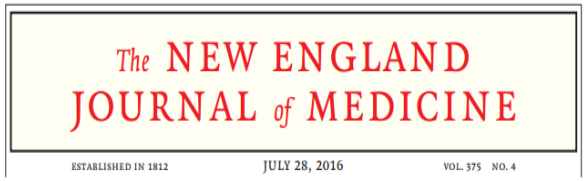
Son Diyabet Çalışmalarından Mesajlar

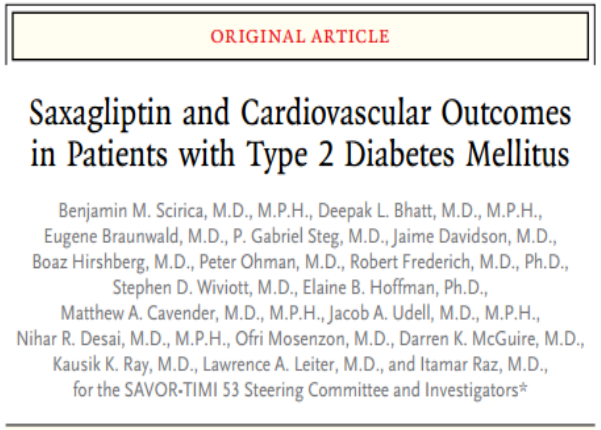


The NEW ENGLAND JOURNAL of MEDICINE

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

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

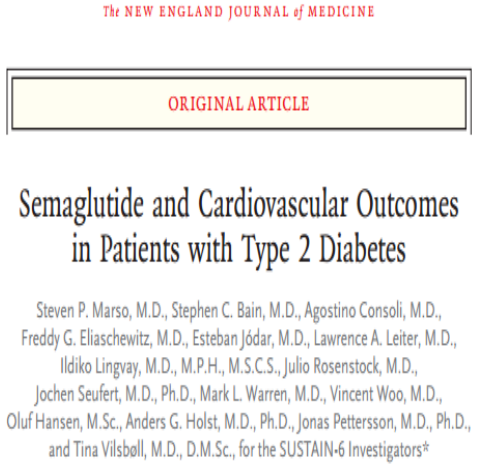
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette 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*



ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mosenzon, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

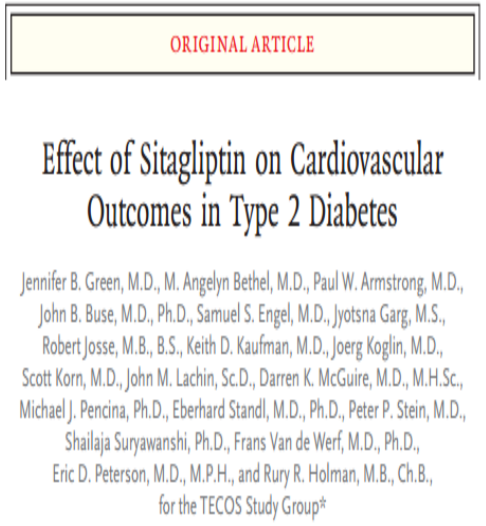


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

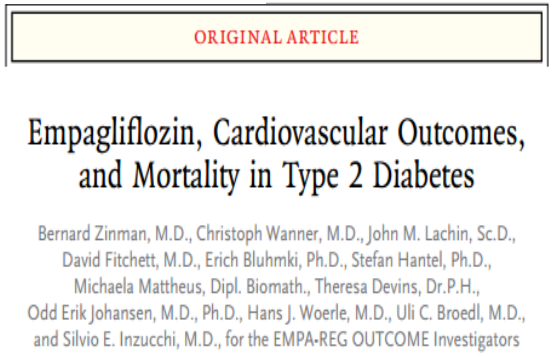
Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*



ORIGINAL ARTICLE

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D., John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S., Robert Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D., Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc., Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B., for the TECOS Study Group*



ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Dr Miraç Vural Keskinler
Dr Aytekin Oğuz

KARDİYOVASKÜLER GÜVENLİK ÇALIŞMALARI

- 2008 yılından itibaren FDA yeni çıkacak olan antihiperglisemik ajanlar için;
  - Kardiyovasküler hastalık riski yüksek olan hastalarda
  - En az 2 yıl sürecek
  - Bağımsız bir komitenin değerlendireceği güvenlik çalışması şartını getirmiştir

T2DM'ta KV Sonlanımları Değerlendiren Farklı Çalışmalar: «Yakın Zamanda Tamamlanmış ya da Devam Eden»

Çalışma Adı	Molekül	Hedef Hasta	Zamanlama
SAVOR	Saxagliptin	N=16,492	Başlangıç 2010; Tamamlanmış
EXAMINE	Alogliptin	N=5384	Başlangıç 2009; Tamamlanmış
TECOS	Sitagliptin	N=14,000	Başlangıç 2008; Tamamlanmış
CAROLINA	Linagliptin	N=6000	Başlangıç 2010; Bitiş 2018
CARMELINA	Linagliptin	N=8300	Başlangıç 2013; Bitiş 2018
ELIXA	Lixisenatide	N=6000	Başlangıç 2010; Tamamlanmış
EXSCEL	Exenatide	N=9500	Başlangıç 2010; Bitiş 2017
LEADER	Liraglutide	N=9340	Başlangıç 2010; Tamamlanmış
REWIND	Dulaglutide	N=9622	Başlangıç 2011; Bitiş 2019
SUSTAIN 6	Semaglutide	N=3260	Başlangıç 2013; Tamamlanmış
EMPA-REG OUTCOME	Empagliflozin	N=7000	Başlangıç 2010-Tamamlanmış
CANVAS	Canagliflozin	N=4410	Başlangıç 2009; Bitiş 2018
C-SCADE 8	Empagliflozin	N=7000	Başlangıç 2010; Bitiş 2018
DECLARE	Dapagliflozin	N=17,150	Başlangıç 2013; Bitiş 2019

Primer sonlanım noktaları

- **Primer sonlanım noktaları**
  - **KV ölüm**
  - **MI**
  - **İnme**
  - **Kararsız anjina nedeniyle hastaneye yatış (**TECOS,ELIXA,CAROLINA)

Tip 2 Diyabette Liraglutid ve Kardiyovasküler Sonuçlar (LEADER®)

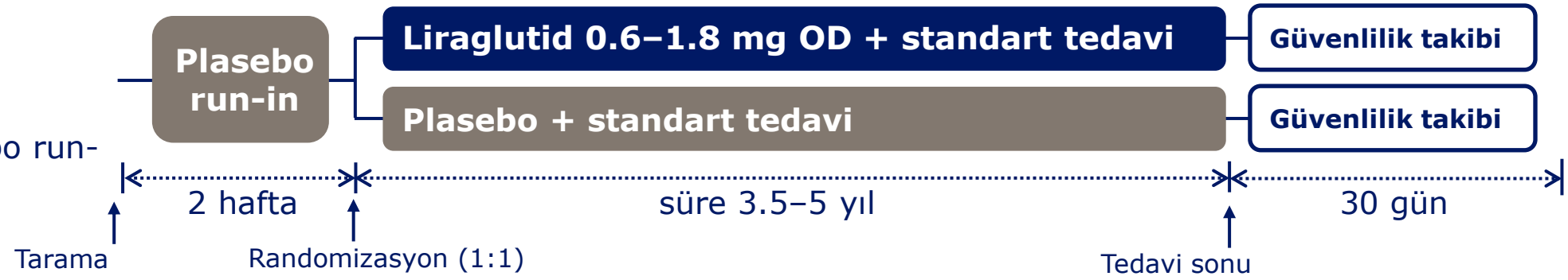
S.P. Marso, G.H. Daniels, K.B. Frandsen, P. Kristensen, J.F.E. Mann, M.A. Nauck, S.E. Nissen, S. Pocock, N.R. Poulter, L.S. Ravn, W.M. Steinberg, M. Stockner, B. Zinman, R.M. Bergenstal, and J.B. Buse

Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

LEADER: Çalışma tasarımı

9340 hasta

- Çift kör
- 2 haftalık plasebo run-in dönemi



Ana dahil etme kriterleri

- T2DM, HbA_{1c} ≥7.0%
- Antidiyabetik ilaç almamış; OAD'ler ve/veya bazal/premix insulin
- Yaş≥50 yıl ve bilinen KV hastalık veya kronik renal yetmezlik **veya**
- Yaş≥60 yıl ve KV hastalık için risk faktörleri

Ana dışlama kriterleri

- T1DM
- GLP-1RA, DPP-4i, pramlintid veya hızlı etkili insülin
- Kişisel veya ailesel MEN-2 veya MTC öyküsü

CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Primer sonlanım noktası

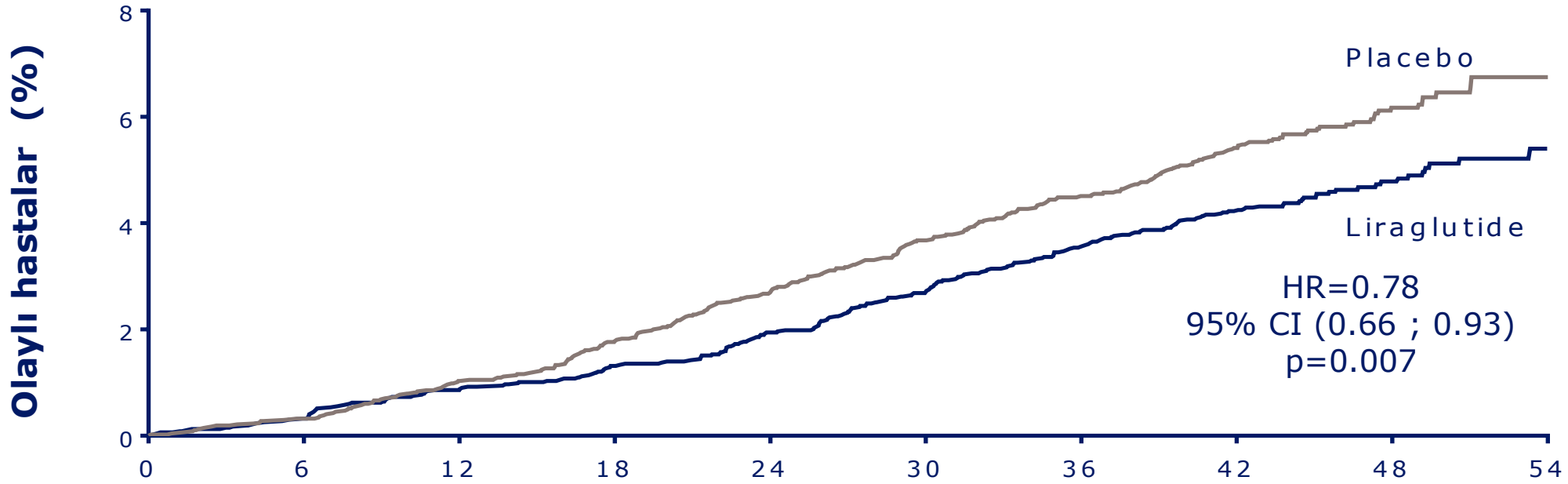
KV ölüm, non-fatal miyokardiyal enfarktüs veya non-fatal inme

Riskli hastalar

Liraglutid	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Plasebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal miyokardiyal enfarktüs , or non-fatal inme. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the Risk Oranı s with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 ay, because less than 10% of the patients had an observation time beyond 54 ay.
CI: confidence interval; CV: cardiovascular; HR: Risk Oranı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

KV Ölüm

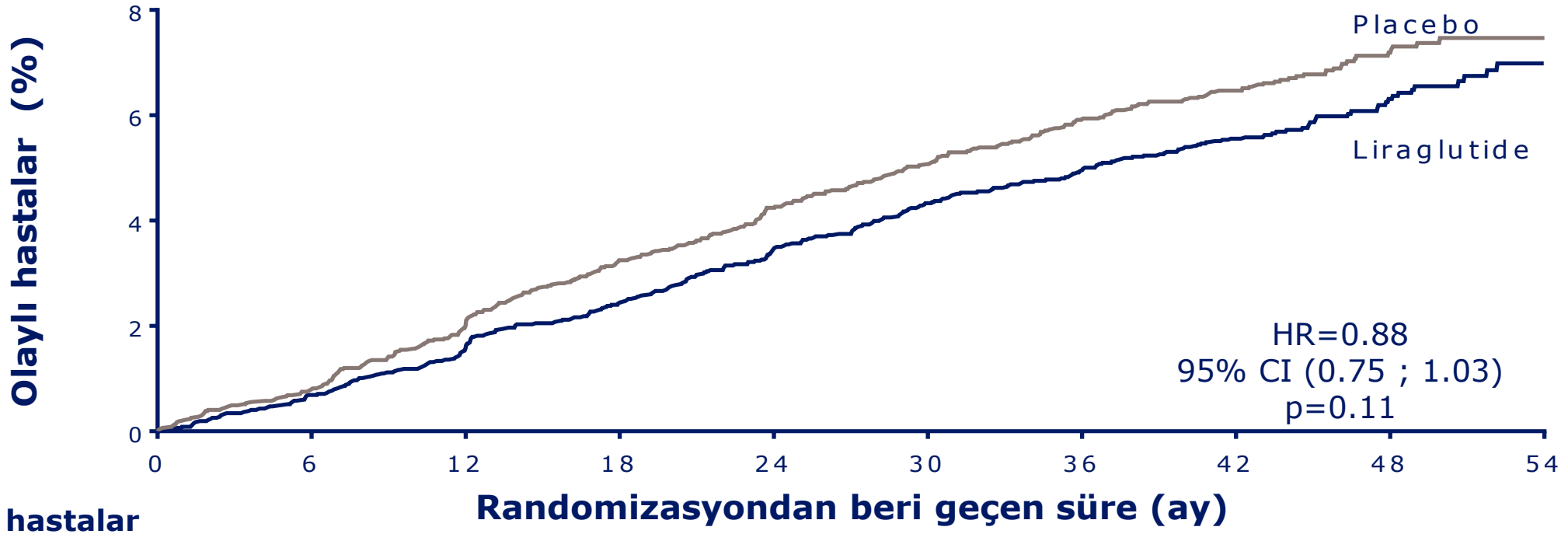


Riskli hastalar

Liraglutid	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Plasebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the Risk Oranı s with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 ay, because less than 10% of the patients had an observation time beyond 54 ay.
CI, confidence interval; CV, cardiovascular; HR, Risk Oranı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Non-fatal miyokardiyal enfarktüsü

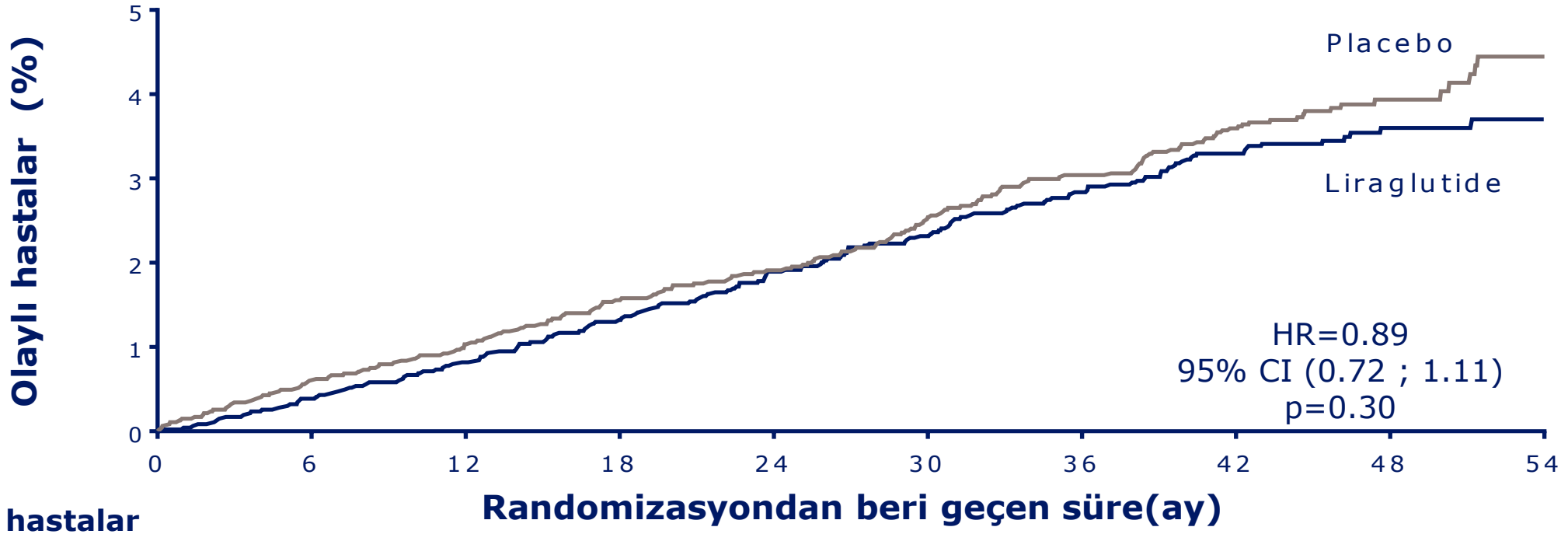


Riskli hastalar

Liraglutid	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Plasebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the Risk Oranı s with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 ay, because less than 10% of the patients had an observation time beyond 54 ay.
CI, confidence interval; HR, Risk Oranı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Non-fatal inme

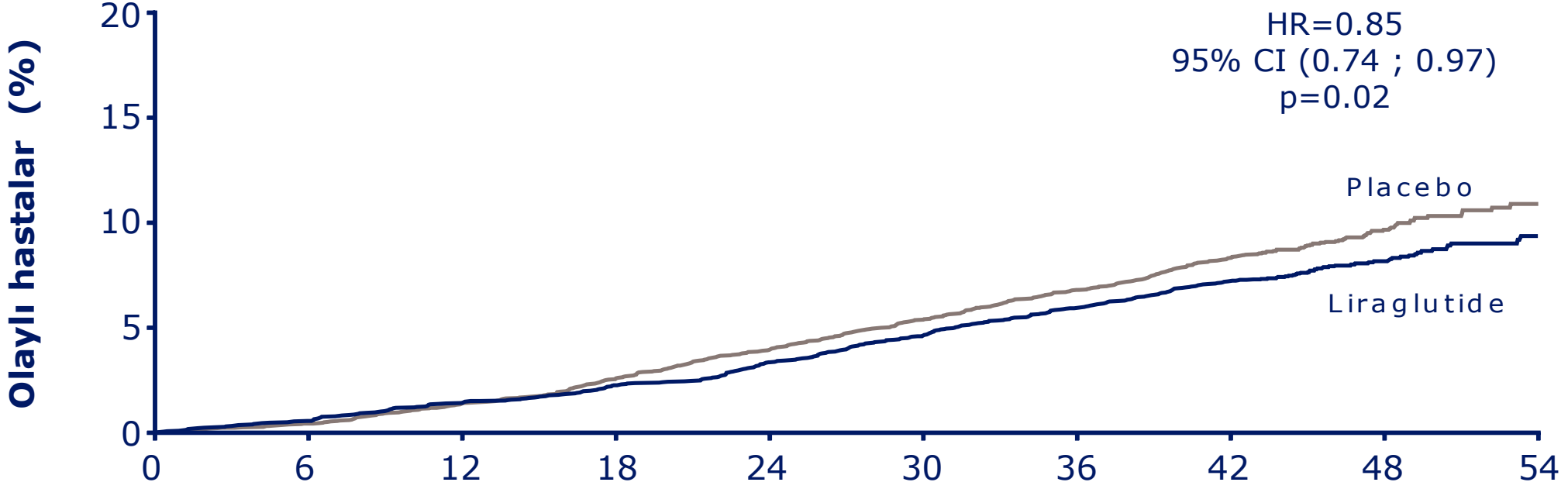


Riskli hastalar

Liraglutid	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Plasebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the Risk Oranı s with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 ay, because less than 10% of the patients had an observation time beyond 54 ay.
CI, confidence interval; HR, Risk Oranı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Tüm sebeplerden ölüm

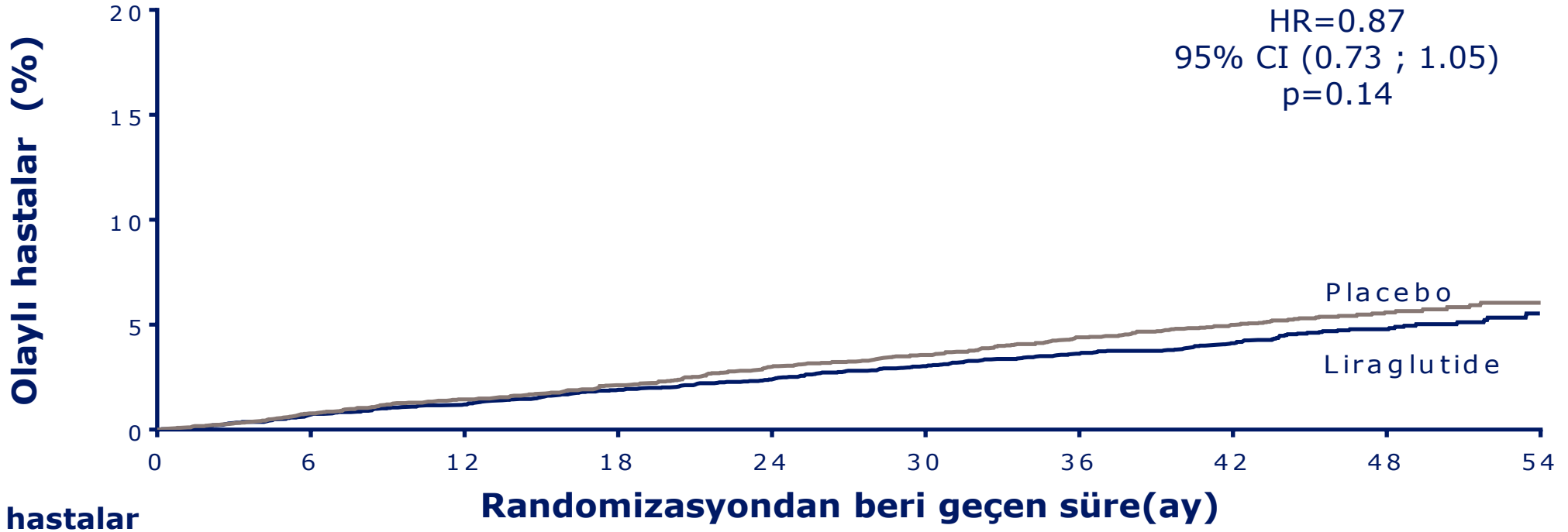


Riskli hastalar

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

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the Risk Oranı s with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 ay, because less than 10% of the patients had an observation time beyond 54 ay.
CI, confidence interval; HR, Risk Oranı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Kalp yetmezliği için hospitalizasyon

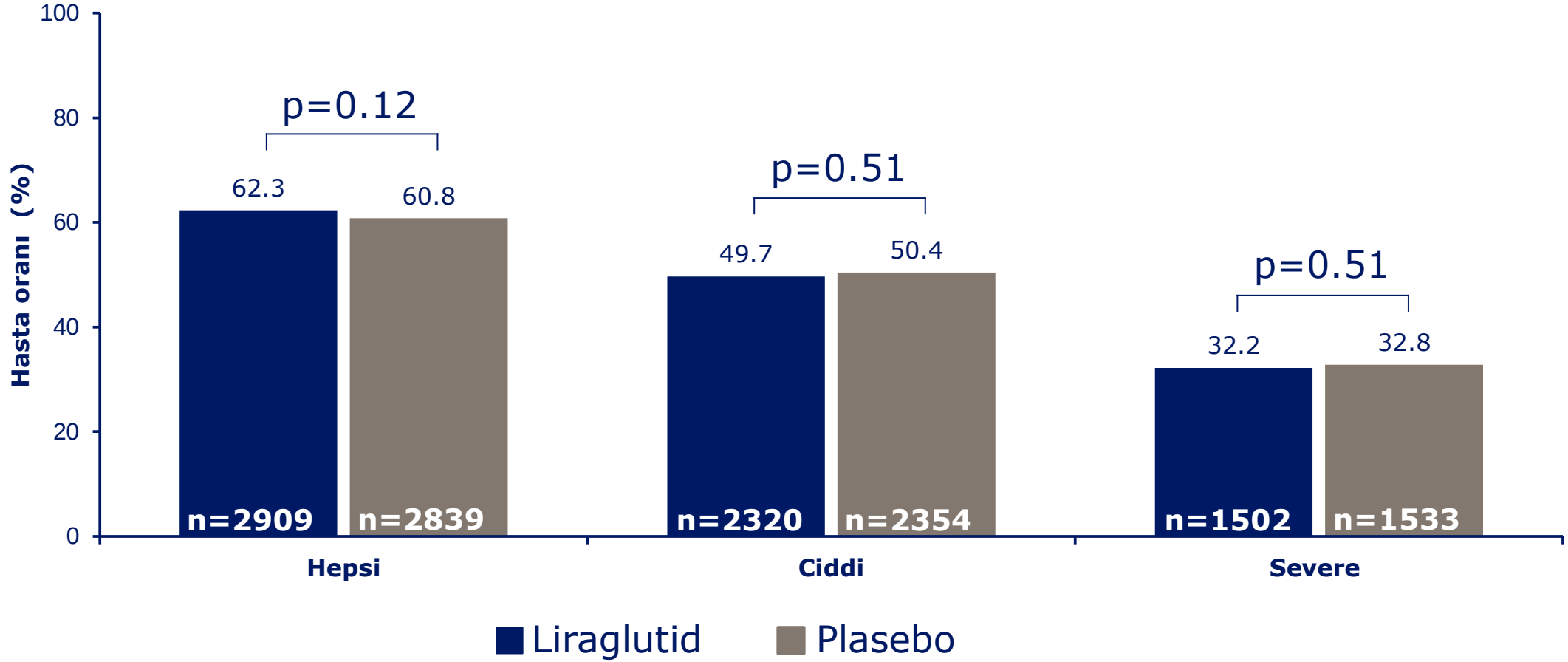


Riskli hastalar

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

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the Risk Oranı s with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 ay, because less than 10% of the patients had an observation time beyond 54 ay.
CI, confidence interval; HR, Risk Oranı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

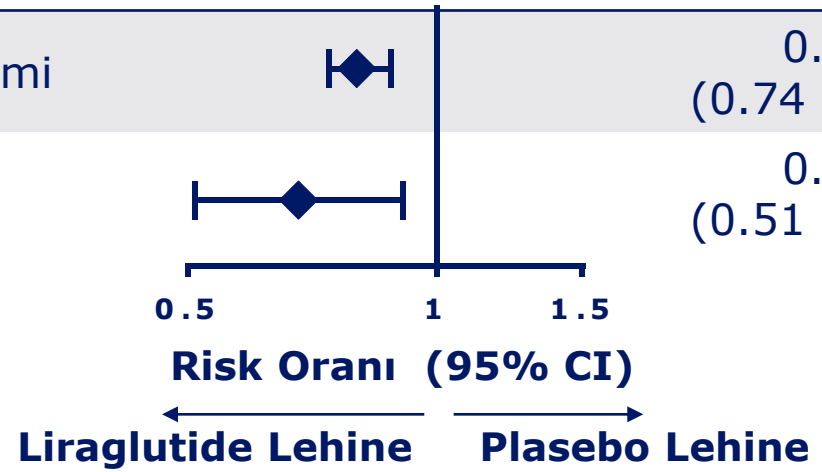
Advers olaylar



Full analysis set.
A Ciddi advers olay was defined as an experience that at Tümü dose resulted in Tümü of the following: death, a life-threatening experience, in-patient hospitalisation or prolongation of hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, important medical events that may jeopardise the patient based upon appropriate medical judgement. A Şiddetli advers olay was defined as a non-Ciddi advers olay that resulted in considerable interference with the patient's daily activities. N, Hasta sayısı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Hipoglisemi

	Risk oranı (95% CI)	p-değeri	Liraglutid N	Liraglutid %	Plasebo N	Plasebo %
Doğrulanmış hipoglisemi	0.80 (0.74 ; 0.88)	<0.001	2039	43.7	2130	45.6
Şiddetli hipoglisemi	0.69 (0.51 ; 0.93)	0.016	114	2.4	153	3.3



Confirmed hypoglycaemia was defined as plasma glucose level of less than 56 mg per decilitre (3.1 mmol per litre) or a Şiddetli event. Şiddetli hypoglycaemia was defined as hypoglycaemia for which the patient required assistance from a third party. Analysed using a negative binomial regression model.
CI, confidence interval.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Pankreatik kanser

Aşağıdakilerle belirlenen pankreatik kanser:	Liraglutid	Plasebo
Neoplazm kararı .	13	5
Ölüm (KV veya non-KV)	0	4
Neoplazm + ölüm	**13**	**9**

AE, advers olay; CV, cardiovascular.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Pankreatit (teyit edilmiş)

	Liraglutid		Plasebo		p-değeri
	N	%	N	%	
Akut pankreatit	18	0.4	23	0.5	0.44
Kronik pankreatit	0	0.0	2	0.0	0.16

Full analysis set. The occurrence of pankreatit was adjudicated by the event adjudication committee. p-değeris were calculated by means of Pearson's chi-square test
%, Hasta oranı ; N, Hasta sayısı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

SON ÇALIŞMALARA GENEL BAKIŞ

PRİMER SONLANIMLAR-1

TECOS (Sitagliptin)
SAVOR-TIMI (Saxagliptin)
EXAMINE (Alogliptin)
ELIXA (Lixisenatid)

NON-INFERIOR
Primer sonlanım noktası plasebo ile benzer bulunmuştur

PRİMER SONLANIMLAR-2

EMPA-REG (Empagliflozin)

LEADER (Liraglutid)

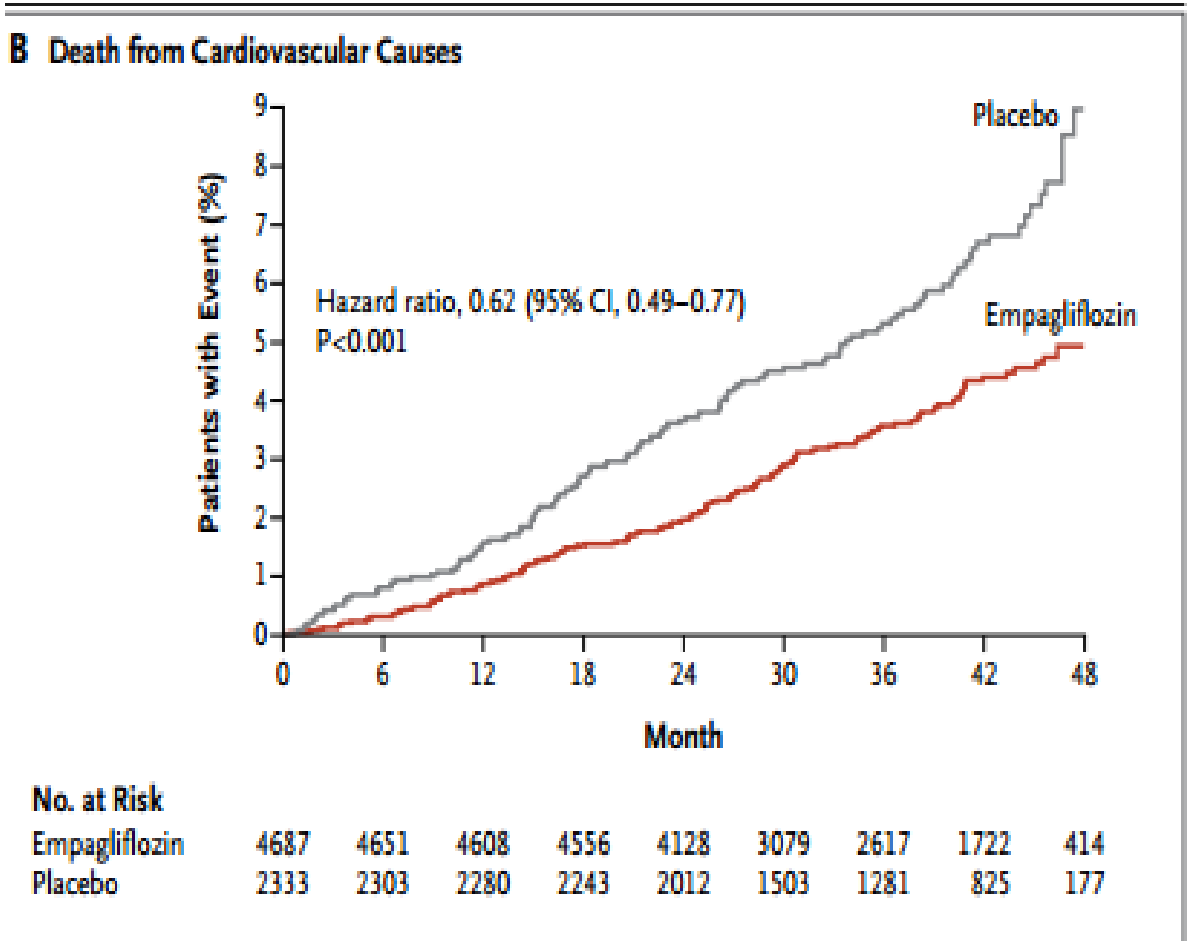
SUSTAIN-6 (Semaglutid)

Primer sonlanım noktaları plaseboya göre daha iyi

KARDİYOVASKÜLER ÖLÜM

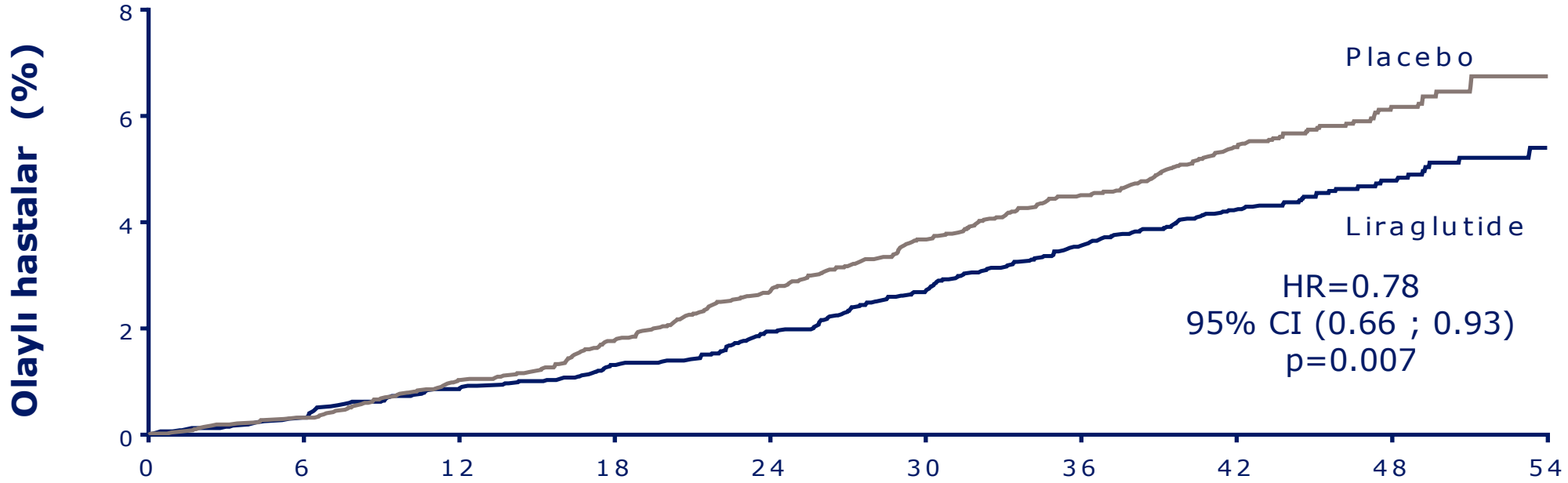
- ✓ Tamamlanmış çalışmalardaki yeni ajanların hiçbirisi kardiyovasküler ölümü plaseboya göre ARTIRMAMIŞTIR!
- ✓ **EMPA-REG ve LEADER** çalışmalarında kardiyovasküler ölüm plaseboya kıyasla AZALMIŞTIR!

EMPA-REG



KARDİYOVASKÜLER ÖLÜMÜN %38 ORANINDA AZALDIĞI GÖRÜLDÜ!

Kardiyovasküler ölüm
LEADER



Riskli hastalar

Liraglutid	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Plasebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the Risk Oranı s with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 ay, because less than 10% of the patients had an observation time beyond 54 ay.
CI, confidence interval; CV, cardiovascular; HR, Risk Oranı .
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

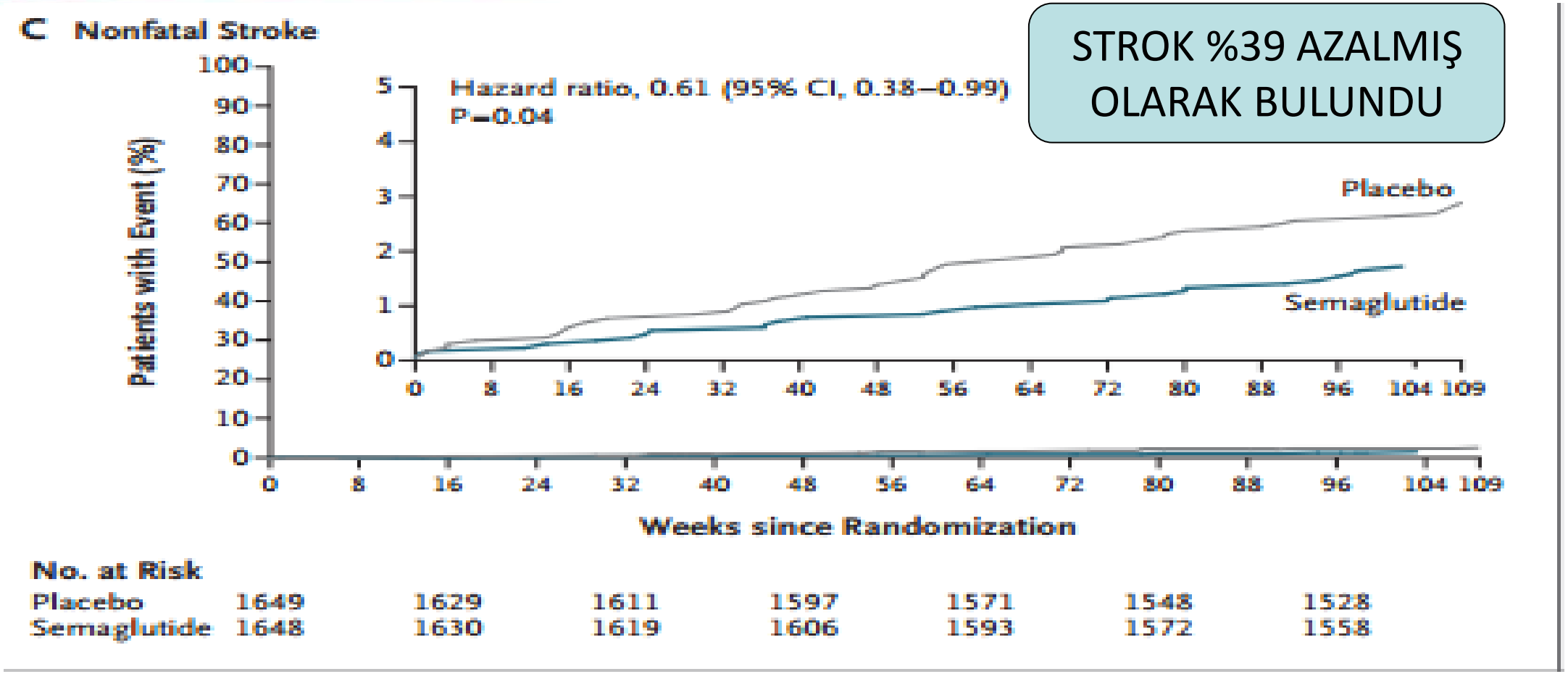
FATAL/NONFATAL MI

- Tüm klinik çalışmalar plasebo ile kıyaslandığında NON-INFERIOR!
- Hiçbirisinde MI sıklığında artış görülmüyor.

STROK

- Çalışmaların hiçbiri plaseboya kıyasla strok gelişimini ARTIRMAMIŞTIR!
- EMPA-REG çalışmasında istatiksel olarak anlamlı olmayan bir artış mevcut!

SUSTAIN-6 çalışmasında semaglutid kolunda plaseboya kıyasla strok oranında AZALMA saptanmıştır.



STROK %39 AZALMIŞ OLARAK BULUNDU

KALP YETMEZLİĞİNE BAĞLI HASTANEYE YATIŞ

- EXAMINE (Alogliptin)
- TECOS (Sitagliptin)
- ELIXA (Lixisenatid)
- SUSTAIN-6 (Semaglutid)

PLASEBO İLE BENZER SAPTANMIŞTIR!

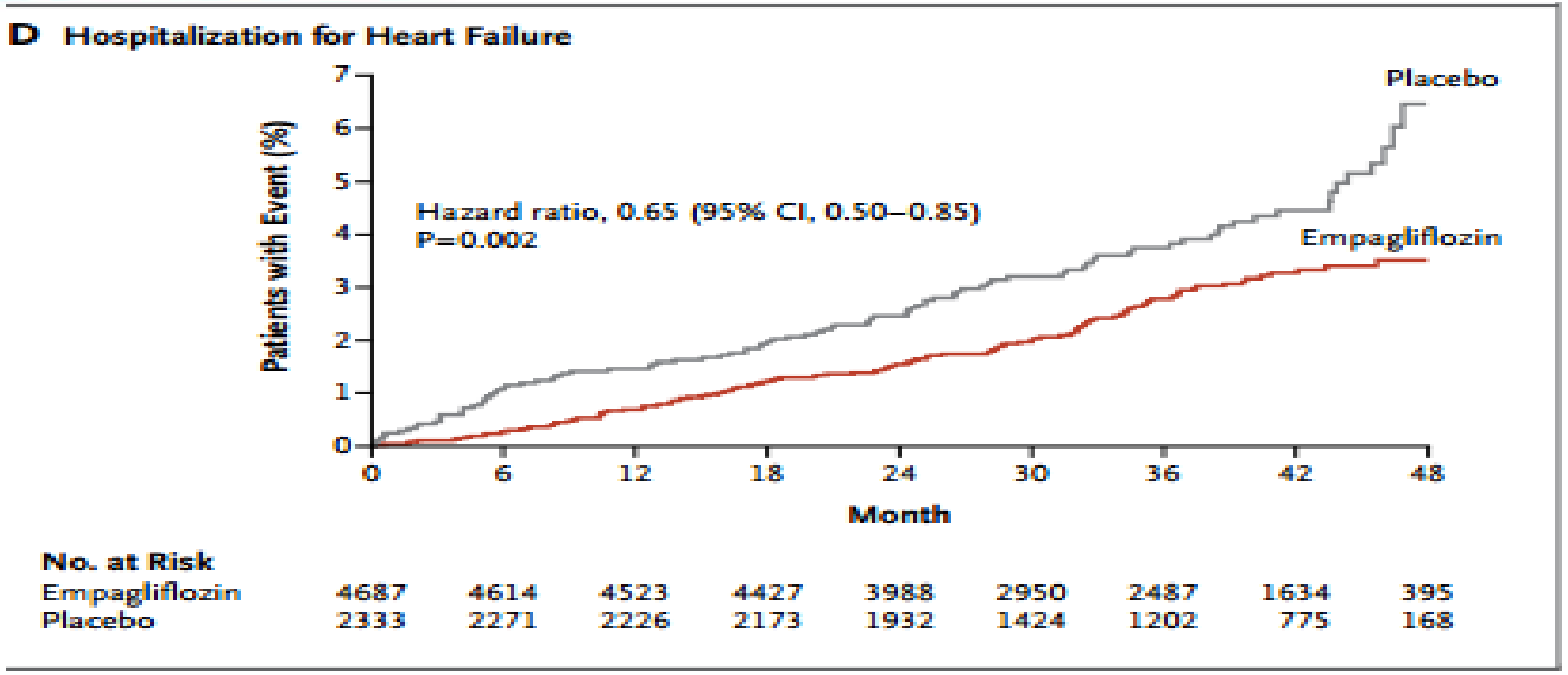
KALP YETERSİZLİĞİNE BAĞLI HASTANEYE YATIŞ SAVOR-TIMI

Etkililik sonlanma noktası	Saksagliptin n (%)* (N = 8,280)	Plasebo n (%)* (N = 8,212)	RO (%95 GA)	*P* değeri
KV ölüm	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
MI	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
İskemik inme	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
UA için hastane yatışı	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
KY için hastane yatışı	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Koroner revask. için Hastane yatışı	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18

* 2 yıl sonra sunulan K-M olay oranı.

Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684.

KALP YETERSİZLİĞİNE BAĞLI HASTANEYE YATIŞ
EMPA-REG



HİPOGLİSEMİ

- Tüm klinik araştırmalarda plaseboya benzer oranda görülmüş.
- İSTİSNA:
- 1-SAVOR-TIMI çalışmasında, saxagliptinle SU ve insülin kombinasyonu yapılan grupta hipoglisemi ARTMIŞ!
- 2- LEADER çalışmasında, liraglutid kolunda plaseboya kıyasla ciddi hipoglisemi daha az görülüyor.

PANKREATİT

- SAVOR-TIMI (Saxagliptin)
- TECOS (Sitagliptin)
- EXAMINE (Alogliptin)
- ELIXA (Lixisenatid)
- LEADER (Liraglutid)
- SUSTAIN-6 (Semaglutid)
- EMPA-REG (Empagliflozin)

Pankreatik olaylardaki artış istatiksel olarak anlamlı DEĞİLDİR!

SUSTAIN-6 VE RETİNOPATİ

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N = 1648)		Placebo (N = 1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

ÖZET OLARAK
Primer sonlanım noktası

Çalışma	Non-inferior	Süperior
SAVOR (Saxagliptin)	√	
TECOS (Sitagliptin)	√	
EXAMINE (Alogliptin)	√	
ELIXA (Lixisenatid)	√	
LEADER (Liraglutid)		√
SUSTAIN-6 (Semaglutid)		√
EMPA-REG (Empagliflozin)		√

GENEL KAPSAMLI KARŞILAŞTIRMA

Çalışma	Primer sonlanım	Kardiyovasküler ölüm	MI	Strok	USAP nedeniyle yatış	KKY nedeniyle yatış
TECOS (Sitagliptin)	**BENZER**	**BENZER**	**BENZER**	**BENZER**	**BENZER**	**BENZER**
SAVOR (Saxagliptin)	**BENZER**	**BENZER**	**BENZER**	**BENZER**	**BENZER**	**ARTMIŞ**
EXAMINE (Alogliptin)	**BENZER**	**BENZER**	**BENZER**	**BENZER**	**BENZER**	**BENZER**
LEADER (Liraglutid)	**DAHA İYİ**	**AZALMIŞ**	**BENZER**	**BENZER**	**BENZER**	**BENZER**
SUSTAIN-6 (Semaglutid)	**DAHA İYİ**	**BENZER**	**BENZER**	**AZALMIŞ**	**BENZER**	**BENZER**
ELIXA (Lixisenatid)	**BENZER**	**BENZER**	**BENZER**	**BENZER**	**BENZER**	**BENZER**
EMPA-REG (Empagliflozin)	**DAHA İYİ**	**AZALMIŞ**	**BENZER**	**ARTMIŞ (P anlamsız)**	**BENZER**	**AZALMIŞ**

TEŞEKKÜR EDERİM