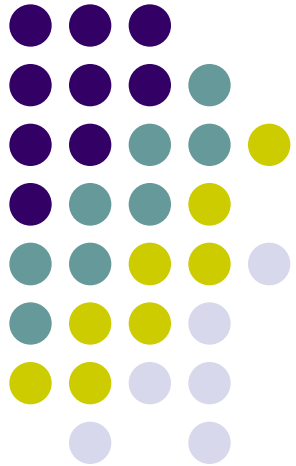
Son 10 Yılda Diyabetik Hastaların Dahil Edildiği Randomize Klinik Çalışmalardan Öğrendiklerimiz:

Renal Sonlanım

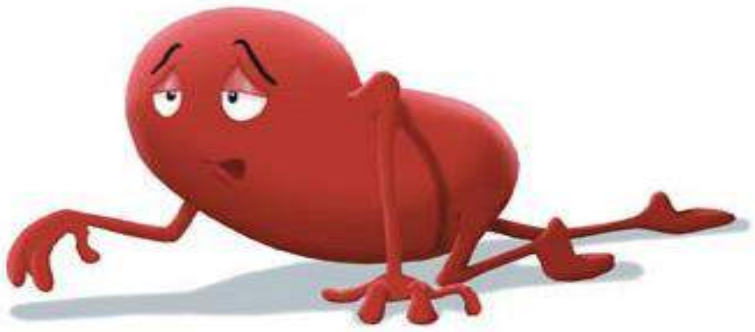
Prof. Dr. Ayşegül Atmaca
Ondokuz Mayıs Üniversitesi
Tıp Fakültesi Endokrinoloji Bilim Dalı

19-23 Nisan 2017, Girne
53. Ulusal Diyabet Kongresi



Diyabet ve Böbrek

- Diyabet kronik böbrek hastalığının bir numaralı nedenidir
- Tanı almış veya almamış diyabetlilerin %40'ında KBH var



Plantinga ve ark, Clin J Am Soc Nephrol, 2010

- Proliferatif retinopati --- ampütasyon riski 25X ↑

  KAH riski 2-3X ↑

  Juutlainen ve ark, Diabetes Care, 2007

- A1c'de her %1'lik ↑ --- KVH %18 ↑

  Di Angelantonio ve ark, JAMA, 2014

Konvansiyonel Tedaviler

Sıkı Kontrol

UKPDS	ACCORD	ADVANCE	VADT
•Orta yaşlı, yeni tanı •≥ 65 yaş dışlanmış •Mikrovasküler komplikasyonları önlüyor •Takipte MI ve mortalite üzerine olumlu (%15 ↓)	•Orta yaşlı, yaşlı, ort.yaş 60, 8-11 yıllık DM, KVH +		
	•3.7 yılda sonlandırılıyor •Mortalite ↑ •MI, inme, KV mortalite aynı •Hipoglisemi (özellikle yaşlılarda)	•5 yıl takip •Mortalite aynı •KV yarar aynı •Nefropati ↓ • 65 yaş altı ve üstü sonuçlar benzer	•>5 yıl takip •KV olay ve mortalite aynı •Albüminüri ↓ •DM süresi önemli (<15 yıl vs ≥20 yıl)

UK Prospective Study (UKPDS) Group, Lancet, 1998
Gerstein ve ark, N Engl J Med, 2008
Miller ve ark, BMJ, 2010
Patel ve ark, N Engl J Med, 2008
Duckworth ve ark, N Engl J Med, 2009

UKPDS

Herhangi mikrovasküler son nokta

Herhangi diyabet ile ilişkili son nokta

Albüminüri	%34 ↓
Kreatinin 2 kat artış	%67 ↓
Üre 2 kat artış	%74 ↓

← Hazard ratio vs. diet (%95 CI)

UKPDS33, Lancet, 1998

10 Yıllık İzlem (UKPDS)

Son Nokta	1997: Rölatif risk Azalımı (%)	p	2007: Rölatif risk Azalımı (%)	p
Herhangi diyabete-bağlı son nokta	12	0.029	9	0.040
Mikrovasküler Hastalık	25	0.0099	24	0.001
MI	16	0.052	15	0.014
Bütün sebeplere bağlı mortalite	6	0.44	13	0.007

Holman ve ark, N Engl J Med, 2008

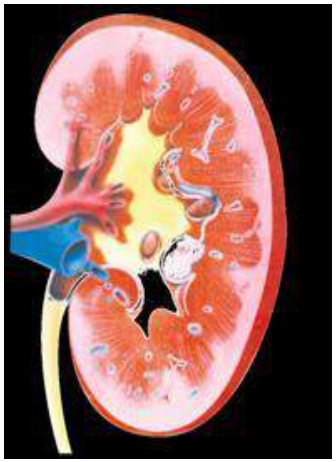
ADVANCE - Nefropati

Yeni / ilerleyen nefropati

Rölatif risk azalması

% 21

p = 0.006



Yeni makroalbüminüri

Rölatif risk azalması

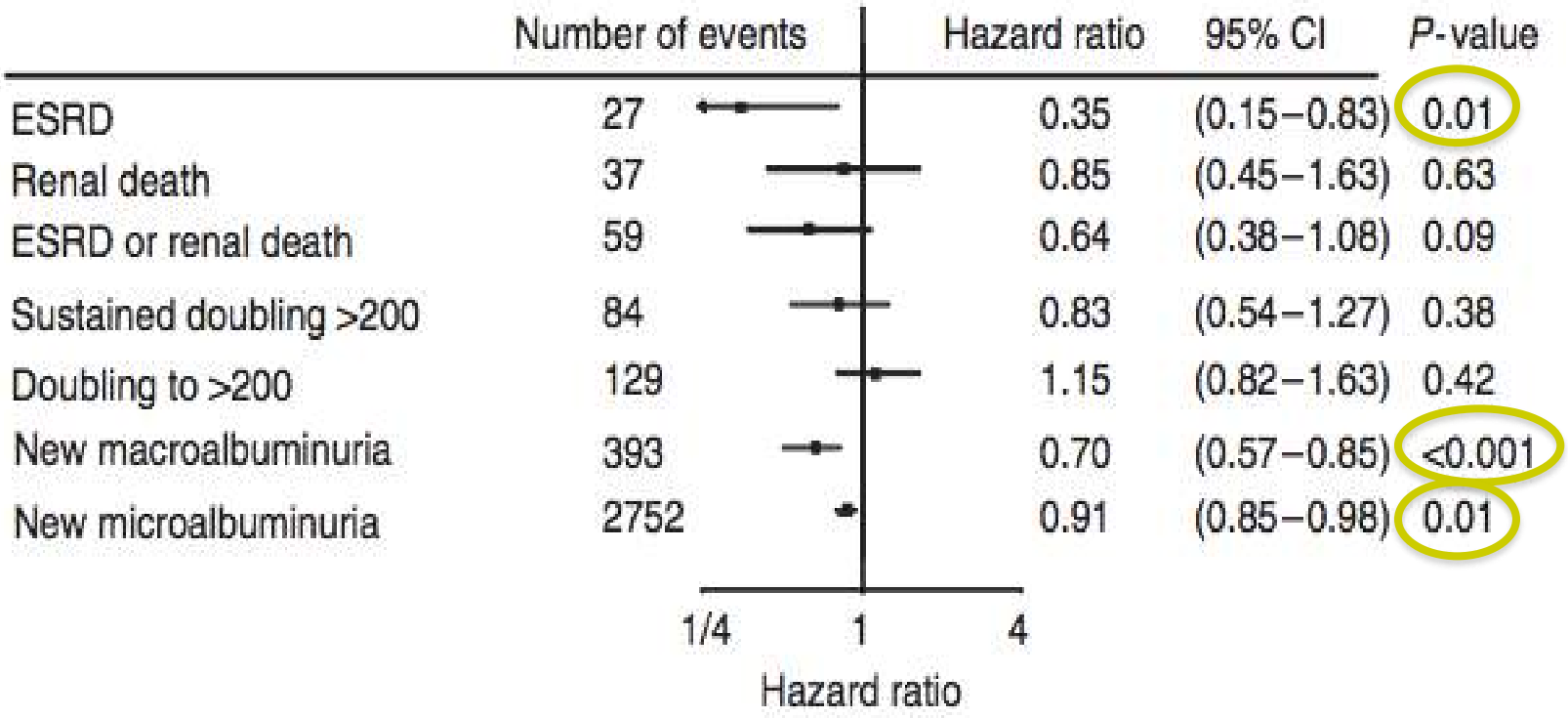
% 30

p = 0.001

ADVANCE Colloborative Group, N Engl J Med, 2008

Intensive glucose control improves kidney outcomes in patients with type 2 diabetes

Vlado Perkovic[1], Hiddo Lambers Heerspink[2], John Chalmers[1], Mark Woodward[1,3], Min Jun[1], Qiang Li[1], Stephen MacMahon[1,4], Mark E. Cooper[5], Pavel Hamet[6], Michel Marre[7], Carl Erik Mogensen[8], Neil Poulter[9], Giuseppe Mancia[10], Alan Cass[1], Anushka Patel[1] and Sophia Zoungas[1,11], for the ADVANCE Collaborative Group



Perkovic ve ark, Kidney Int, 2013

ADVANCE-ON

- İntensif kontrol uzun vadede (yaklaşık 10 yıl)
  - Mortalite
  - Majör makrovasküler olaylar
  - Majör mikrovasküler olaylar

üzerine yararı veya zararı yoktur

Ancak,

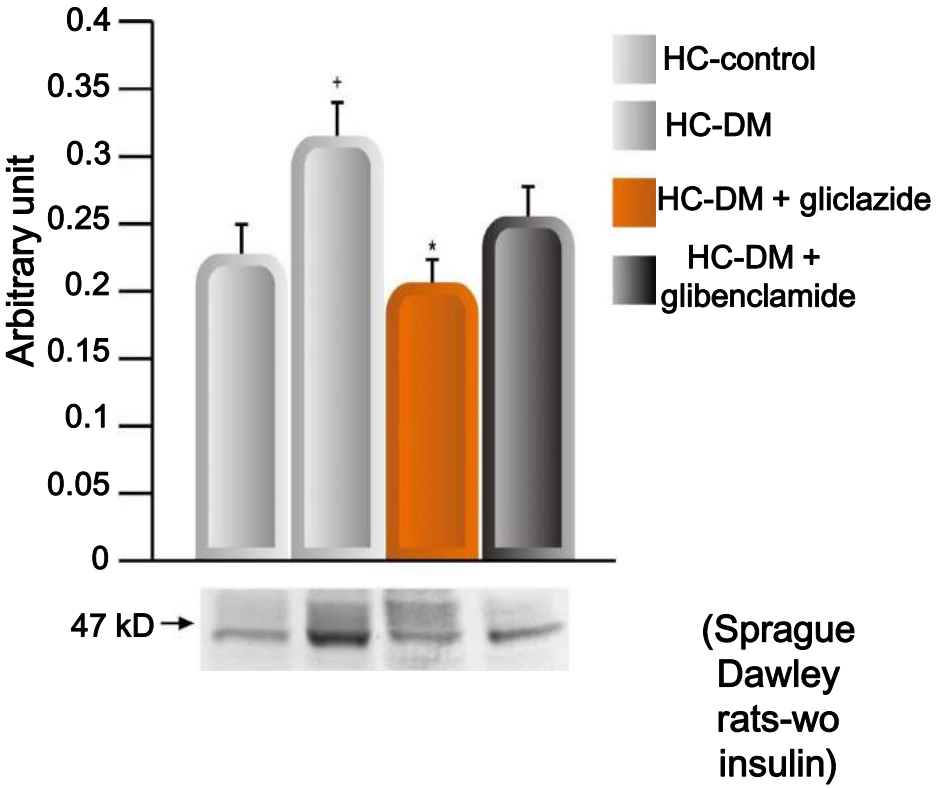
- Son dönem böbrek yetmezliği riskini azaltıcı etkisi uzun vadede devam eder.

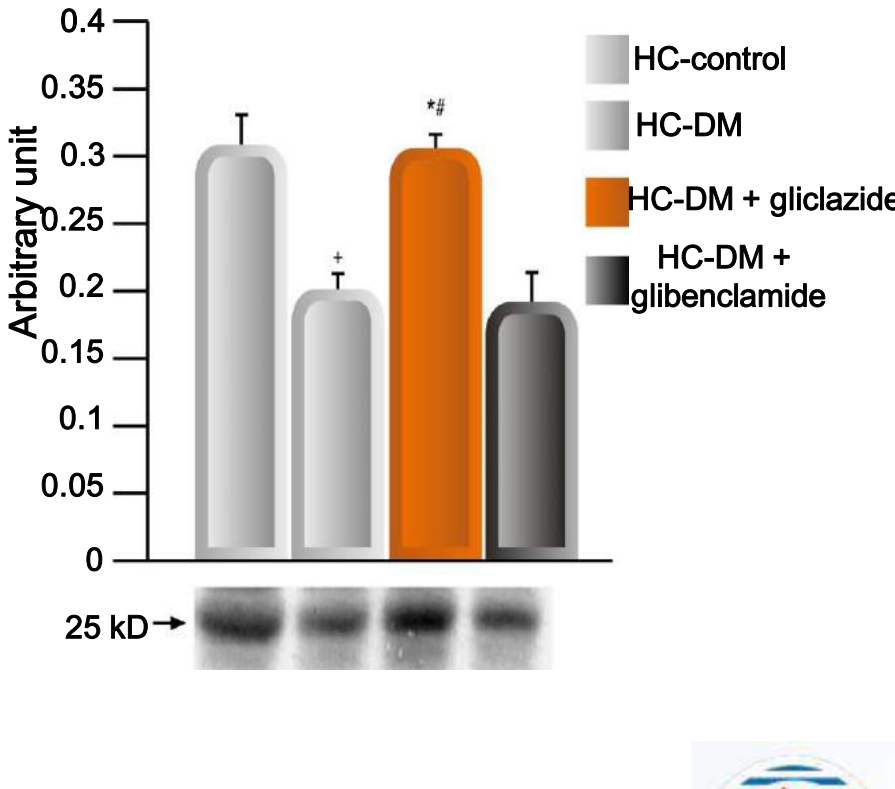
Rölatif risk azalması 46%

95% CI: 15 to 66%, $p<0.01$

Zoungas ve ark, N Engl J Med, 2014

Serbest radikaller üzerine Gliklazid etkisi
Böbrek dokusunda NADPH oksidaz p47phox protein ekspresyonu (oksidatif stresin kaynağı)





Onozato ve ark, Kidney Int, 2004

Observation on Renal Outcomes in the Veterans Affairs Diabetes Trial

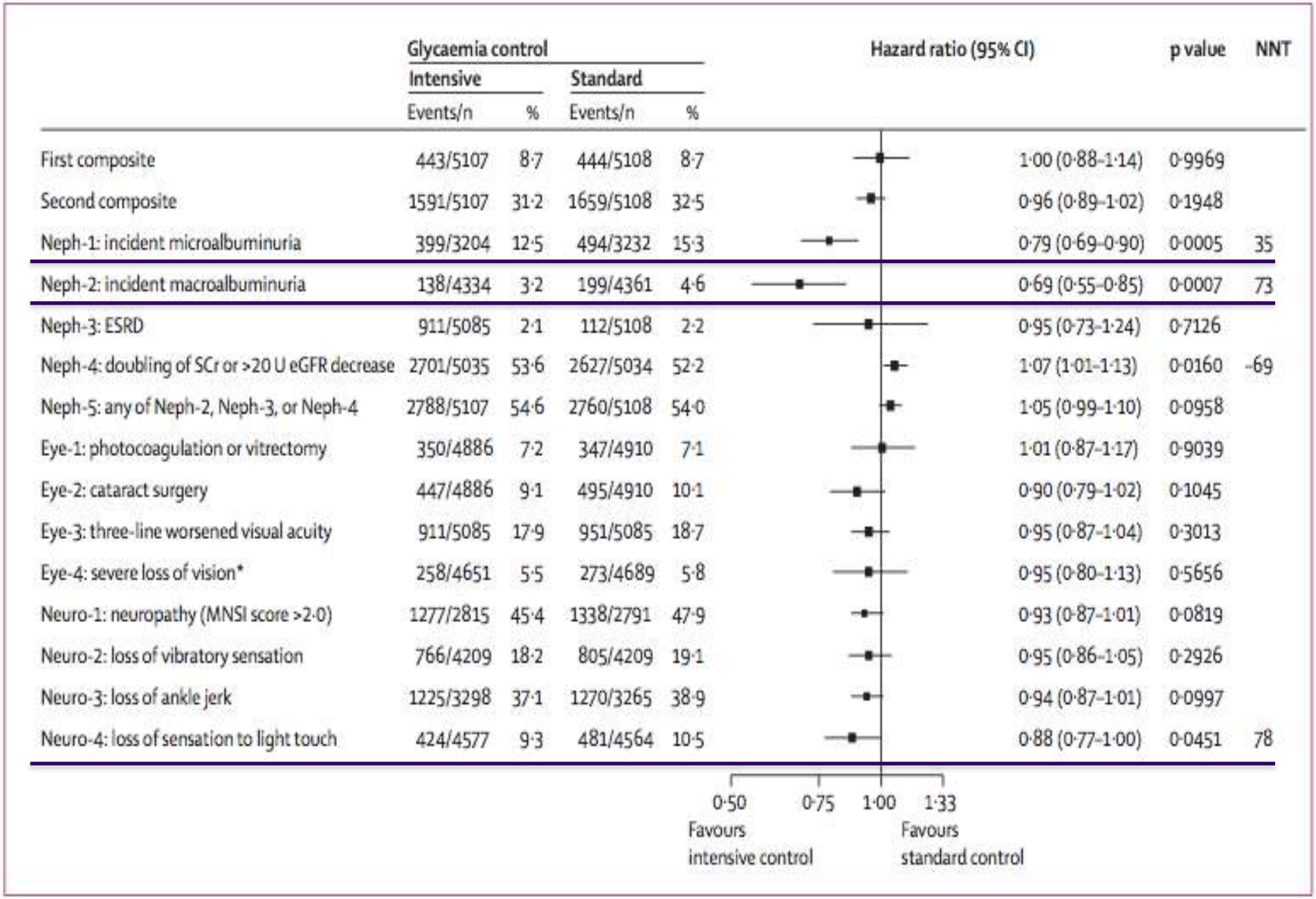
LILY AGRAWAL, MD[1]
NASRIN AZAD, MD[1]
NICHOLAS V. EMANUELE, MD[1]
GIDEON D. BAHN, PHD[2]
DERRICK G. KAUFMAN, MS[2]
THOMAS E. MORITZ, MS[2]
WILLIAM C. DUCKWORTH, MD[3]
CARLOS ABRAIRA, MD[4]
FOR THE VETERANS AFFAIRS DIABETES TRIAL (VADT) STUDY GROUP*

glucose control had minimal effec
the incidence of renal failure, but
was a significant reduction (P = 0.0
any worsening of the urine albumi
creatinine ratio (ACR) in the INT g

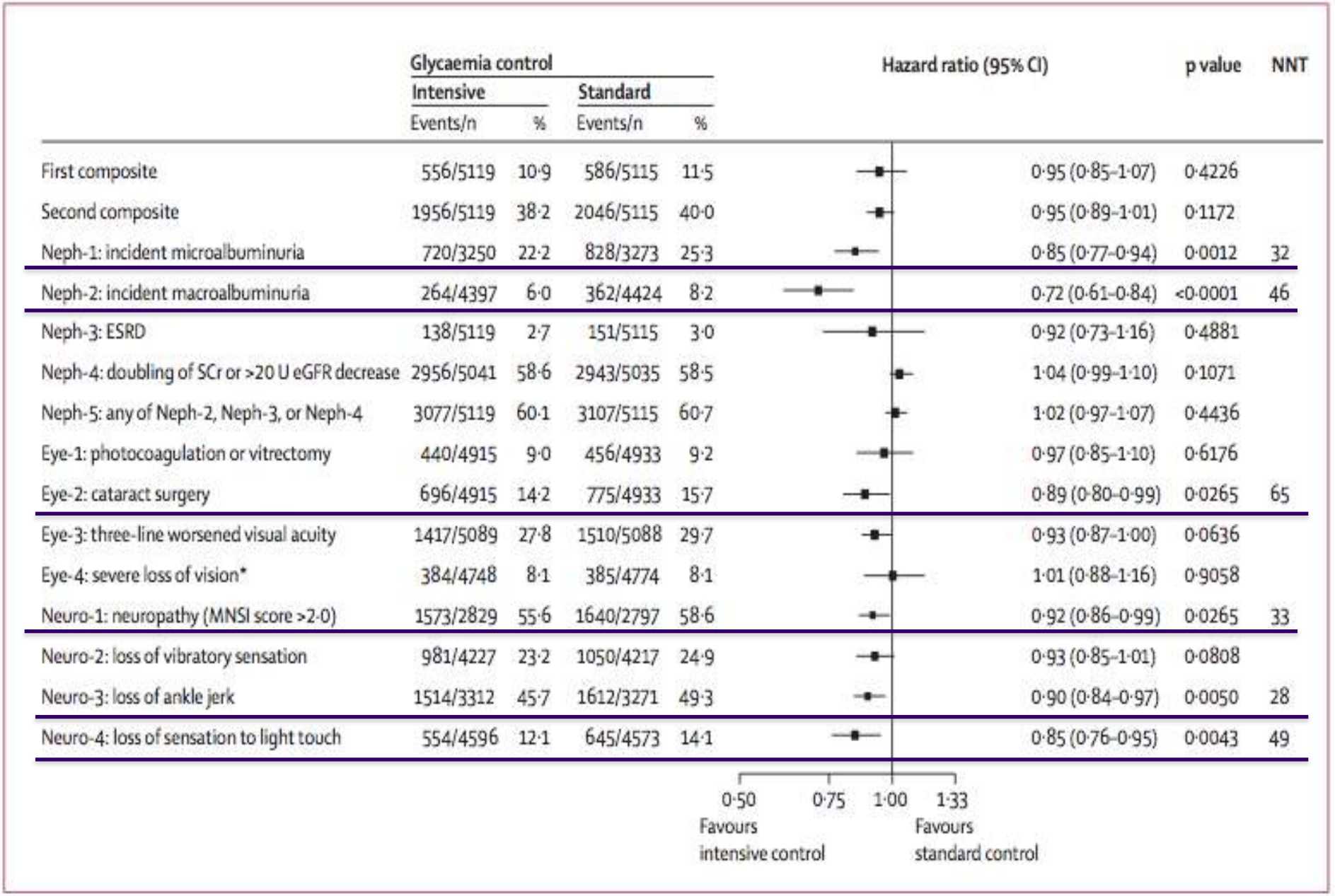
Nephropathy			
Serum creatinine			
Doubling of level	78/884 (8.8)	78/882 (8.8)	0.99
>3 mg/dl (265 μmol/liter)	16/884 (1.8)	18/882 (2.0)	0.72
Glomerular filtration rate <15 ml/min	11/884 (1.2)	7/882 (0.8)	0.35
Change in albumin level			
From normal to microalbuminuria	61/463 (13.2)	43/442 (9.7)	0.12
From normal to macroalbuminuria	7/463 (1.5)	1/442 (0.2)	0.07
From microalbuminuria to macroalbuminuria	29/240 (12.1)	19/251 (7.6)	0.10
From normal to microalbuminuria or macroalbuminuria	68/463 (14.7)	44/442 (10.0)	0.03
From normal to microalbuminuria to macroalbuminuria	36/703 (5.1)	20/693 (2.9)	0.04
Any increase in albuminuria	97/703 (13.8)	63/693 (9.1)	0.01

İleri mikrovasküler hasar, düşük bazal DKB ve yüksek bazal BKİ olanlarda intensif kontrol daha etkin

Duckworth ve ark, N Engl J Med, 2009
Agrawal ve ark, Diabetes Care, 2011



Ismail-Beigi ve ark, Lancet, 2010



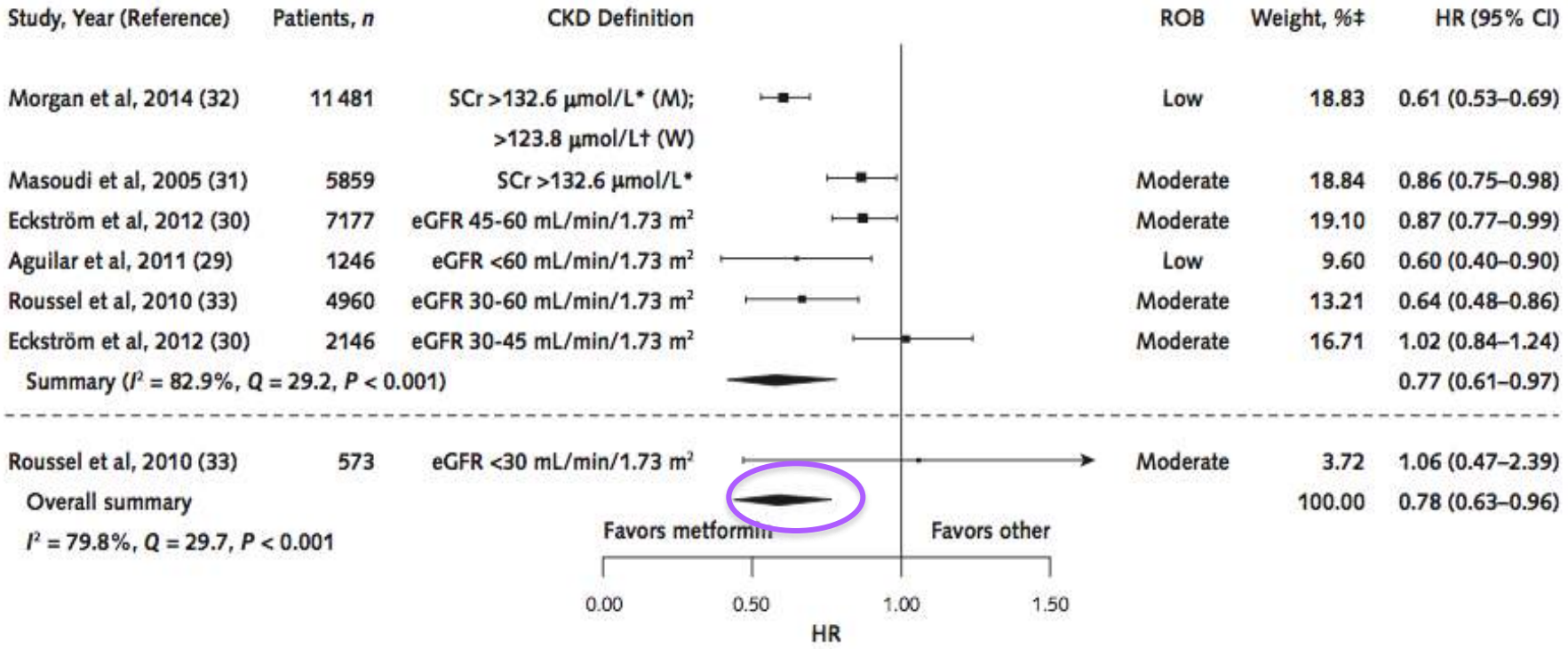
Ismail-Beigi ve ark, Lancet, 2010

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease

A Systematic Review

Matthew J. Crowley, MD, MHS; Clarissa J. Diamantidis, MD, MHS; Jennifer R. McDuffie, PhD; C. Blake Cameron, MD, MBI; John W. Stanifer, MD, MSc; Clare K. Mock, MD; Xianwei Wang, MD; Shuang Tang, PhD; Avishek Nagi, MS; Andrzej S. Kosinski, PhD; and John W. Williams Jr., MD, MHS

Figure 2. Meta-analysis of all-cause mortality among patients with moderate to severe CKD receiving treatment regimens including metformin versus those receiving regimens without metformin.



Crowlley ve ark, Ann Intern Med, 2017

Metformin

- Kreatinin: ≥1.4 mg/dl erkekte ≥1.5 mg/dl ise kullanma
- GFR düşükse kullanma! <30?? <45??
- Randomize kontrollü çalışma yok
- Birçok organizasyon (ADA/EASD) endikasyonu genişletmek istiyor

FDA önerileri

- Kreatinin yerine GFR kullan
- GFR <30 ise kontrendike
- GFR 30-45 ise önerilmez
- Metformin altında GFR <45 olursa dikkatli kullanılabilir
- Metformin düzeyi takibi ?? (<3 mg/L)
- Evre 3'de 4-6 ayda bir GFR ölçüü

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

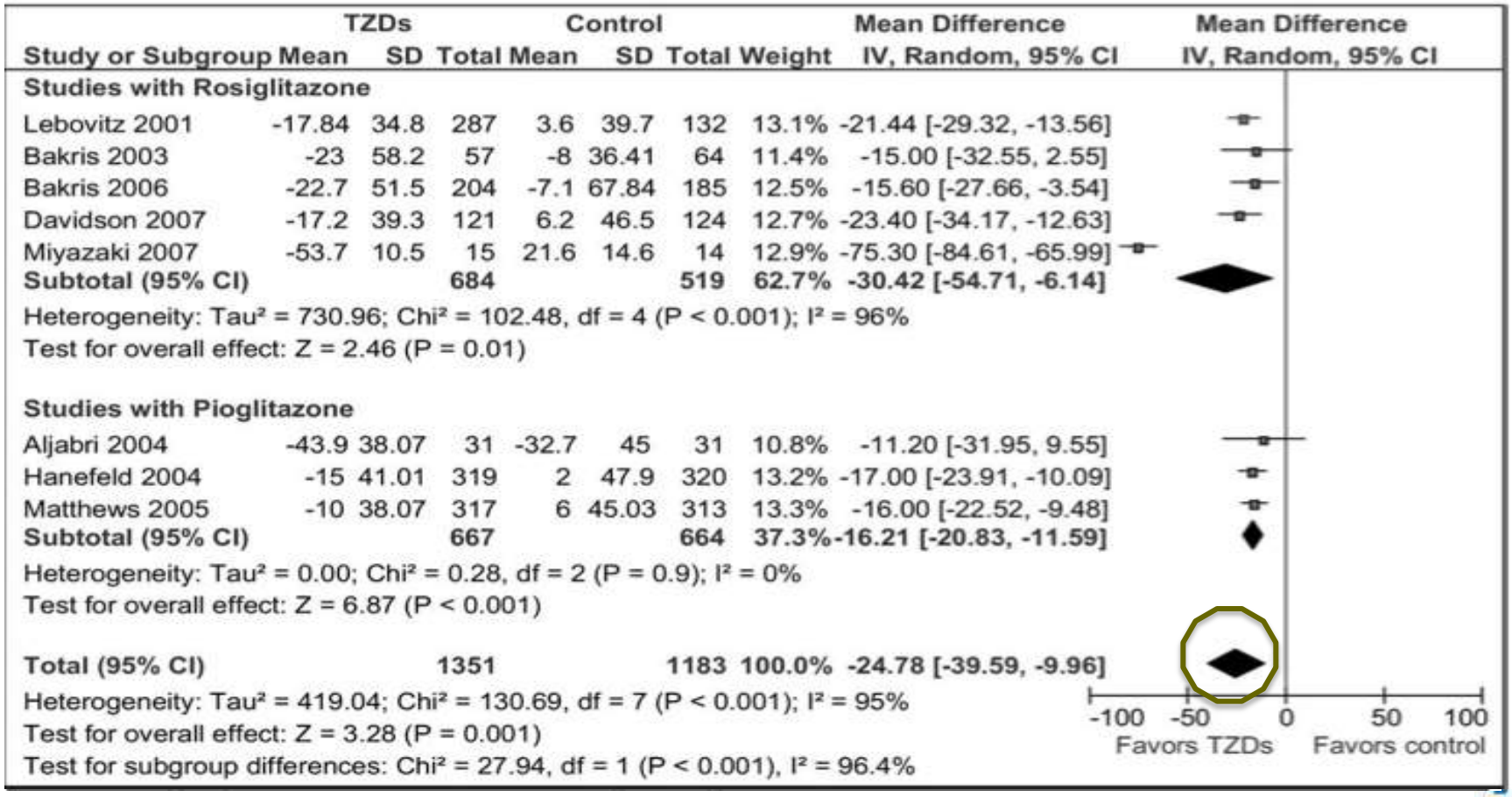
- 5238 hasta, 34.5 ay, %11.6'da GFR <60 ml/dk/1.73 m^2
- Mikroalbüminüri ve kreatinin sonuçları benzer
- Makrovasküler sonlanım KBH'da %25.6 vs KBH olmayanlarda %19.6, p<0.0001

Groups of patients	N Pio vs Pbo	Primary composite endpoint	Main secondary endpoint	All-cause mortality	Specific endpoint (see footnote)
Presence of chronic kidney disease	274 vs 323	HR = 0.75, 0.55–1.03; P = NA	HR = 0.66, 0.45–0.98; P = NA	HR = 0.75, 0.55–1.03; P = NA[a]	NA
Absence of chronic kidney disease	2292 vs 2265	HR = 0.94, 0.83–1.07;	HR = 0.89, 0.75–1.05;	HR = 1.09, 0.87–1.38;	NA

Dormandy ve ark, Lancet, 2005
Schneider ve ark, J Am Soc Nephrol, 2008

Effect of Thiazolidinediones on Albuminuria and Proteinuria in Diabetes: A Meta-analysis

Pantelis A. Sarafidis, MD, MSc, PhD, Panagiotis C. Stafylas, MD, MSc, Panagiotis I. Georgianos, MD, Athanasios N. Saratzis, MD, and Anastasios N. Lasaridis, MD, PhD



Sarafidis ve ark, Am J Kidney Dis, 2010

TZD - Mekanizmalar

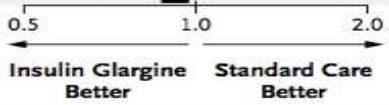
- KŞ regülasyonu
- İnsülin düzeylerinde düşme
- KB'da düşme
- Tübüler ve glomeruler proliferasyonun inhibisyonu (ECM,TGF-β, büyüme faktörü ↓)
- Sitokinlerde azalma, antiinflamatuvar etki
- RAAS ↓
- Endotel fx düzelme
- Oksidatif stres ↓
- PAI-1 ↓

Sarafidis ve ark, Cardiovac Ther, 2011

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

Outcome	Insulin Glargine (N=6264) no. (%)	Insulin Glargine (N=6264) no./100 patient-yr	Standard Care (N=6273) no. (%)	Standard Care (N=6273) no./100 patient-yr	Hazard Ratio (95% CI)	P Value
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	**1323 (21.1)**	**3.87**	**1363 (21.7)**	**3.99**	**0.97 (0.90–1.05)**	**0.43**
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52

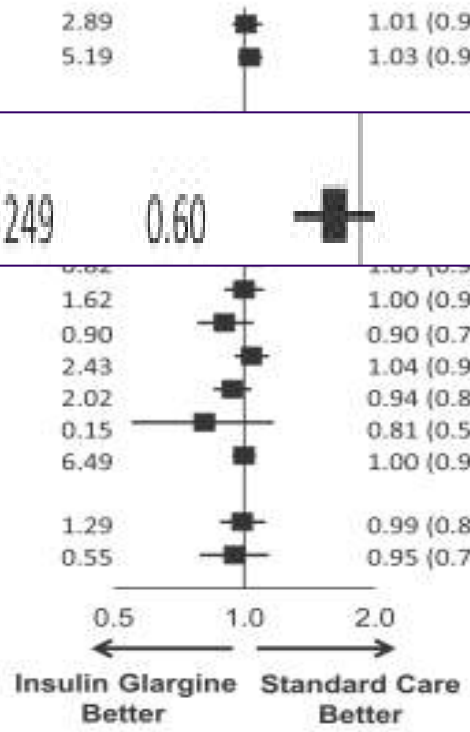


Gerstein ve ark, N Engl J Med, 2012

Cardiovascular and Other Outcomes Postintervention With Insulin Glargine and Omega-3 Fatty Acids (ORIGINALE)

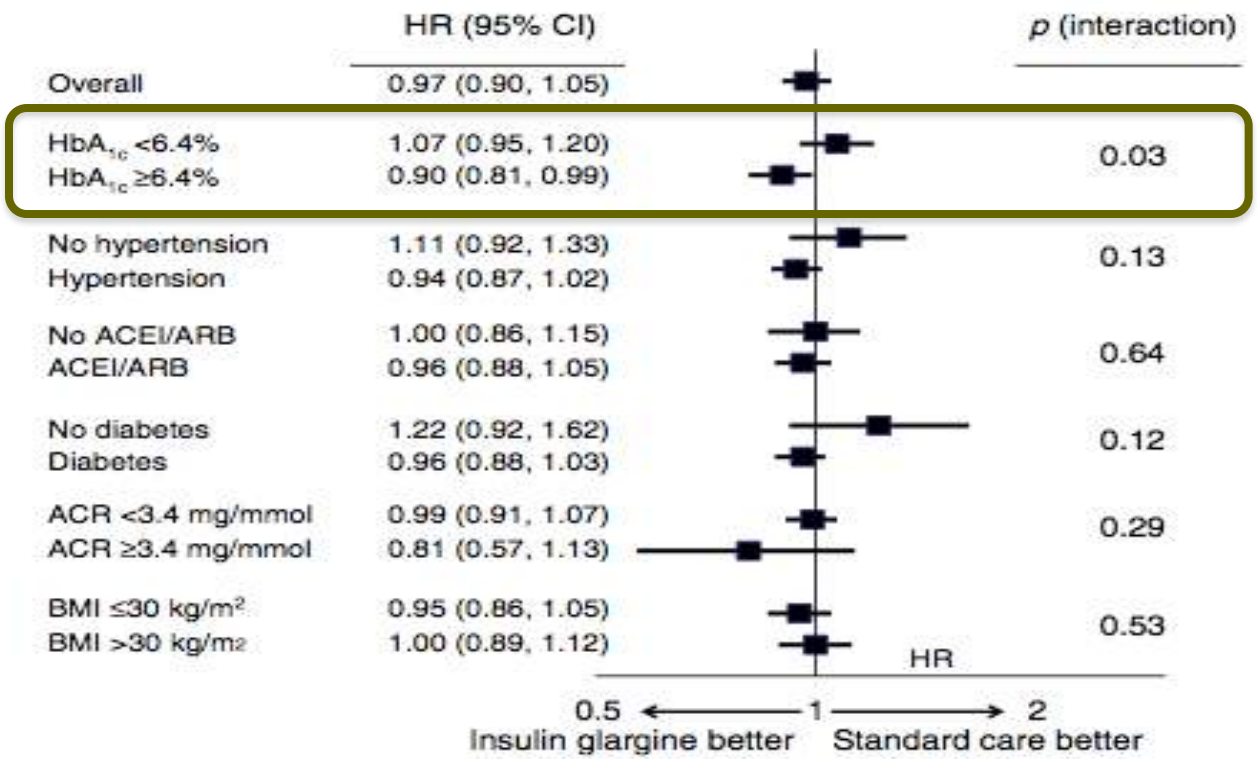
Diabetes Care 2016;39:709–716 | DOI: 10.2337/dc15-1676

	Insulin Glargine Events	/100 py	Standard Care Events	/100 py	Hazard Ratio (95%CI)	P
First coprimary outcome	1185	2.95	1165	2.89	1.01 (0.94-1.10)	0.72
Second coprimary outcome	1958	5.38	1910	5.19	1.03 (0.97-1.10)	0.38
Clinical microvascular outcomes	221	0.53	249	0.60	0.89 (0.74-1.07)	0.20
Death from cardiovascular causes	694	1.62	695	1.62	1.00 (0.90-1.11)	0.94
Hospitalization for congestive heart failure	336	0.82	370	0.90	0.90 (0.78-1.05)	0.18
Revascularization	972	2.56	934	2.43	1.04 (0.95-1.14)	0.35
Angina	741	1.92	779	2.02	0.94 (0.85-1.04)	0.24
Limb or digit amputation	50	0.12	62	0.15	0.81 (0.55-1.17)	0.25
Cardiovascular hospitalization	2168	6.55	2167	6.49	1.00 (0.94-1.06)	0.96
Any cancer	524	1.28	529	1.29	0.99 (0.88-1.12)	0.91
Death from cancer	225	0.52	236	0.55	0.95 (0.79-1.14)	0.61



Punthakee ve ark, Diabetes Care, 2016

Basal insulin glargine and microvascular outcomes in dysglycaemic individuals: results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial



Gibert ve ark, Diabetologia, 2014

Yeni Tedaviler

Majör Sonlanım Çalışmaları

SAVOR

ELIXA

EMPA-REG

EXAMINE

LEADER

TECOS

SUSTAIN-6

Başlangıç GFR (ml/dk)	eGFR (MDRD)	Placebo	Alogliptin
≥90		N = 440	N = 399
	Başlangıç eGFR	103.2	104.8
	ΔeGRF	-4.5	-6.7
<90 ve ≥60		N = 1446	N = 1530
	Başlangıç eGFR	75.0	74.6
	ΔeGRF	1.0	0.6
<60 ve ≥30		N = 714	N = 694
	Başlangıç eGFR	48.4	48.5
	ΔeGRF	2.1	1.1
<30		N = 79	N = 78
	Başlangıç eGFR	22.9	22.6
	ΔeGRF	1.6	0.2
	Diyaliz ihtiyacı	22 (%0.8)	24 (%0.9)

White ve ark, Am Heart J, 2011
White ve ark, N Engl J Med, 2013

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*

- 16492 hasta, median 2.1 yıl
- GFR

>50 ml/dk: 5 mg

≤50 ml/dk: 2.5 mg

Scirica ve ark, N Engl J Med, 2013

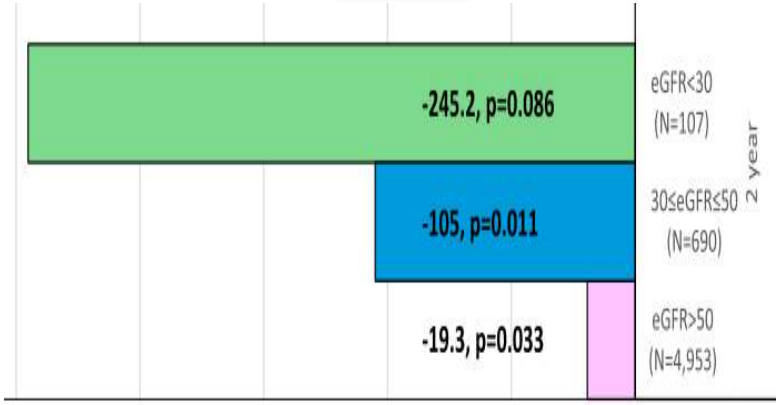
Effect of Saxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial

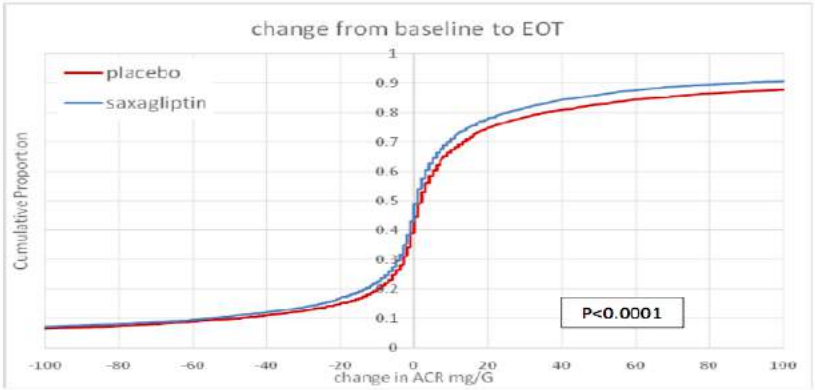
DOI: 10.2337/dc16-0621

Ofri Mosenzon,[1] Gil Leibowitz,[2] Deepak L. Bhatt,[3] Avivit Cahn,[2] Boaz Hirshberg,[4] Cheryl Wei,[5] KyungAh Im,[3] Aliza Rozenberg,[1] Ilan Yanuv,[1] Christina Stahre,[6] Kausik K. Ray,[7] Nayyar Iqbal,[5] Eugene Braunwald,[3] Benjamin M. Scirica,[3] and Itamar Raz[1]

Table 2—Change in categorical ACR (<30, 30–300, and >300 mg/g) from baseline to EOT by baseline ACR categories and treatment arms

		ACR at EOT					
		Saxagliptin			Placebo		
ACR at baseline (mg/g)	*P* value	<30	30–300	>300	<30	30–300	>300
<30	0.021*	3,152 (84.2)[a]	555 (14.8)[d]	36 (1.0)[e]	2,993 (82.2)[a]	617 (16.9)[d]	31 (0.8)[e]
30–300	<0.001**	451 (28.9)[b]	929 (59.5)[a]	181 (11.6)[d]	352 (23.4)[b]	904 (60.1)[a]	249 (16.5)[d]
>300	0.049***	23 (4.3)[c]	148 (27.7)[b]	363 (68.0)[a]	15 (3.0)[c]	115 (23.4)[b]	362 (73.6)[a]





Mosenzon ve ark, Diabetes Care, 2017

Effect of Saxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial

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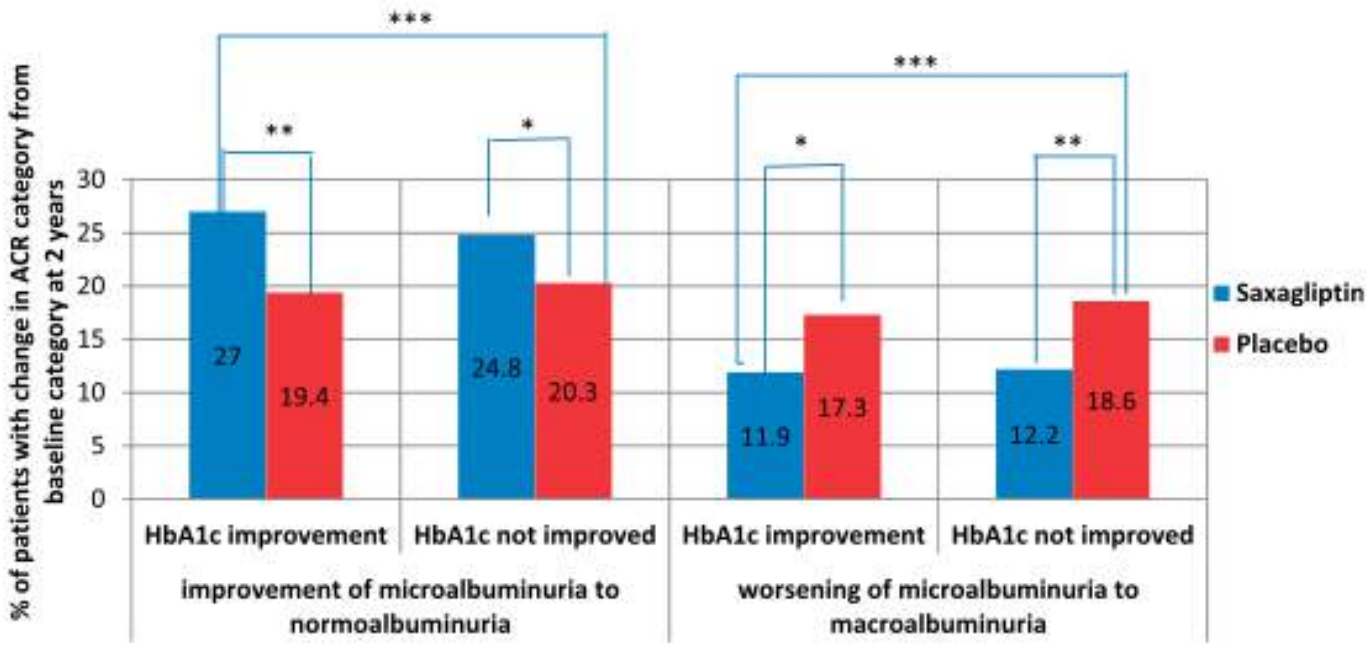
Ofri Mosenzon,[1] Gil Leibowitz,[2] Deepak L. Bhatt,[3] Avivit Cahn,[2] Boaz Hirshberg,[4] Cheryl Wei,[5] KyungAh Im,[3] Aliza Rozenberg,[1] Ilan Yanuv,[1] Christina Stahre,[6] Kausik K. Ray,[7] Nayyar Iqbal,[5] Eugene Braunwald,[3] Benjamin M. Scirica,[3] and Itamar Raz[1]



eGFR, kreatininin 2 katına çıkması,diyalize başlama, renal transplantasyon, kreatinin >6 mg/dL açısından fark yok (p = 0.46)

Mosenzon ve ark, Diabetes Care, 2017

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*

- 14671 hasta, 3 yıl
- eGFR (1, 2, 3a, 3b)

>50 mL/dk: 100 mg/gün

30-50 mL/dk: 50 mg/gün

<30 mL/dk: 25 mg/gün

Green ve ark, Am Heart J, 2013
Green ve ark, N Engl J Med, 2015

Effect of Sitagliptin on Kidney Function and Respective Cardiovascular Outcomes in Type 2 Diabetes: Outcomes From TECOS

Diabetes Care 2016;39:2304–2310 | DOI: 10.2337/dc16-1415

Table 3—Estimated mean 4-year eGFR and UACR between-treatment group differences (sitagliptin minus placebo), overall and by baseline eGFR stages

	Baseline value	Mean between-group treatment difference (95% CI)†	*P* value†
eGFR (*N* = 13,604), mL/min/1.73 m^2			
Overall	75.1 ± 21.0	−1.34 (−1.76 to −0.91)	<0.0001
Stage 1 (eGFR ≥90 mL/min/1.73 m^2)	104 ± 14	−0.22 (−1.19 to 0.75)	
Stage 2 (eGFR 60–89 mL/min/1.73 m^2)	73 ± 9	−1.42 (−2.05 to −0.79)	
Stage 3a (eGFR 45–59 mL/min/1.73 m^2)	53 ± 4	−1.33 (−2.45 to −0.21)	Interaction *P* = 0.14
Stage 3b (eGFR 30–44 mL/min/1.73 m^2)	39 ± 4	−2.25 (−4.27 to −0.23)	
UACR (*N* = 3,832), mg/g			
Overall	11.1 (3.9, 35.0)	−0.18 (−0.35 to −0.02)	0.031
Stage 1 (eGFR ≥90 mL/min/1.73 m^2)	11.0 (4.7, 30.2)	−0.18 (−0.53 to 0.16)	
Stage 2 (eGFR 60–89 mL/min/1.73 m^2)	9.7 (3.5, 29.2)	−0.20 (−0.42 to 0.02)	
Stage 3a (eGFR 45–59 mL/min/1.73 m^2)	14.3 (4.1, 55.4)	−0.30 (−0.70 to 0.09)	Interaction *P* = 0.68
Stage 3b (eGFR 30–44 mL/min/1.73 m^2)	27.7 (9.7, 126.6)	0.23 (−0.54 to 1.00)	

- Klinik anlam? --- Progresyon yok (Renal yetmezlik %3.3 vs 3.6)[1]
- Bazal A1c veya A1c değişimi ile açıklanmaz
- Diğer DPP4-İ ile de gözlenmiş[2]

Cornel ve ark, Diabetes Care, 2016

[1] Scott, Drugs, 2017

[2] Cooper ve ark, Am J Kidney Dis, 2015

Linagliptin Lowers Albuminuria on Top of Recommended Standard Treatment in Patients With Type 2 Diabetes and Renal Dysfunction

PER-HENRIK GROOP, MD, DMSC[1,2,3]
MARK E. COOPER, MBBS, PHD[3]
VLADO PERKOVIC, MBBS, PHD[4]
ANGELA EMSER, PHD[5]
HANS-JUERGEN WOERLE, MD[5]
MAXIMILIAN VON EYNATTEN, MD[5]

OBJECTIVE—Preclinical data suggest that linagliptin, a dipeptidyl peptidase-4 inhibitor, may lower urinary albumin excretion. The ability of linagliptin to lower albuminuria on top of renin-angiotensin-aldosterone system (RAAS) inhibition in humans was analyzed by pooling data from four similarly designed, 24-week, randomized, double-blind, placebo-controlled, phase III trials.

RESEARCH DESIGN AND METHODS—A pooled analysis of four completed studies identified 217 subjects with type 2 diabetes and prevalent albuminuria (defined as a urinary albumin-to-creatinine ratio [UACR] of 30−3,000 mg/g creatinine) while receiving stable doses of RAAS inhibitors. Participants were randomized to either linagliptin 5 mg/day (n = 162) or placebo (n = 55). The primary end point was the percentage change in geometric mean UACR from baseline to week 24.

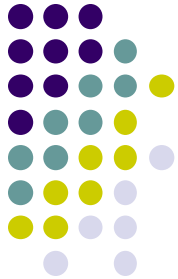
RESULTS—UACR at week 24 was reduced by 32% (95% CI −42 to −21; $P < 0.05$) with linagliptin compared with 6% (95% CI −27 to +23) with placebo, with a between-group difference of 28% (95% CI −47 to −2; $P = 0.0357$). The between-group difference in the change in HbA_{1c} from baseline to week 24 was −0.61% (−6.7 mmol/mol) in favor of linagliptin (95% CI −0.88 to −0.34% [−9.6 to −3.7 mmol/mol]; $P < 0.0001$). The albuminuria-lowering effect of linagliptin, however, was not influenced by race or HbA_{1c} and systolic blood pressure (SBP) values at baseline or after treatment.

CONCLUSIONS—Linagliptin administered in addition to stable RAAS inhibitors led to a significant reduction in albuminuria in patients with type 2 diabetes and renal dysfunction. This observation was independent of changes in glucose level or SBP. Further research to prospectively investigate the renal effects of linagliptin is underway.

Diabetes Care 36:3460–3468, 2013

Kidney Disease End Points in a Pooled Analysis of Individual Patient–Level Data From a Large Clinical Trials Program of the Dipeptidyl Peptidase 4 Inhibitor Linagliptin in Type 2 Diabetes

Mark E. Cooper, MBBS, PhD,[1] Vlado Perkovic, MBBS, PhD,[2] Janet B. McGill, MD,[3] Per-Henrik Groop, MD, DMSC,[1,4,5] Christoph Wanner, MD,[6] Julio Rosenstock, MD,[7] Uwe Hehnke, MSc,[8] Hans-Juergen Woerle, MD,[8] and Maximilian von Eynatten, MD[8]



- 13 faz 2, 3 çalışma
- 3505 linagliptin, 1961 plasebo
- Yeni veya kötüleşen mikroalbüminüri
- Yeni veya kötüleşen makroalbüminüri
- Kreatininde ≥2.8 mg/dl artış
- eGFR'nin %50 azalması
- Akut böbrek yetmezliği
- Herhangi bir nedene bağlı ölüm

- SONUÇ
- Linagliptin 448 olay (%12.8)
- Plasebo 306 (%15.6)
- %16 risk azaltımı
- HR, 0.84; 95% CI, 0.72-0.97; P = 0.02

Cooper ve ark, Diabetes Care, Am J Kidney Dis, 2015

The efficacy and safety of dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus patients with severe renal impairment: a meta-analysis

An updated systematic review and

Systematic Literature Review of DPP-4 Inhibitors in Patients with Type 2 Diabetes Mellitus and Renal Impairment

CLINICAL STUDY

The efficacy and safety of dipeptidyl peptidase-4 inhibitors for treatment

Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: Meta-analysis of placebo-controlled randomized clinical trials

M.B. Rehman[a,*], B.V. Tudrej[b], J. Soustre[b], M. Buisson[c], P. Archambault[b], D. Pouchain[d], H. Vaillant-Roussel[e,h], F. Gueyffier[f], J.-L. Faillie[c], M.-C. Perault-Pochat[g], C. Cornu[c], R. Boussageon[b]

Rationale, design, and baseline characteristics in Evaluation of LIXisenatide in Acute Coronary Syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo

- Son 180 gün içinde ACS geçiren T2 DM hastaları
- 6068 hasta, median 25 ay

eGFR (mL/dk/1.73 m^2)	%	ACR (mg/g)	%
<30	0.1	<30	74.3
30-60	23.1	30-300	19.2
60-90	53.4	≥300	6.5
≥90	23.4		

Bentley-Lewis ve ark, Am Heart J, 2015

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Marc A. Pfeffer, M.D., Ph.D., Brian Claggett, Ph.D., Rafael Diaz, M.D., Kenneth Dickstein, M.D., Ph.D., Hertzel C. Gerstein, M.D., Lars V. Køber, M.D., Francesca C. Lawson, M.D., Lin Ping, M.D., Xiaodan Wei, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Aldo P. Maggioni, M.D., John J.V. McMurray, M.D., Ph.D., Jeffrey L. Probstfield, M.D., Matthew C. Riddle, M.D., Scott D. Solomon, M.D., and Jean-Claude Tardif, M.D., for the ELIXA Investigators*

Median ACR	Plasebo (N = 2830)	Lixisenitide (N = 2803)	
Bazal	10.4	10.0	
6. ay	11.5	10.2	
18. ay	12.5	11.1	
24. ay	13.4	11.9	
% değişim: 0-24 ay	%34	%24	p = 0.004
Post hoc (A1c'ye göre düzeltilmiş)	%32	%26	p = 0.07

Pfeffer ve ark, N Engl J Med, 2015

Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial

Melanie J. Davies,[1] Stephen C. Bain,[2] Stephen L. Atkin,[3] Peter Rossing,[4] David Scott,[5] Minara S. Shamkhalova,[6] Heidrun Bosch-Traberg,[7] Annika Syrén,[7] and Guillermo E. Umpierrez[8]

Diabetes Care 2016;39:222–230 | DOI: 10.2337/dc14-2883

Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

Nefropati

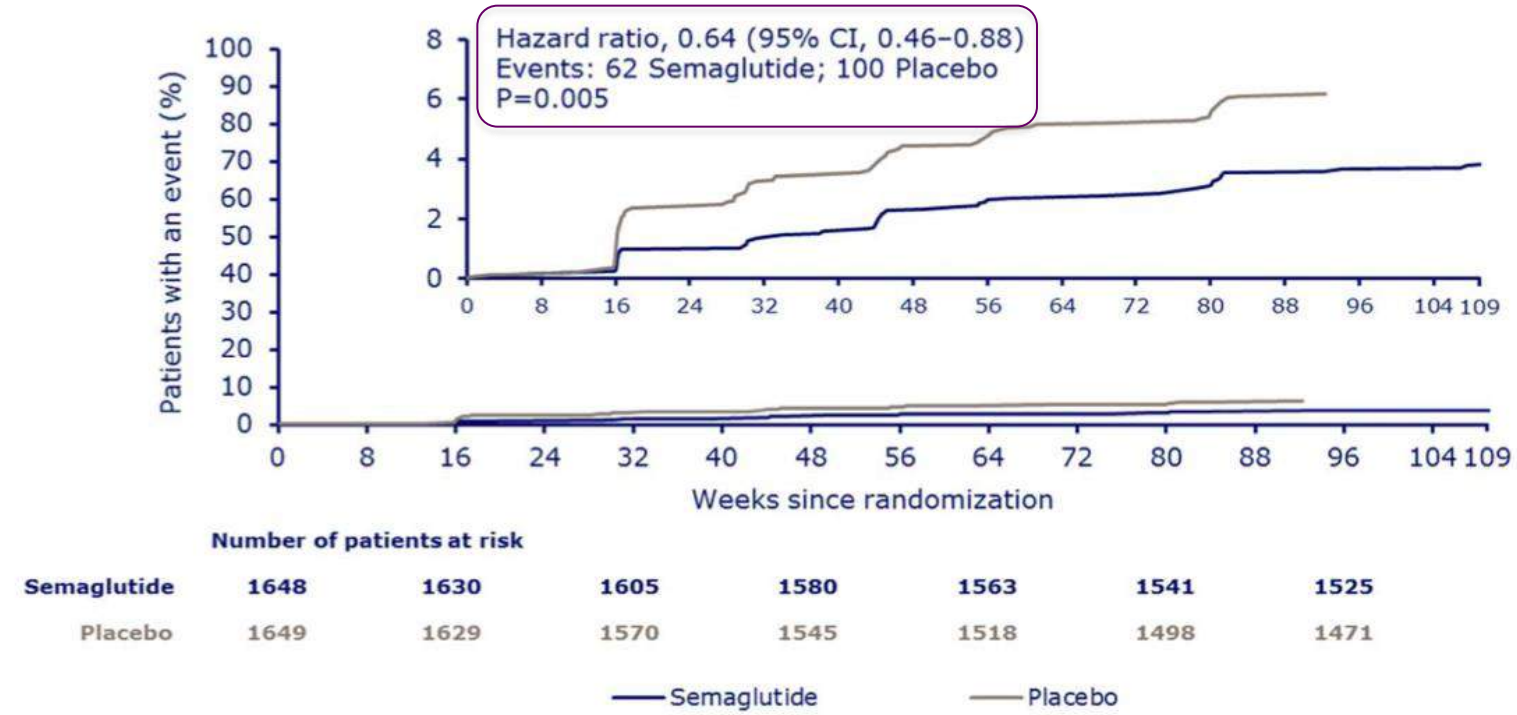
- Yeni makroalbüminüri
- Kreatinin 2 katına çıkması
- Kreatinin klerensi (MDRD) <45 ml/dk/1.73 m^2

Marso ve ark, N Engl J Med, 2016
Davies ve ark, Diabetes Care,2016

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*

B. New or worsening nephropathy



Marso ve ark, N Engl J Med, 2016

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

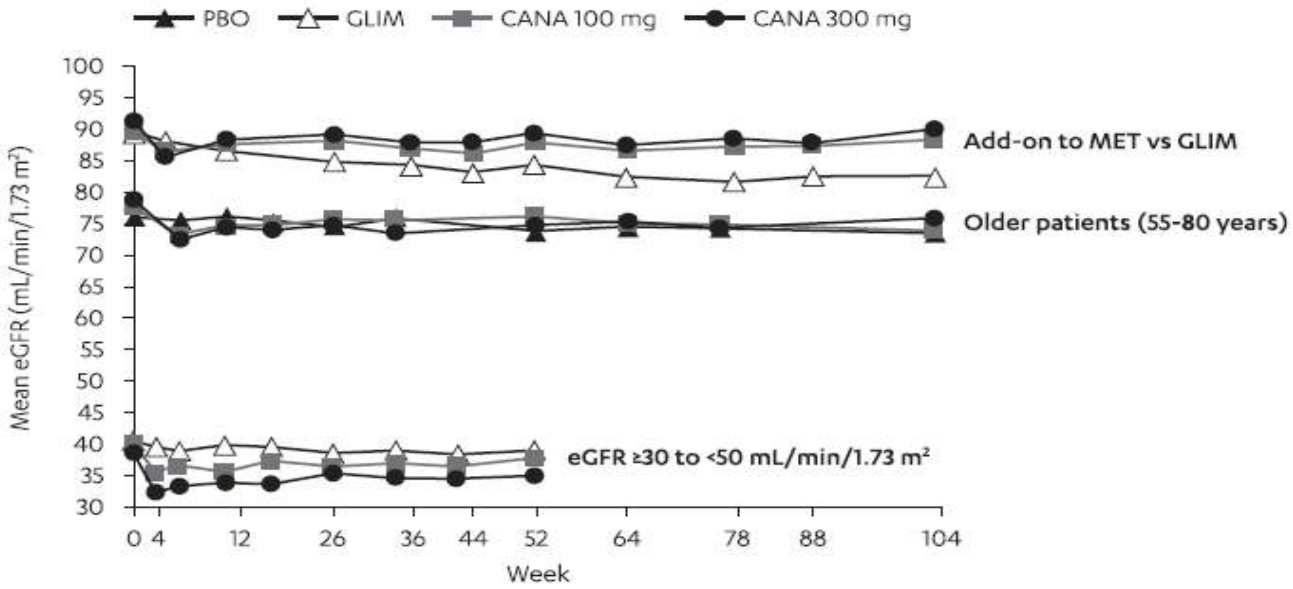
Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., 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*

	Semaglutide (N = 1648)		Plasebo (N = 1649)		Hazard ratio (%95 CI)		p
	N (%)	İnsidans hızı/100 hasta yılı	N (%)	İnsidans hızı/100 hasta yılı			
Yeni/kötüleşen nefropati	62 (3.8)	1.86	100 (6.1)	3.06	0.64	0.46; 0.88	0.005
Persistan makroalbüminüri	44 (2.7)	1.31	81 (4.9)	2.47	0.54	0.37; 0.77	0.001
Kreatinin 2 katına çıkması ve GFR <45	18 (1.1)	0.53	14 (0.8)	0.41	1.25	0.64; 2.58	0.48
Renal replasman tedavisi	11 (0.7)	0.32	12 (0.7)	0.35	0.91	0.4; 2.7	0.83

Marso ve ark, N Engl J Med, 2016

Canagliflozin

- İlk haftada eGFR **3-8** ml/dk/1.73m^2 azalır.
- 3. haftanın sonunda bazal seviyelerine döner.
- 52-104. haftada sabit kalır.
  - GFR azalması ilaç kesilince reversible



Perkovic ve ark, Curr Med Res Opin, 2015

Renal effects of canagliflozin in type 2 diabetes mellitus

Vlado Perkovic, Meg Jardine, Ujjwala Vijapurkar & Gary Meininger

Early transient reductions in estimated glomerular filtration rate were observed with canagliflozin; these changes generally stabilized or attenuated over time and reversed after discontinuation, suggesting no renal

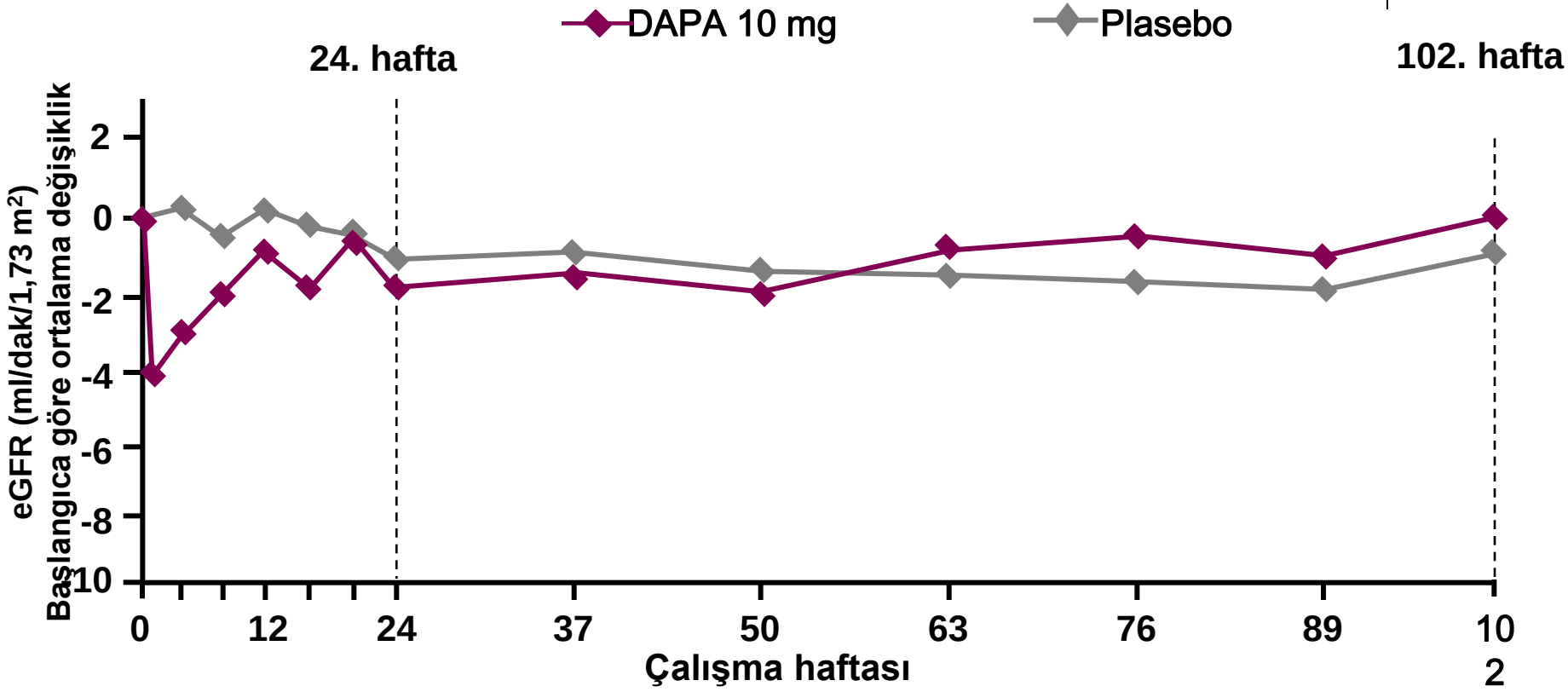
Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study–Renal (CANVAS-R): A randomized, placebo-controlled trial

function status; however, patients with moderately impaired kidney function experienced hyperkalemia more frequently with canagliflozin 300 mg compared with patients treated with either canagliflozin 100 mg or placebo. Canagliflozin was not associated with increased cardiovascular risk across studies; however, relatively few events among patients with impaired renal function meant that the analysis was not adequately powered to examine this outcome, and results from separate trials are awaited.

Perkovic ve ark, Curr Med Res Opin, 2015
Neal ve ark, Diabetes Obes Metab, 2017

Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis

Christian Sonesson*, Peter A. Johansson, Eva Johnsson and Ingrid Gause-Nilsson



Sonesson ve ark, Cardiovasc Diabetol, 2016

Dapagliflozin - Renal Sonlanımlar

- Çoğu olay kreatinin değerinde küçük ve geri dönüşümlü artış şeklinde olmuş ve serum kreatinin düzeyinde nadiren başlangıca göre klinik olarak anlamlı dalgalanmalara neden olmuştur

	Plasebo kontrollü havuz (kısa dönem)	
	DAPA 10 mg N=2360	Plasebo N=2295
Bir olay gözlenen toplam hasta sayısı, n (%)	76 (3,2)	42 (1,8)
Renal kreatinin klirensinde azalma	27 (1,1)	16 (0,7)
Böbrek bozukluğu	20 (0,8)	12 (0,5)
Kan kreatinin düzeyinde artış	15 (0,6)	9 (0,4)
Glomerüler filtrasyon hızında azalma	7 (0,3)	3 (0,1)
Böbrek yetmezliği	4 (0,2)	2 (0,1)
Akut böbrek yetmezliği	3 (0,1)	1 (<0,1)
Diğer[a]	6 (0,3)	2 (0,1)

[a]Sistatin C artışı, akut pre-böbrek yetmezliği, anormal renal kreatinin klirensi, anormal böbrek fonksiyonu testi, idrar akışında azalma, idrar çıkışında azalma

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm379659.pdf

Mikroalbüminüri

Table 3. Effects of SGLT2 inhibitors on albumin excretion rate.

Study	*N*	Investigational drug	Comparator	Weeks	Change in albumin excretion rate		
					Investigational drug	Comparator	Difference
Barnett et al. (2014)[88]	292[a]	Empagliflozin 10/25 mg	Placebo	52	−70/−121	114	−185/−236
Barnett et al. (2014)[88]	375[b]	Empagliflozin 25 mg	Placebo	52	−155	29	−184
Barnett et al. (2014)[88]	74[c]	Empagliflozin 25 mg	Placebo	52	−634	−140	−494
Cefalu et al. (2013)[89]	1450	Canagliflozin 100/300 mg	Glimepiride	52	−0.1/−0.9	0.7	−0.8/−1.5
Kohan et al. (2014)[87]	252	Dapagliflozin 5/10 mg	Placebo	104	78.0/−11.7	69.7	8.3/−81.4
Yale et al. (2013)[86]	269	Canagliflozin 100/300 mg	Placebo	52	−117.5/−96.2	15.4	−132.9/−111.6

SGLT2: sodium-glucose cotransporter 2; CKD: chronic kidney disease.
[a]Patients with Stage 2 CKD.
[b]Patients with Stage 3 CKD.
[c]Patients with Stage 4 CKD.

Scherntaner ve ark, Diab Vasc Dis Res, 2014

Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™)

- 7028 hasta, 10 ve 25 mg empagliflozin, median 3.1 yıl

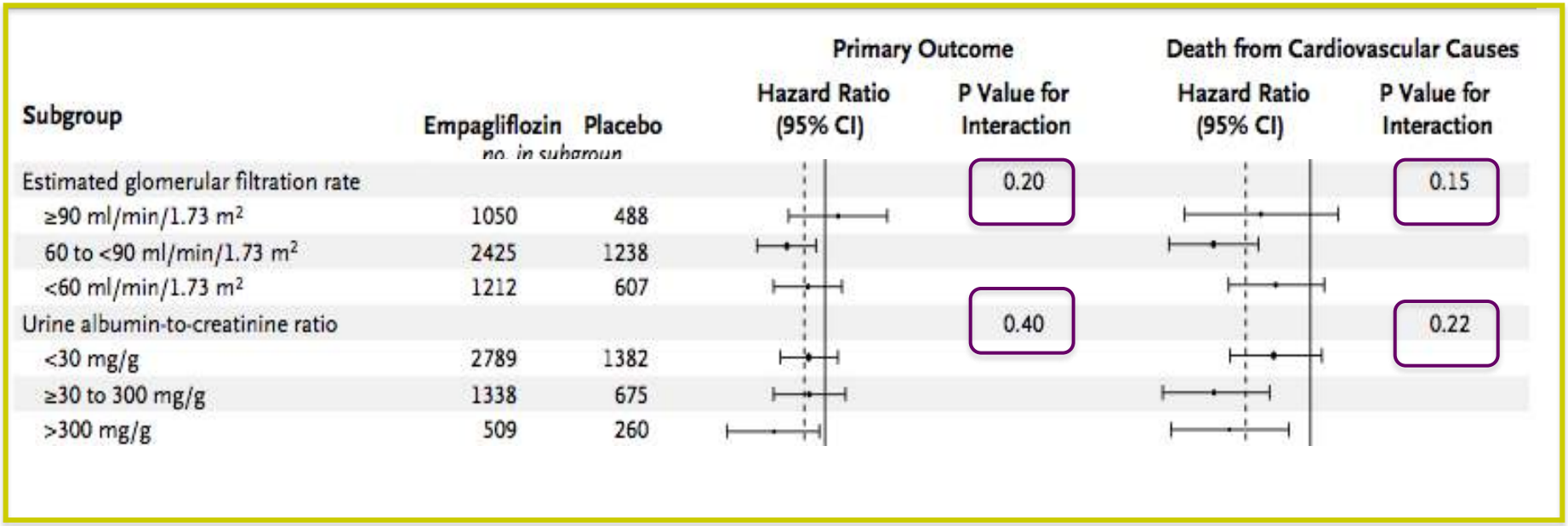
eGFR - MDRD ml/dk/1.73/m^2, ort. (SD)	74(21)
eGFR - MDRD ml/dk/1.73/m^2, n (%) Evre1: ≥90 Evre 2: 60-90 Evre3: 30-60	 1534 (22) 3672 (52) 1796 (26)
ACR – mg/g, median (Q1, Q3)	17.7 (7.1, 72.5)
ACR – mg/g, n (%) 30-300 ≥300	 2011 (29) 771 (11)

- Yeni makroalbüminüri
- Kreatinin 2 katına çıkması
- Kreatinin klerensi (MDRD) <45 ml/dk/1.73 m^2
- Renal replasman
- Renal ölüm

Zinman ve ark, Cardiovasc Diabetol, 2014

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



- ✔ Akut böbrek yetmezliği
- ✔ Akut böbrek hasarı
- ✔ Hiperkalemi

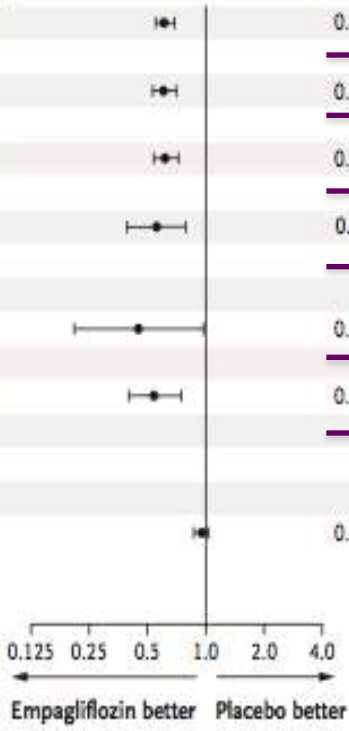
eGFR >60 ve <60 olanlar ayrı analiz edildiğinde plasebo ile benzer

Zinman ve ark, N Engl J Med, 2015

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

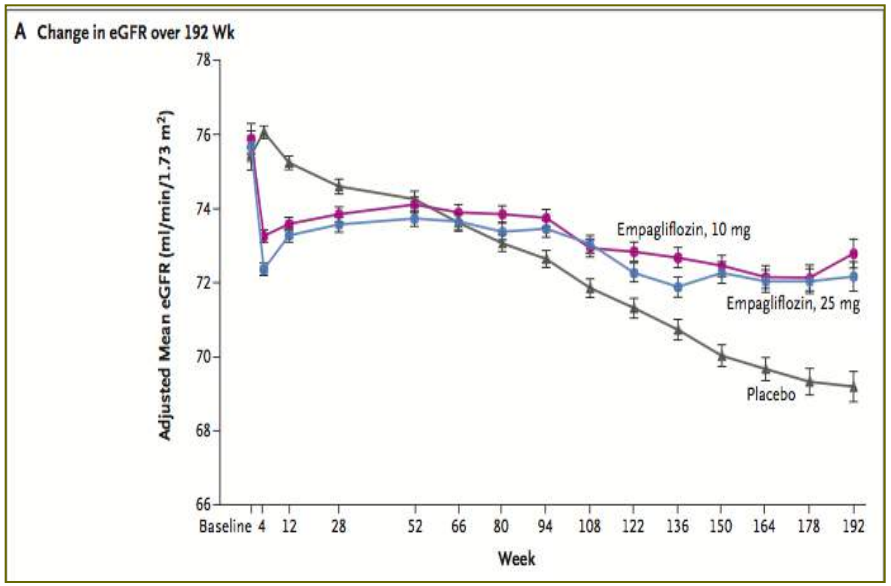
Renal Outcome Measure	Empagliflozin: no. with event/ no. analyzed (%)	Empagliflozin: rate/1000 patient-yr	Placebo: no. with event/ no. analyzed (%)	Placebo: rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25

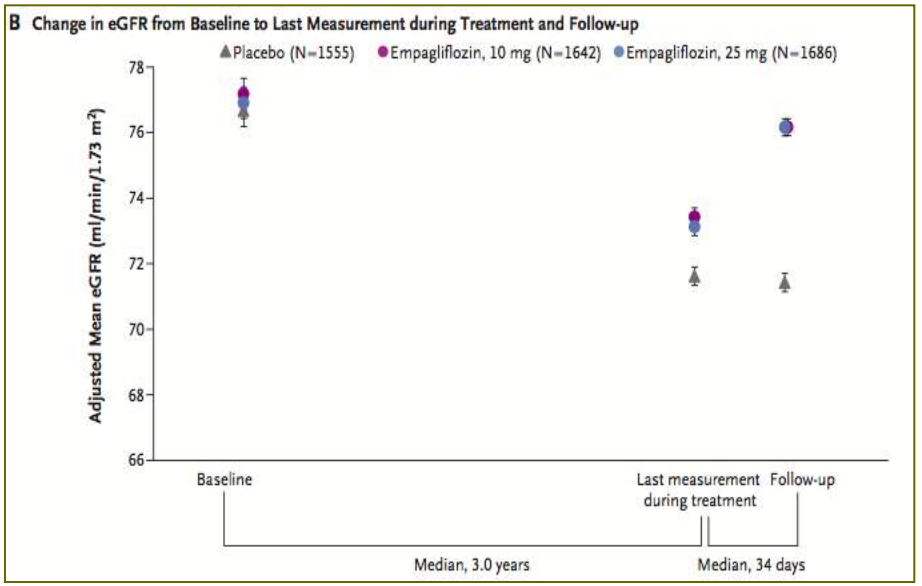


Wanner ve ark, N Engl J Med, 2016

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*





GFR değişimi	Empa 10	Empa 25	Plasebo	p
0-4 hafta (haftalık)	-0.62	-0.82	-0.01	<0.001
4 h-3 yıl (yıllık)	-0.19	-0.19	-1.67	<0.001
Takip (34 gün) (haftalık)	+0.48	+0.55	-0.04	<0.001

Wanner ve ark, N Engl J Med, 2016

SGLT2-İ -- Mekanizmalar

- Renovasküler
- Tübüloglomerüler feedback (Hiperfiltrasyonu ↓)
- İntraglomerüler basınç ↓
- Arteryel stiffness
- Vasküler direnç ↓
- Ürik asit düzeyi ↓
- Renal ve sistemik nörohormonal değişiklikler

LEADER ve EMPA-REG Çıkarımlar

	Liraglutide (LEADER; n=9340)	Empagliflozin (EMPA-REG OUTCOME; n=7020)
Incident or worsening nephropathy	0·78 (0·67–0·92); p=0·003	0·61 (0·53–0·70); p<0·001
New-onset macroalbuminuria	0·74 (0·60–0·91); NR	0·62 (0·54–0·72); p<0·001
Doubling of serum creatinine concentration and eGFR ≤45 mL/min/1·73m²	0·88 (0·66–1·18); NR	0·56 (0·39–0·79); p<0·001
Need for renal replacement therapy	0·87 (0·61–1·24); NR	0·45 (0·21–0·97); p=0·04
Death due to renal disease	1·59 (0·52–4·87); NR	3 (empagliflozin) vs 0 (placebo);* NR

- Empagliflozinin, yeni albüminüri üzerine etkisi yok
- Glisemik kontrol sonuçlara etkili
- Nonglisemik etkiler (KB, kilo, ürik asit….)
- Renal fizyoloji üzerine etkiler – liraglutide için net değil

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):

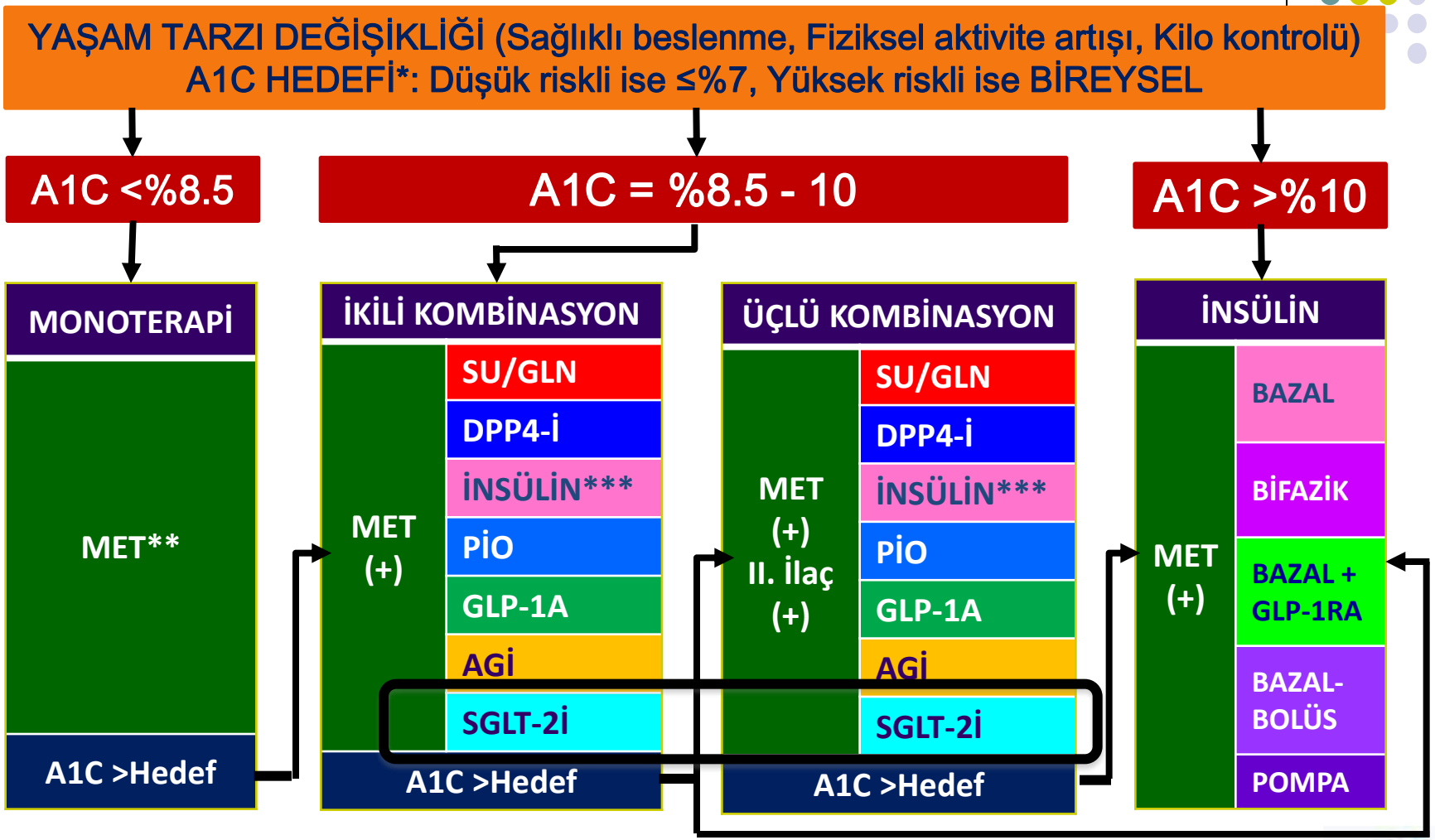
Triple Therapy — Metformin + — Lifestyle Management

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)

TEMD TİP 2 DİYABETTE TEDAVİ ALGORİTMASI - 2016



*Tedavi değişikliği için A1C >%7 veya bireysel hedefin üstünde olmalı. **Monoterapide MET tercih edilir, ancak MET kontrendike veya intolerans varsa diğer oral anti-diyabetiklerden biri başlanabilir. ***Bazal insülin tercih edilmeli, gerekirse bifazik insülin de başlanabilir. (MET: Metformin, DPP4-İ: Dipeptidil peptidaz 4 inhibitörü, SU: Sulfonilüre, GLN: Glinid, PİO: Pioglitazon, GLP-1A: Glukagon benzeri peptid 1 analoğu, AGİ: Alfa glukozidaz inhibitörü).

TEMD Diabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi ve İzlem Kılavuzu 2016

Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min)

FREE

Guideline development group; Henk Bilo; Luis Coentrão; Cécile Couchoud; Adrian Covic; Johan De Sutter; Christiane Drechsler; Luigi Gnudi; David Goldsmith; James Heaf; Olof Heimburger; Kitty J. Jager; Hakan Nacak; Maria José Soler; Liesbeth Van Huffel; Charlie Tomson; Steven Van Laecke; Laurent Weekers; Andrzej Wieçek; Davide Bolignano; Maria Haller; Evi Nagler; Ionut Nistor; Sabine van der Veer; Wim Van Biesen

	KBH-1	KBH-2	KBH-3	KBH-4	KBH-5ND	KBH-5D
Metformin			1.5g-850 mg/gün*	500 mg/gün**	Dikkatle değerlendirin/Daha fazla veri gerekli	
Gliklazid	Düşük dozlarda başlanmalı, her 1-4 haftada doz titre edilmelidir					
Glimepirid	Dozu 1 mg/gün'e düşürün				Kaçınılmalıdır	
Repaglinid					Mevcut deneyimler sınırlıdır	
Akarboz				En düşük doz kullanılmalı ve <50 mg olmalıdır		
Pioglitazon						
Sitagliptin			50 mg/gün'e düşürün	25 mg/gün'e düşürün		
Vildagliptin			Günde bir defa 50 mg'ye düşürün			
Saksagliptin			Günde bir defa 2.5 mg'ye düşürün			
Linagliptin						
Eksenatid		Dozu 1 ila 2 defa 5 mg'ye düşürün		Kaçınılmalıdır		
Liraglutid	Mevcut deneyimler sınırlıdır					

Bilo ve ark, Nephrol Dial Transplant, 2015

GFR'ye Göre SGLT2 İnhibitörü Dozları

Dapagliflozin	Canagliflozin	Empagliflozin
GFR<60 mL/dak/1.73 m Ise Kullanımı yok	GFR <45 mL/dak/1.73 m2 ise Kullanımı yok ≥45 to <60 mL/dak/1.73 m2 Ise Maks. 100 mg	GFR <45 mL/dak/1.73 m2 ise Kullanımı yok

Renal yetmezlikte SGLT2 inhibitörlerinin etkinliği azalmaktadır

eGFR <45 ml/dk/1.73 m^2 ise etkinlik çok azalır sıfıra yakındır

eGFR 45-60 ml/dk/1.73 m^2 ise HbA1c %0.3-0.45 azalır

eGFR>60 ml/dk/1.73 m^2 ise etkinlik sağlıklı kişiler ile benzerdir

Scheen, Drugs, 2015

Akılda Kalması Gerekenler

	SAVOR	TECOS	EXAMINE	ORIGIN	ELIXA	LEADER	EMPA-REG
Body weight change, kg	−0.4	N/A	Neutral	+1.1*	−0.6*	−2.3*	−1.4*
Renal endpoints	Albuminuria improved	No effect	No effect	No effect	Lower increase in albuminuria	Lower rate of nephropathy events	Lower progression of CKD
Efficacy							
HbA1c change, %	−0.3*	−0.3*	−0.36*	−0.3*	−0.4*	−0.4*	−0.3*

- Glisemik kontrol nefropati üzerine olumlu
- İlaç gruplarının renal sonlanımlara katkısı farklı
- Gliklazide MR, pioglitazon, liraglutide, semaglutide ve empagliflozin renoprotektif görünüyor
- Primer sonlanım çalışmalarına ihtiyaç var
- eGFR düştükçe kullanımları kısıtlı
- Tüm diyabet hastalarına uyarlanamaz (çoğu çalışma KVH veya risk faktörü olanlada, beyaz popülasyonda)

Avogaro ve ark, Cardiovasc Diabetol, 2016

Devam Eden Çalışmalar

- CARMELINA — Linagliptin
- MARLINA-T2D — Linagliptin
- RENALIS — Linagliptin
- EXTEND-CRS — Exenetide
- ELIXIRS — Lixisenetide
- AWARD-7 — Dulaglutide
- DERIVE — Dapagliflozin
- CANVAS-R — Canagliflozin
- CREDENCE — Canagliflozin

Teşekkürler...

atmaca_aysegul@yahoo.com