33]
Subtotal (95% CI)		**3682**		**2053**	**74.0%**	**1.35 [0.70, 2.59]**
Total events	39		14			
Heterogeneity: Tau² = 0.00; Chi² = 7.34, df = 9 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI) *		**4235**		**2611**	**100.0%**	**1.24 [0.68, 2.27]**
Total events	41		16			
Heterogeneity: Tau² = 0.00; Chi² = 7.85, df = 12 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%						

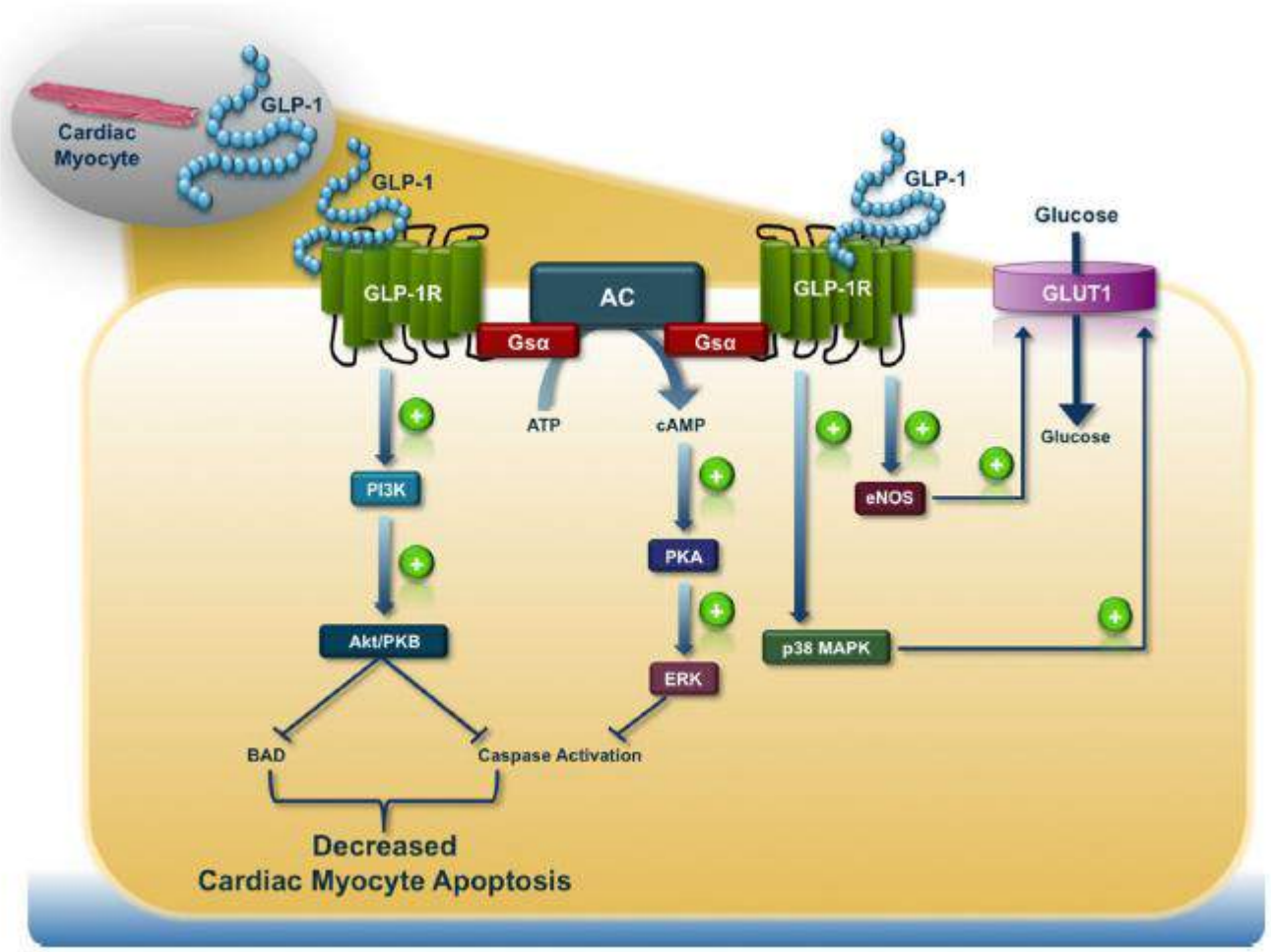
Kardiyovasküler etkiler

İnkretinlerin kardiyovasküler etki mekanizmaları



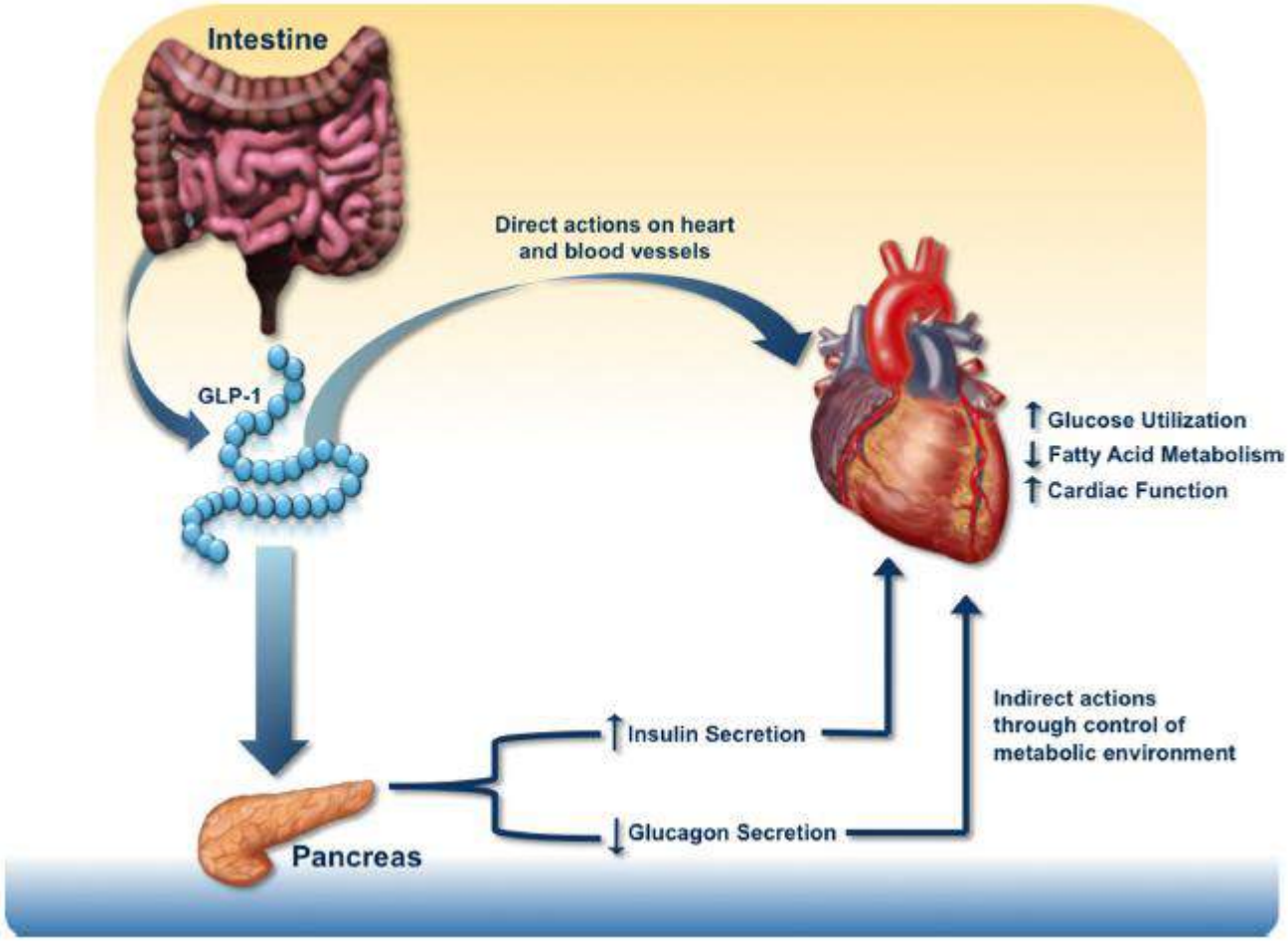
Cardiovascular Diabetology 2013, **12**:130

Kardiyak myositte GLP-1 bağımlı sinyal yolakları



Endocrine Reviews, April 2012, 33(2):187–215

GLP-1 analoglarının indirekt kardiyak etkileri

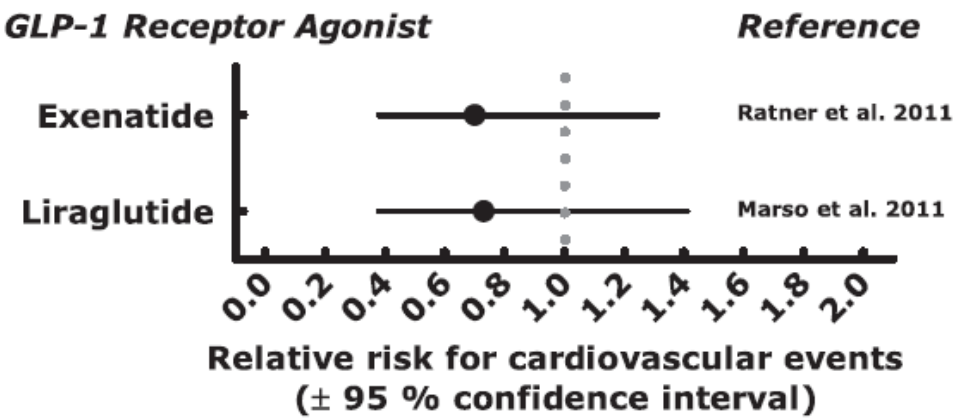


Endocrine Reviews, April 2012, 33(2):187–215

GLP-1 agonistleri ile yürütülen kardiyovasküler güvenlik çalışmaları

GLP-1 agonisti	Çalışma	Katılımcı sayısı	Başlangıç tarihi	Bitiş tarihi
Taspoglutide	T-EMERGE-8	2118	01/2010	GIS yan etkileri ve alerjik reaksiyonlar nedeniyle durduruldu.
Liraglutide	LEADER	9340	08/2010	01/2016
Exenatide	EXSCEL	9500	06/2010	03/2017
Lixisenatide	ELIXA	6000	06/2010	09/2014
Dulaglutide haftalık	REWIND	9622	07/2011	04/2019
Semaglutide	SUSTAIN 6	3260	02/2013	01/2016

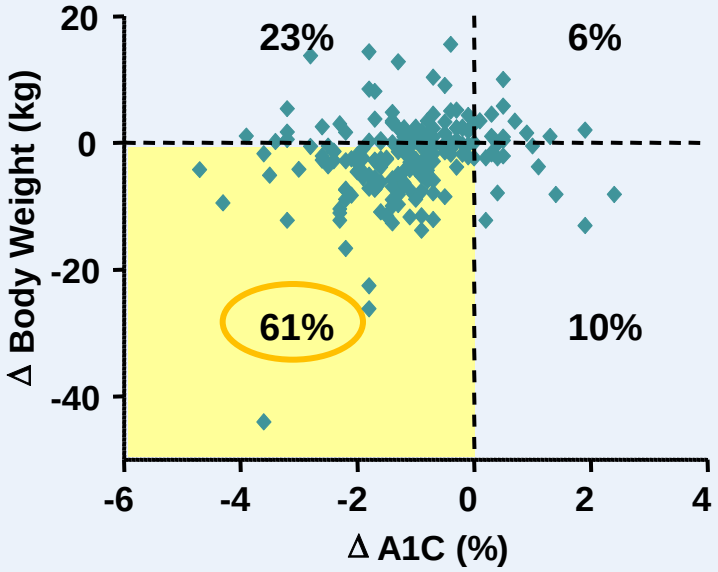
Kardiyovasküler olaylar



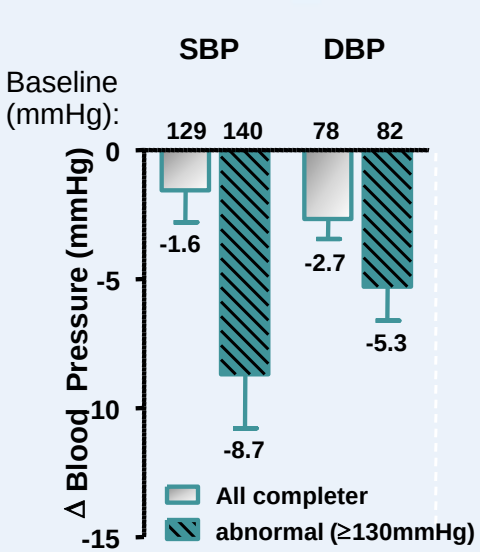
Nauck M, Diabetes Care, 2013

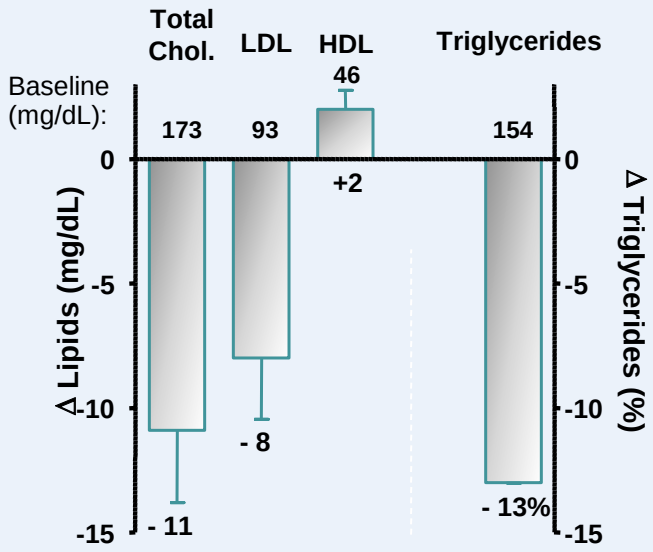
Exenatide ile 4 yıllık izlem sonunda kardiyovasküler etkiler

A1C and kg değişimi



Kardiyometabolik etkiler

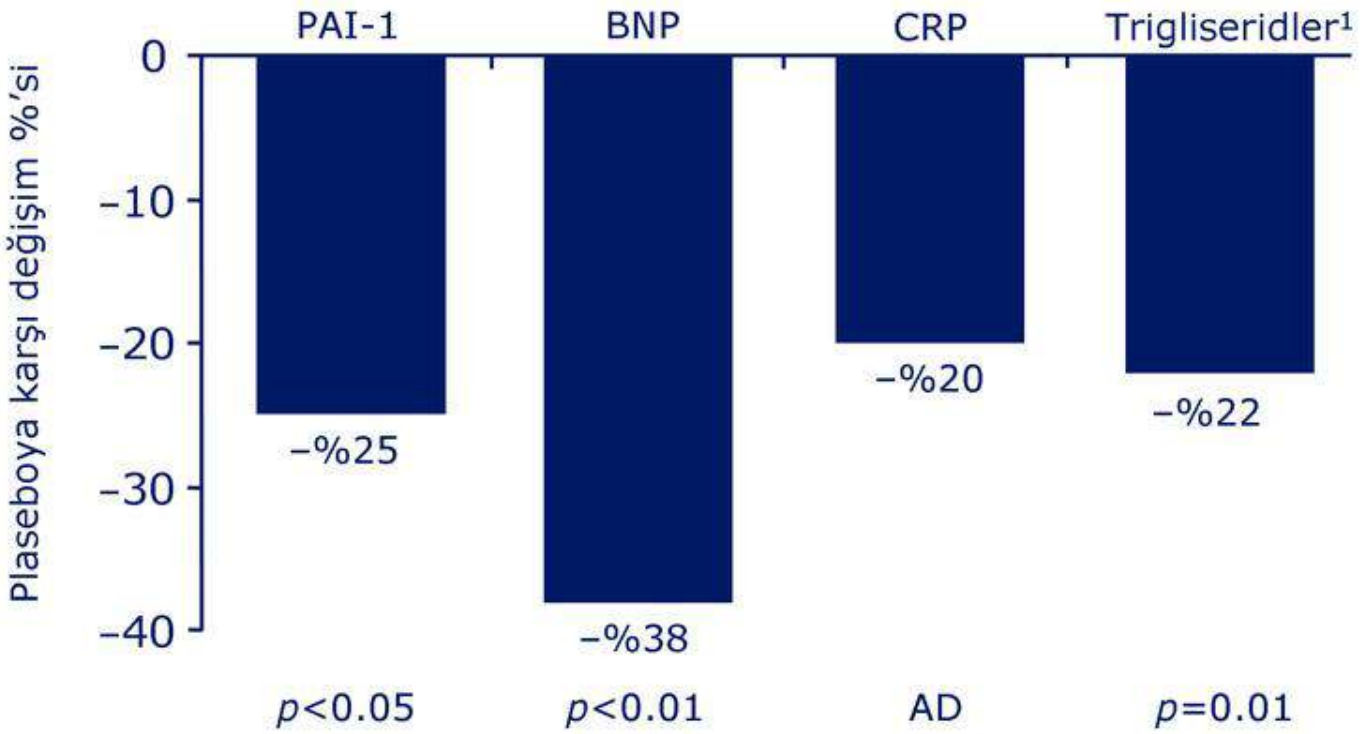




MacConell, et al., ADA Scientific Sessions 2012; June 9th 11:30am – 12:30pm, Poster Session #1156-P.

Liraglutid KV biyobelirteçlerini iyileştirir

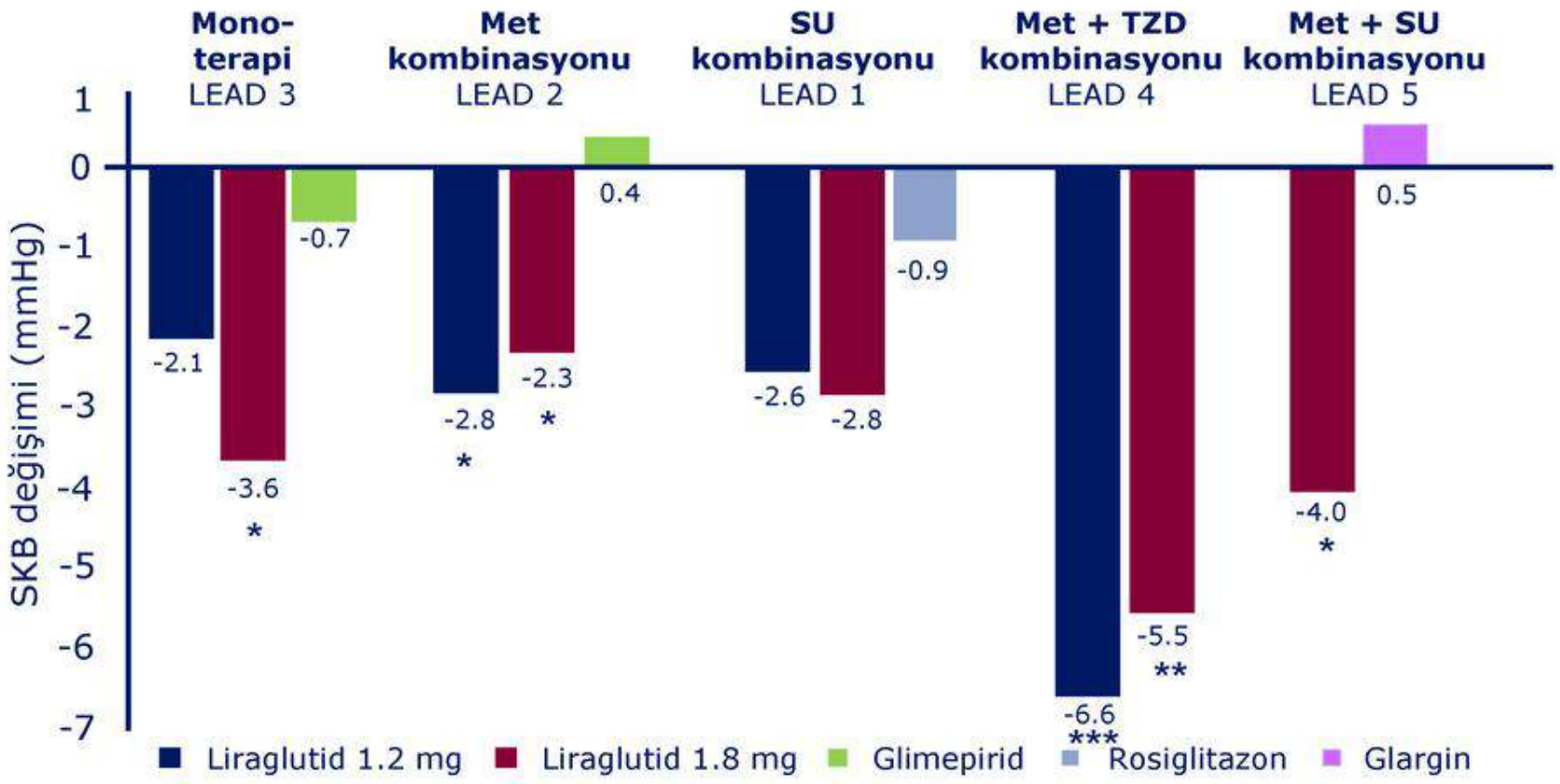
Liraglutid 1.90 mg/gün ile 14 haftalık tedavi



Plasebo karşısında *p* değerleri;
PAI-1 = plazminojen aktive edici inhibitörü; BNP = B-tipi natriüretik peptid;
CRP = C-reaktif protein;

Courrèges *et al. Diab Med* 2008:[1]Vilsbøll *et al. Diab Care* 2007;30:1608-10.Madsbad S. Diabetic Medicine 25,1125–1131

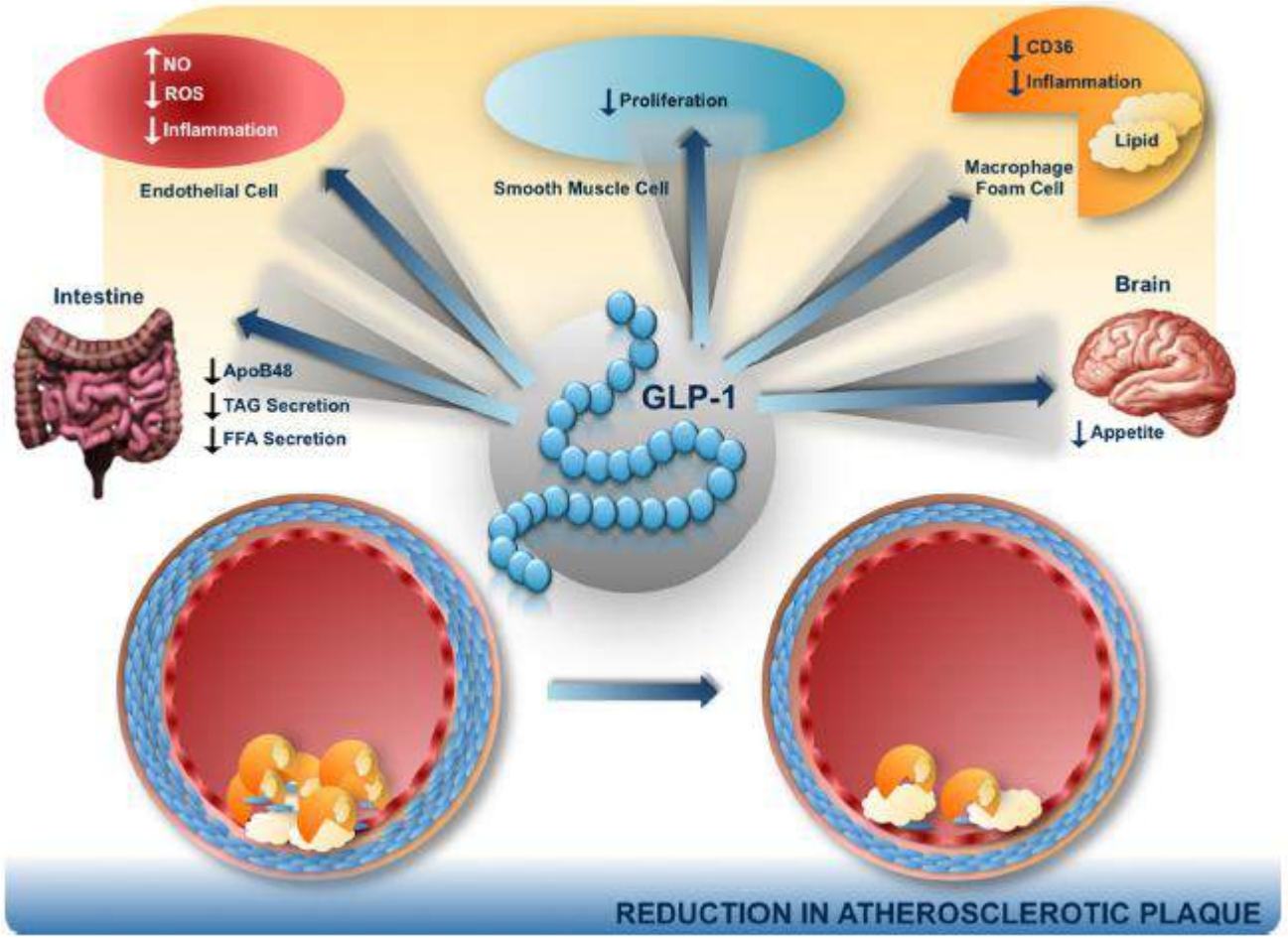
T2D tedavisinde kullanıldığında, liraglutid SKB'yi sürekli biçimde düşürür



***p<0.0001 **p<0.001 *p<0.05 vs. Başlangıç

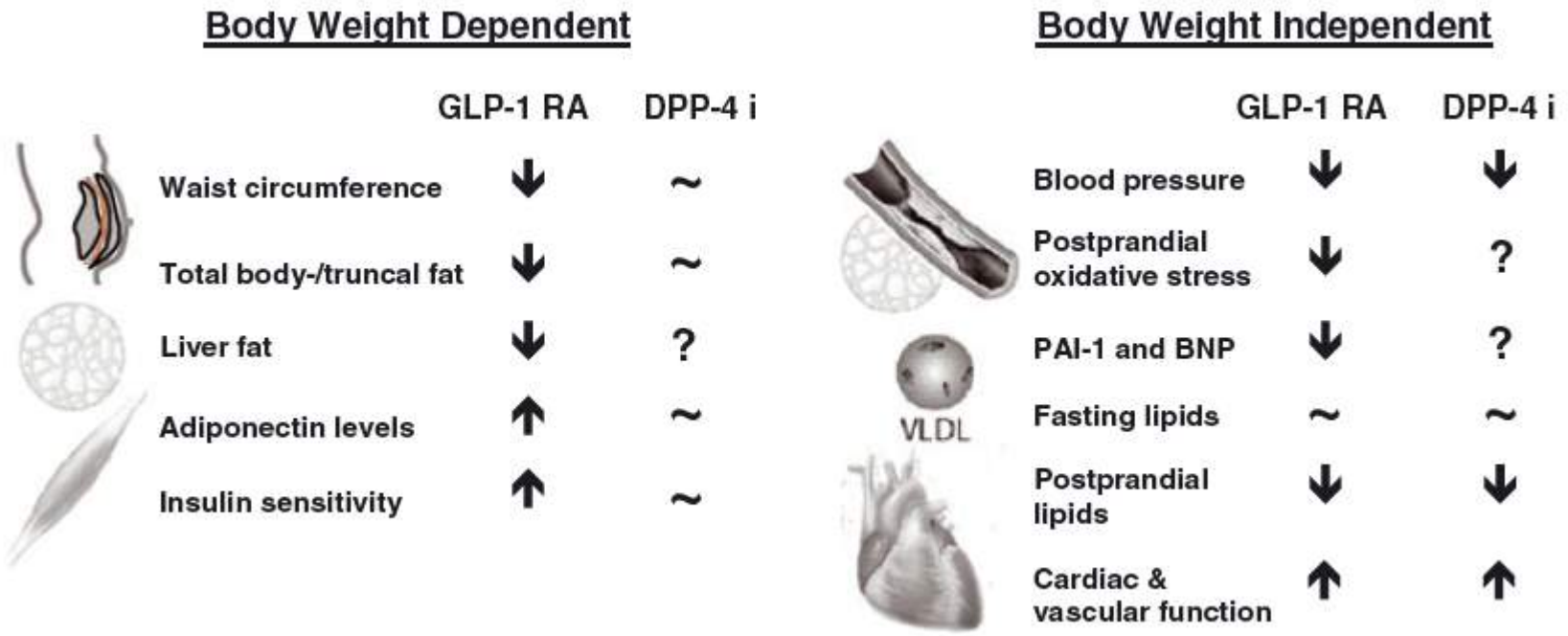
Orijinal veriler Colagiuri *et al. Diabetes* 2008;57(Suppl. 1):A16'da olduğu gibi sunulmuştur.

GLP-1 analoglarının antiaterosklerotik potansiyel etkisi için olası mekanizmalar



Endocrine Reviews, April 2012, 33(2):187–215

GLP-1 analoglarının antiaterosklerotik potansiyel etkisi için olası mekanizmalar



Diabetes, Obesity and Metabolism 15: 593–606, 2013.

Klinik çalışmalarda advers etkiler

Exanatide: Güvenlik metaanalizi

19 studies included

Inclusion criteria:

- 12 to 30 weeks in duration
- Population = type 2 diabetes
- Placebo- or comparator (insulin)-controlled study
- Efficacy and safety endpoints

Placebo-controlled studies	Duration (weeks)	Concomitant medications	Exenatide (N = ITT)	Comparator (N = ITT)	Total (N)	ClinicalTrials.gov Identifier
Apovian et al[16]	24	Met and/or SFU	96	98	194	NCT 00375492
Buse et al[2]	30	SFU	254	123	377	NCT 00039026
Buse et al[20]	30	Basal INS w/wout Met and/or TZD	137	122	259	NCT 00765817
DeFronzo et al[3]	30	Met	223	113	336	NCT 00039013
DeFronzo et al[14]	20	TZD	92	45	137	NCT 00135330
Gao et al[10]	16	Met and/or SFU	234	233	467	NCT 00324363
Gill et al[15]	12	Met and/or TZD	28	26	54	NCT 00516074
Kadowaki et al[11]	12	SFU w/wout Met	111	40	151	NCT 00382239
Kadowaki et al[17]	24	SFU w/ Met, TZD, or GAA-I, or SFU	144	35	179	NCT 00577824
Kendall et al[4]	30	Met and SFU	486	247	733	NCT 00035984
Liutkus et al[19]	26	TZD w/wout Met	111	54	165	NCT 00603239
Moretto et al[12]	24	None	155	77	232	NCT 00381342
Zinman et al[6]	16	TZD w/wout Met	121	112	233	NCT 00099320
Insulin-controlled studies	**Duration (weeks)**	**Concomitant medications**	**Exenatide (N = ITT)**	**Comparator (N = ITT)**	**Total (N)**	**ClinicalTrials.gov Identifier**
Barnett et al[7]	16	Met and SFU	136	127	263	NCT 00082407
Davies et al[13]	26	Met, TZD, or SFU (alone/combin)	118	117	235	NCT 00360334
Davis et al[8]	16	Met and/or SFU	33	16	49	NCT 00099333
Gallwitz et al[5]	26	Met w/wout SFU	247	233	480	NCT 00434954
Heine et al[5]	26	Met and SFU	282	267	549	NCT 00082381
Nauck et al[9]	52	Met and SFU	253	248	501	NCT 00082407
Total			**3261**	**2333**	**5594**	

Table 1 Summary of treatment-emergent adverse events and discontinuations

Patients with treatment-emergent AEs	Exenatide BID (N = 3261)	Pooled comparator (N = 2333)	Risk difference
	n (%)	n (%)	(95% CI)[b]
With one or more AEs	2653 (81.4)	1613 (69.1)	12.3 (9.9, 14.5)
With study drug-related AEs[a]	1569 (48.1)	372 (15.9)	32.2 (29.9, 34.4)
With GI-related AEs	1677 (51.4)	495 (21.2)	30.2 (27.8, 32.6)
With serious AEs	119 (3.6)	90 (3.9)	−0.3 (−1.2, 0.8)
With serious drug-related AEs[a]	14 (0.4)	5 (0.2)	0.2 (−0.1, 0.5)
Deaths	2 (<0.1)	3 (<0.1)	0 (−0.2, 0.1)
Discontinued due to AEs	255 (7.8)	43 (1.8)	6.0 (4.9, 7.0)
Discontinued due to drug-related AEs[a]	207 (6.3)	18 (0.8)	5.5 (4.7, 6.5)
Discontinued due to serious AEs	25 (0.8)	17 (0.7)	0.1 (−0.4, 0.5)
Discontinued due to serious drug-related AEs[a]	5 (0.2)	2 (0.1)	0.1 (−0.1, 0.2)
Discontinued due to GI-related AEs	173 (5.3)	7 (0.3)	5.0 (4.2, 5.8)

Notes: [a]Determined by the investigator to be possibly, probably, or definitely drug-related; [b]RD = Exenatide IR (%) minus pooled comparator IR (%).
Abbreviations: AEs, adverse events; BID, twice daily; CI, confidence interval; GI, gastrointestinal.

Exenatide: Güvenlik metaanalizi

Table 2 Summary of treatment-emergent adverse events by system organ class

System organ class[a]	Exenatide BID (N = 3261) n (%)	Pooled comparator (N = 2333) n (%)	Risk difference (95% CI)[b]
Blood and lymphatic system disorders	34 (1.0)	17 (0.7)	0.3 (−0.2, 0.8)
Cardiac disorders	68 (2.1)	53 (2.3)	−0.2 (−1.0, 0.6)
Congenital, familial, and genetic disorders	2 (<0.1)	1 (0.0)	<0.1 (−0.1, 0.1)
Ear and labyrinth disorders	49 (1.5)	52 (2.2)	−0.7 (−1.5, 0.0)
Endocrine disorders	10 (0.3)	2 (<0.1)	0.2 (−0.0, 0.4)
Eye disorders	90 (2.8)	65 (2.8)	0 (−0.9, 0.8)
Gastrointestinal disorders	1677 (51.4)	495 (21.2)	30.2 (27.8, 32.6)
General disorders and administration site conditions	586 (18.0)	283 (12.1)	5.9 (4.0, 7.7)
Hepatobiliary disorders	24 (0.7)	15 (0.6)	0.1 (−0.3, 0.5)
Immune system disorders	50 (1.5)	29 (1.2)	0.3 (−0.3, 0.9)
Infections and infestations	971 (29.8)	731 (31.3)	−1.5 (−4.0, 0.9)
Injury, poisoning, and procedural complications	234 (7.2)	153 (6.6)	0.6 (−0.7, 2.0)
Investigations	231 (7.1)	94 (4.0)	3.1 (1.9, 4.2)
Metabolism and nutrition disorders	1128 (34.6)	719 (30.8)	3.8 (1.3, 6.3)
Musculoskeletal and connective tissue disorders	471 (14.4)	356 (15.3)	−0.9 (−2.7, 1.1)
Neoplasms, benign, malignant, and unspecified	36 (1.1)	18 (0.8)	0.3 (−0.2, 0.8)
Nervous system disorders	602 (18.5)	332 (14.2)	4.3 (2.3, 6.2)
Pregnancy, puerperium, and perinatal conditions	1 (0.0)	0 (0.0)	0 (−0.0, 0.1)
Psychiatric disorders	153 (4.7)	77 (3.3)	1.4 (0.4, 2.4)
Renal and urinary disorders	69 (2.1)	53 (2.3)	−0.2 (−0.9, 0.6)
Reproductive system and breast disorders	64 (2.0)	34 (1.5)	0.5 (−0.2, 1.2)
Respiratory, thoracic, and mediastinal disorders	313 (9.6)	220 (9.4)	0.2 (−1.4, 1.7)
Skin and subcutaneous tissue disorders	260 (8.0)	163 (7.0)	1.0 (−0.4,2.4)
Social circumstances	5 (0.2)	1 (0.0)	0.2 (−0.0, 0.3)
Surgical and medical procedures	86 (2.6)	47 (2.0)	0.6 (−0.2, 1.4)
Vascular disorders	107 (3.3)	78 (3.3)	0 (−1.0, 0.9)

Notes: [a]Events listed by system organ class are indicated by number (n) of patients who experienced an adverse event; [b]RD = Exenatide IR (%) minus pooled comparator IR (%).
Abbreviations: BID, twice daily; CI, confidence interval.

Exanatide: Güvenlik metaanalizi

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Cardiac disorders	68 (2.1)	53 (2.3)	−0.2 (−1.0, 0.6)
Congenital, familial, and genetic disorders	2 (<0.1)	1 (0.0)	<0.1 (−0.1, 0.1)
Ear and labyrinth disorders	49 (1.5)	52 (2.2)	−0.7 (−1.5, 0.0)
Endocrine disorders	10 (0.3)	2 (<0.1)	0.2 (−0.0, 0.4)
Eye disorders	90 (2.8)	65 (2.8)	0 (−0.9, 0.8)
Gastrointestinal disorders	1677 (51.4)	495 (21.2)	30.2 (27.8, 32.6)
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Nervous system disorders	602 (18.5)	332 (14.2)	4.3 (2.3, 6.2)
Pregnancy, puerperium, and perinatal conditions	1 (0.0)	0 (0.0)	0 (−0.0, 0.1)
Psychiatric disorders	153 (4.7)	77 (3.3)	1.4 (0.4, 2.4)
Renal and urinary disorders	69 (2.1)	53 (2.3)	−0.2 (−0.9, 0.6)
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Social circumstances	5 (0.2)	1 (0.0)	0.2 (−0.0, 0.3)
Surgical and medical procedures	86 (2.6)	47 (2.0)	0.6 (−0.2, 1.4)
Vascular disorders	107 (3.3)	78 (3.3)	0 (−1.0, 0.9)

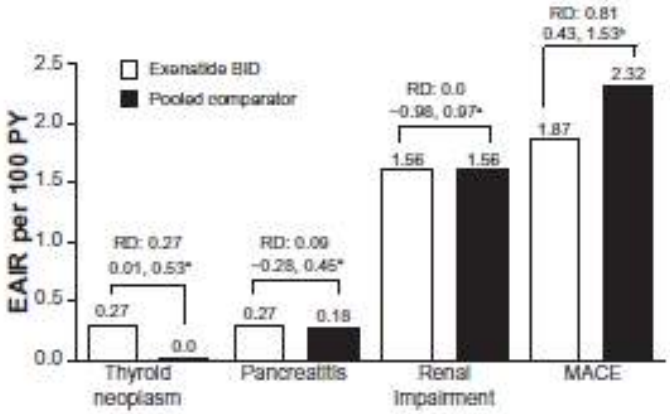
Notes: [a]Events listed by system organ class are indicated by number (n) of patients who experienced an adverse event; [b]RD = Exenatide IR (%) minus pooled comparator IR (%).
Abbreviations: BID, twice daily; CI, confidence interval.

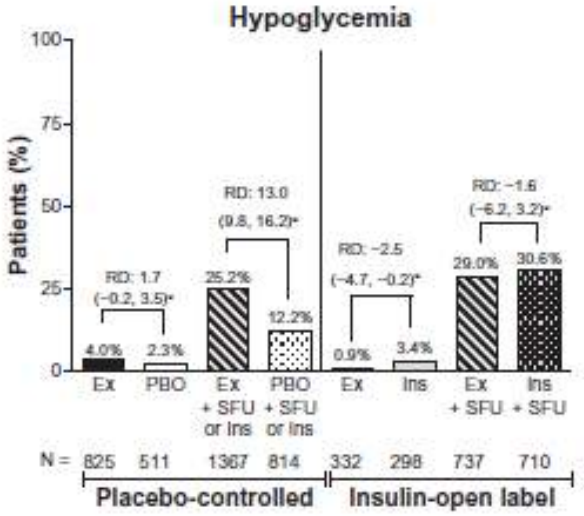
Exanatide: Güvenlik metaanalizi

Table 3 Frequent (≥5%) treatment-emergent adverse events

Preferred term*	Exenatide BID (N = 3261) n (%)	Pooled comparator (N = 2333) n (%)	Risk difference (95% CI)
Nausea	1202 (36.9)	193 (8.3)	28.6 (26.6, 30.6)
Vomiting	442 (13.6)	67 (2.9)	10.7 (9.3, 12.0)
Diarrhea	346 (10.6)	127 (5.4)	5.2 (3.8, 6.6)
Dizziness	173 (5.3)	78 (3.3)	2.0 (0.9, 3.0)
Headache	275 (8.4)	173 (7.4)	1.0 (−0.4, 2.4)
Nasopharyngitis	288 (8.8)	219 (9.4)	−0.6 (−2.1, 1.0)
Upper respiratory tract infection	193 (5.9)	137 (5.9)	0 (−1.2, 1.3)

Notes: Events listed by preferred term (MedDRA v 13.0 terms) are indicated by number (n) of patients who experienced an adverse event.
Abbreviations: BID, twice daily; CI, confidence interval.





Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2012:5

Haftalık exanatide: Duration-2 çalışması

	Exenatide once weekly (n=160)		Sitagliptin (n=166)		Pioglitazone (n=165)	
	Patients	Events	Patients	Events	Patients	Events
Non-cardiac chest pain	0	0	1 (1%)	1	1 (1%)	1
Coronary artery occlusion	0	0	0	0	2 (1%)	2
Cerebrovascular accident	0	0	1 (1%)	1	1 (1%)	1
Pancreatitis	0	0	0	0	2 (1%)	2
Papillary thyroid cancer	0	0	1 (1%)	1	0	0
Nausea	38 (24%)	62	16 (10%)	22	8 (5%)	9
Diarrhoea	29 (18%)	39	16 (10%)	21	12 (7%)	13
Upper-respiratory-tract infection	6 (4%)	7	15 (9%)	16	17 (10%)	20
Headache	15 (9%)	16	15 (9%)	19	7 (4%)	9
Vomiting	18 (11%)	29	4 (2%)	4	5 (3%)	7
Urinary-tract infection	10 (6%)	10	9 (5%)	10	6 (4%)	7
Peripheral oedema	2 (1%)	3	5 (3%)	5	13 (8%)	14
Injection-site pruritus	8 (5%)	8	8 (5%)	13	2 (1%)	2
Sinusitis	5 (3%)	5	2 (1%)	2	11 (7%)	12
Fatigue	9 (6%)	10	0	0	5 (3%)	9
Constipation	9 (6%)	9	3 (2%)	4	2 (1%)	2

Lancet 2010; 376: 431–39

Sonuç

- Mevcut veriler ışığında inkretin tabanlı tedavilerin güvenlik verileri takip edilmeldir.
- Bugün için inkretin tabanlı tedavileri almakta olan hastaların tedavilerin değiştirilmesi veya tedaviden vaz geçilmesini gerekli kılan güçlü kanıtlar bulunmamaktadır.
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