Empagliflozin ve Linagliptin ile Renal Yaklaşım

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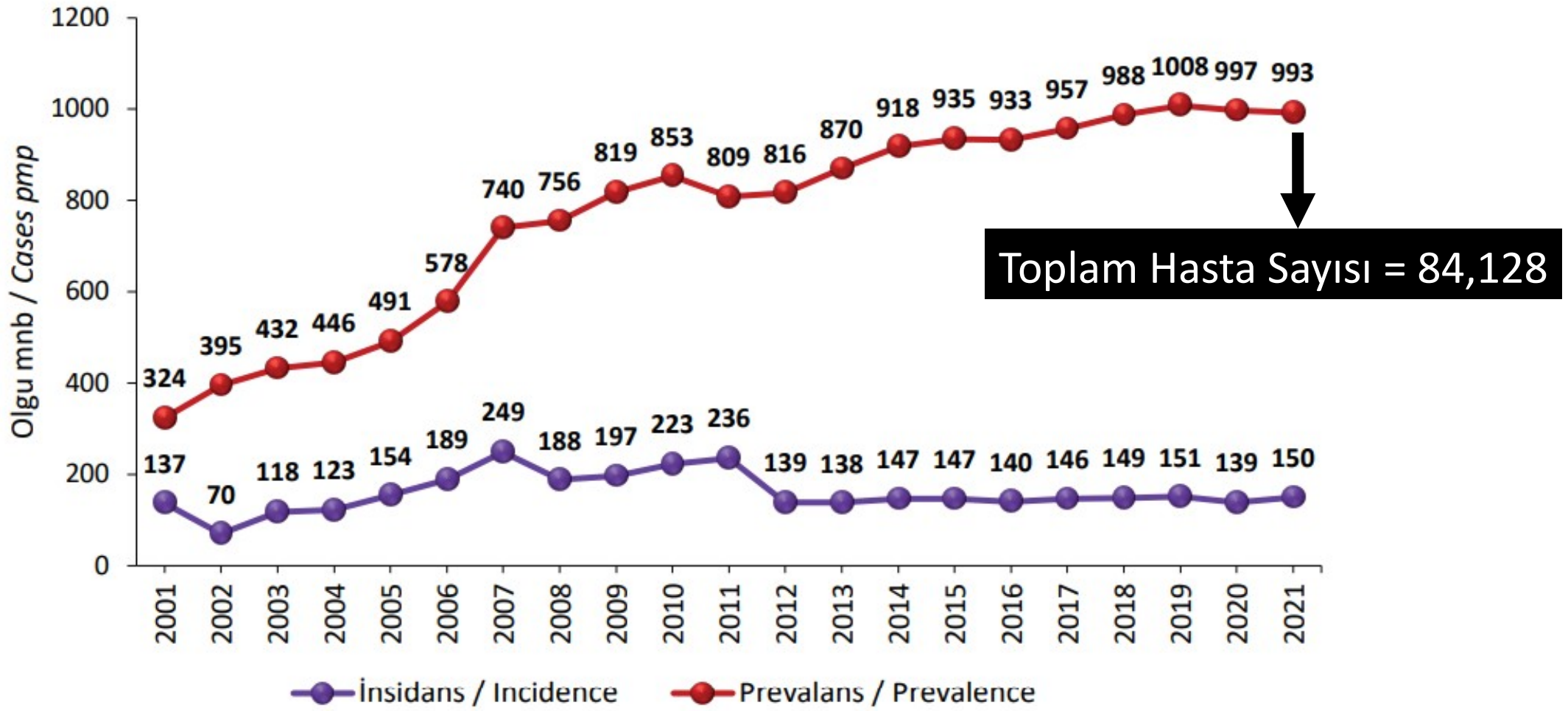
Türkiye'de RRT Gerektiren Son Dönem Böbrek Hastalığının İnsidansı ve Prevalansı



Registry of the Nephrology, Dialysis and Transplantation in Turkey

SDBH Olan 84,000 Hasta

Nephrol Dial Transplant (2011) 26: 1862–1871
doi: 10.1093/ndt/gfq656
Advance Access publication 4 November 2010

A population-based survey of Chronic REnal Disease In Turkey—the CREDIT study

Erişkin Popülasyonun %15.7'si

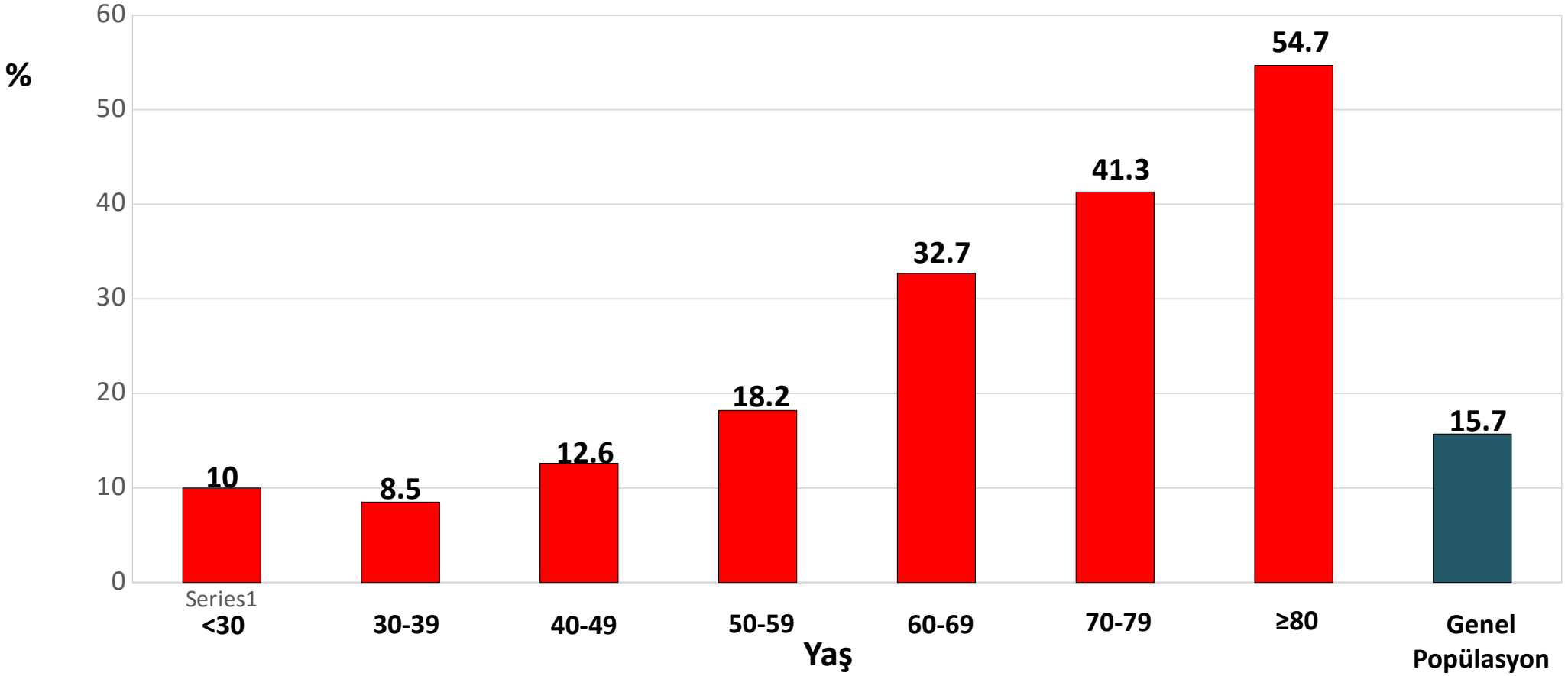
Department of Medicine, Erciyes University Medical Faculty, Kayseri, Turkey, [3]Nephrology Division, Department of Medicine, Gazi University Medical Faculty, Ankara, Turkey, [4]Nephrology Division, Department of Medicine, Ankara University Medical Faculty, Ankara, Turkey, [5]Nephrology Division, Department of Medicine, Hacettepe University Medical Faculty, Ankara, Turkey, [6]Nephrology Division, Department of Medicine, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey, [7]Nephrology Division, Department of Medicine, Istanbul University Istanbul Medical Faculty, Istanbul, Turkey, [8]Nephrology Division, Department of Medicine, Dicle University Medical Faculty, Diyarbakir, Turkey, [9]Nephrology Division, Department of Medicine, Dokuz Eylül University Medical Faculty, Izmir, Turkey, [10]Nephrology Division, Department of Medicine, Ege University Medical Faculty, Izmir, Turkey and [11]Nephrology Division, Goztepe Training and Research Hospital, Istanbul, Turkey

Kronik böbrek hastalığı, GFR'de (basitleştirilmiş MDRD formülü ile hesaplanmış) azalma ile birlikte veya azalma olmaksızın böbrek hasarı olarak tanımlanmıştır.

CREDIT Çalışması

(Chronic REnal Disease In Turkey)

Kronik Böbrek Hastalığının Değişik Yaş Gruplarında Prevalansı

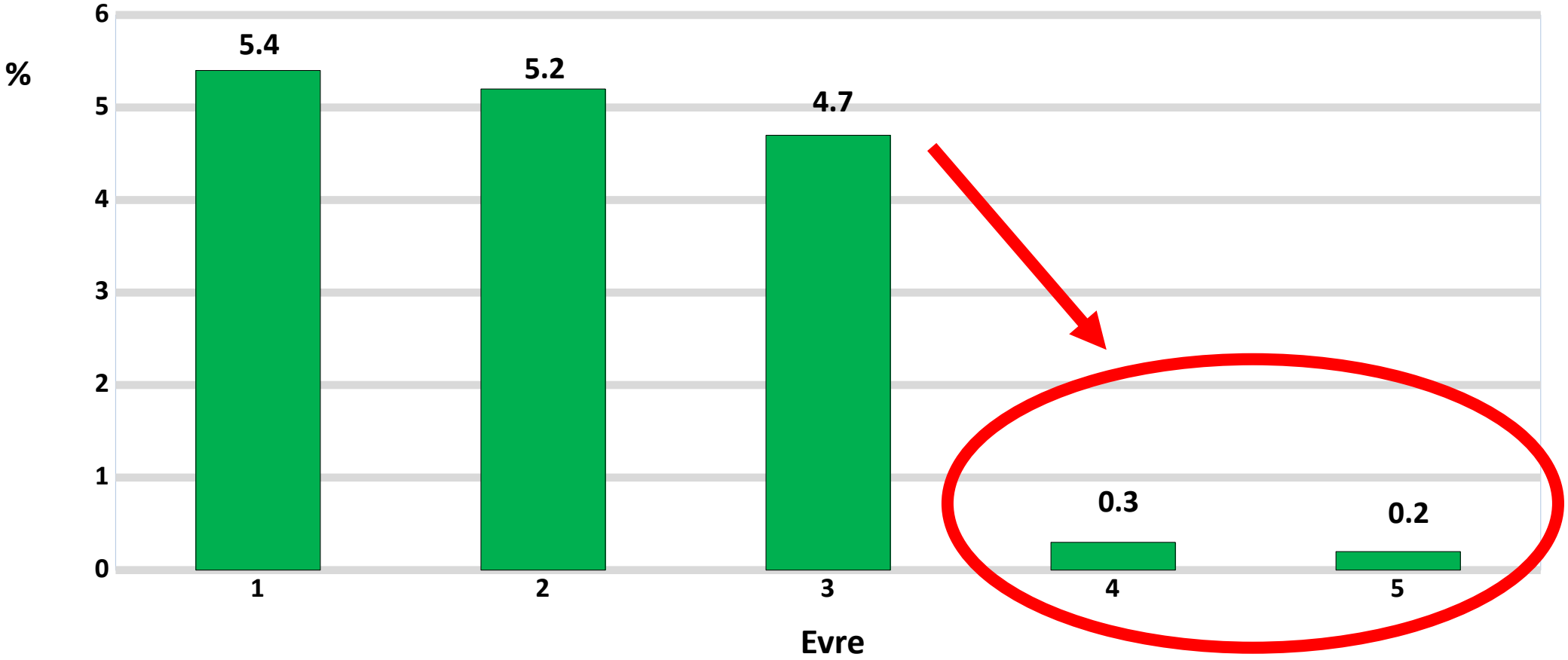


Süleymanlar et al: Nephrol Dial Transplant 26: 1862 – 1871, 2011

CREDIT Çalışması

(Chronic REnal Disease In Turkey)

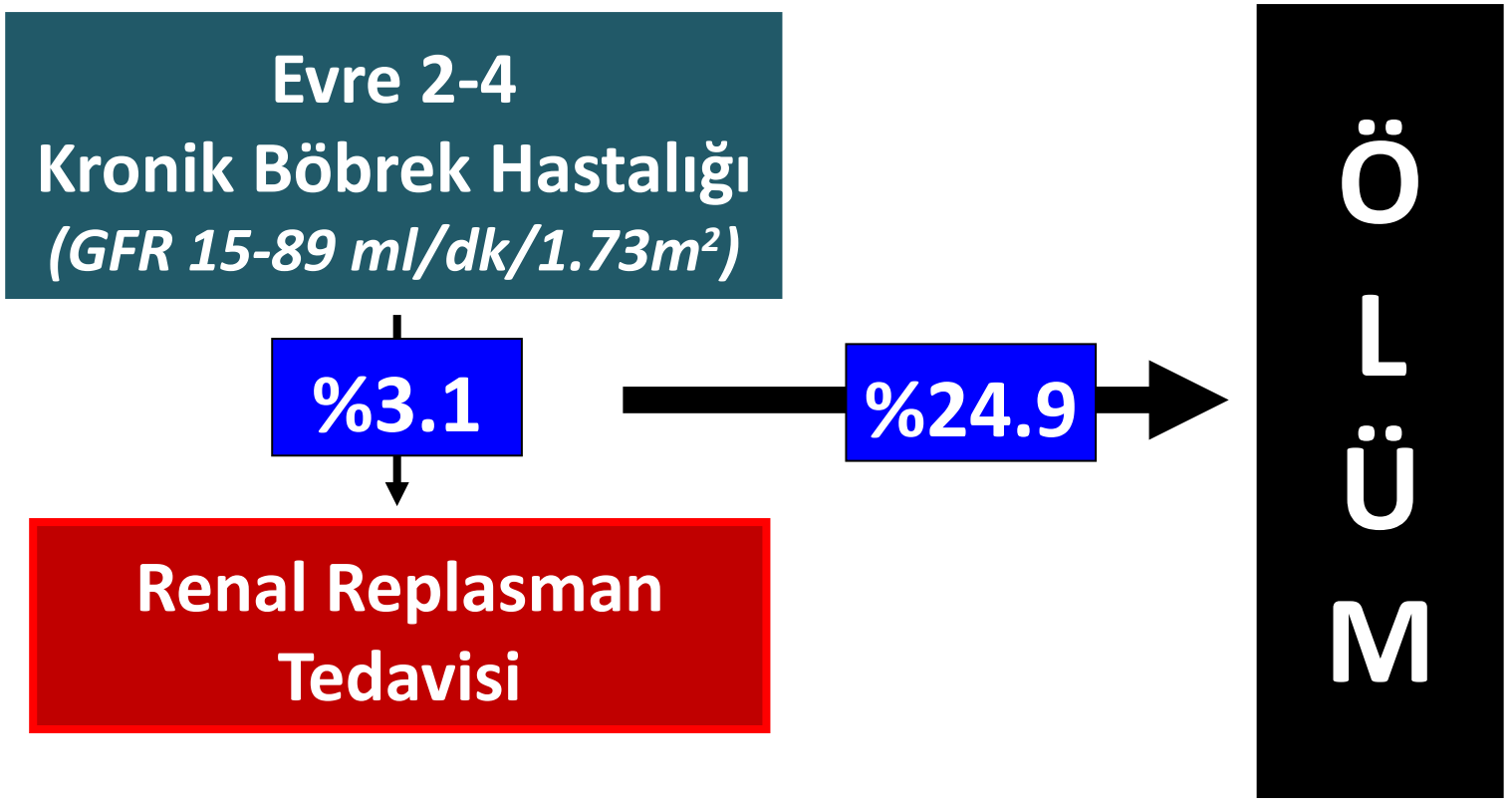
Kronik Böbrek Hastalığının Evrelerinin Prevalansı



Süleymanlar et al: Nephrol Dial Transplant 26: 1862 – 1871, 2011

Kronik Böbrek Hastalığının Doğal Seyri

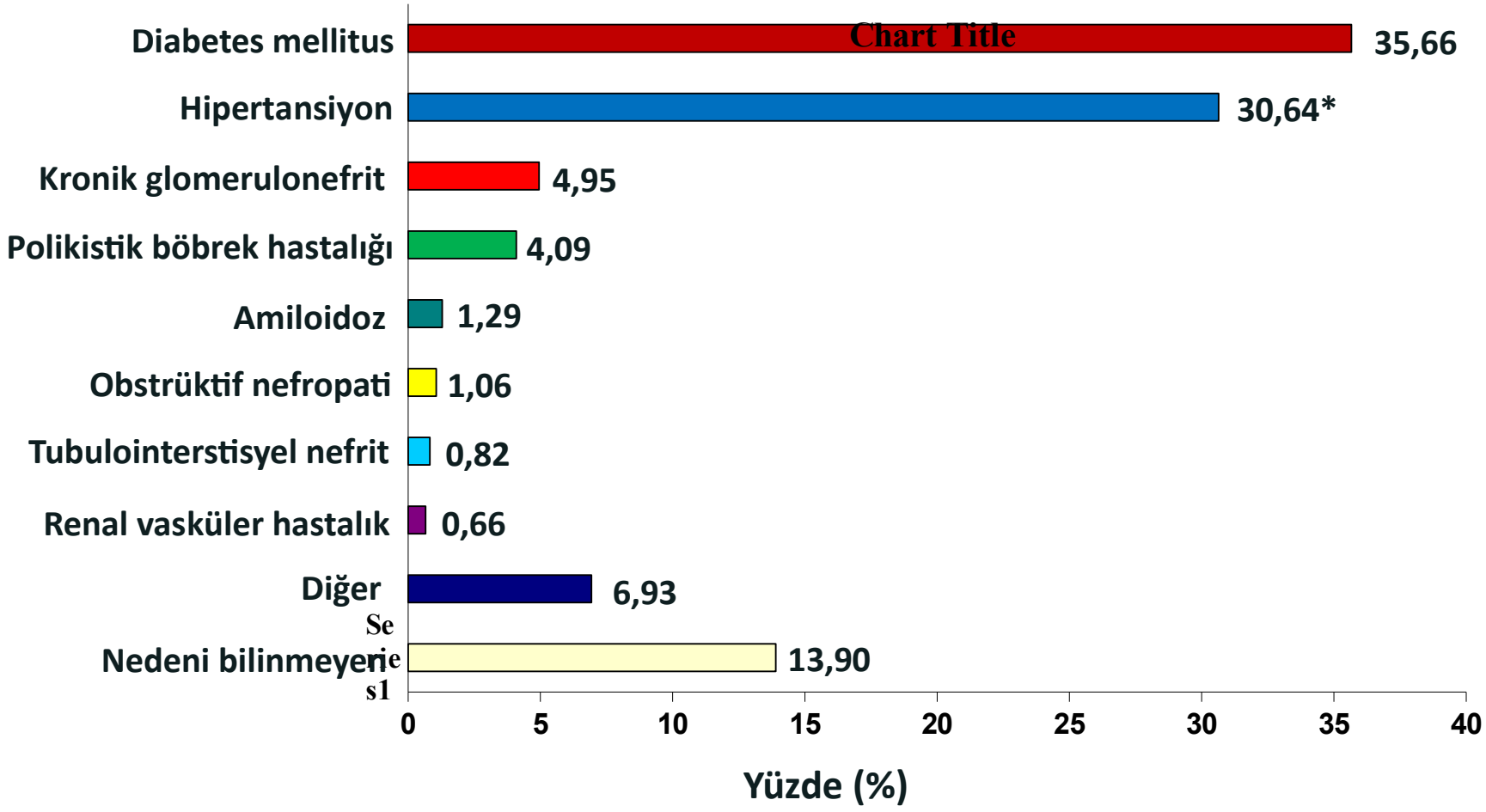
27,998 Hastanın* 5.5 Yıl Boyunca Takibi



Keith et al.: Arch Intern Med 164: 659-663, 2004

*Third National Health and Nutrition Examination Survey (NHANES III)

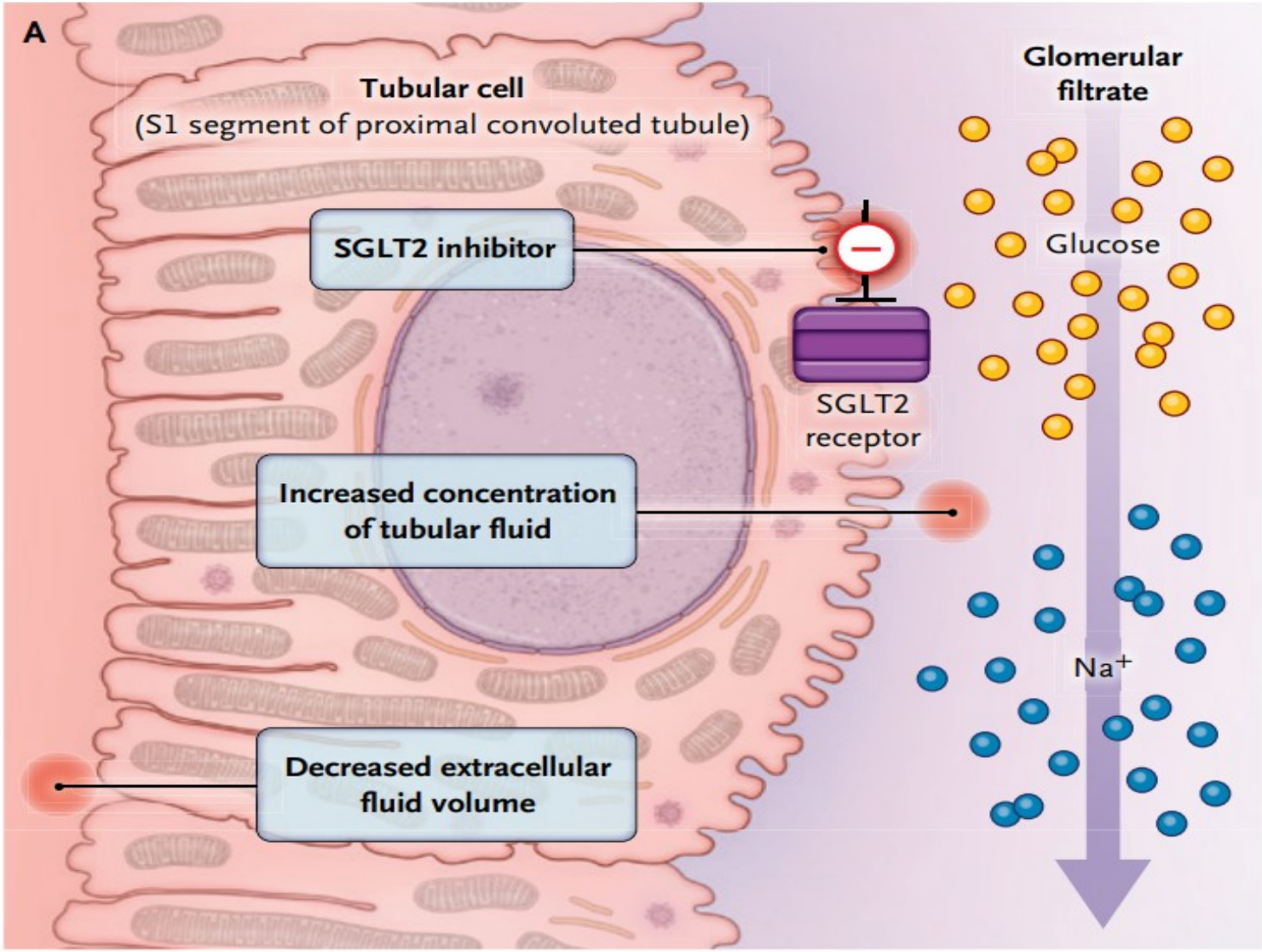
Hemodiyaliz Hastalarında Böbrek Yetersizliğinin Nedenleri



*Hipertansiyonun primer değil, kronik böbrek yetmezliğine bağlı oluşan sekonder hipertansiyon olduğuna dair kuvvetli şüpheler vardır.

Registry of The Nephrology, Dialysis and Transplantation in Turkey, Registry 2021

SGLT2 İnhibitörleri



Braunwald: N Engl J Med 386; 2024-2034, 2022

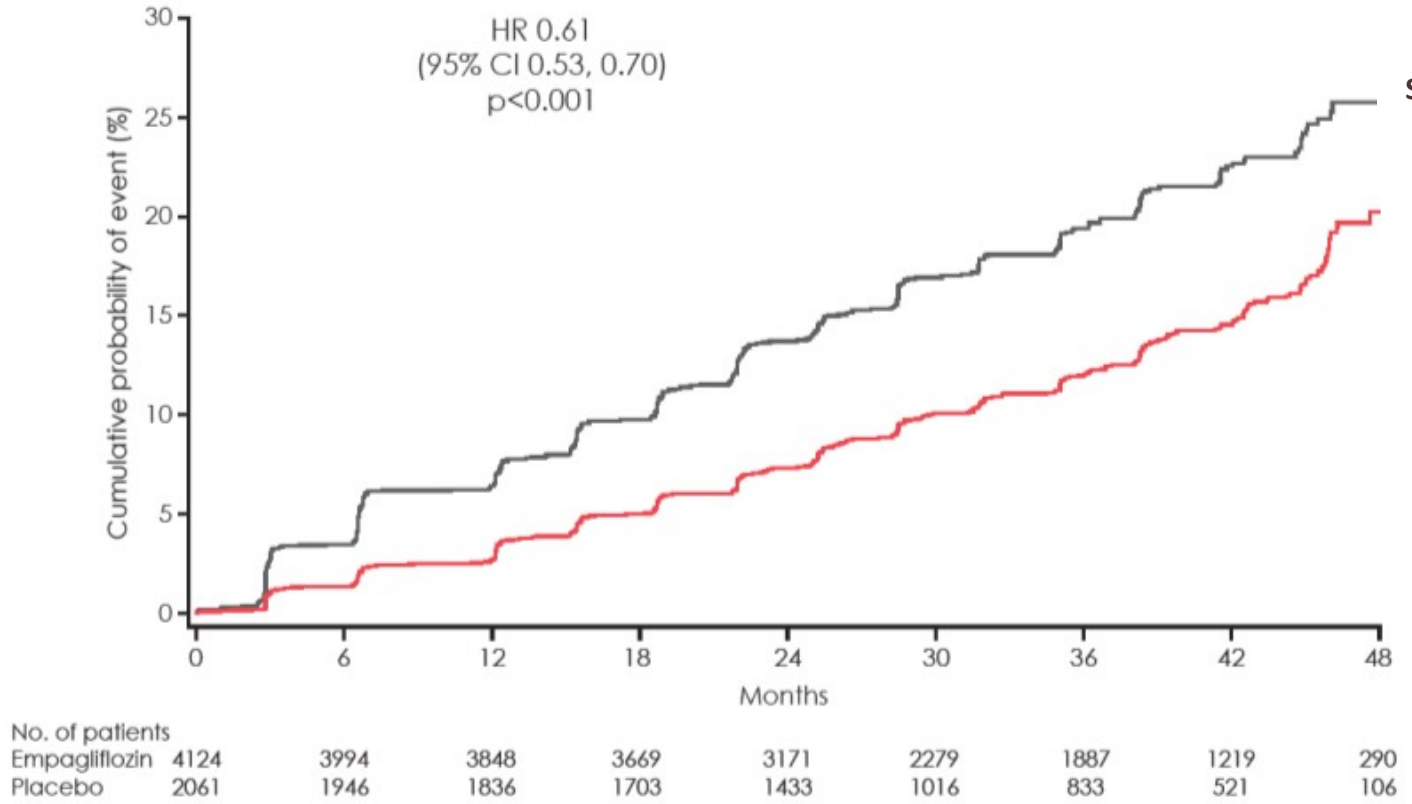
EMPA-REG OUTCOME Çalışması

Characteristic	Patients with eGFR of 59 ml per Minute per 1.73 m^2 or Less		Patients with eGFR of 60 ml per Minute per 1.73 m^2 or More	
	Placebo (N=607)	Empagliflozin (N=1212)	Placebo (N=1726)	Empagliflozin (N=3473)
Age — yr	67.1±8.2	67.1±7.6	61.9±8.6	61.7±8.5
Male sex — no. (%)	418 (68.9)	816 (67.3)	1262 (73.1)	2518 (72.5)
Body-mass index†	30.9±5.4	31.0±5.5	30.6±5.2	30.5±5.2
Glycated hemoglobin — %‡	8.03±0.85	8.07±0.86	8.10±0.84	8.07±0.84
Interval of >10 yr since diagnosis of type 2 diabetes — no. (%)	422 (69.5)	794 (65.5)	917 (53.1)	1876 (54.0)
Blood pressure — mm Hg				
Systolic	136.4±18.7	136.1±18.0	135.6±16.7	135.0±16.6
Diastolic	74.6±10.3	74.5±9.9	77.6±10.0	77.4±9.5
Estimated glomerular filtration rate — ml/min/1.73 m^2	48.6±7.8	48.4±8.2	82.7±16.6	83.1±17.1
Urinary albumin-to-creatinine ratio — no. (%)§				
<30	283 (46.6)	566 (46.7)	1099 (63.7)	2223 (64.0)
30 to 300	205 (33.8)	411 (33.9)	470 (27.2)	926 (26.7)
>300	115 (18.9)	223 (18.4)	145 (8.4)	286 (8.2)
Cholesterol — mg/dl				
Low-density lipoprotein¶	85.0±36.1	84.4±35.8	84.8±35.1	86.5±36.0
High-density lipoprotein‖	42.9±10.7	44.2±12.5	44.4±11.5	44.7±11.7
Triglycerides — mg/dl‖	180.4±107.4	173.5±108.1	167.2±125.6	169.4±136.4
Coronary artery disease	482 (79.4)	938 (77.4)	1281 (74.2)	2606 (75.0)
History of stroke**	156 (25.7)	293 (24.2)	397 (23.0)	791 (22.8)
Peripheral artery disease††	130 (21.4)	314 (25.9)	349 (20.2)	667 (19.2)
Cardiac failure‡‡	89 (14.7)	174 (14.4)	155 (9.0)	288 (8.3)
Concomitant medication — no. (%)				
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	502 (82.7)	1031 (85.1)	1366 (79.1)	2766 (79.6)
Beta-blocker	415 (68.4)	829 (68.4)	1083 (62.7)	2226 (64.1)
Diuretic	355 (58.5)	710 (58.6)	633 (36.7)	1336 (38.5)
Calcium-channel blocker	227 (37.4)	446 (36.8)	561 (32.5)	1082 (31.2)
Statin	461 (75.9)	966 (79.7)	1312 (76.0)	2663 (76.7)
Aspirin	495 (81.5)	981 (80.9)	1432 (83.0)	2894 (83.3)
Metformin	369 (60.8)	711 (58.7)	1365 (79.1)	2746 (79.1)
Sulfonylurea	234 (38.6)	480 (39.6)	758 (43.9)	1534 (44.2)
Insulin	357 (58.8)	699 (57.7)	778 (45.1)	1551 (44.7)

Wanner C et al. N Engl J Med. 2016;375(4):323-34.

EMPA-REG OUTCOME Çalışması

Yeni Ortaya Çıkan veya Kötüleşen Nefropati*



Plasebo + Standart Tedavi (n=2061)

Empagliflozin + Standart Tedavi (n=4124)

%39 RRR

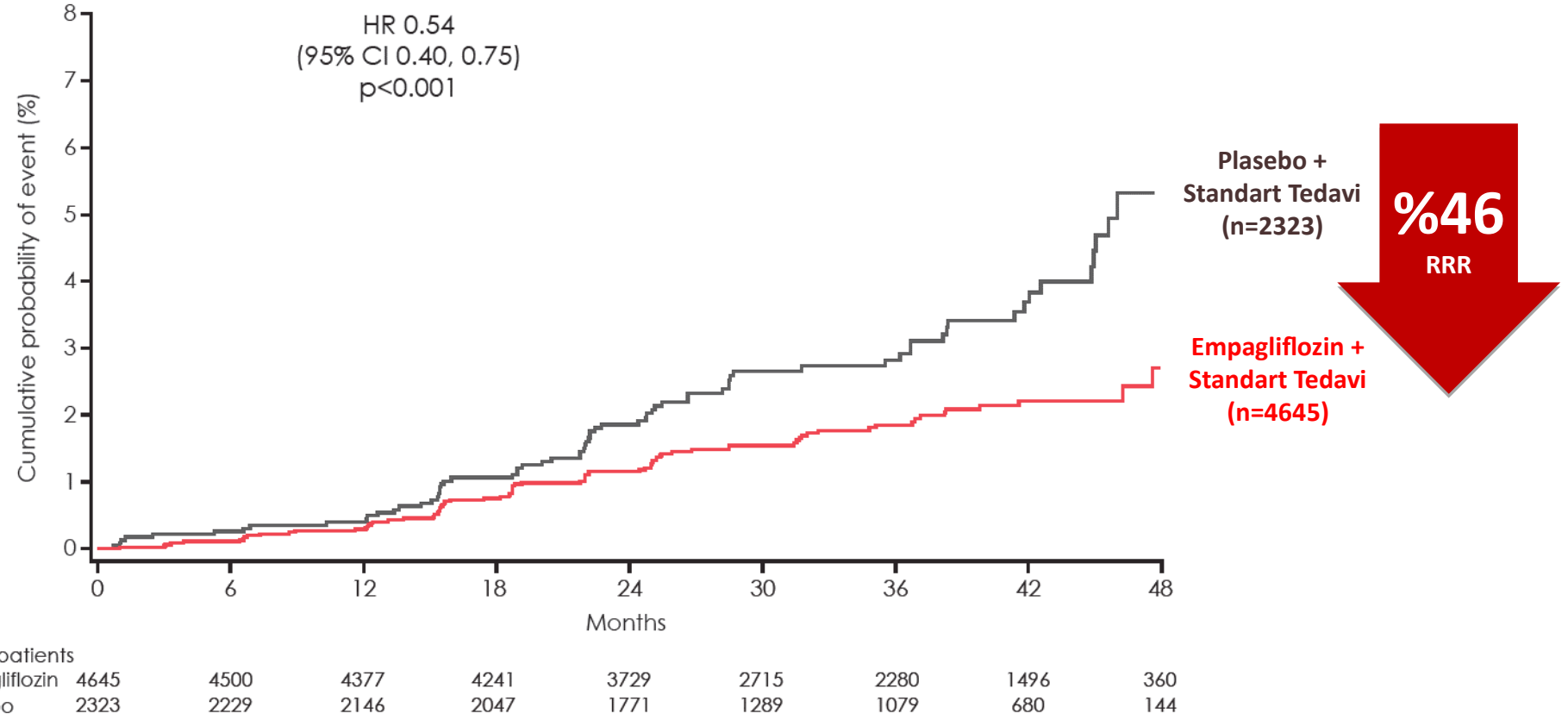
≥1 doz çalışma ilacı ile tedavi edilmiş hastalarda Kaplan-Meier tahmini. Tehlike oranları Cox regresyon analizlerine dayanmaktadır.
HR, tehlike oranı; GA, güven aralığı. Önceden belirtilmiş analizler.

***Makroalbüminüriye ilerleme, serum kreatinin düzeyinin 2 katına çıkması, RRT gereksinimi veya böbrek hastalığına bağlı ölüm**

Wanner C et al. N Engl J Med. 2016;375(4):323-34.

EMPA-REG OUTCOME Çalışması

Serum Kreatininin İki Katına Çıkması, Renal Replasman Tedavisinin Başlatılması veya Renal Hastalığa Bağlı Ölüm



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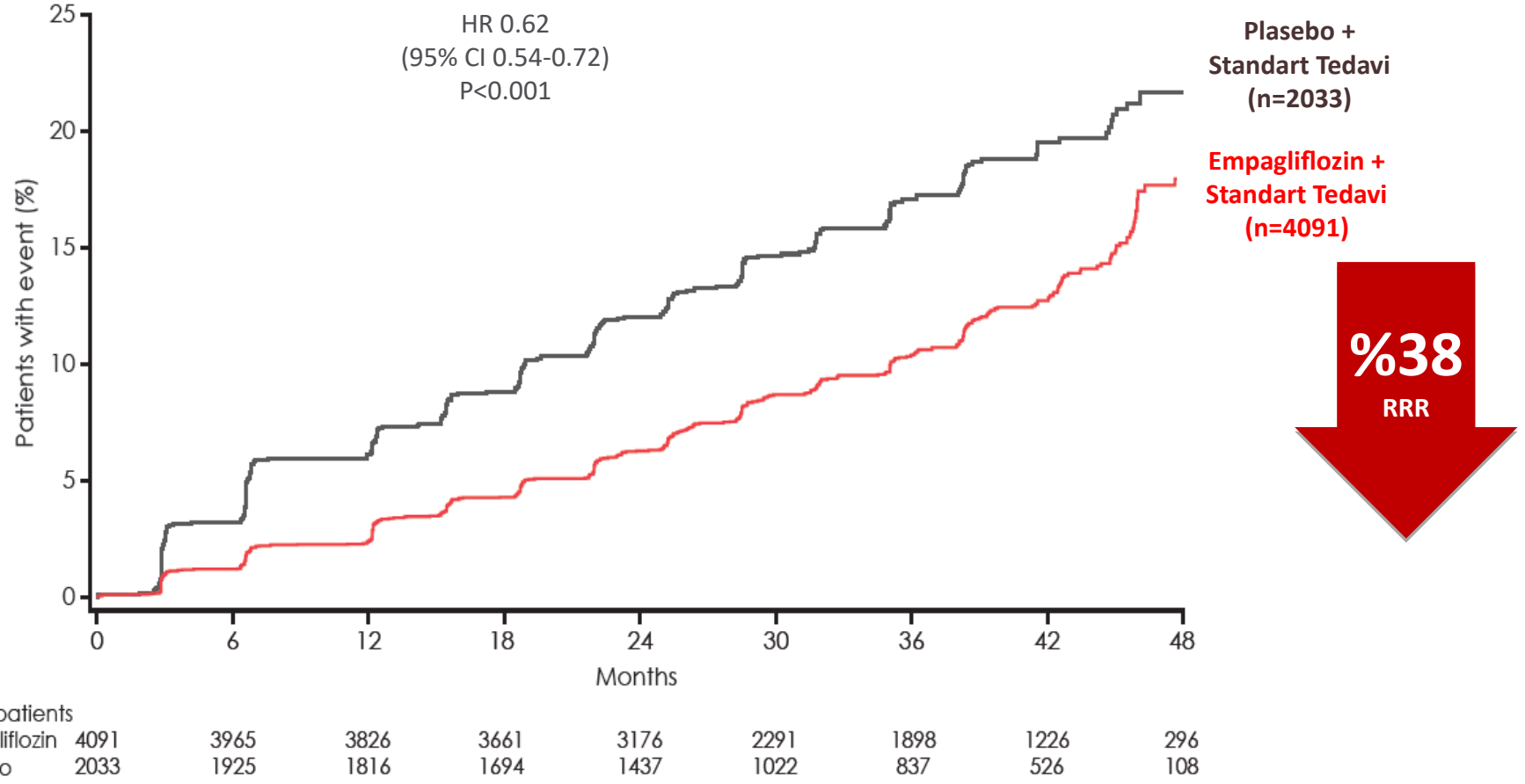
HR, tehlike oranı; GA, güven aralığı. Önceden belirtilmiş analizler.

Wanner C et al. N Engl J Med. 2016;375(4):323-34.

EMPA-REG OUTCOME Çalışması

Makroalbüminüri Gelişmesi

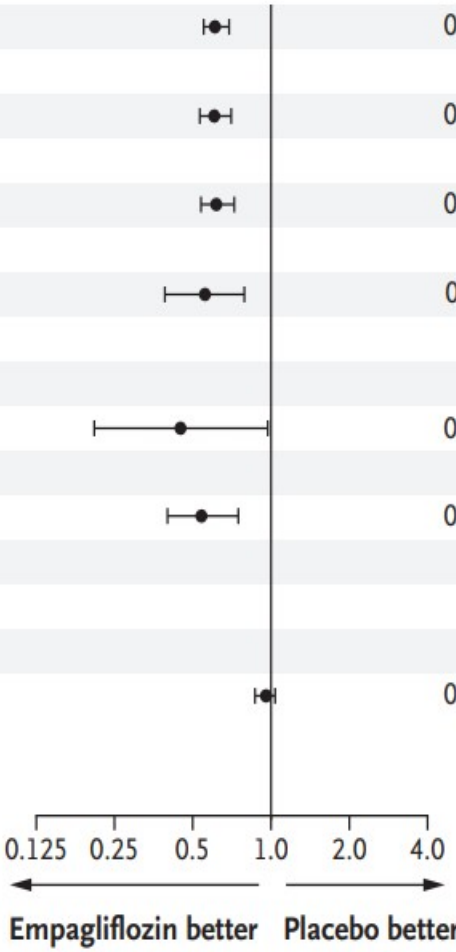


Wanner C et al. N Engl J Med. 2016;375(4):323-34.

EMPA-REG OUTCOME Çalışması

Renal Sonuçlar

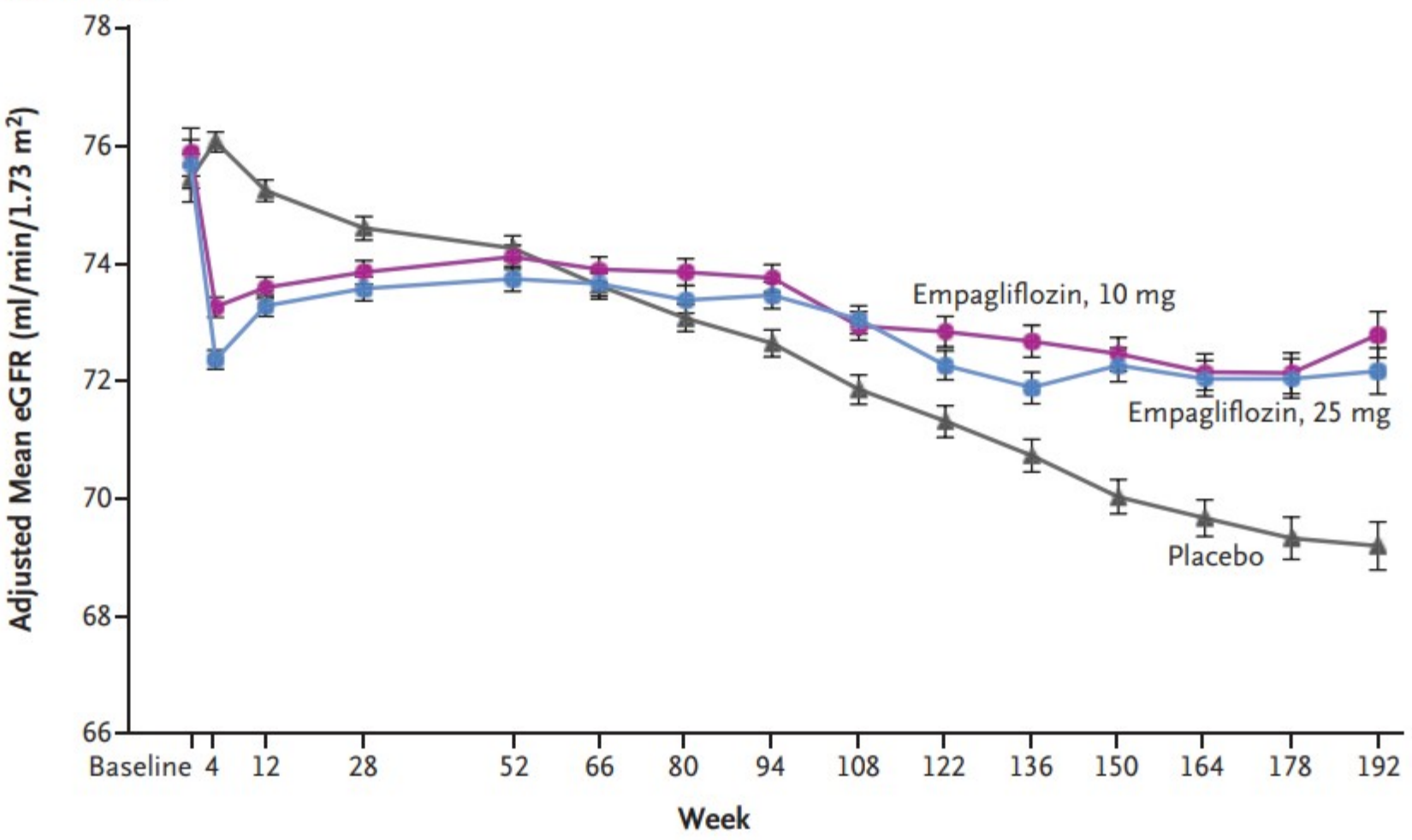
Renal Outcome Measure	Empagliflozin: *no. with event/ no. analyzed (%)*	Empagliflozin: *rate/1000 patient-yr*	Placebo: *no. with event/ no. analyzed (%)*	Placebo: *rate/1000 patient-yr*	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (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 C et al. N Engl J Med. 2016;375(4):323-34.

EMPA-REG OUTCOME Çalışması

192 Hafta Boyunca eGFR (CKD-EPI)



Wanner C et al. N Engl J Med. 2016;375(4):323-34.

EMPEROR-Reduced Çalışması

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

- Sınıf II, III ve IV kalp yetersizliği olan ve ejeksiyon fraksiyonu ≤%40 olan 3730 hasta
- Empagliflozin 10 mg ve plasebo grupları
- Birincil birleşik sonlanım noktası: Kardiyovasküler nedenlere bağlı ölüm veya kalp yetersizliğinin kötüleşmesine bağlı hastaneye yatış
- Ortanca takip süresi: 16 ay

Packer et al: N Engl J Med 383: 1413-1424, 2020

EMPEROR-Reduced Çalışması

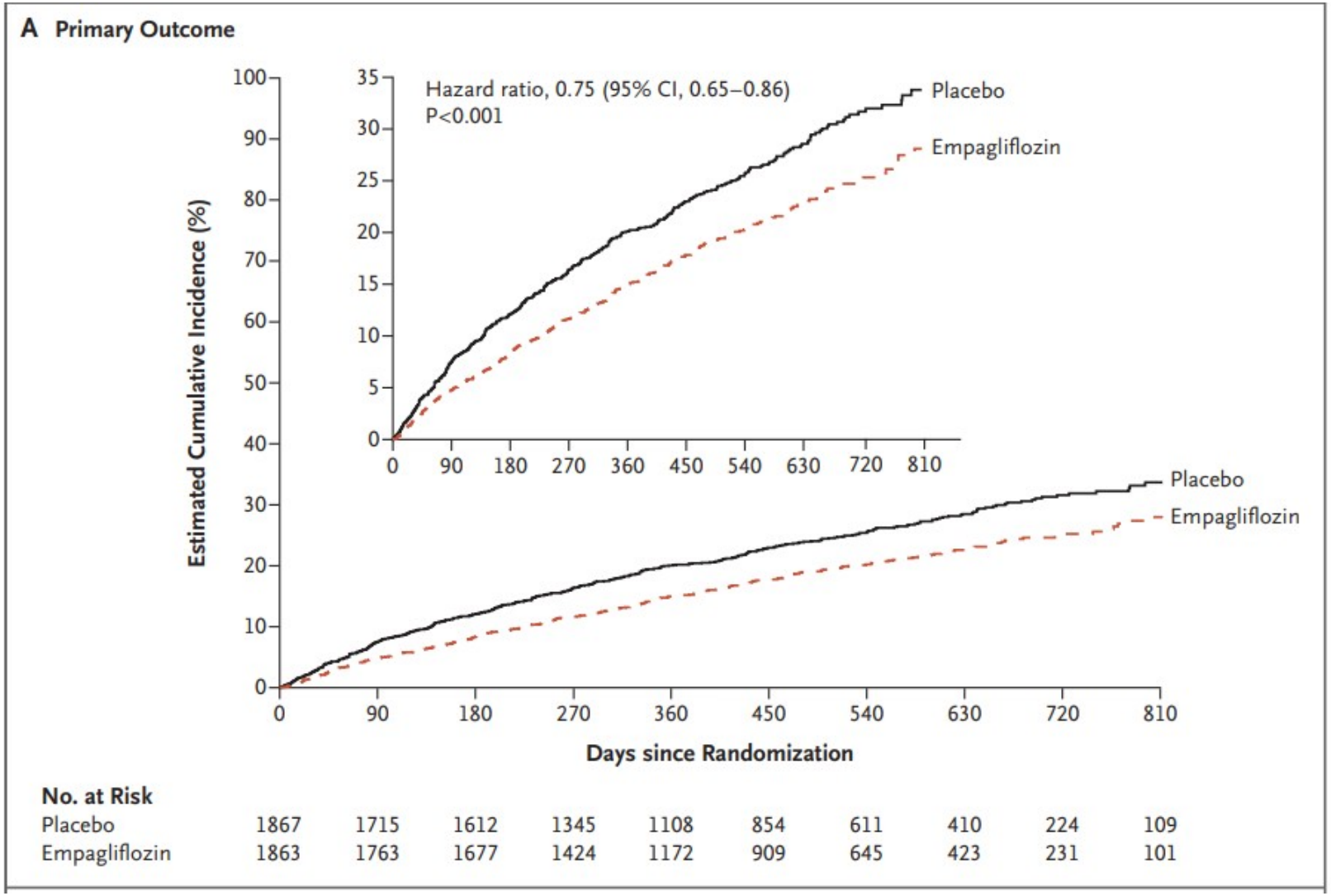
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	578 (31.0)	593 (31.8)
Cardiac resynchronization therapy‖	220 (11.8)	222 (11.9)

Packer et al: N Engl J Med 383: 1413-1424, 2020

EMPEROR-Reduced Çalışması

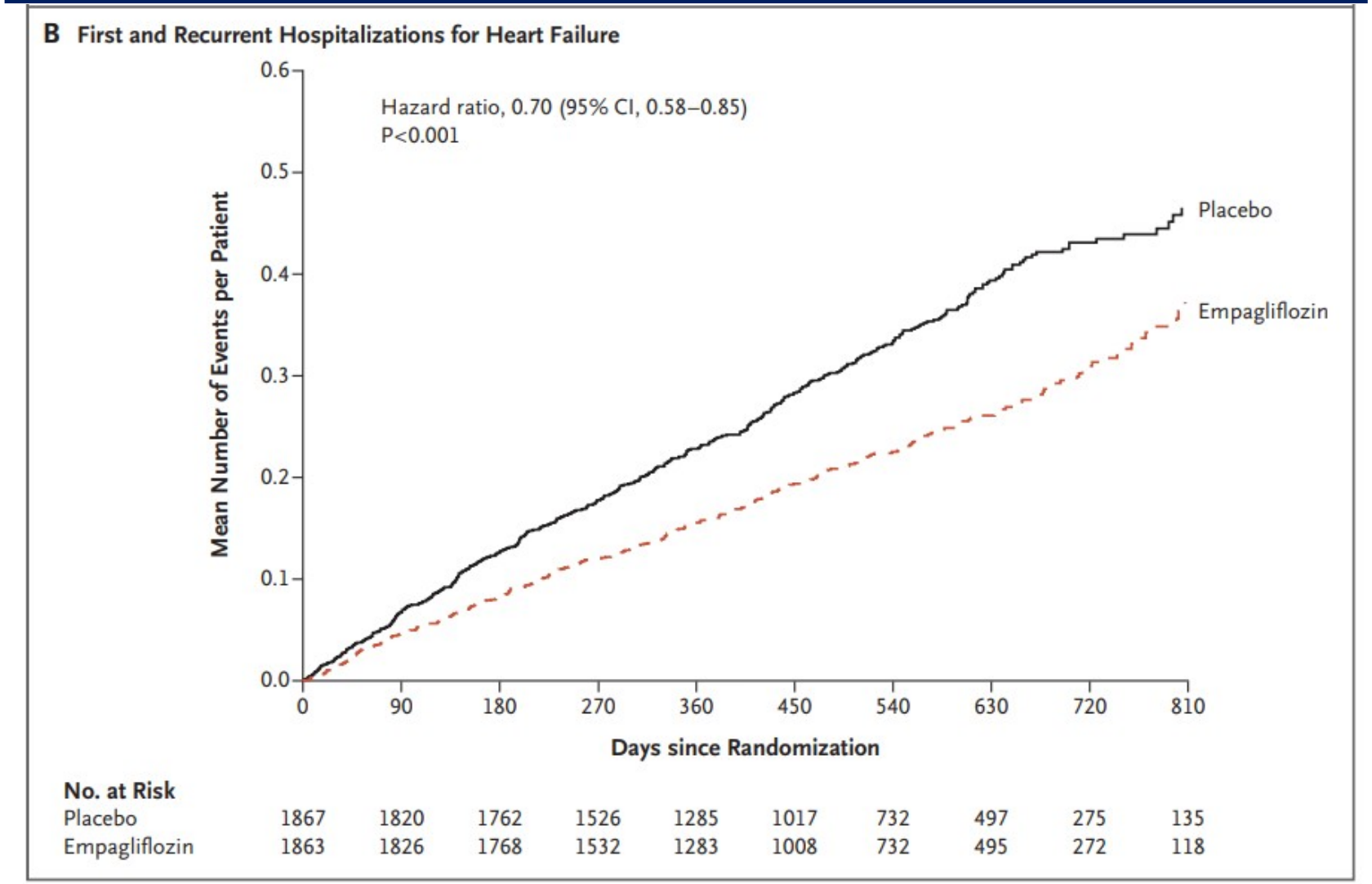
Kardiyovasküler Nedenlere Bağlı Ölüm veya Kalp Yetersizliğine Bağlı Hastaneye Yatış



Packer et al: N Engl J Med 383: 1413-1424, 2020

EMPEROR-Reduced Çalışması

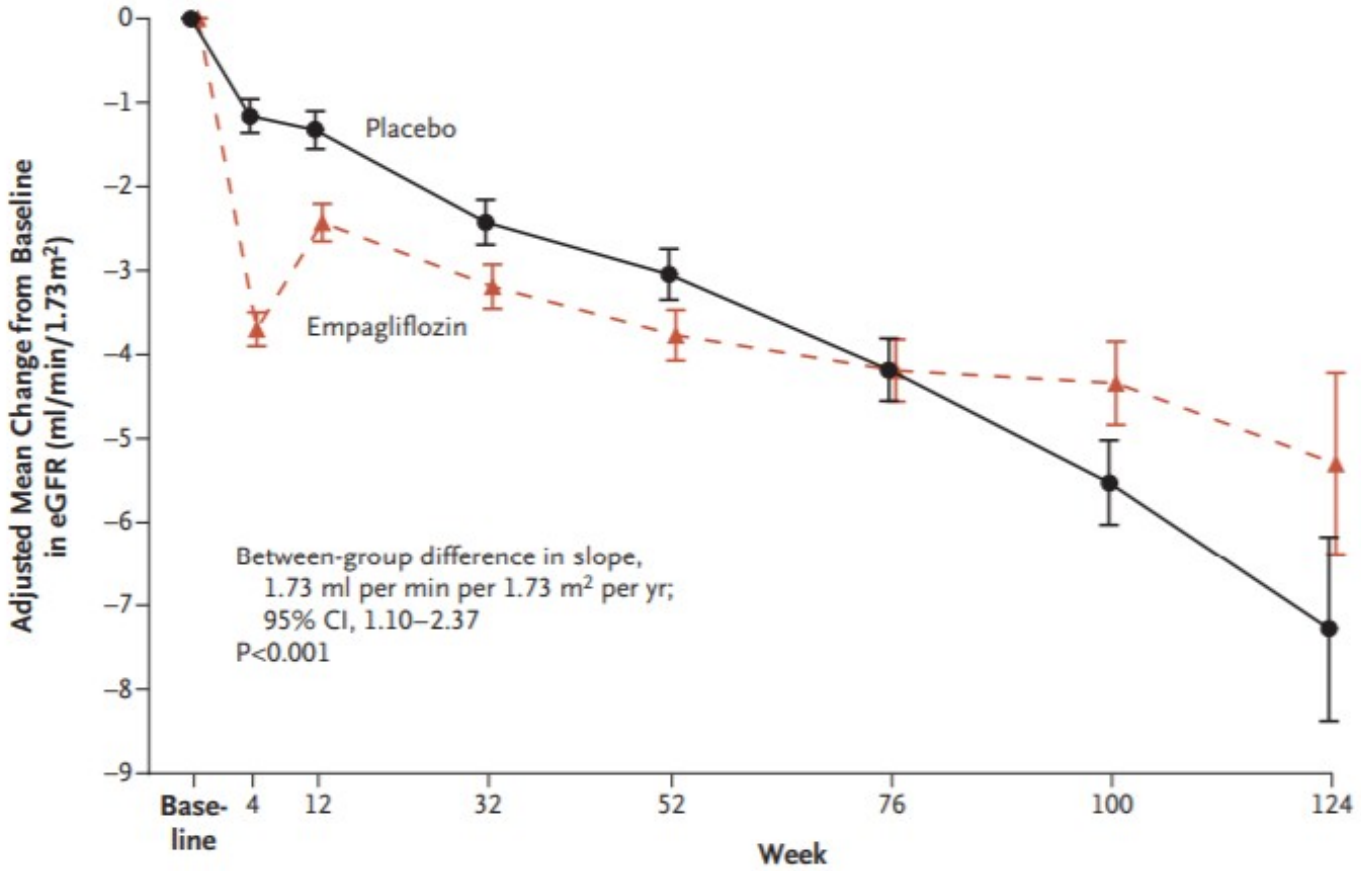
Kalp Yetersizliğine Bağlı Toplam Hastaneye Yatış



Packer et al: N Engl J Med 383: 1413-1424, 2020

EMPEROR-Reduced Çalışması

eGFR'deki Değişiklik



No. at Risk								
Placebo	1792	1765	1683	1500	1146	745	343	76
Empagliflozin	1799	1782	1720	1554	1166	753	356	80

Packer et al: N Engl J Med 383: 1413-1424, 2020

EMPEROR-Reduced Çalışması

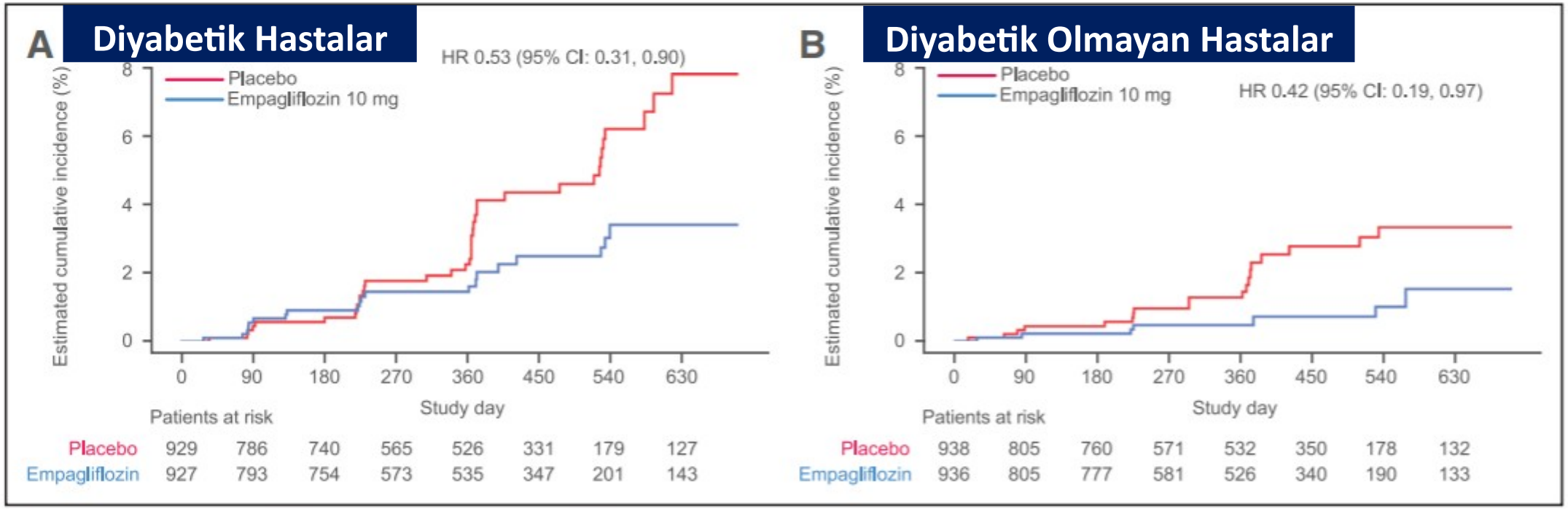
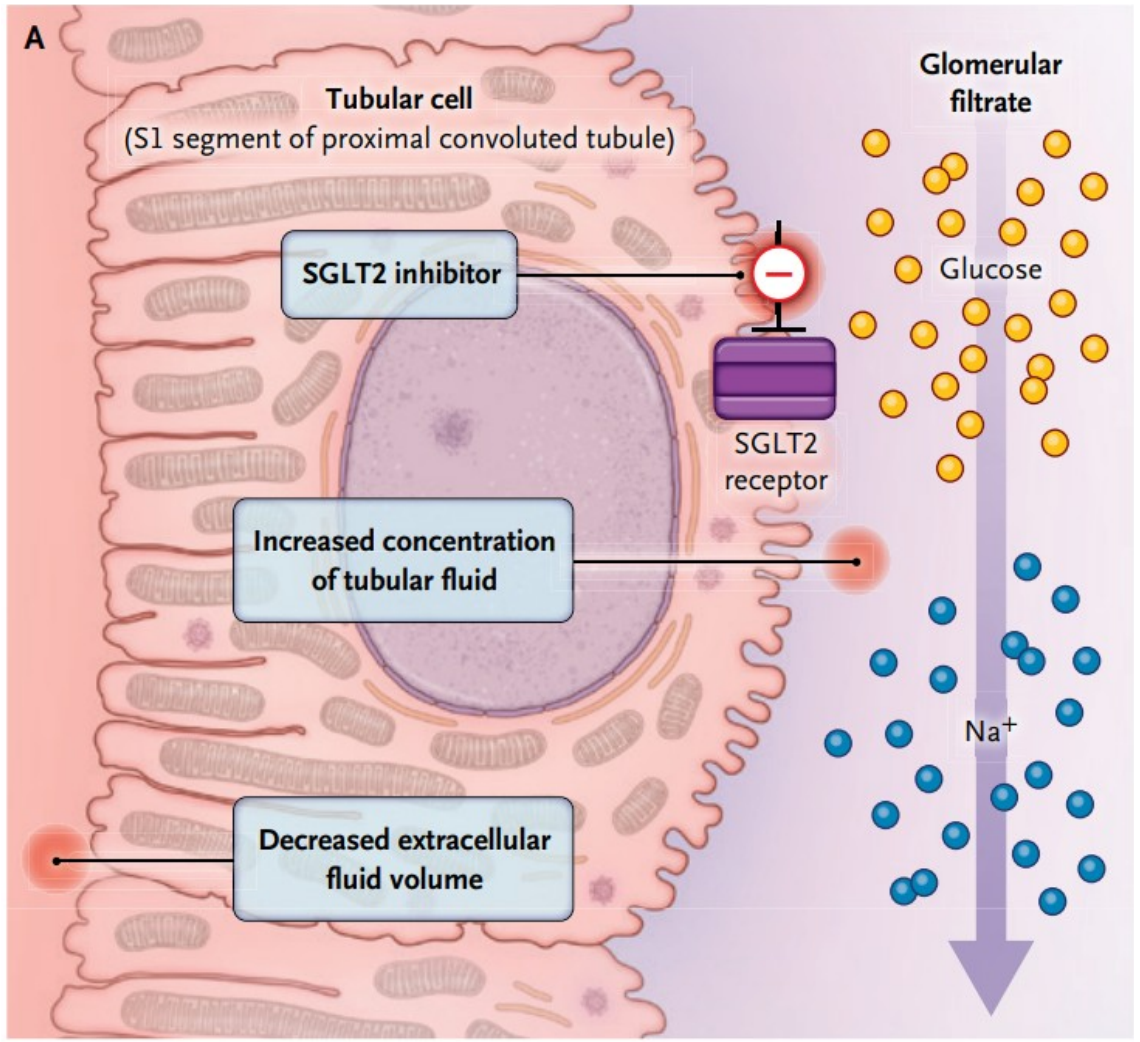
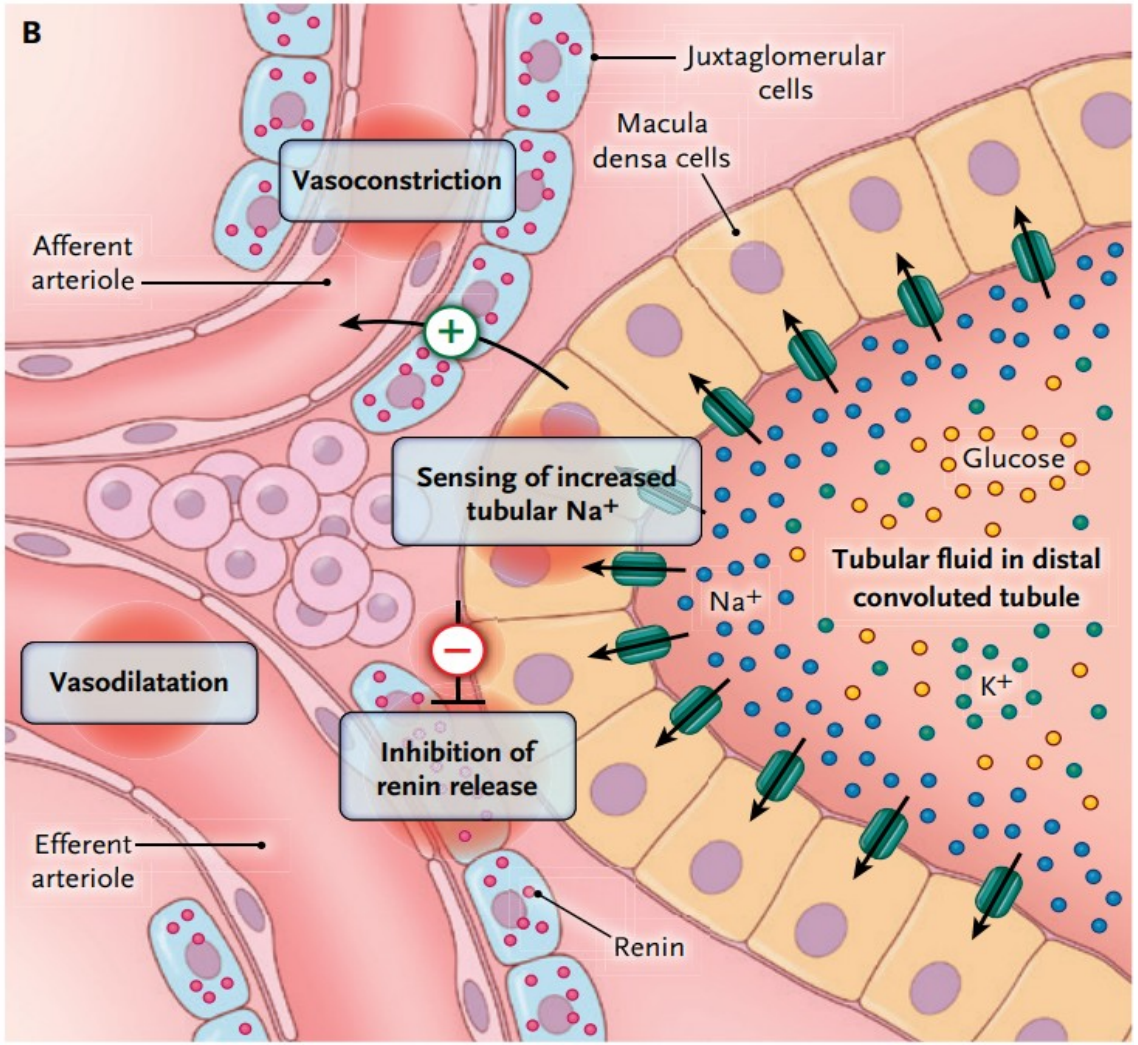


Figure 4. Effect of empagliflozin on renal composite end point.
Effect of empagliflozin on renal composite end point in (**A**) patients with diabetes and (**B**) patients without diabetes. Composite renal end point is defined as chronic dialysis, renal transplant, sustained reduction of ≥40% eGFR, or sustained eGFR <15 mL/min/1.73 m² for patients with eGFR ≥30 mL/min/1.73 m² at baseline (<10 mL/min/1.73 m² for patients with eGFR <30 mL/min/1.73 m² at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. In accordance with usual practice, cumulative incidence plots were truncated when the number of patients being followed in individual subgroups became extremely sparse. HR indicates hazard ratio.

Anker et al: Circulation 143: 337-349, 2021

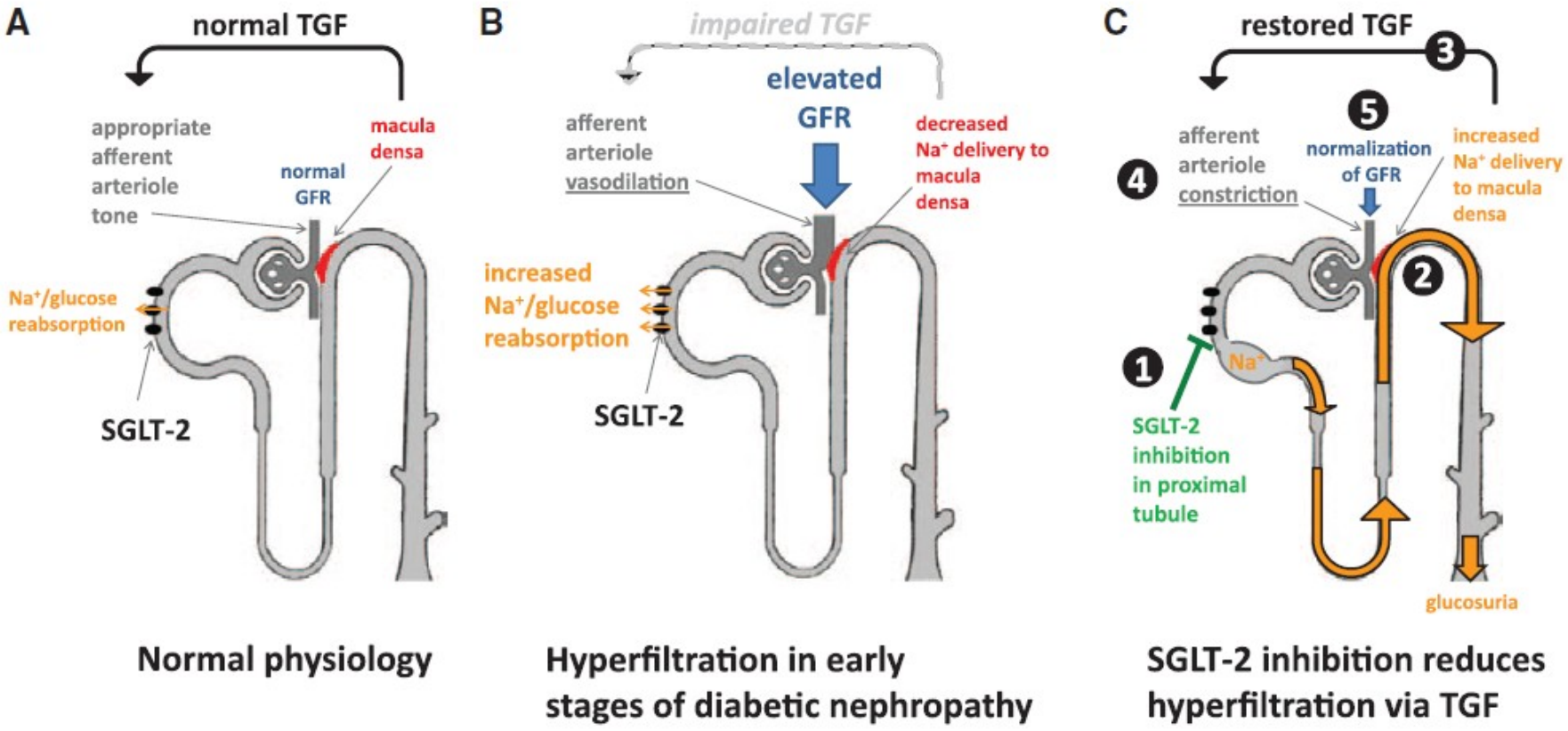
SGLT2 İnhibitörleri





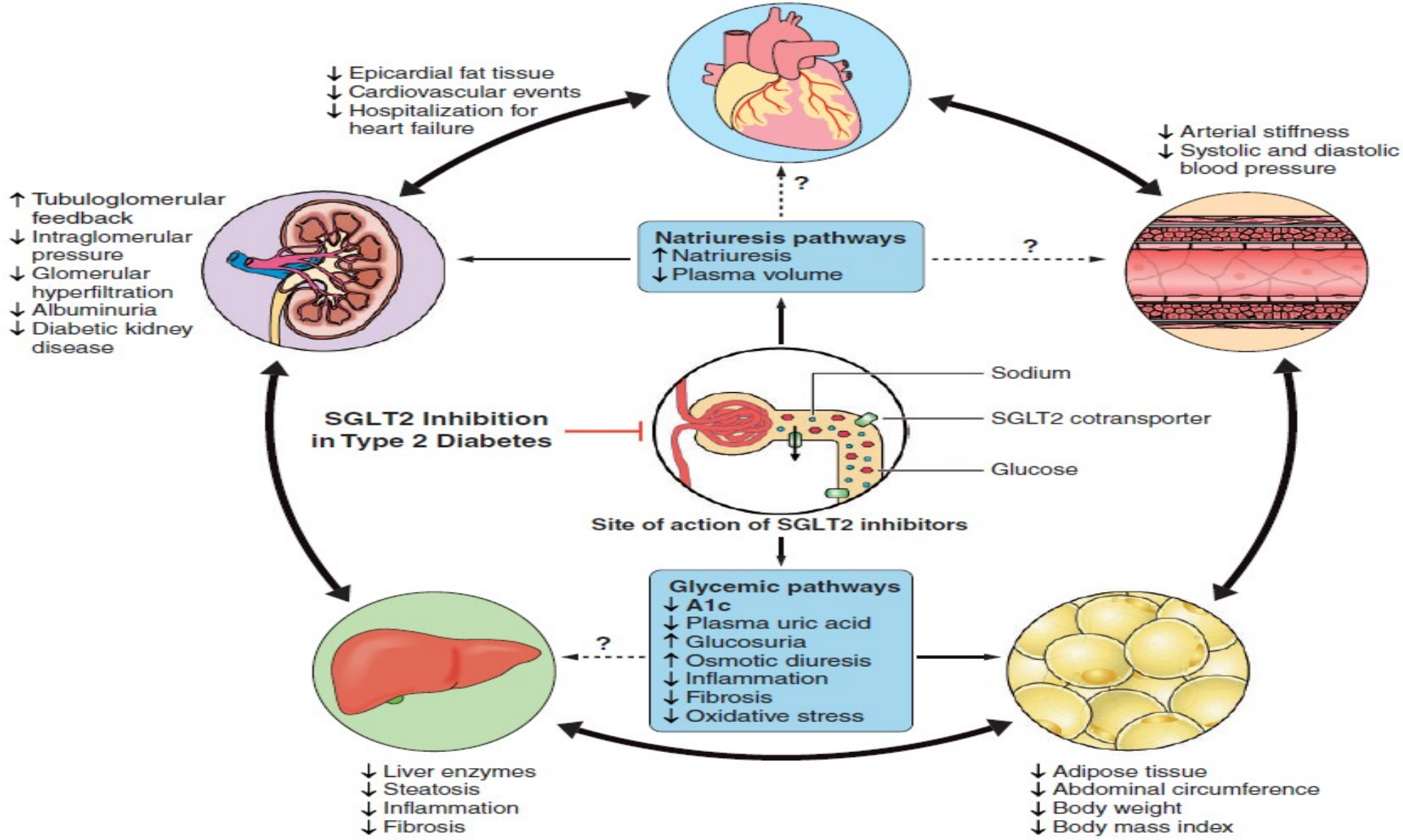
Braunwald: N Engl J Med 386; 2024-2034, 2022

SGLT2 İnhibitörlerinin Tubuloglomerüler "Feedback" Üzerine Olumlu Etkisi



Cherney et al: Circulation 129: 587-597, 2014

SGLT İnhibitörlerinin Metabolik ve Kardiyorenal Koruyucu Etkileri



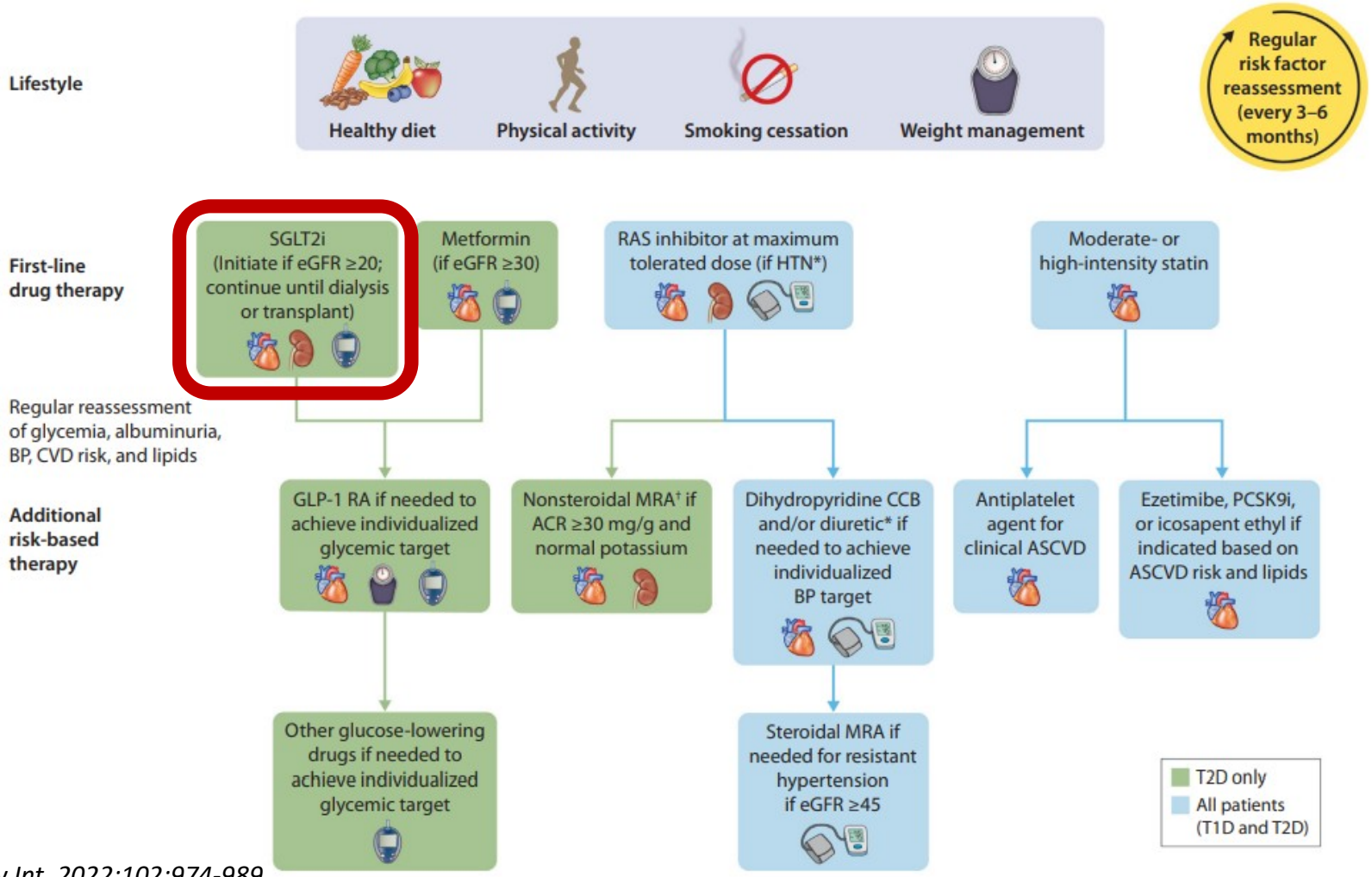
Cherney et al: Nephrol Dial Transplant 35: i3-i12, 2020

SGLT2 İnhibitörlerinin Kullanımında Dikkat Edilmesi Gereken Pratik Hususlar

- **Tedaviye başlandıktan sonraki ilk haftalarda eGFR'deki akut ve geçici düşüş**
  - %30'un altındaki düşüşlerde ilaç kesilmemelidir.
  - %30'un üzerinde düşüş varsa
    - Hacim durumu değerlendirilmeli ve diüretiklerin dozu azaltılmalıdır.
    - NSAİ ilaç kullanımı varsa kesilmelidir.
    - Nadiren ozmotik hasara (ozmotik nefrozis) bağlı geriye dönüşümlü tübüler toksisite gelişebilir.
- **Hücre dışı sıvı hacminde azalmaya neden olan akut hastalıklarda (alım azlığı, kusma ve/veya diyare) SGLT2 inhibitörünü kesin**
- **Kan basıncındaki semptomatik düşüş**
  - Diüretiklerin dozunu azaltmayı düşünün.
  - Renin anjiyotensin aldosteron blokerlerinin dozunu azaltmaktan kaçının.
- **Hipoglisemi**
  - eGFR >60 ml/dk. olan hastalarda daha sıktır.
  - Endokrinolog ile birlikte takip ederek insülin dozunu %10-20 azaltmayı veya sülfanilüre dozunu azaltmayı düşünün.
  - eGFR düştükçe hipoglisemi riski azalır ve eGFR <30 ml/dk. olan hastalarda hipoglisemi beklenmez.
- **Uzun dönemdeki yararları dikkate alındığında, SGLT2 inhibitörü tedavisinin kullanılması için her türlü gayret gösterilmelidir.**

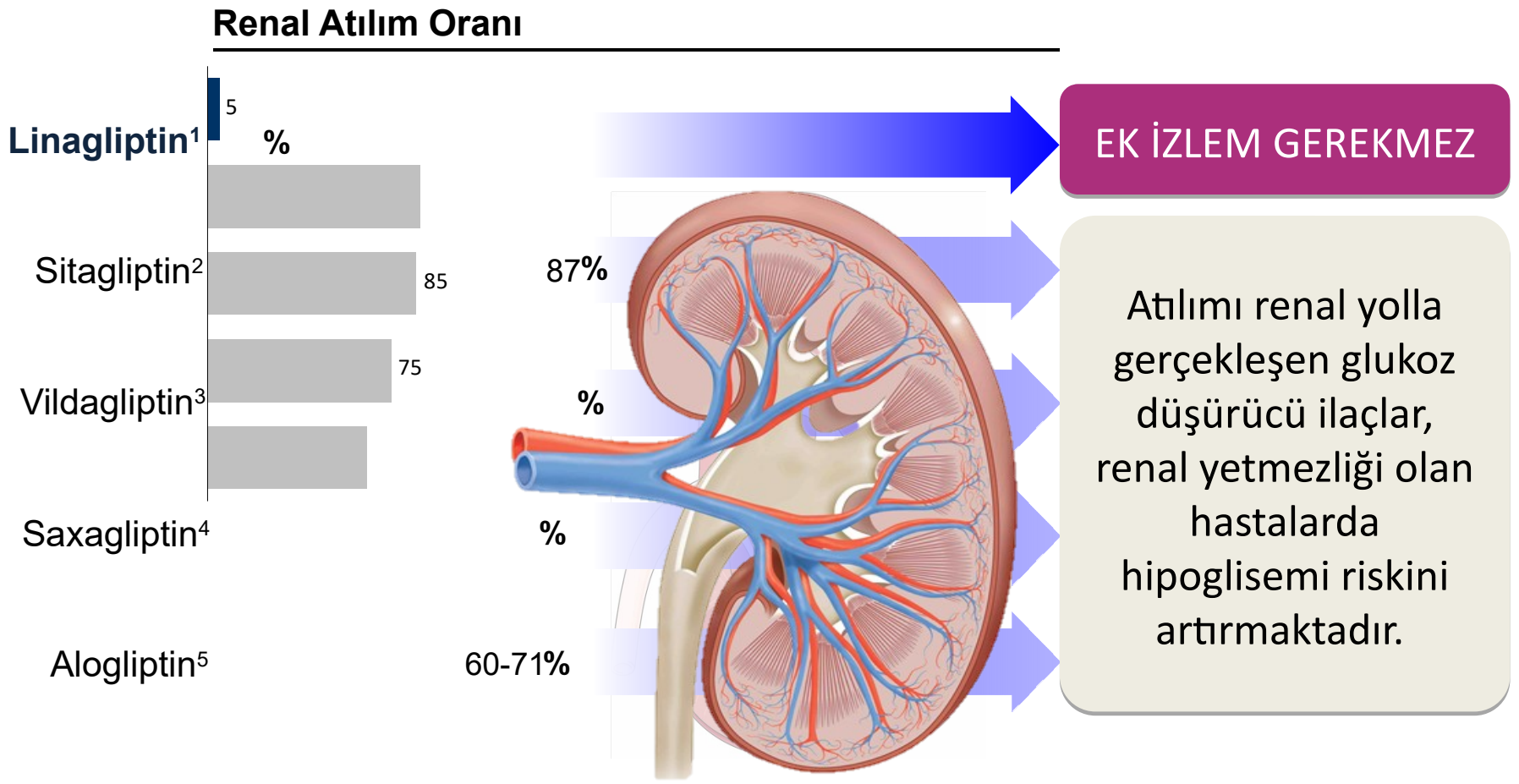
Palmer, Clegg: CJASN 18: 279-289, 2023

Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)



De Boer et al: Kidney Int. 2022;102:974-989

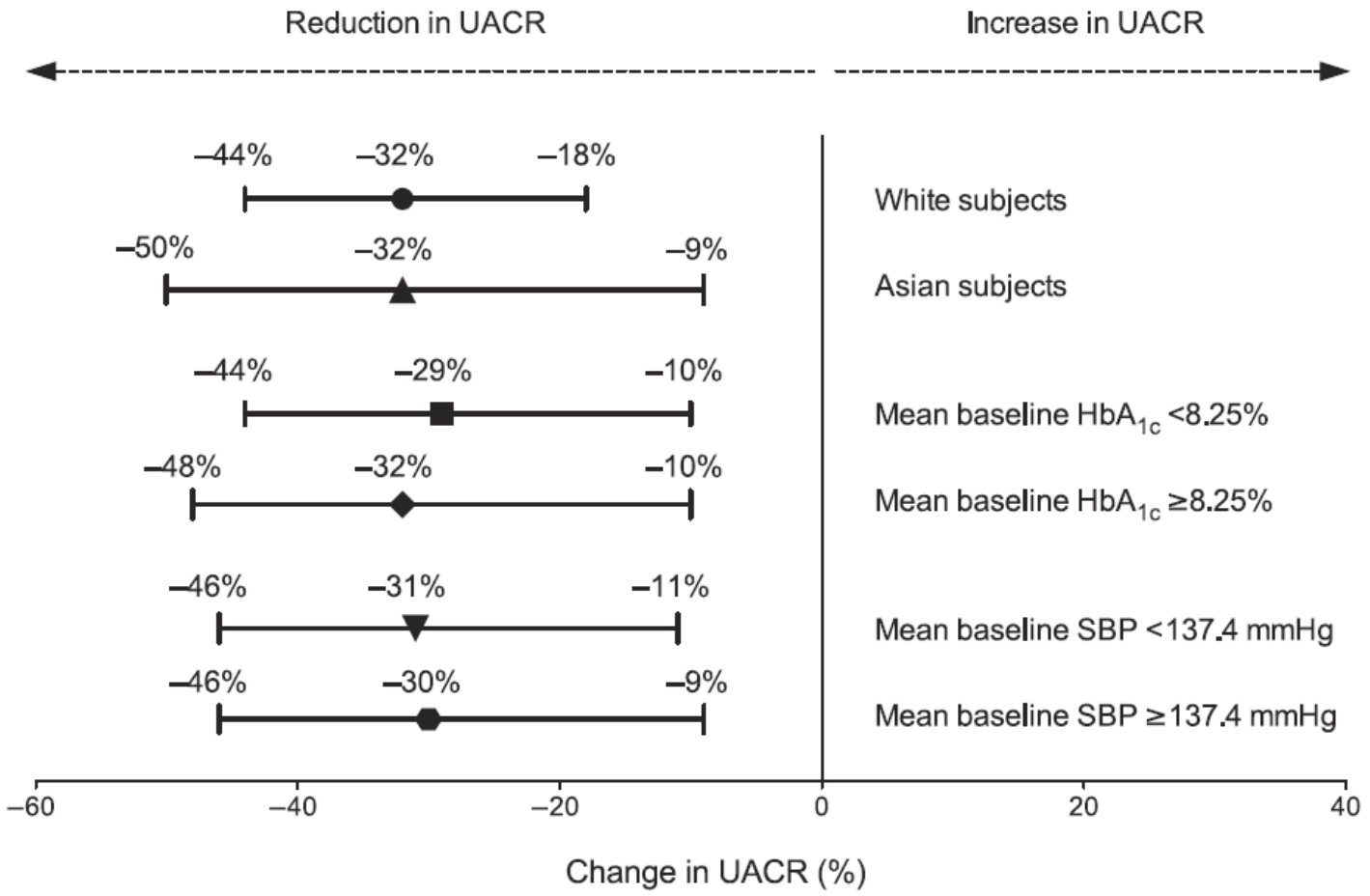
Linagliptin Büyük Oranda Safra ve Bağırsaklar Yoluyla Atılan İlk DPP-4 İnhibitörüdür



Linagliptin KUB; Vincent SH et al: Drug Metab Dispos. 2007;35:533–538; He H et al: Drug Metab Dispos. 2009;37:536–544. Saksagliptin KUB; Christopher R et al: Clin Ther. 2008;30:513–527.

Diyabetik Nefropatisi Olan Hastalarda Linagliptin Albüminüriyi Azaltır

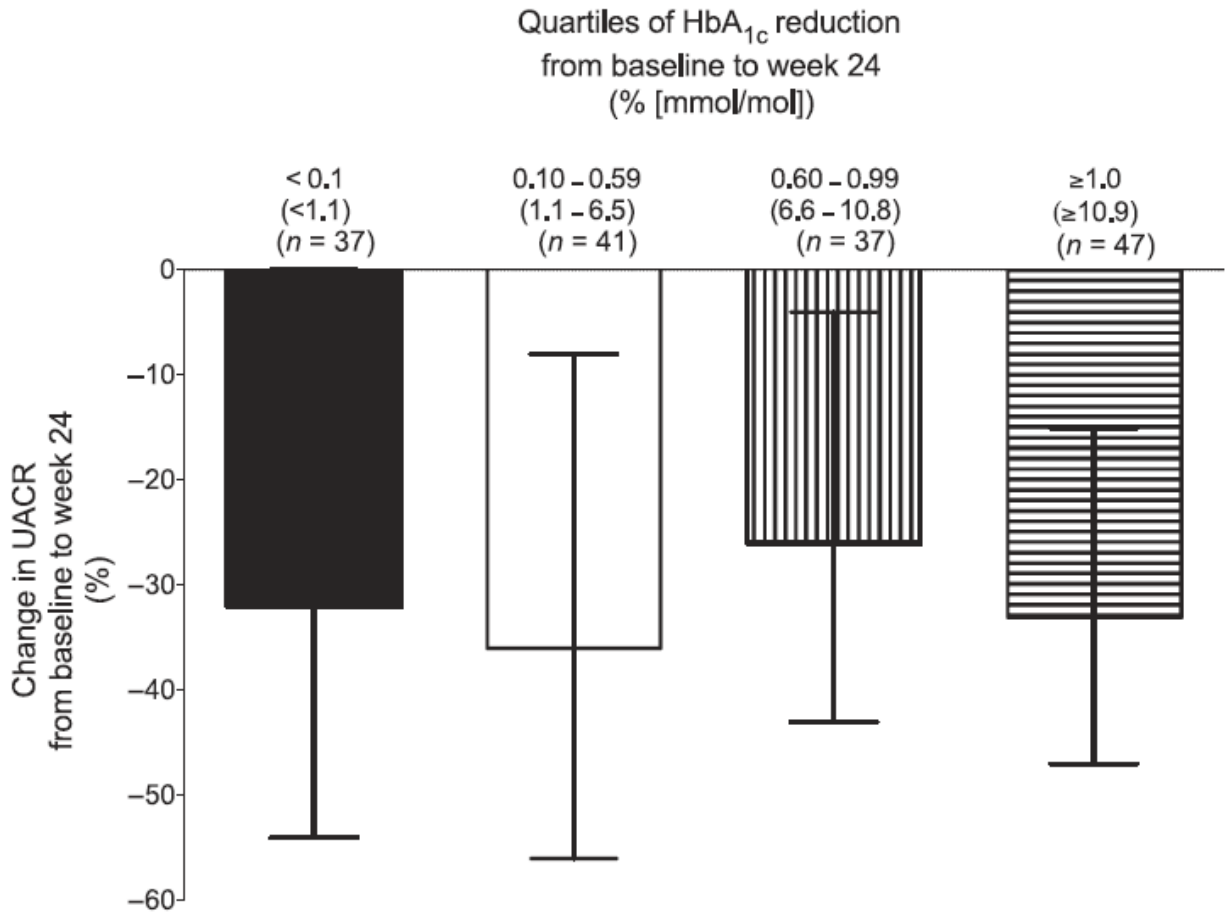
Dört adet randomize, çift-kör, plasebo kontrollü faz 3 çalışmanın analizi



Groop PH et al: Diabetes Care 36: 3460-3468, 2013

Linagliptinin Albüminüriyi Azaltıcı Etkisi HbA1c Düşüşünden Bağımsızdır

Dört adet randomize, çift-kör, plasebo kontrollü faz 3 çalışmanın analizi



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JAMA | Original Investigation

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk
The CARMELINA Randomized Clinical Trial

Julio Rosenstock, MD; Vlado Perkovic, MBBS, PhD; Odd Erik Johansen, MD, PhD; Mark E. Cooper, MBBS, PhD; Steven E. Kahn, MB, ChB; Nikolaus Marx, MD; John H. Alexander, MD, MHSc; Michael Pencina, PhD; Robert D. Toto, MD; Christoph Wanner, MD; Bernard Zinman, MD; Hans Juergen Woerle, MD; David Baanstra, MSc, MBA; Egon Pfarr, MSc; Sven Schnaidt, MSc; Thomas Meinicke, MD; Jyothis T. George, MBBS, PhD; Maximillian von Eynatten, MD; Darren K. McGuire, MD, MHSc; for the CARMELINA Investigators

Primer sonlanım: 3P-MACE

Aşağıdaki bileşenlerden herhangi birinin ilk kez ortaya çıkmasına kadar geçen süre:

1. **KV ölüm (ölümcül inme ve ölümcül MI dahil)**
2. **Ölümcül-olmayan MI (sessiz MI hariç)**
3. **Ölümcül-olmayan inme**

Önceden belirtilmiş sekonder sonlanım: Birleşik renal veri

Aşağıdaki bileşenlerden herhangi birinin ilk kez ortaya çıkmasına kadar geçen süre:

1. **Renal ölüm**
2. **Devam eden son-dönem böbrek hastalığı**
3. **GFR'de ≥%40 oranında devam eden azalma**

3P-MACE, 3-noktalı majör advers kardiyovasküler olaylar; KV, kardiyovasküler; eGFR, tahmini glomerüler filtrasyon hızı; MI, miyokard enfarktüsü

Rosenstock J et al: JAMA 2018; Rosenstock J et al. Cardiovasc Diabetol 2018;17:39

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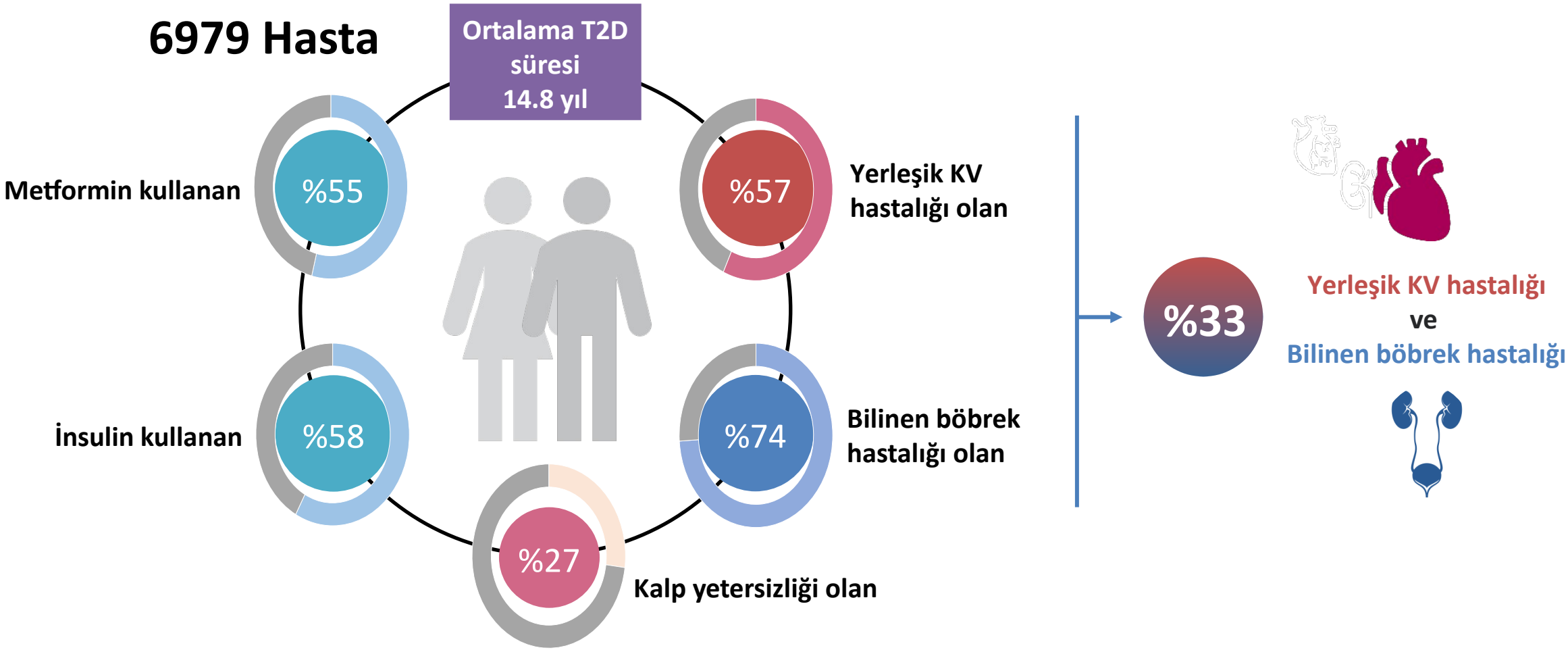

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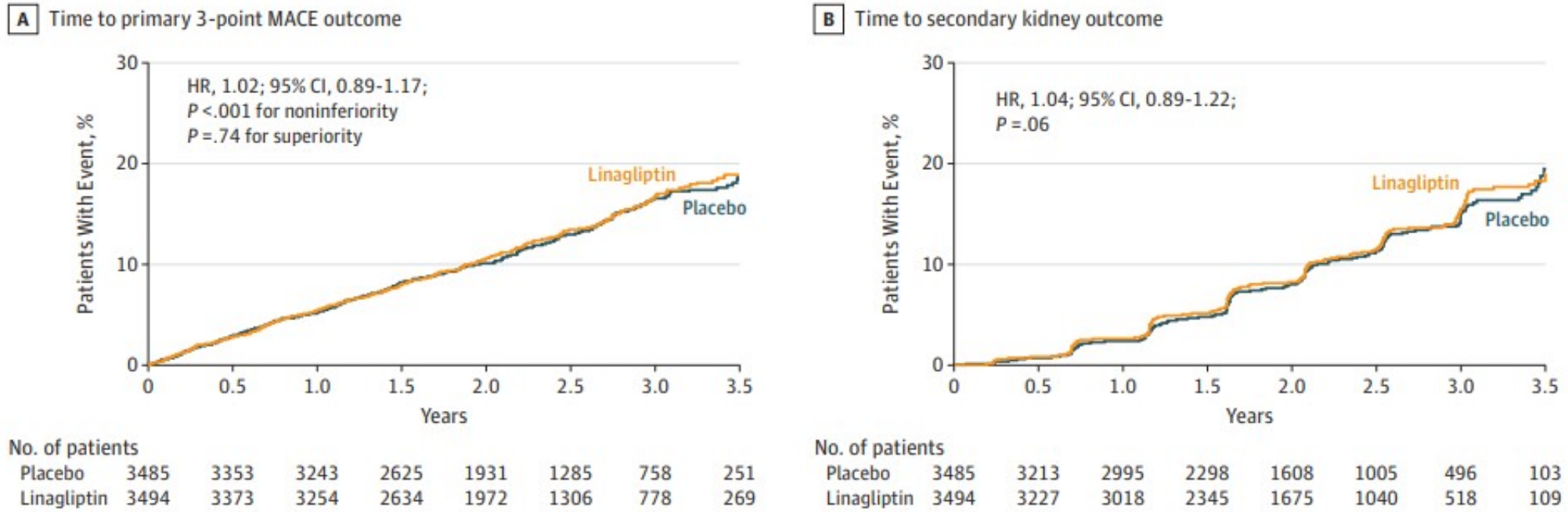


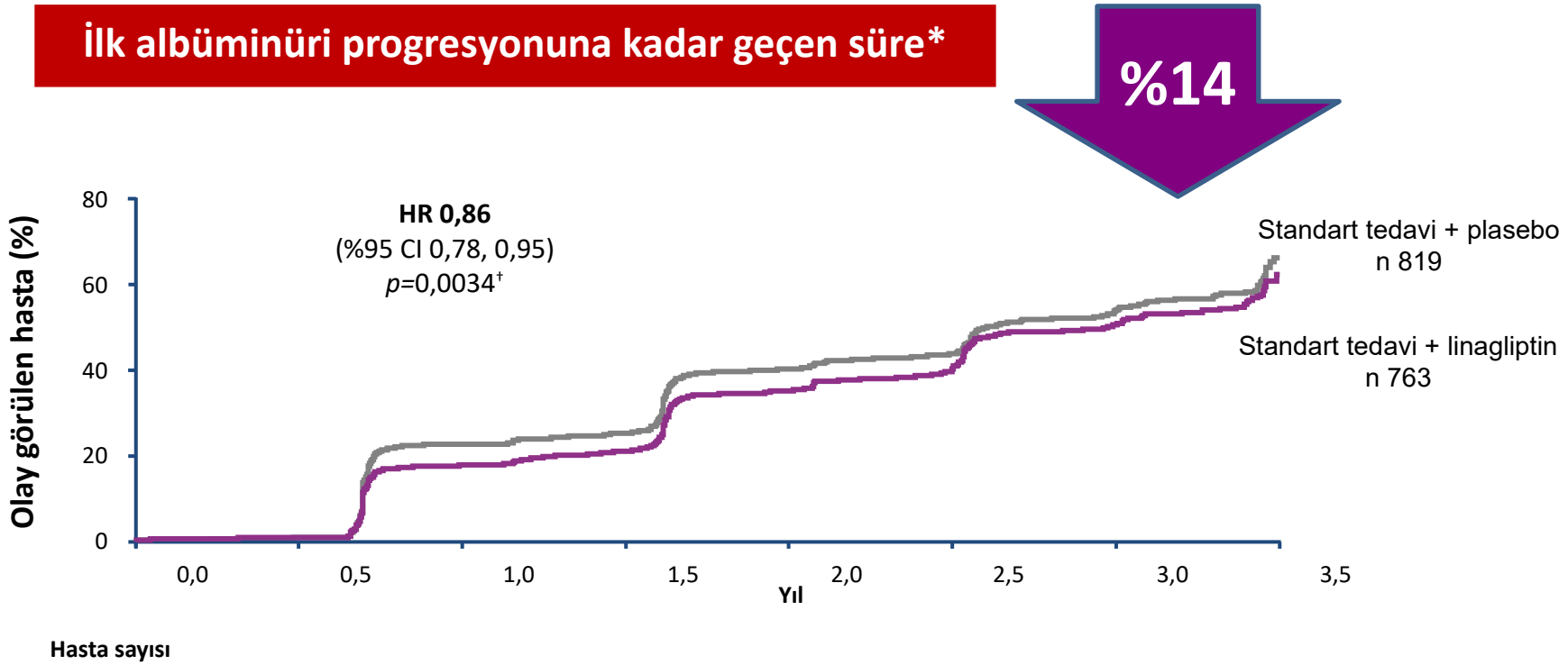
Hazard ratio (HR) based on Cox regression analyses in patients treated with at least 1 dose of study drug. A, Time to 3-point major adverse cardiovascular event (MACE) primary outcome (first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Median observation time was 2.1 (interquartile range [IQR], 1.5-2.9) years for linagliptin and 2.1 (IQR, 1.5-2.8) years for placebo.

B, Time to secondary kidney outcome (first sustained end-stage renal disease, death due to renal failure, or sustained decrease of ≥40% in estimated glomerular filtration rate from baseline). Median observation time was 1.9 (IQR, 1.2-2.6) years for linagliptin and 1.7 (IQR, 1.2-2.5) years for placebo.

Rosenstock J et al: JAMA 2018; Rosenstock J et al. Cardiovasc Diabetol 2018;17:39

Linagliptin ile Albüminüri Progresyonunda Anlamlı Azalma Sağlanmıştır

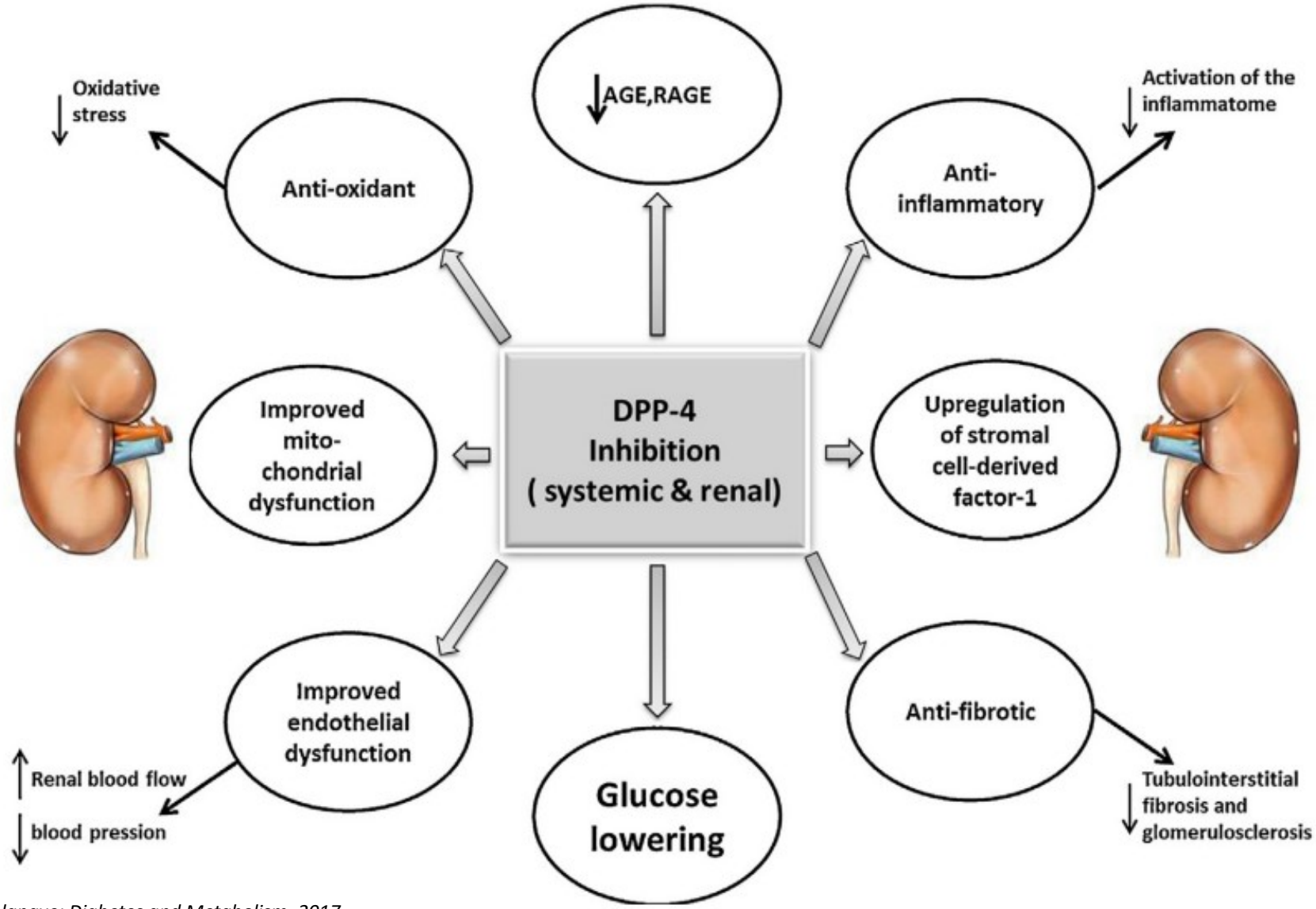
İlk albüminüri progresyonuna kadar geçen süre*



Linagliptin olay oranı 21,36/100 PY Plasebo olay oran 2.4.54/100 PY
Tedavi edilen set, Kaplan-Meier tahmini. Tedavi grubuna (p=0,0034) ve bölgeye (p<0,0001) ilişkin terimler içeren Cox regresyon modeline dayanılarak tehlike oranı ve %95 CI
*normoalbüminüriden mikro- veya makroalbüminüriye ya da mikroalbüminüriden makroalbüminüriye kadar değişiklik; †iki yönlü

Rosenstock J et al: JAMA 2018; Rosenstock J et al. Cardiovasc Diabetol 2018;17:39

DPP-4 İnhibisyonu ile Renoproteksiyon Mekanizmaları



Scheen, Delanaye: Diabetes and Metabolism, 2017

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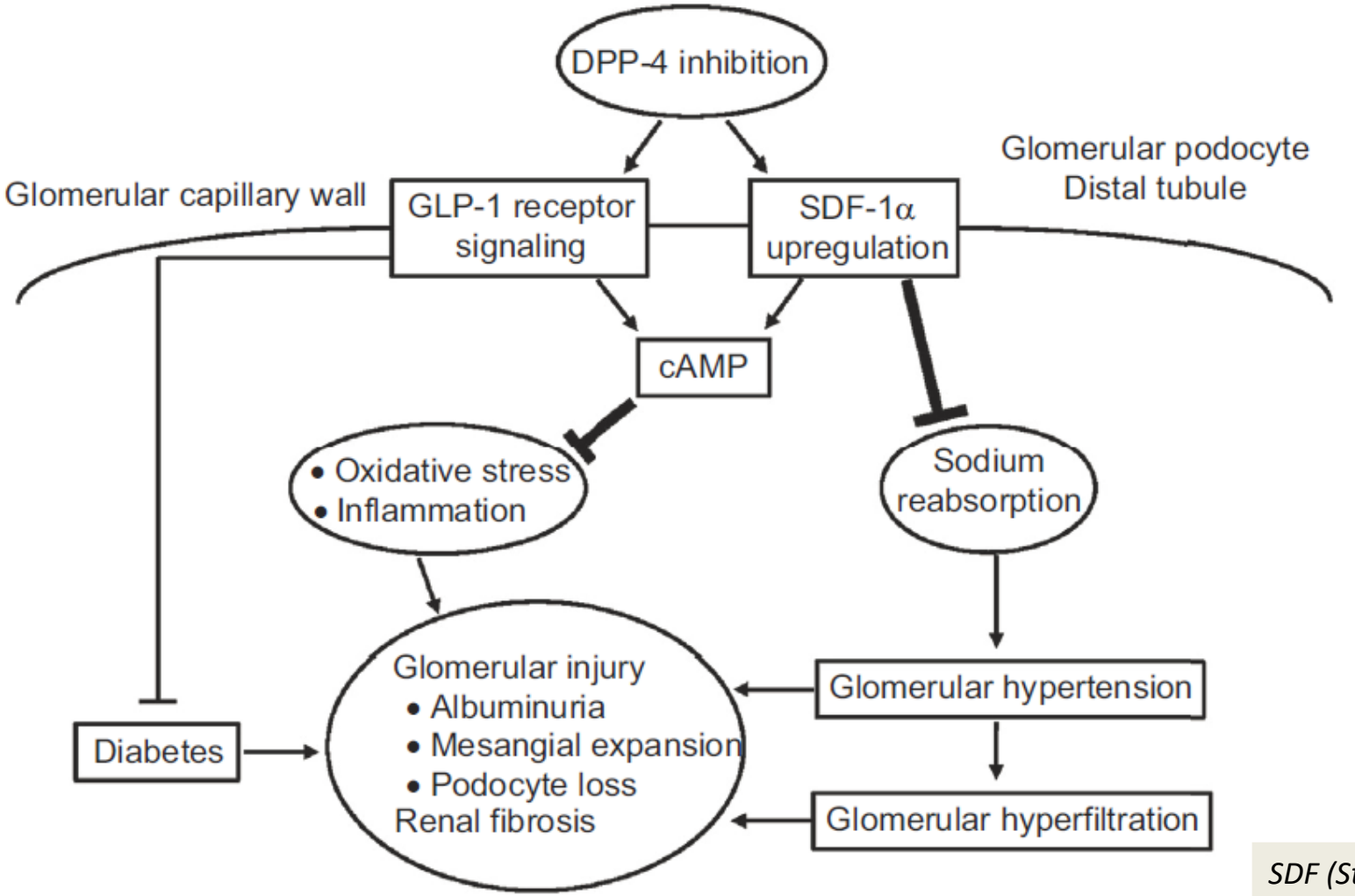
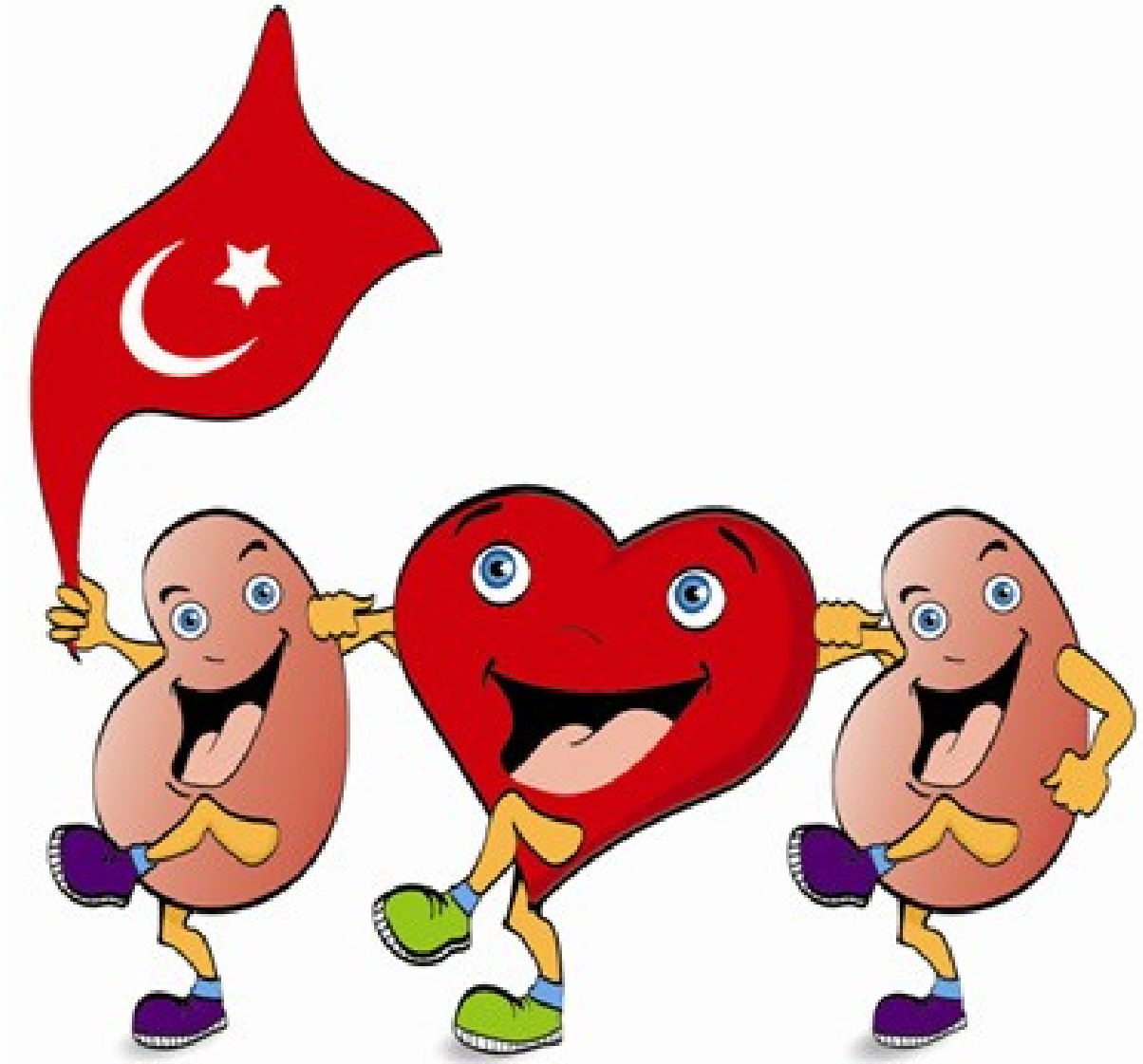


SDF (Stromal cell-derived factor)

Takashima et al: Kidney Int 90: 783-796, 2016



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