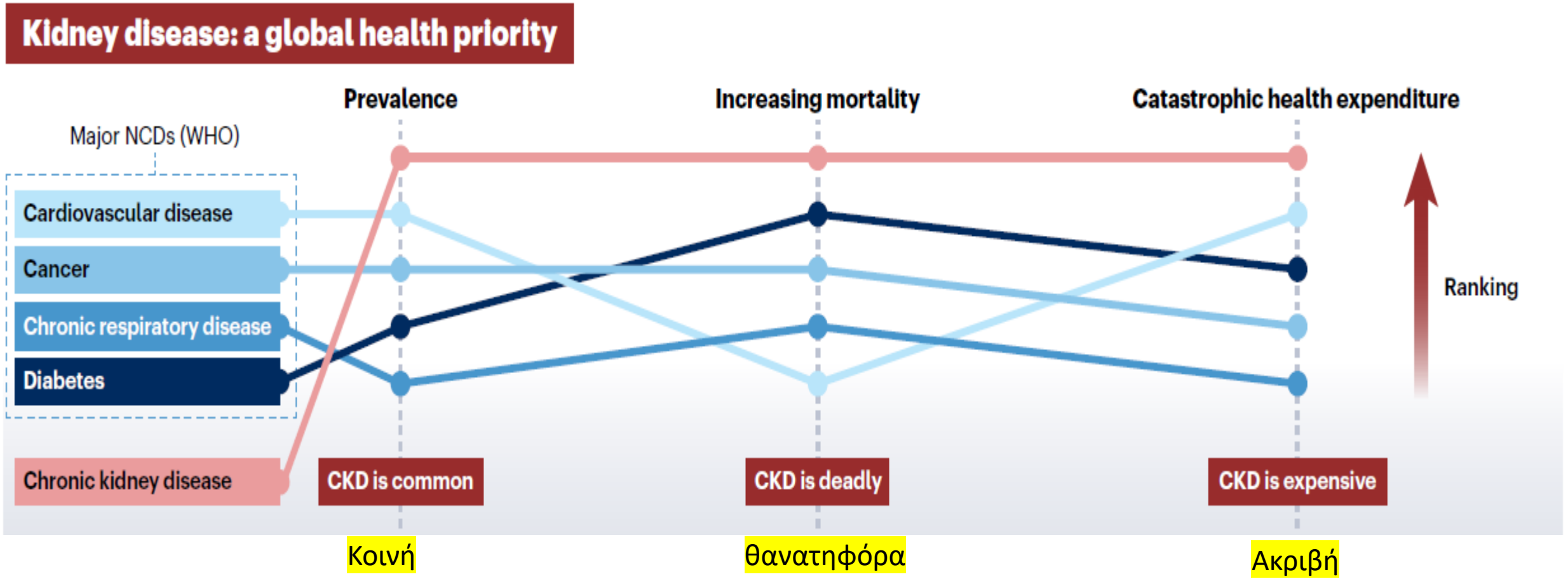
Επαναπροσδιορίζοντας την προστασία της νεφρικής λειτουργίας με τους SGLT2 αναστολείς

Όλγα Μπαλάφα

Διευθύντρια ΕΣΥ

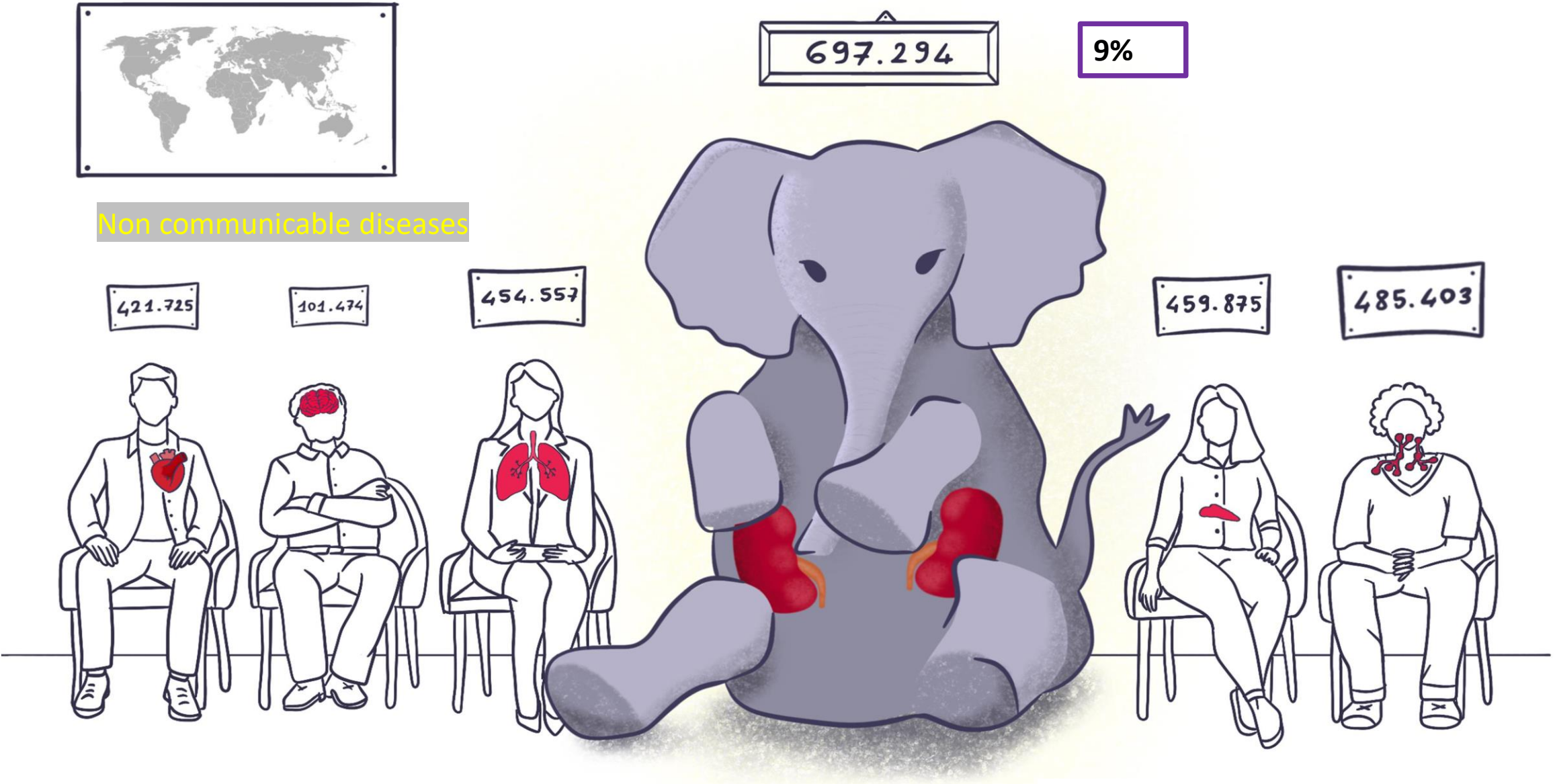
Νεφρολογική Κλινική Πανεπιστημιακού Νοσοκομείου Ιωαννίνων

ΧΝΝ σημαντικό υγειονομικό πρόβλημα



CKD the elephant in the room

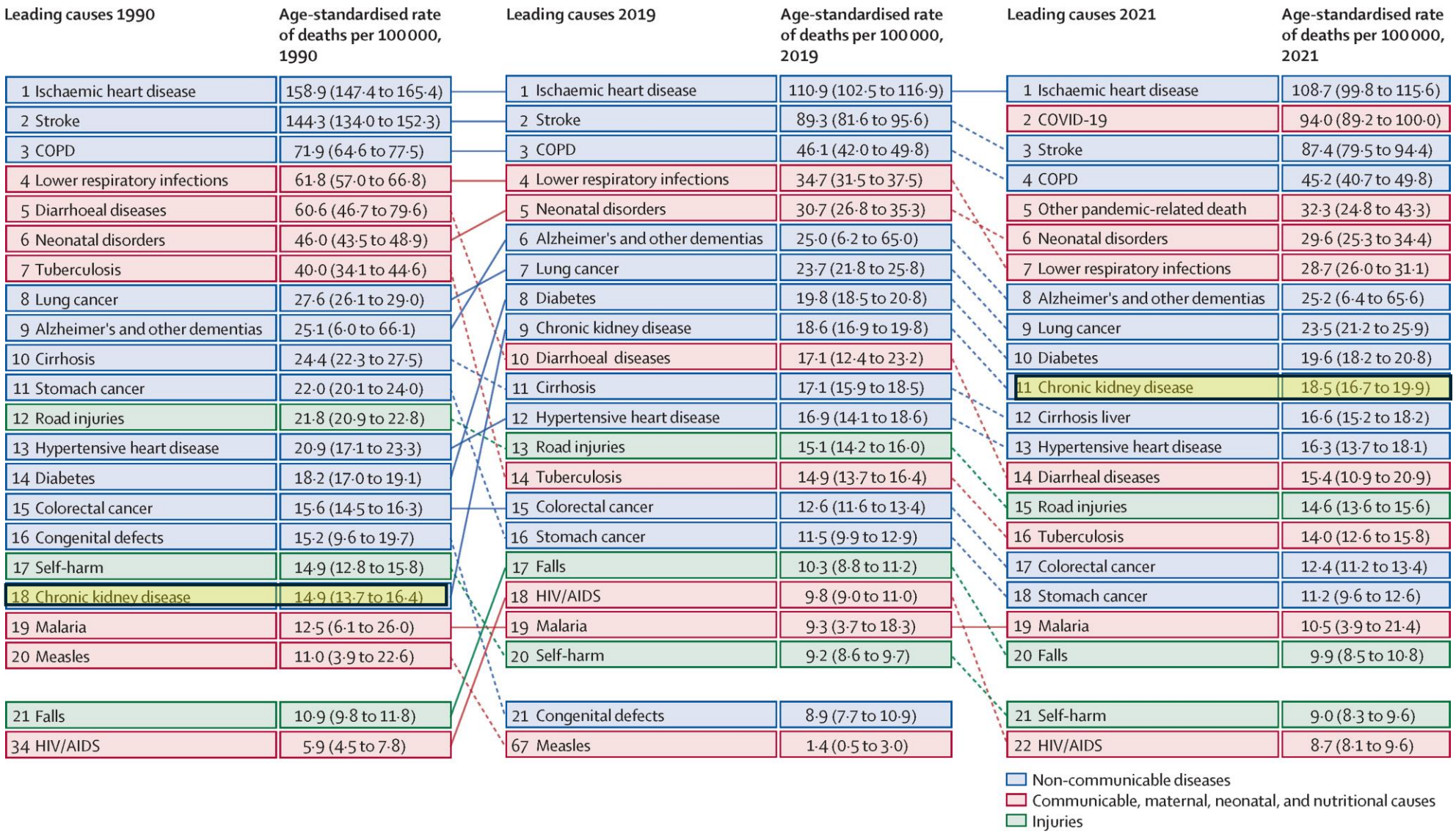
Non communicable diseases



Torra R. Nephrol Dial Transplant, 2024

Causes of global deaths and age-standardised death rates

Global Burden of Disease Study



Lancet, 2024

Overall	Urine albumin-creatinine ratio, mg/g					Urine albumin-creatinine ratio, mg/g				
eGFRcr	<10	10–29	30–299	300–999	1000+	<10	10–29	30–299	300–999	1000+
	All-cause mortality: 82 cohorts 26 444 384 participants; 2 604 028 events					Myocardial infarction: 64 cohorts 22 838 356 participants; 451 063 events				
105+	1.6	2.2	2.9	4.3	5.8	1.1	1.4	2.0	2.7	3.8
90–104	ref	1.3	1.8	2.6	3.1	ref	1.3	1.6	2.2	3.2
60–89	1.0	1.3	1.7	2.2	2.8	1.1	1.3	1.6	2.2	3.1
45–59	1.3	1.6	2.0	2.4	3.1	1.4	1.7	2.0	2.8	3.7
30–44	1.8	2.0	2.5	3.2	3.9	1.9	2.0	2.4	3.2	4.3
15–29	2.8	2.8	3.3	4.1	5.6	2.7	3.1	3.1	4.2	5.1
<15	4.6	5.0	5.3	6.0	7.0	4.6	5.6	4.8	6.0	6.0
	Cardiovascular mortality: 76 cohorts 26 022 346 participants; 776 441 events					Stroke: 68 cohorts 24 746 436 participants; 461 785 events				
105+	1.4	2.0	3.0	4.1	5.4	1.2	1.6	2.2	3.1	4.3
90–104	ref	1.3	1.9	2.7	3.6	ref	1.3	1.6	2.4	3.1
60–89	1.0	1.4	1.7	2.4	3.2	1.1	1.3	1.7	2.2	3.0
45–59	1.4	1.7	2.2	2.8	3.8	1.4	1.6	1.9	2.3	2.9
30–44	2.0	2.3	2.8	3.7	4.6	1.6	1.7	2.0	2.4	3.0
15–29	3.2	3.1	3.5	5.0	6.5	1.8	2.1	2.1	2.7	3.0
<15	6.1	6.4	6.4	7.3	8.2	3.2	2.8	2.9	3.2	3.8
	Kidney failure with replacement therapy: 57 cohorts 25 466 956 participants; 158 846 events					Heart failure: 61 cohorts 24 603 016 participants; 1 132 443 events				
105+	0.5	1.2	2.9	7.7	25	1.2	1.7	2.7	4.2	6.9
90–104	ref	1.8	4.3	12	43	ref	1.3	2.0	2.8	4.2
60–89	2.3	4.9	10	27	85	1.1	1.4	1.9	2.7	4.2
45–59	13	19	37	89	236	1.6	1.8	2.4	3.4	5.0
30–44	50	58	115	240	463	2.2	2.5	3.1	4.2	6.5
15–29	283	301	443	796	1253	3.6	3.5	4.1	5.8	8.1
<15	770	1040	1618	2297	2547	5.1	5.7	5.8	7.9	9.9
	Acute kidney injury: 49 cohorts 23 914 614 participants; 1 408 929 events					Atrial fibrillation: 50 cohorts 22 886 642 participants; 1 068 701 events				
105+	1.0	1.6	2.4	3.7	5.5	1.1	1.3	1.7	2.4	3.5
90–104	ref	1.4	2.1	3.2	5.0	ref	1.2	1.5	1.9	2.3
60–89	1.6	2.2	3.1	4.3	6.7	1.0	1.2	1.4	1.7	2.2
45–59	3.5	4.0	5.1	6.9	9.0	1.2	1.3	1.5	1.8	2.4
30–44	5.6	5.9	6.8	8.6	11	1.4	1.5	1.7	2.0	2.4
15–29	8.3	8.0	8.5	9.9	10	1.9	1.8	2.0	2.6	3.0
<15	8.5	11	7.9	5.5	5.7	2.6	2.5	3.1	3.6	4.2
	Hospitalization: 49 cohorts 25 426 722 participants; 8 398 637 events					Peripheral artery disease: 54 cohorts 24 830 794 participants; 378 924 events				
105+	1.4	1.7	2.1	2.1	2.3	0.9	1.4	1.9	2.8	5.0
90–104	ref	1.1	1.3	1.5	1.7	ref	1.3	1.9	2.8	4.3
60–89	1.0	1.1	1.3	1.5	1.8	1.0	1.3	1.8	2.5	3.8
45–59	1.3	1.3	1.5	1.7	2.1	1.5	1.7	2.1	2.9	4.2
30–44	1.5	1.5	1.6	1.9	2.3	2.0	1.9	2.5	3.6	5.0
15–29	1.8	1.8	1.9	2.4	2.8	3.3	3.3	3.8	5.7	8.1
<15	2.7	2.8	3.0	3.2	3.8	9.1	9.0	9.6	13	14

XNNIII

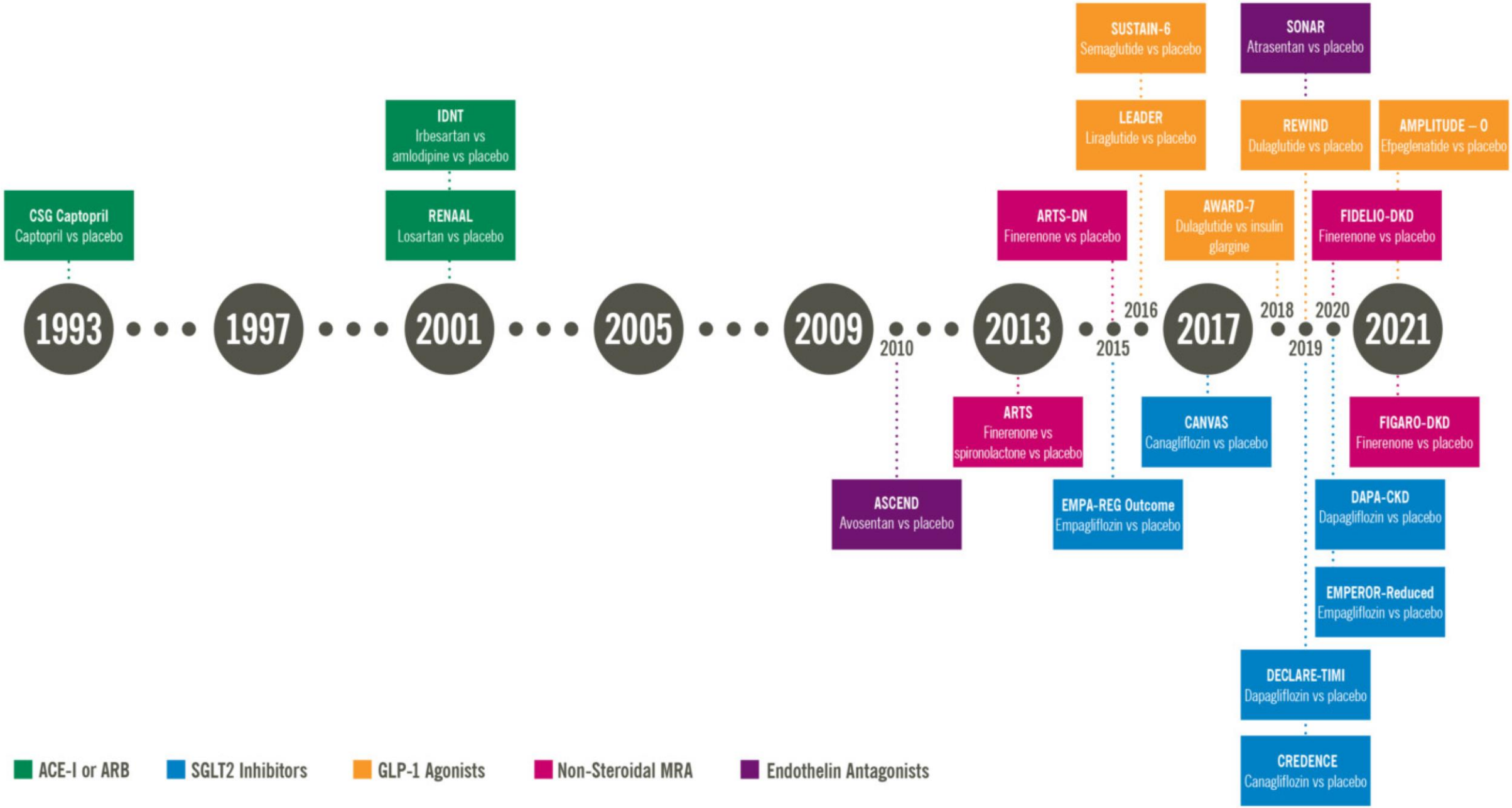
EM

AEE

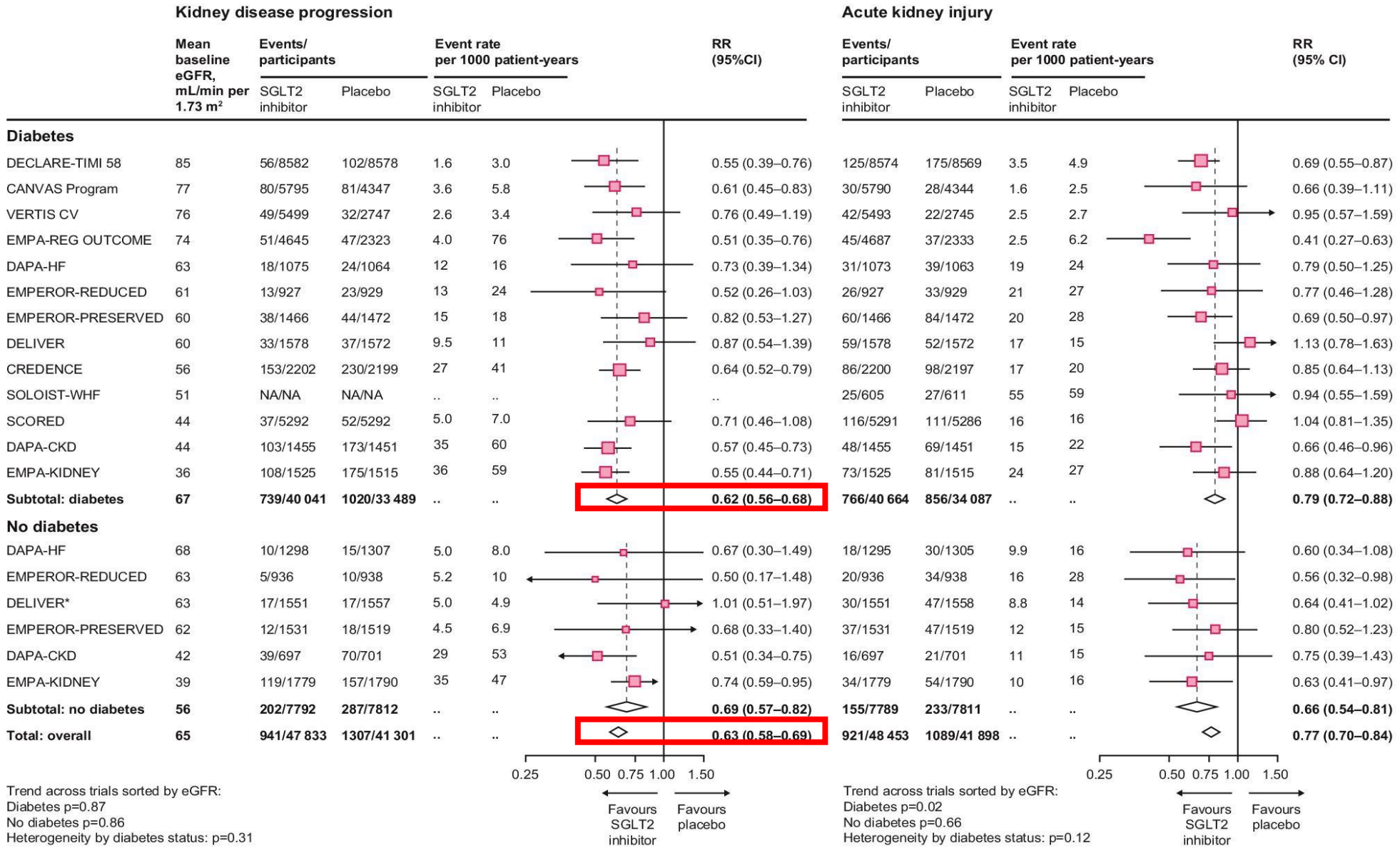
KA

KM

KDIGO, 2024


CSG Captopril
Captopril vs placebo
IDNT
Irbesartan vs amlodipine vs placebo
RENAAL
Losartan vs placebo
SUSTAIN-6
Semaglutide vs placebo
SONAR
Atrasentan vs placebo
LEADER
Liraglutide vs placebo
REWIND
Dulaglutide vs placebo
AMPLITUDE – O
Efpeglenatide vs placebo
ARTS-DN
Finerenone vs placebo
AWARD-7
Dulaglutide vs insulin glargine
FIDELIO-DKD
Finerenone vs placebo
1993
1997
2001
2005
2009
2010
2013
2015
2016
2017
2018
2019
2020
2021
ARTS
Finerenone vs spironolactone vs placebo
CANVAS
Canagliflozin vs placebo
FIGARO-DKD
Finerenone vs placebo
ASCEND
Avosentan vs placebo
EMPA-REG Outcome
Empagliflozin vs placebo
DAPA-CKD
Dapagliflozin vs placebo
EMPEROR-Reduced
Empagliflozin vs placebo
DECLARE-TIMI
Dapagliflozin vs placebo
CREDENCE
Canagliflozin vs placebo
ACE-I or ARB
SGLT2 Inhibitors
GLP-1 Agonists
Non-Steroidal MRA
Endothelin Antagonists

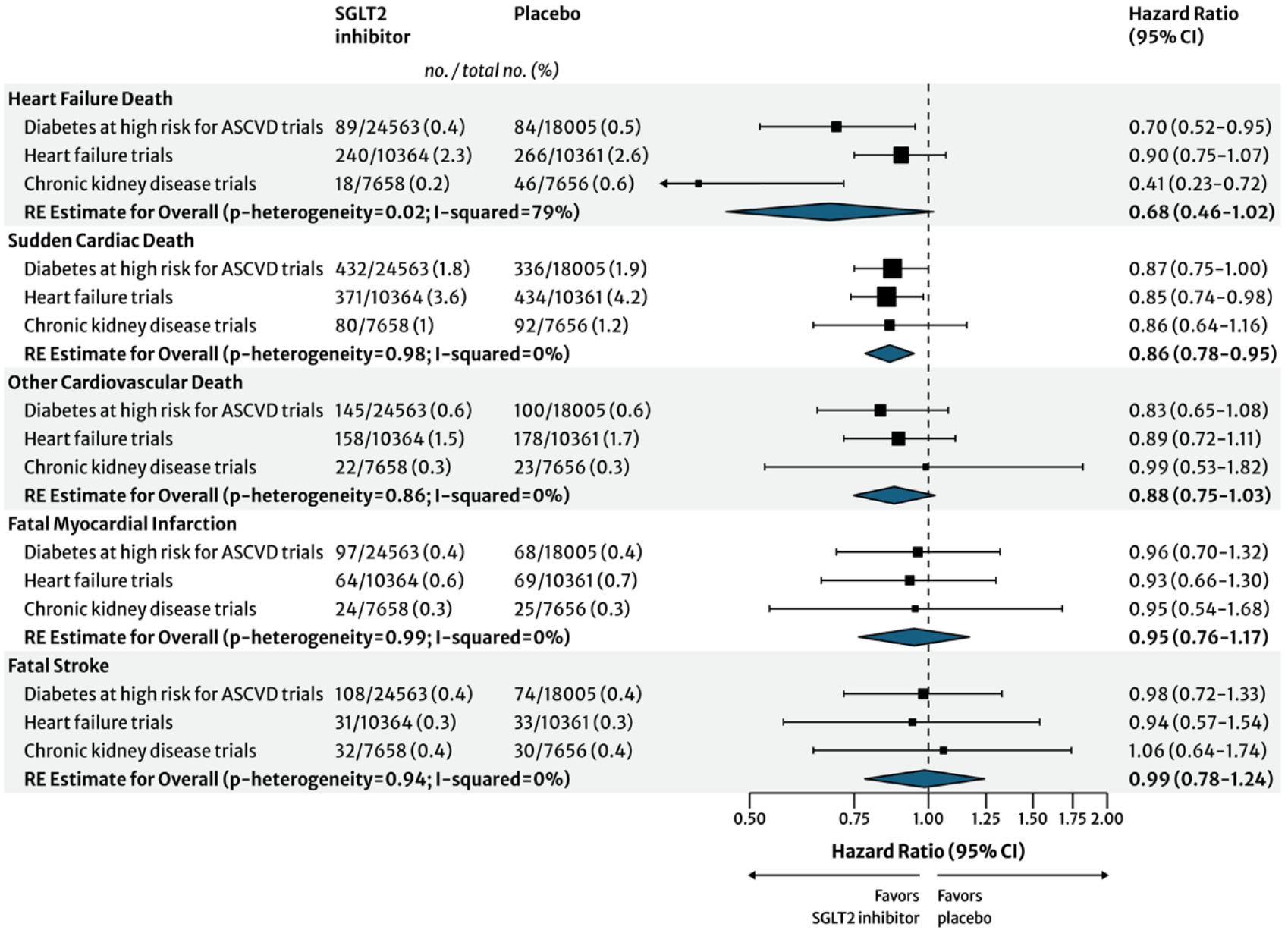
SGLT2i και νεφρική έκβαση meta-analysis



↓ 37%

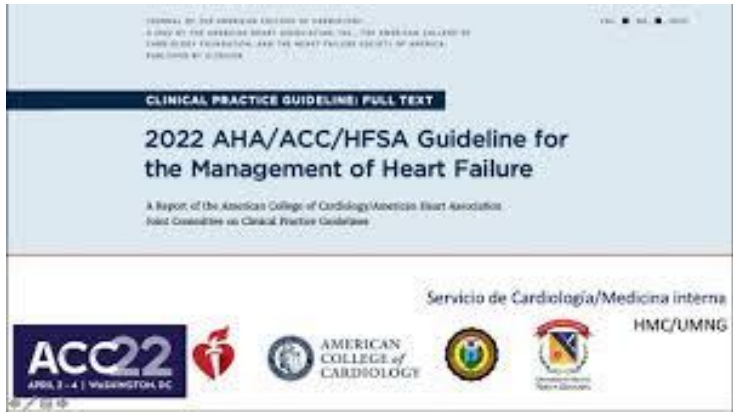
SGLT2i και καρδιαγγειακή έκβαση meta-analysis

78000 ασθενείς



32%

Circulation 2024



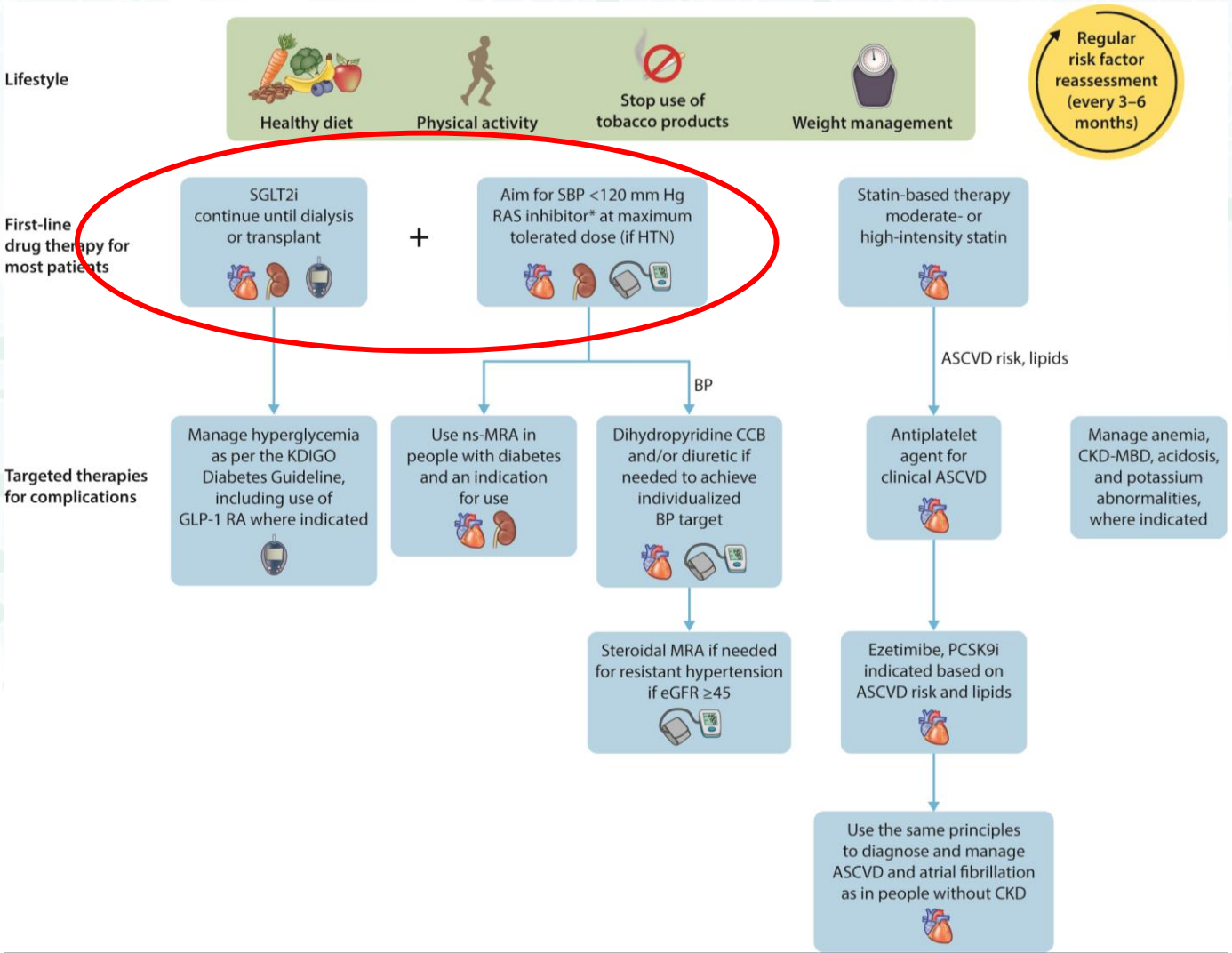
Guideline Directed Medical Therapy Across Heart Failure Stages

Use this tool to reference guideline directed medical therapy (GDMT) across the four ACC/AHA stages of Heart Failure (HF) as outlined in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. See the guideline for specific patient population criteria.

GDMT of major medication classes	Stage A At-Risk for Heart Failure	Stage B Pre-Heart Failure	Stage C & D Stage C: Symptomatic Heart Failure & Stage D: Advanced Heart Failure HFrEF LVEF ≤40%	HFmrEF LVEF 41-49%	HFpEF LVEF ≥50%
	SGLT2i in pts with DM (1)	SGLT2i in pts with DM (1)	ARNI in NYHA II-III; ACEi or ARB in NYHA II-IV (1)	Diuretics, as needed (1)	Diuretics, as needed (1)
		ACEi (1)	Beta blocker (1)	SGLT2i (2a)	SGLT2i (2a)
		ARB if ACEi intolerant (1)	MRA (1)	ACEi, ARB, ARNi (2b)	ARNi (2b)
		Beta blocker (1)	SGLT2i (1)	MRA (2b)	MRA (2b)
			Diuretics, as needed (1)	Beta blocker (2b)	ARB (2b)
			Hydral-nitrates for NYHA III-IV, in African American pts (1)		

MANAGEMENT – RASI AND SGLT2I

Treatments that delay progression of CKD with a strong evidence base include RASi and SGLT2i. In people with CKD and heart failure, SGLT2i confer benefits irrespective of albuminuria.



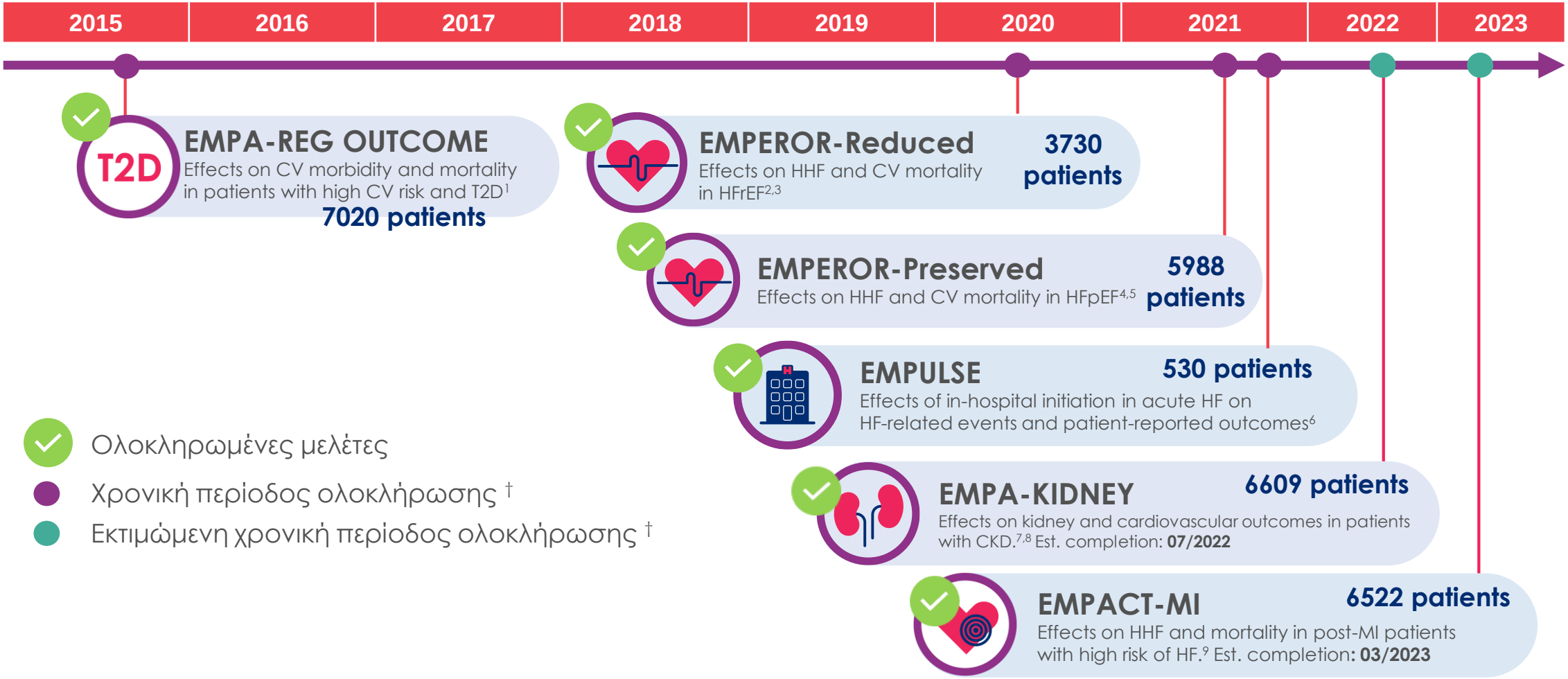
Tale of salt and sugar…

- 1835 C. Petersen : απομόνωσε φλωριζίνη από το φλοιό της ρίζας της μηλιάς για τη θεραπεία της ελονοσίας
- 1886 von Mering : ανακάλυψε ότι προκαλεί γλυκοζουρία
- 1960 : επαναρρόφηση γλυκόζης και νατρίου στο εγγύς σωληνάριο
- 1962 Alvarado και Crane : η φλωριζίνη (γλυκόζη με δυο αρωματικούς δακτυλίους) αναστέλλει αυτή τη συμμεταφορά -στα ζώα εγχυόμενη προκαλεί υπογλυκαιμία (αλλά μη απορροφούμενη pos)
- I996, Kyoto University / Tanuba Seiygyu Co. (Ιαπωνία) : παρασκεύασαν χημικά τον πρώτο SGLT2i
- 2000 : παραγωγή του T-1095, SGLT2i που δόθηκε σε διαβητικά ποντίκια και μείωσε επίπεδα γλυκόζης
- 2012 και 2015 EMA και FDA : ενέκριναν dapagliflozin, canagliflozin και empagliflozin ως αντιδιαβητικά δεύτερης γραμμής σε ΣΔΙΙ (μείωση HgbA1c 0.6%, μέτρια μείωση ΣΒ και ΑΠ)
- 2008 FDA : απαίτησε τα αντιδιαβητικά φάρμακα να έχουν αποδεδειγμένη καρδιαγγειακή ασφάλεια

Braunwald Eugene. Eur Heart Journal, 2022

Το κλινικό πρόγραμμα EMPOWER:
ένα κάρδιο-νέφρο-μεταβολικό πρόγραμμα με **>200,000 ασθενείς***

Στόχος: Επιβεβαίωση των δεδομένων της EMPA-REG OUTCOME σε ασθενεις με ΚΑ και ΧΝΝ με ή Χωρίς Δτ2



EMPA-REG OUTCOME®

1

Η Μελέτη EMPA-REG OUTCOME®

Νεφρικά Δεδομένα

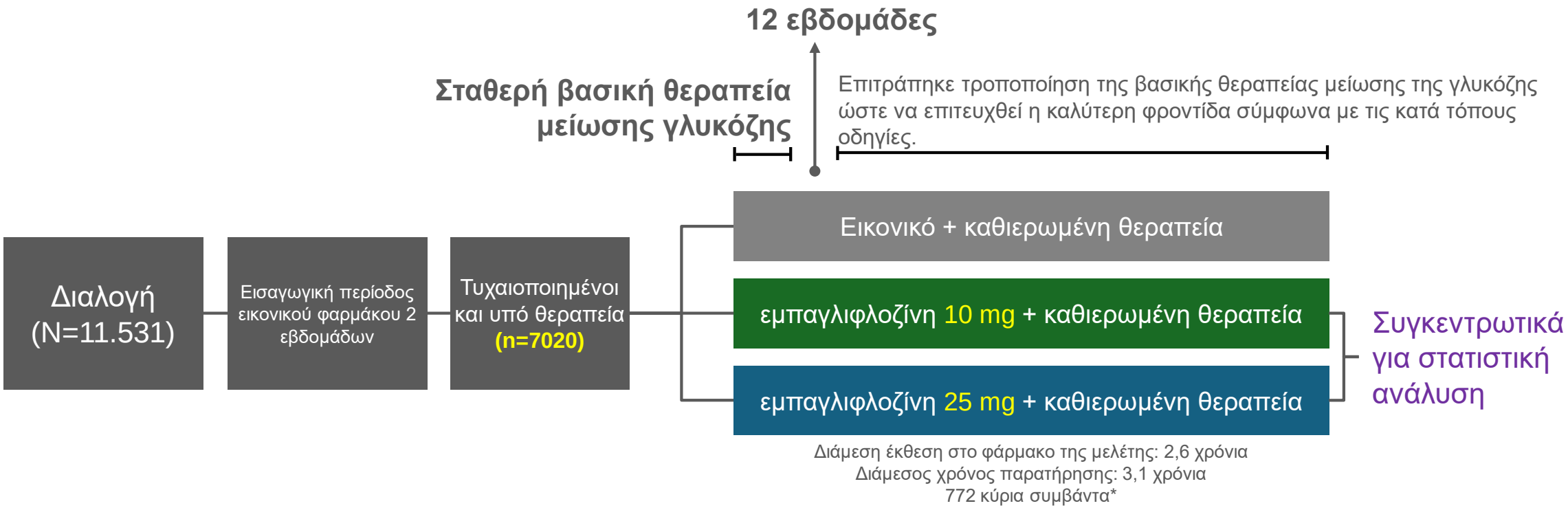
Ασθενείς με Δτ2 και **Καρδιαγγειακή Νόσο**[1]

Zinman B, et al. N Engl J Med. 2015;373:2117–2128

Wanner C, et al. N Engl J Med. 2016;375:323–334

Σχεδιασμός της Μελέτης EMPA-REG OUTCOME

Στόχος: να εξεταστούν οι μακροπρόθεσμες επιδράσεις της εμπαγλιφλοζίνης έναντι του εικονικού φαρμάκου, επιπλέον της καθιερωμένης θεραπείας, στη ΚΔ νοσηρότητα και θνησιμότητα σε ασθενείς με ΣΔτ2 και εγκατεστημένη ΚΔ νόσο



Οποιαδήποτε επιπλέον θεραπεία θεωρείται απαραίτητη για την ευημερία του ασθενή μπορεί να χορηγείται κατά τη διακριτική ευχέρεια του ερευνητή

EMPA-REG OUTCOME®

Η εμπαγλιφλοζίνη επέδειξε σημαντικές Κάρδιο-προστατευτικές επιδράσεις σε ασθενείς με ΣΔτ2 & εγκατεστημένη ΚΔ νόσο

Πρωτεύον τελικό σημείο

3P-MACE

14% (RRR)

HR=0.86, 95% CI: 0.74–0.99,
p<0.001 for non-inferiority
p=0.04 for superiority

Άλλα τελικά σημεία

ΚΔ θάνατος

38% (RRR)

HR=0.62, 95% CI: 0.49–0.77,
p<0.001

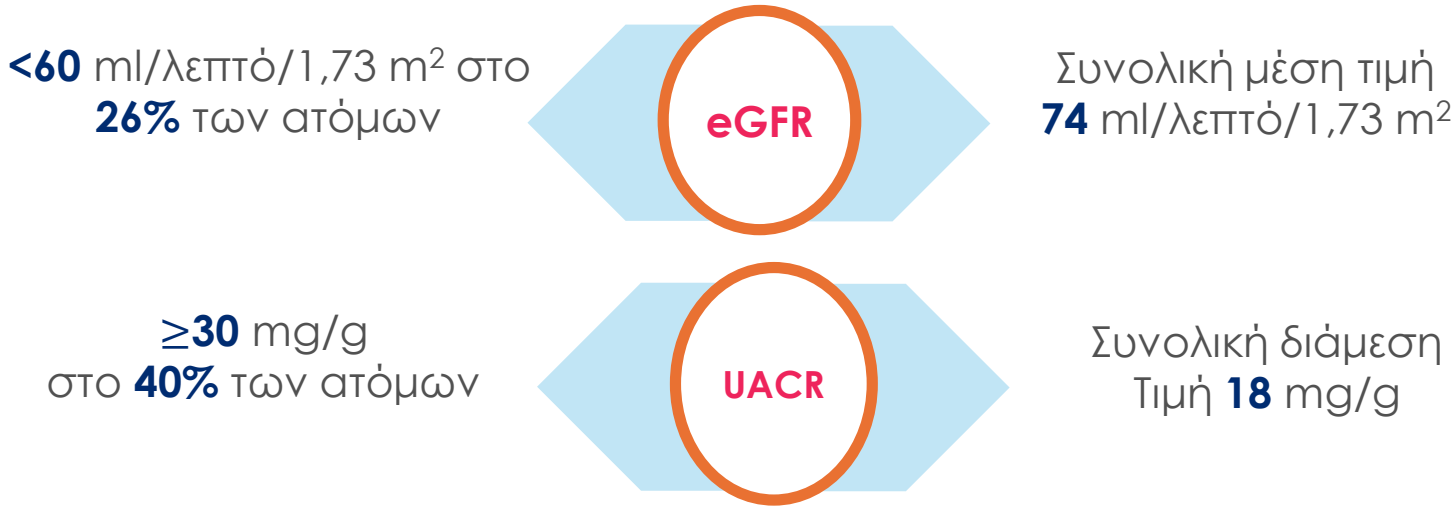
Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

1. Zinman B et al. N Engl J Med 2015;373:2117; 2. Wanner C et al. N Engl J Med 2016;375:323

Η εμπαγλιφλοζίνη βελτίωσε τις νεφρικές εκβάσεις έναντι του εικονικού φαρμάκου

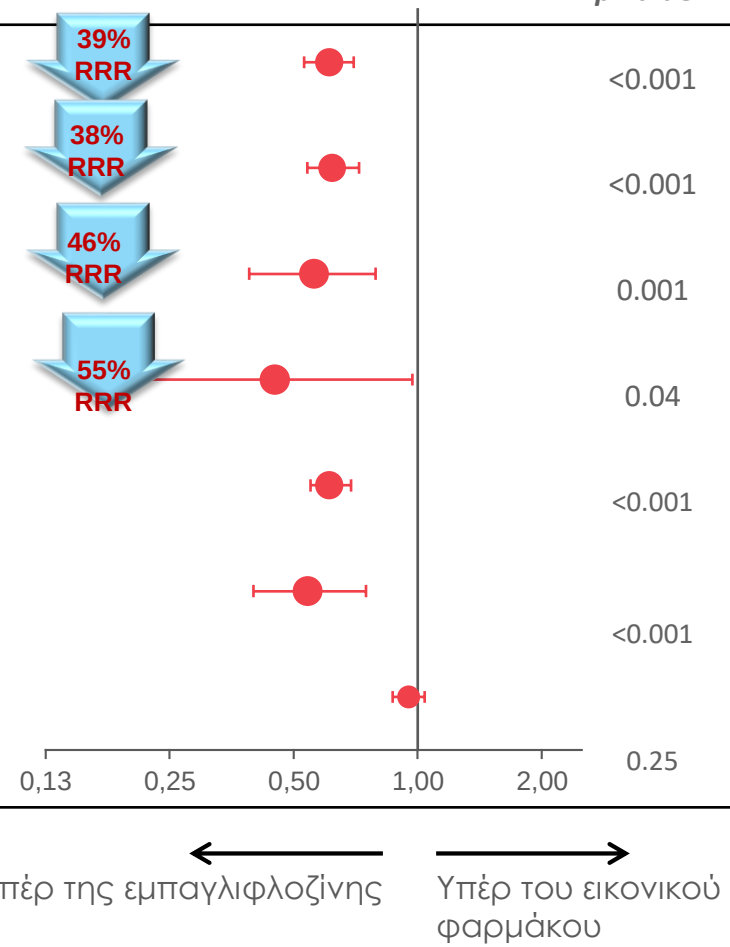
7020 άτομα με ΣΔτ2 και υψηλό ΚΔ κίνδυνο



11.0% macroalbuminuria

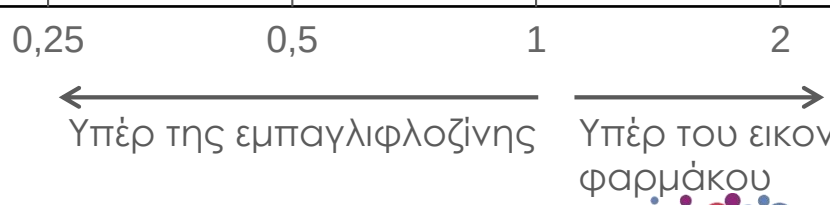
EMPA-REG OUTCOME® ανάλυση νεφρικών δεδομένων

	n με συμβάν / N αναλύθηκαν (%)				
	Εμπαγλιφλοζίνη	Placebo	HR (95% CI)		*p*-value*
Νέα εμφάνιση ή επιδείνωση νεφροπάθειας[†]	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)	39% RRR	<0.001
Εξέλιξη σε Μακρο-αλβουμινουρία	459/4091 (11.2)	330/2033 (16.2)	0.62 (0.54, 0.72)	38% RRR	<0.001
Διπλασιασμός κρεατινίνης ορού(eGFR<45ml/min)	70/4645 (1.5)	60/2323 (2.6)	0.56 (0.39 , 0.79)	46% RRR	0.001
Έναρξη θεραπείας νεφρικής υποκατάστασης	13/4687 (0.3)	14/2333 (0.6)	0.45 (0.21, 0.97)	55% RRR	0.04
Νέα εμφάνιση ή επιδείνωση νεφροπάθειας ή ΚΔ θάνατος	675/4170 (16.2)	497/2102 (23.6)	0.61 (0.55, 0.69)		<0.001
Διπλασιασμός κρεατινίνης ορού,[‡] Έναρξη θεραπείας νεφρικής υποκατάστασης ή θάνατος από νεφρική νόσο	81/4645 (1.7)	71/2323 (3.1)	0.54 (0.40, 0.75)		<0.001
Εμφάνιση αλβουμινουρίας σε ασθενείς χωρίς αλβουμινουρία κατά την έναρξη [§]	1430/2779 (51.5)	703/1374 (51.2)	0.95 (0.87, 1.04)		0.25



Νεφρικές εκβάσεις σύμφωνα με τις κατηγορίες eGFR και UACR στην έναρξη

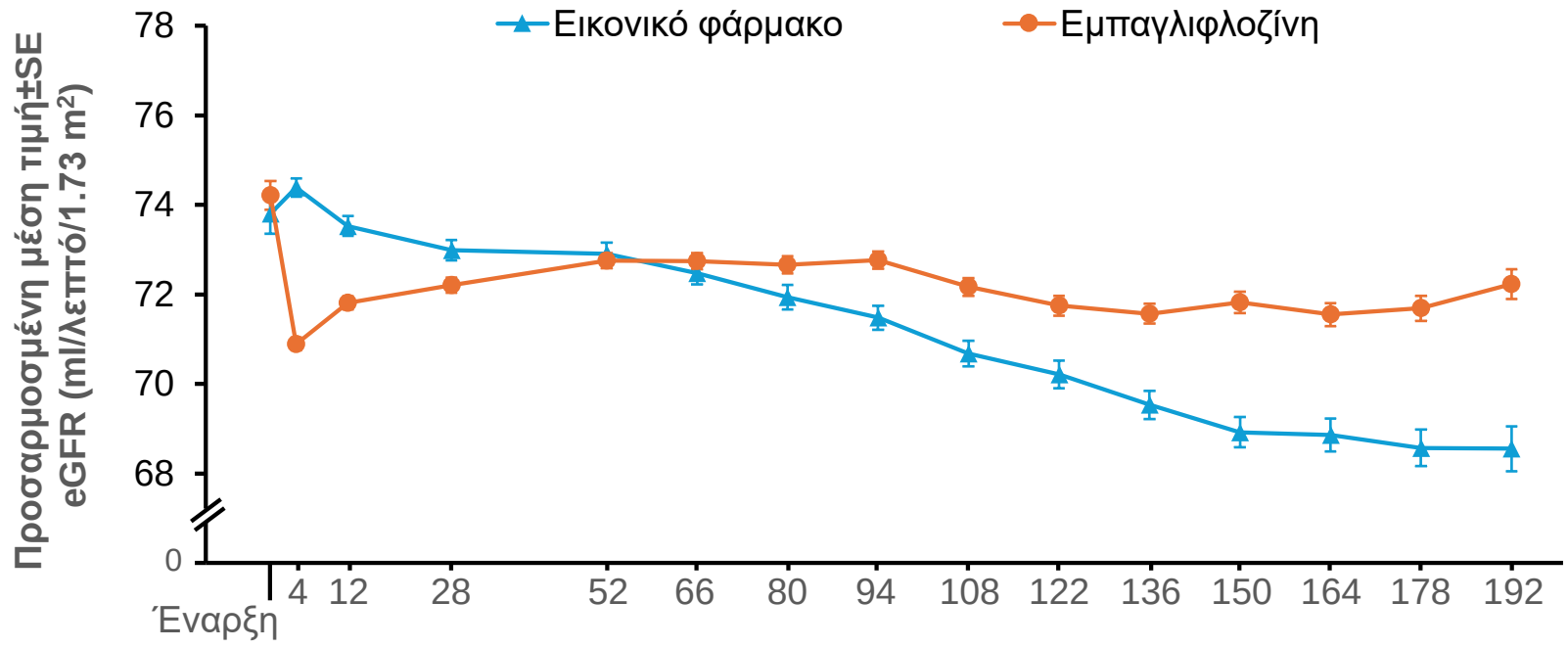
	εμπαγλιφλοζίνη	Εικ. φάρμακο	HR (95% CI)	Τιμή-*p* για αλληλεπίδραση
	Ασθενείς που αναλύθηκαν			
Όλοι οι ασθενείς	4124	2061		
eGFR				0,40
≥90 mL/λεπτό/1.73 m²	962	452		
60 έως <90ml/λεπτό/1.73 m²	2179	1112		
45 έως <60ml/λεπτό/1.73 m²	707	341		
< 45 mL/λεπτό/1.73 m²	276	156		
UACR				0,87
<30 mg/g	2737	1361		
≥30 mg/g	1344	687		



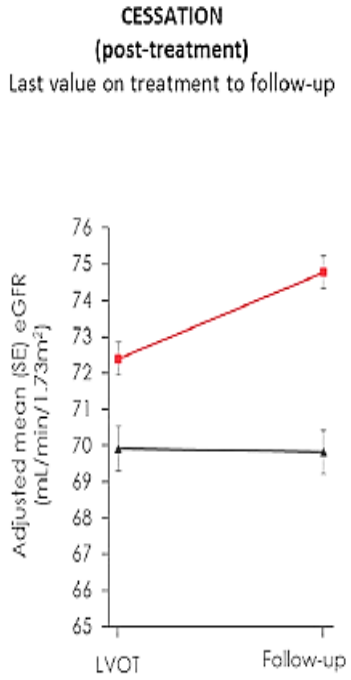
Η μείωση στον κίνδυνο εμφάνισης ή επιδείνωσης νεφροπάθειας* ήταν σταθερή σε όλες τις κατηγορίες eGFR και UACR στην έναρξη

EMPA-REG OUTCOME®

Η εμπαγλιφλοζίνη επιβράδυνε την έκπτωση του eGFR στην πάροδο του χρόνου



Αρ. ασθενών														
Εικονικό φάρμακο	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
empagliflozin	4644	4578	4533	4451	4318	4225	4018	4131	3710	3103	2654	2387	2087	1623	1037



Wanner C *et al. J Am Soc Nephrol* 2018;29:2755

Abrupt Decline in Estimated Glomerular Filtration Rate after Initiating Sodium-Glucose Cotransporter 2 Inhibitors Predicts Clinical Outcomes: A Systematic Review and Meta-Analysis

≥18 y/o, initiating SGLT2i for DM, HF or CKD

Initial eGFR dip vs. no-dip groups

Primary outcome

Slope of eGFR decline

MD=0.640 (95% CI: 0.437–0.843)

Secondary outcomes

MAKE

HR=0.010 (95% CI: 0.869–1.173)

HHF and CV death

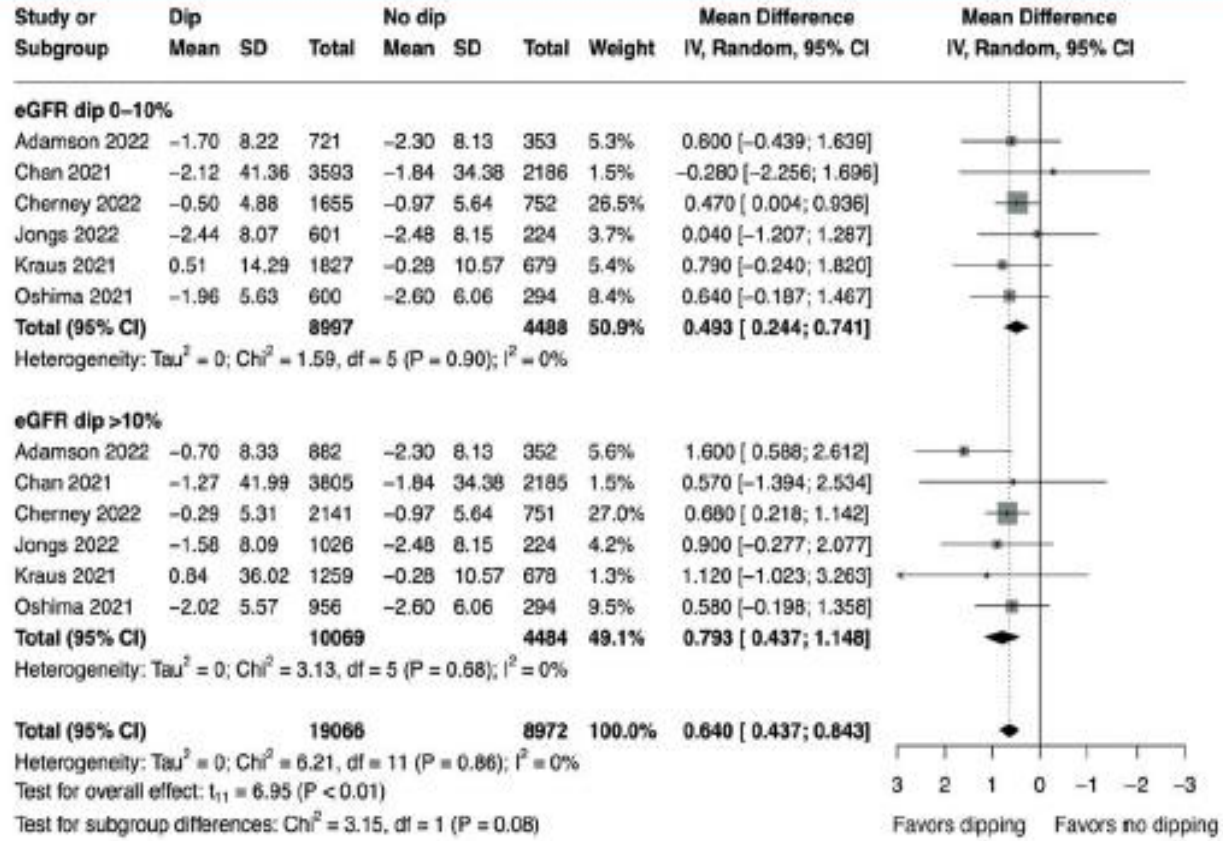
HR=0.824 (95% CI: 0.633–1.074)

HHF

HR=1.059 (95% CI: 0.574–1.952)

All-cause mortality

HR=0.830 (95% CI: 0.589–1.170)



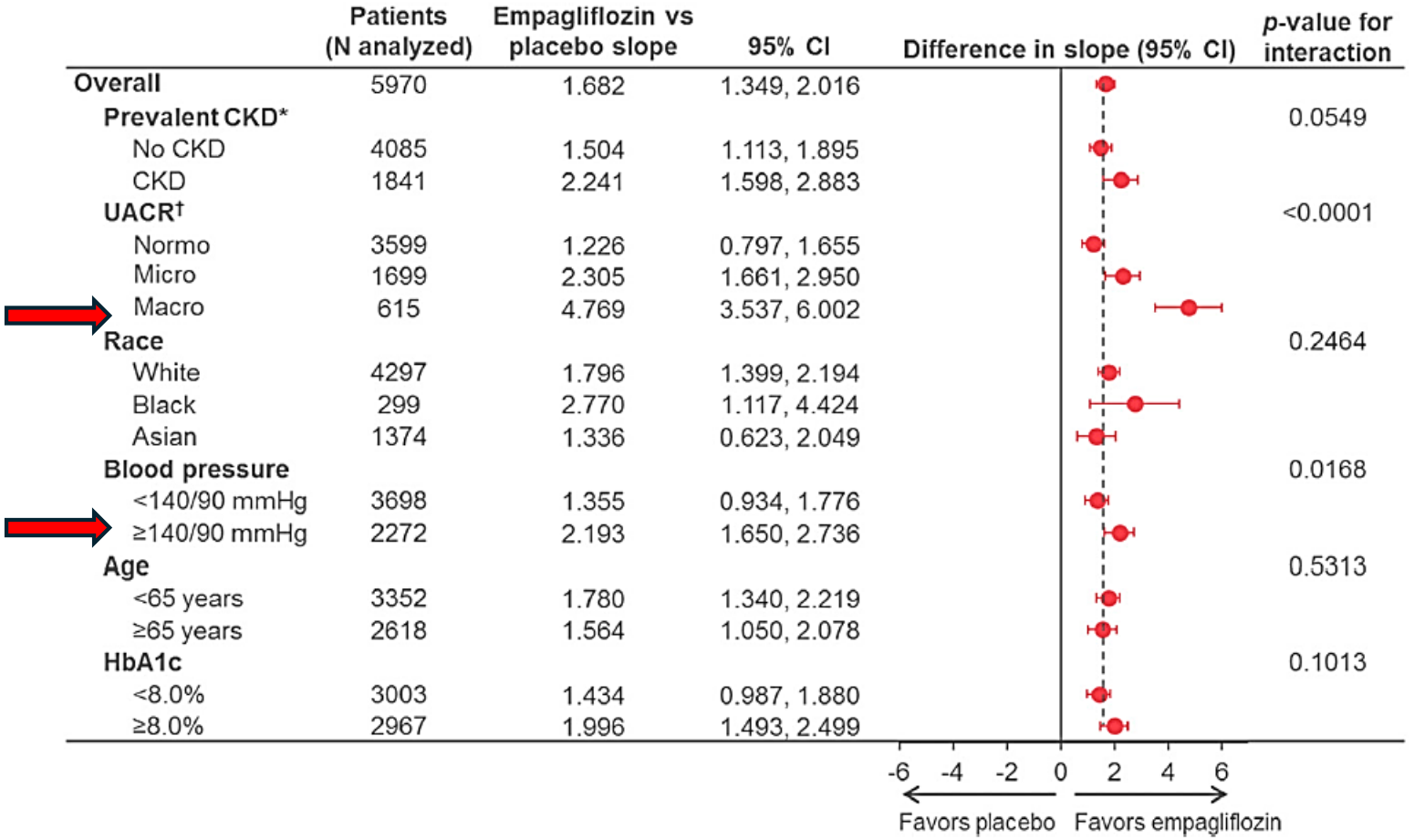
Study or Subgroup	Dip Mean	SD	Total	No dip Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
eGFR dip 0–10%								
Adamson 2022	−1.70	8.22	721	−2.30	8.13	353	5.3%	0.600 [−0.439; 1.639]
Chan 2021	−2.12	41.36	3593	−1.84	34.38	2186	1.5%	−0.280 [−2.256; 1.696]
Cherney 2022	−0.50	4.88	1655	−0.97	5.64	752	26.5%	0.470 [0.004; 0.936]
Jongs 2022	−2.44	8.07	601	−2.48	8.15	224	3.7%	0.040 [−1.207; 1.287]
Kraus 2021	0.51	14.29	1827	−0.29	10.57	679	5.4%	0.790 [−0.240; 1.820]
Oshima 2021	−1.96	5.63	600	−2.60	6.06	294	8.4%	0.640 [−0.197; 1.467]
Total (95% CI)			**8997**			**4488**	**50.9%**	**0.493 [0.244; 0.741]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.59$, df = 5 (P = 0.90); $I^2 = 0\%$								
eGFR dip >10%								
Adamson 2022	−0.70	8.33	882	−2.30	8.13	352	5.6%	1.600 [0.588; 2.612]
Chan 2021	−1.27	41.99	3805	−1.84	34.38	2185	1.5%	0.570 [−1.394; 2.534]
Cherney 2022	−0.29	5.31	2141	−0.97	5.64	751	27.0%	0.680 [0.218; 1.142]
Jongs 2022	−1.58	8.09	1026	−2.48	8.15	224	4.2%	0.900 [−0.277; 2.077]
Kraus 2021	0.84	36.02	1259	−0.28	10.57	678	1.3%	1.120 [−1.023; 3.263]
Oshima 2021	−2.02	5.57	956	−2.60	6.06	294	9.5%	0.580 [−0.198; 1.358]
Total (95% CI)			**10069**			**4484**	**49.1%**	**0.793 [0.437; 1.148]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.13$, df = 5 (P = 0.68); $I^2 = 0\%$								
Total (95% CI)			**19066**			**8972**	**100.0%**	**0.640 [0.437; 0.843]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 6.21$, df = 11 (P = 0.86); $I^2 = 0\%$								
Test for overall effect: $t_{11} = 6.95$ (P < 0.01)								
Test for subgroup differences: $Chi^2 = 3.15$, df = 1 (P = 0.08)								

Conclusion

An initial eGFR dip after initiating SGLT2i may lead to less eGFR decline over time.
The risks of adverse cardiovascular outcomes were similar between the dipping and non-dipping groups.

DIABETES & METABOLISM JOURNAL dmj

Η εμπαγλιφλοζίνη μικρότερη eGFR κλίση σε όλες τις υποκατηγορίες



Wanner C *et al. J Am Soc Nephrol* 2018;29:2755

EMPEROR-Reduced

EMPEROR- Preserved

2

3

Οι Μελέτες EMPEROR-Reduced® & EMPEROR-Preserved®

Νεφρικά Δεδομένα

Ασθενείς με ή Χωρίς Δτ2 και **Καρδιακή Ανεπάρκεια**

Milton P. et al. N Engl J Med. 2020 Oct 8;383(15):1413-1424.
Anker S et al. N Engl J Med. 2021,DOI: 10.1056/NEJMoa2107038.

EMPEROR-Reduced

Φάσης III, τυχαιοποιημένη, διπλά τυφλή, ελεγχόμενη με εικονικό φάρμακο δοκιμή

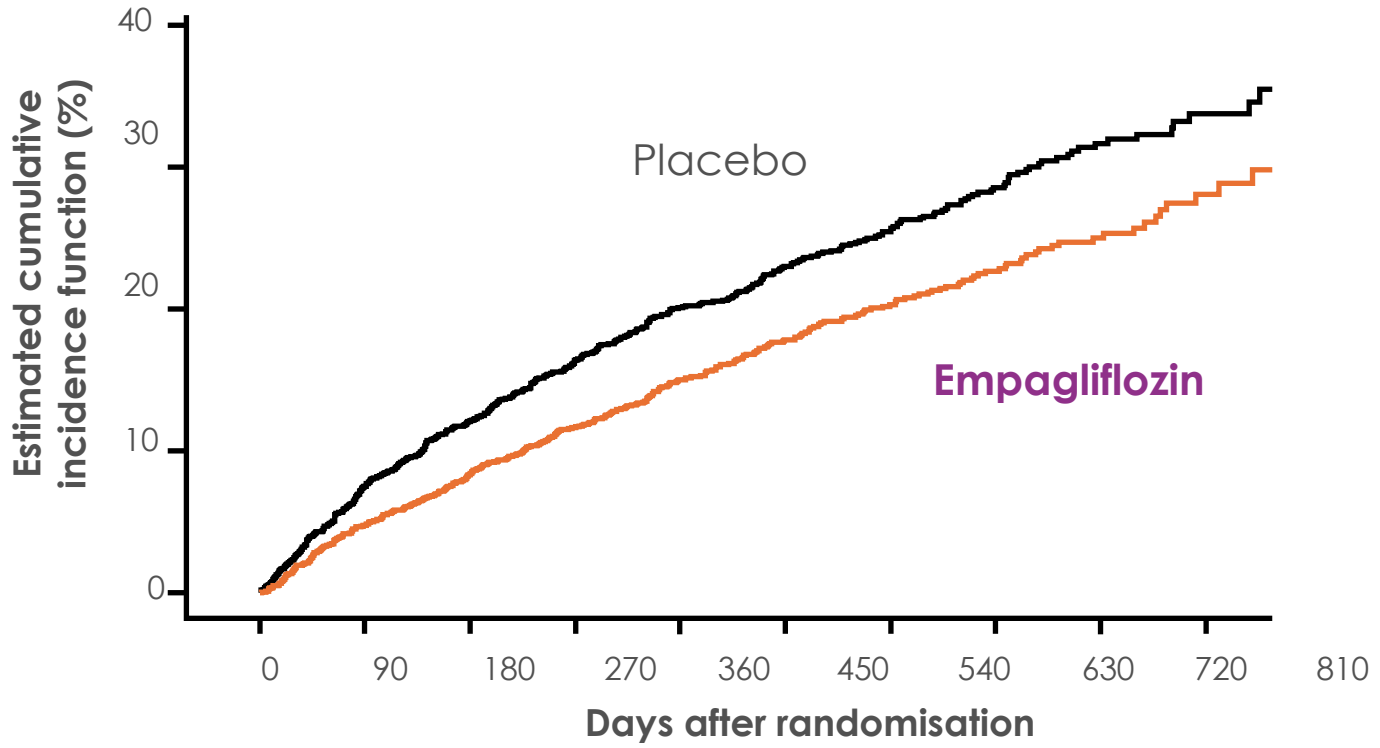
Σκοπός: Η διερεύνηση της ασφάλειας και της αποτελεσματικότητας της εμπαγλιφλοζίνης έναντι του εικονικού φαρμάκου επιπλέον της σύμφωνης με τις οδηγίες ιατρικής θεραπείας σε ασθενείς **με ΚΑ με μειωμένο κλάσμα εξώθησης**

Πληθυσμός: Με και χωρίς Δτ2, ηλικίας≥18 ετών, χρόνια ΚΑ (τάξη NYHA II–IV)

Σχεδιασμός της μελέτης

class II, III, or IV heart failure
and an ejection fraction of 40% or less

Primary endpoint: First adjudicated CV death or hospitalisation for heart failure



Patients at risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

RRR 25%

ARR 5.2%

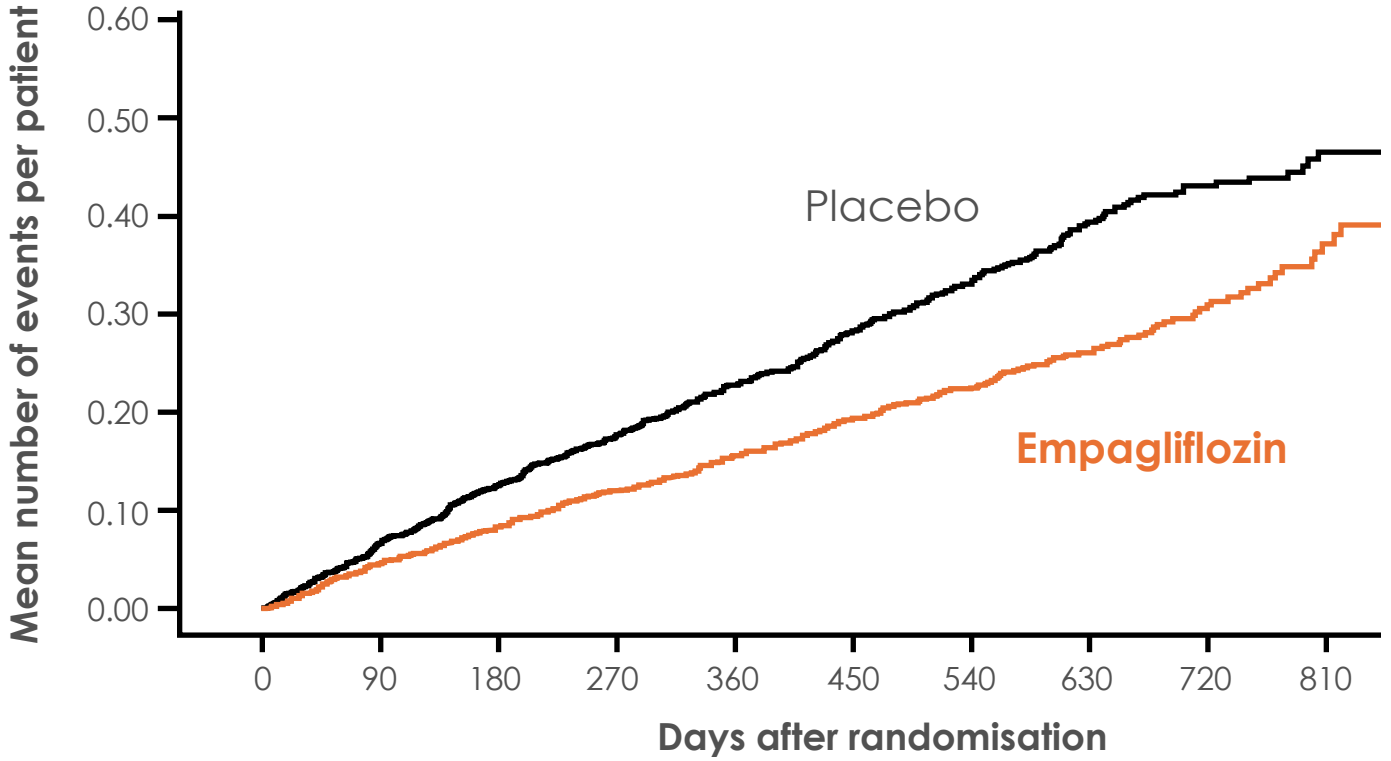
NNT = 19

HR 0.75
(95% CI 0.65, 0.86)
p<0.001

Empagliflozin:
361 patients with event
Rate: 15.8/100 patient-years
Placebo:
462 patients with event
Rate: 21.0/100 patient-years

Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment
CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ARR, absolute risk reduction; RRR, relative risk reduction. NNT: Number needed to treat
Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

Key secondary: Adjudicated total hospitalisations for heart failure (first and recurrent)



Patients at risk

Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

RRR 30%

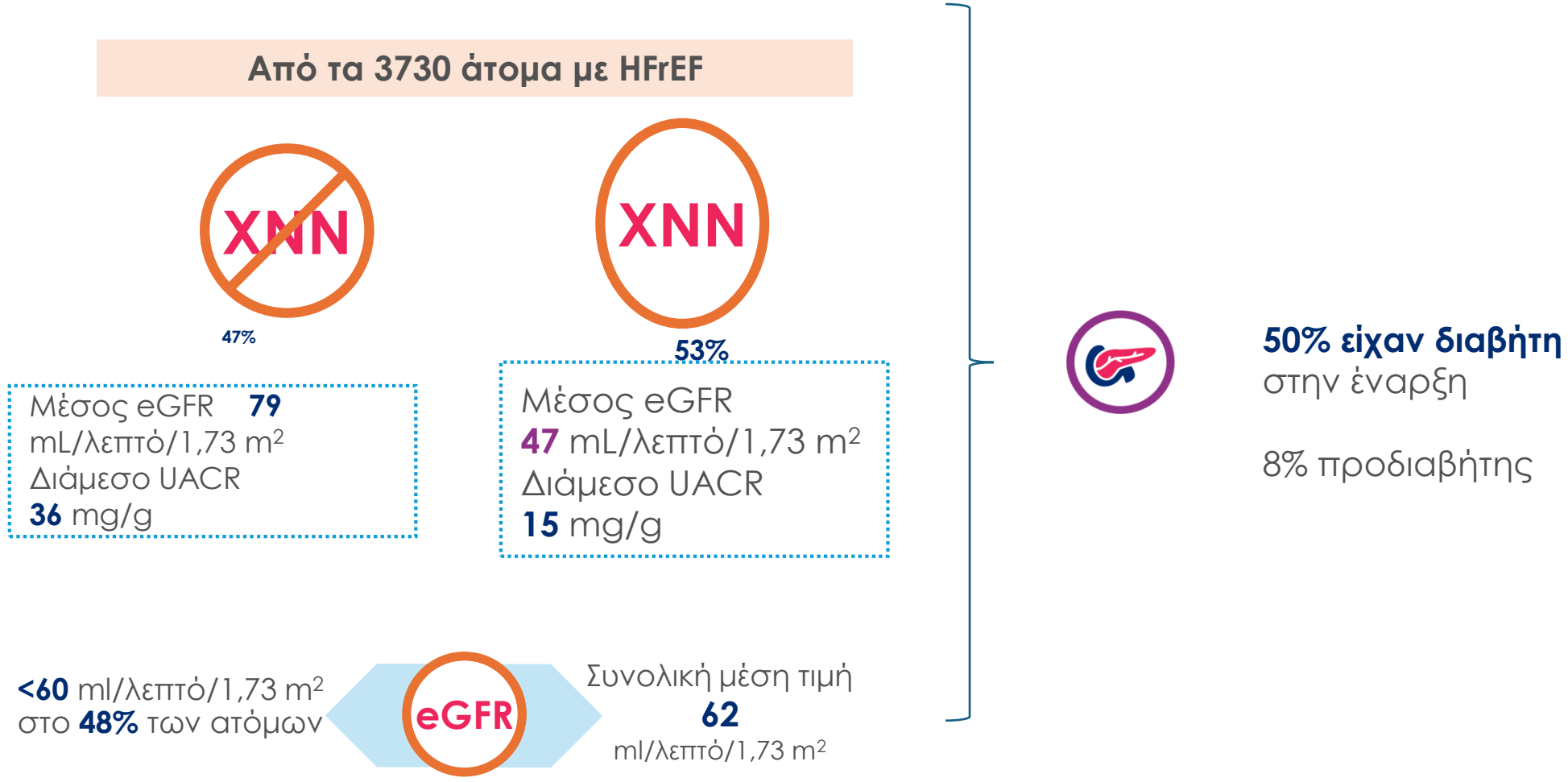
HR 0.70
(95% CI 0.58, 0.85)
p<0.001

Emagliflozin: 388 events
Placebo: 553 events

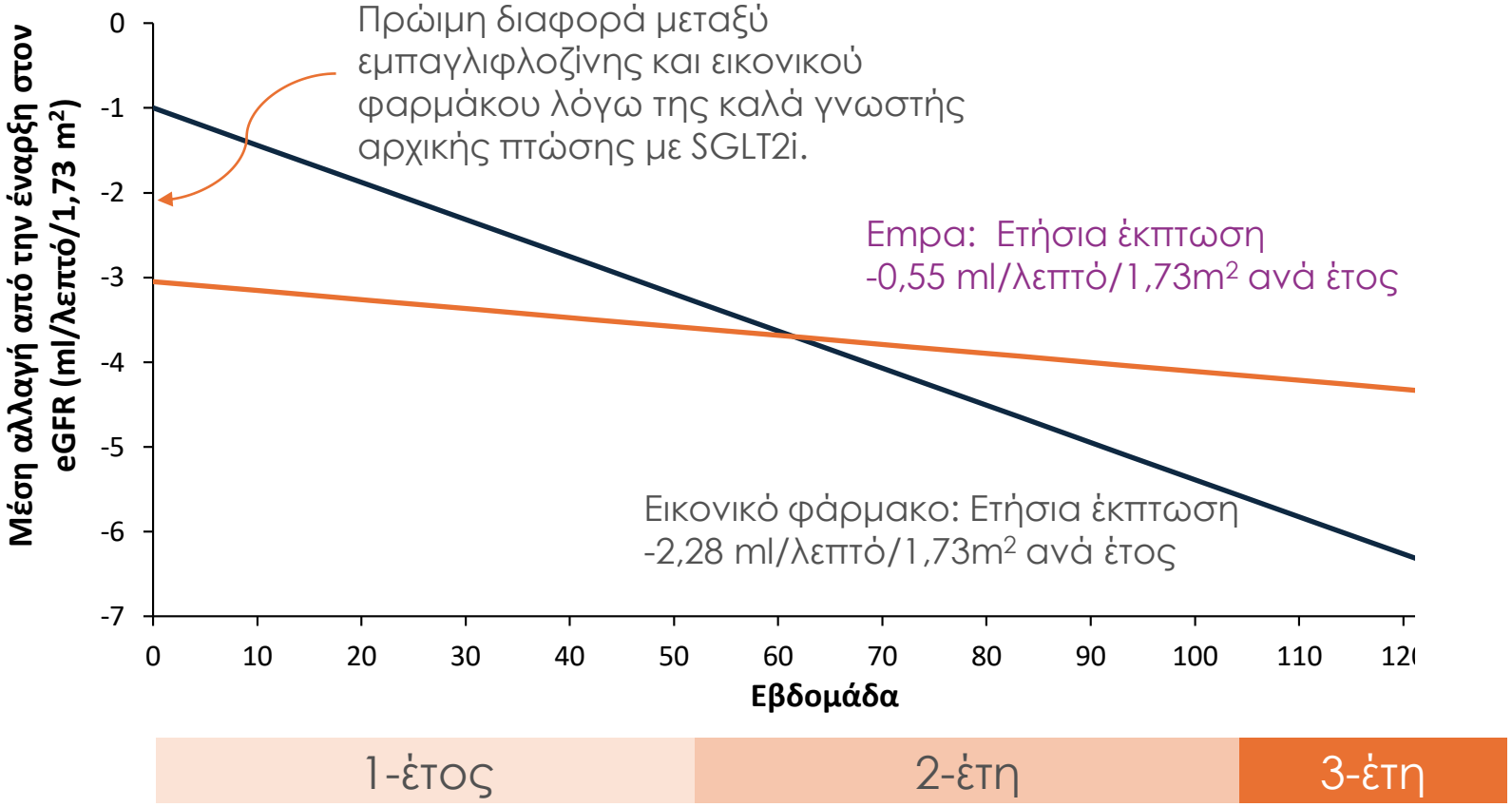
Analysis of first and recurrent HHF accounting for CV death as terminal event using a joint frailty model. Model includes covariates age, baseline eGFR, treatment, region, baseline diabetes status, sex, and baseline LVEF, estimated dependence between adjudicated HHF and adjudicated CV death, and variance of frailty. CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction

Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

Κύριο δευτερεύον τελικό σημείο: Κλίση eGFR



Κύριο δευτερεύον τελικό σημείο: κλίση eGFR



Διαφορά κλίσης eGFR μεταξύ εμπαγλιφλοζίνης και εικονικού φαρμάκου:

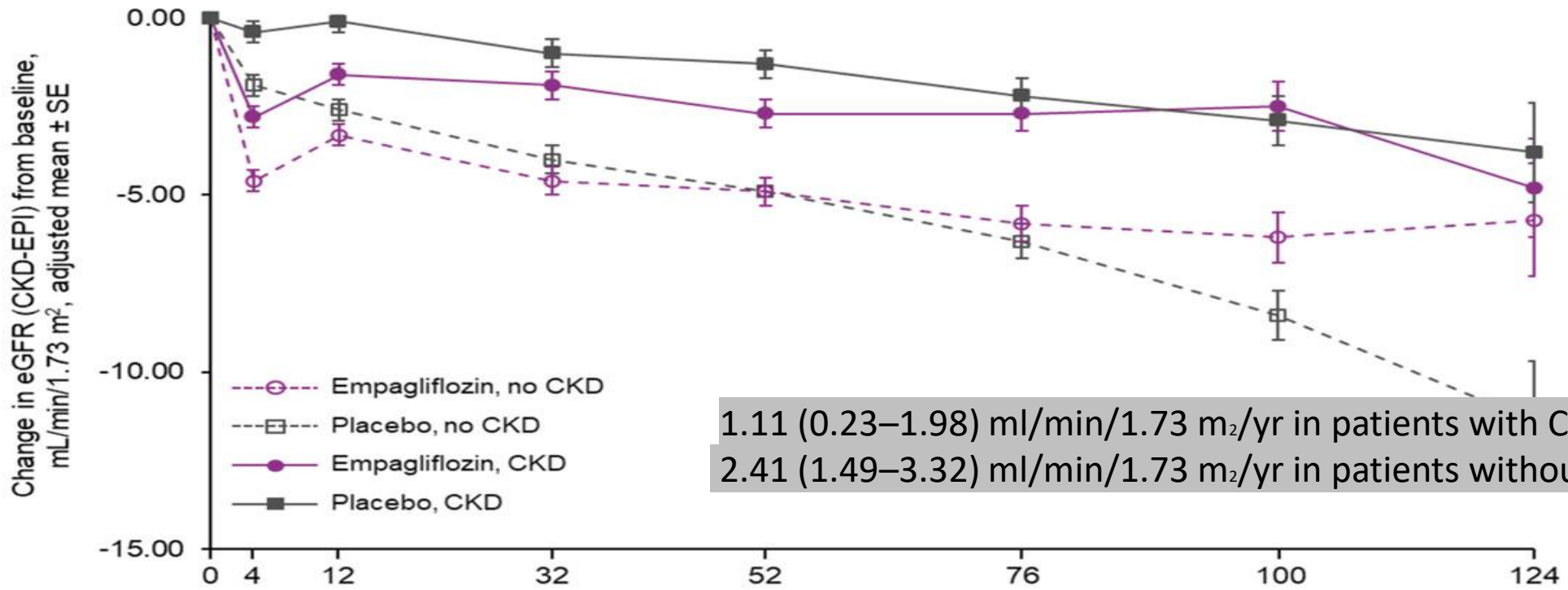
Με διαβήτη:
+ 2,21 ml/λεπτό/1,73 m²/έτος
95% ΔΕ: 1,31 3,10

Χωρίς διαβήτη
+ 1,27 ml/λεπτό/1,73 m²/έτος
95% ΔΕ: 0,38 2,16

Τιμή-*p* αλληλεπίδρασης: 0,15

Επισκόπηση τριών τελικών σημείων που προκαθορίστηκαν για ιεραρχικό έλεγχο

				EMPEROR-Reduced
	Πρωτεύον τελικό σημείο: Αξιολογημένος ΚΔ θάνατος ή νοσηλεία για καρδιακή ανεπάρκεια	Επιβεβαιωτικό*	✓	**HR 0.75** **(95% ΔΕ 0,65, 0,86)** **p< 0,001**
	Βασικό δευτερεύον τελικό σημείο: Αξιολογημένες πρώτες και επαναλαμβανόμενες νοσηλείες για καρδιακή ανεπάρκεια	Επιβεβαιωτικό†	✓	**HR 0.70** **(95% ΔΕ 0,58, 0,85)** **p<0,001**
	Βασικό δευτερεύον τελικό σημείο: Κλίση eGFR	Επιβεβαιωτικό‡	✓	**Διαφορά κλίσης** **1,73 ml/λεπτό/1,73 m²** **ανά έτος,** **(95% ΔΕ 1,1, 2,4)** **p<0,001**



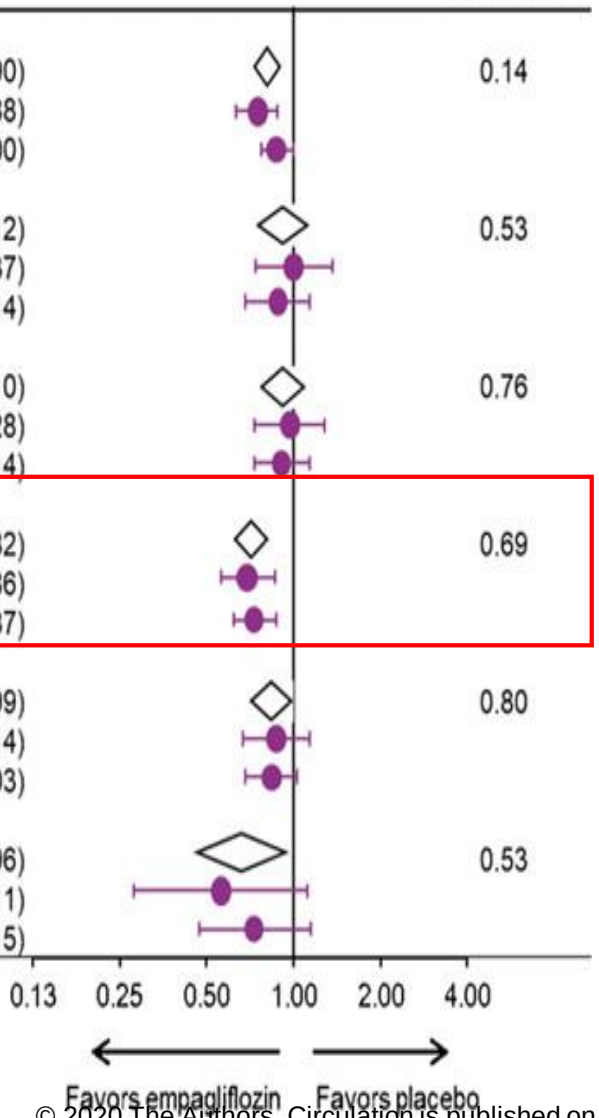
1.11 (0.23–1.98) ml/min/1.73 m_2/yr in patients with CKD

2.41 (1.49–3.32) ml/min/1.73 m_2/yr in patients without CKD

Patients with data at visit								
Empagliflozin no CKD	848	843	815	749	562	370	170	35
Placebo no CKD	833	819	785	727	554	351	155	31
Empagliflozin CKD	949	937	903	803	603	383	186	45
Placebo CKD	957	944	986	772	591	393	187	45

Faiez Zannad. Circulation. Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function, Volume: 143, Issue: 4, Pages: 310-321, DOI: (10.1161/CIRCULATIONAHA.120.051685)

	Empagliflozin 10 mg		Placebo				
	n with event/N analyzed (%)	Rate per 100 patient-years	n with event/N analyzed (%)	Rate per 100 patient-years	HR (95% CI)	HR (95% CI)	*P*-value for interaction
All-cause hospitalization							
All patients	703/1863 (37.7)	36.62	814/1867 (43.6)	45.23	0.81 (0.73, 0.90)		0.14
No prevalent CKD	266/879 (30.3)	28.10	330/867 (38.1)	37.71	0.75 (0.63, 0.88)		
Prevalent CKD*	422/981 (43.0)	42.92	464/997 (46.5)	49.46	0.87 (0.77, 1.00)		
CV death							
All patients	187/1863 (10.0)	7.55	202/1867 (10.8)	8.13	0.92 (0.75, 1.12)		0.53
No prevalent CKD	81/879 (9.2)	6.89	79/867 (9.1)	6.84	1.00 (0.74, 1.37)		
Prevalent CKD*	106/981 (10.8)	8.17	121/997 (12.1)	9.13	0.88 (0.68, 1.14)		
All-cause mortality							
All patients	249/1863 (13.4)	10.06	266/1867 (14.2)	10.71	0.92 (0.77, 1.10)		0.76
No prevalent CKD	96/879 (10.9)	8.17	96/867 (11.1)	8.32	0.97 (0.73, 1.28)		
Prevalent CKD*	153/981 (15.6)	11.79	168/997 (16.9)	12.68	0.91 (0.73, 1.14)		
Composite kidney outcome†, CV death or HHF							
All patients	370/1863 (19.9)	19.95	492/1867 (26.4)	27.81	0.71 (0.62, 0.82)		0.69
No prevalent CKD	147/879 (16.7)	16.67	198/867 (22.8)	23.87	0.69 (0.56, 0.86)		
Prevalent CKD*	223/981 (22.7)	22.98	292/997 (29.3)	31.18	0.73 (0.62, 0.87)		
Composite kidney outcome† or all-cause mortality							
All patients	265/1863 (14.2)	13.37	305/1867 (16.3)	15.60	0.84 (0.71, 0.99)		0.80
No prevalent CKD	102/879 (11.6)	10.97	109/867 (12.6)	12.14	0.87 (0.67, 1.14)		
Prevalent CKD*	163/981 (16.6)	15.53	194/997 (19.5)	18.41	0.84 (0.68, 1.03)		
Acute kidney injury‡							
All patients	46/1863 (2.5)	1.89	67/1867 (3.6)	2.76	0.66 (0.45, 0.96)		0.53
No prevalent CKD	13/879 (1.5)	1.13	22/867 (2.5)	1.95	0.56 (0.28, 1.11)		
Prevalent CKD*	33/981 (3.4)	2.58	45/997 (4.5)	3.48	0.73 (0.47, 1.15)		



Faiez Zannad. Circulation. Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function, Volume: 143, Issue: 4, Pages: 310-321, DOI: (10.1161/CIRCULATIONAHA.120.051685)

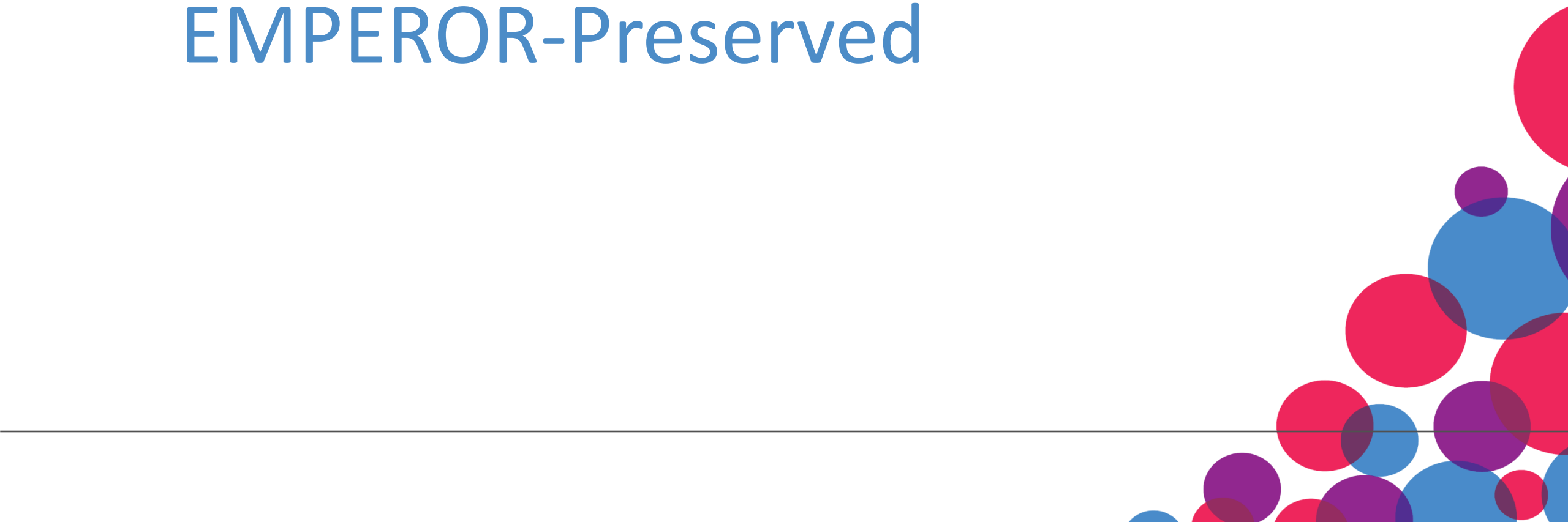
Results of DAPA-HF vs. EMPEROR-Reduced

	DAPA-HF	EMPEROR-REDUCED
Patients	4744	3730
DM	40%	50%
Primary endpoint	CV death, hospitalization for HF, urgent HF visit	CV death, hospitalization for HF
Sacubitril -valsartan	10%	18-21%
Natriuretic peptides median levels	1428-1466	NT-proBNP Median value (IQR) — pg/ml 1887 (1077–3429) 1926
Secondary renal end point	a composite of worsening renal function (sustained decline in the eGFR of 50% or greater, eGFR of <15 ml per minute per 1.73 m2, sustaineddialysis, or renal transplantation), or renal death; and death from any cause	rate of the decline in the e GFR

Dapagliflozin	2372	2294	2226	2141	2008	1570	1153	622	223
Placebo	2370	2276	2200	2117	1975	1537	1132	600	215

Carnicelli A and Mentz R, Circulation 2021

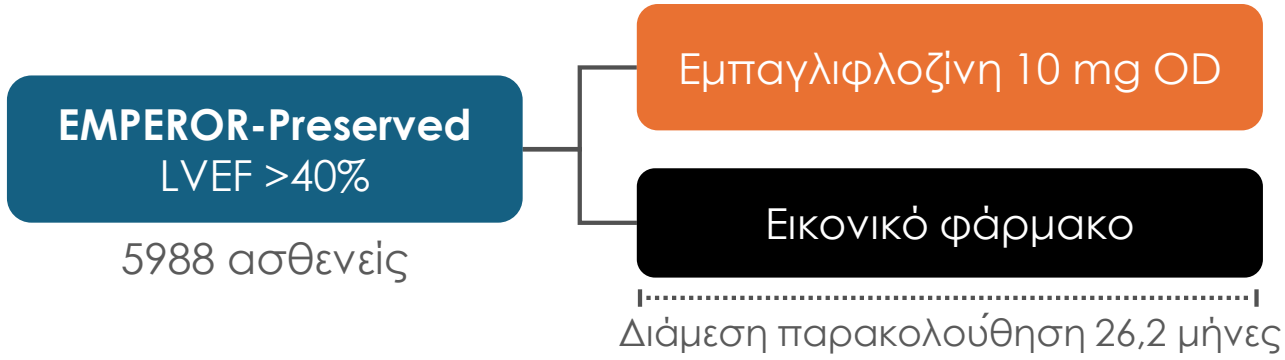
EMPEROR-Preserved



Σχεδιασμός της Μελέτης EMPEROR-Preserved

Σκοπός: Η διερεύνηση της ασφάλειας και της αποτελεσματικότητας της εμπαγλιφλοζίνης έναντι του εικονικού φαρμάκου σε ασθενείς με **ΚΑ** με **διατηρημένο κλάσμα εξώθησης**

Πληθυσμός: Με και χωρίς Δτ2, ηλικίας≥18 ετών, χρόνια ΚΑ (τάξη NYHA II–IV)



EMPEROR-Preserved:

Πρωτεύον τελικό σημείο:
Αξιολογημένος ΚΔ θάνατο
ΝΚΑ

Βασικό δευτερεύον τελικό
Αξιολογημένες πρώτες κα
επαναλαμβανόμενες
ΝΚΑ

Βασικό δευτερεύον τελικό
Κλίση eGFR

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)
Age			
<70 yr	134/1066	152/1084	0.88 (0.70–1.11)
≥70 yr	281/1931	359/1907	0.75 (0.64–0.87)
Sex			
Male	253/1659	297/1653	0.81 (0.69–0.96)
Female	162/1338	214/1338	0.75 (0.61–0.92)
Race			
White	310/2286	370/2256	0.81 (0.69–0.94)
Black	24/133	28/125	0.73 (0.42–1.25)
Asian	54/413	77/411	0.65 (0.46–0.92)
Other	27/164	36/198	0.95 (0.58–1.57)
BMI at baseline			
<30	223/1654	292/1642	0.74 (0.62–0.88)
≥30	192/1343	219/1349	0.85 (0.70–1.03)
Estimated GFR (CKD-EPI) at baseline			
≥60 ml/min/1.73 m^2	152/1493	189/1505	0.81 (0.65–1.00)
<60 ml/min/1.73 m^2	263/1504	321/1484	0.78 (0.66–0.91)
Systolic blood pressure at baseline			
<Median	200/1496	249/1474	0.76 (0.63–0.91)
≥Median	215/1501	262/1517	0.82 (0.68–0.98)

*
Anker S et al. N Engl J Med. 2021,DOI: 10.1056/NEJMoa2107038

EMPEROR-Preserved: η εμπαγλιφλοζίνη επιβράδυνε τον ρυθμό έκπτωσης της νεφρικής λειτουργίας σε άτομα με HFpEF με ή χωρίς διαβήτη

Από τα 5988 άτομα με HFpEF[1]

<60 ml/λεπτό/1,73 m^2 στο **50%** των ατόμων

eGFR

Συνολική μέση τιμή **61**mL/λεπτό/1,73 m^2

49% είχαν διαβήτη
στην έναρξη

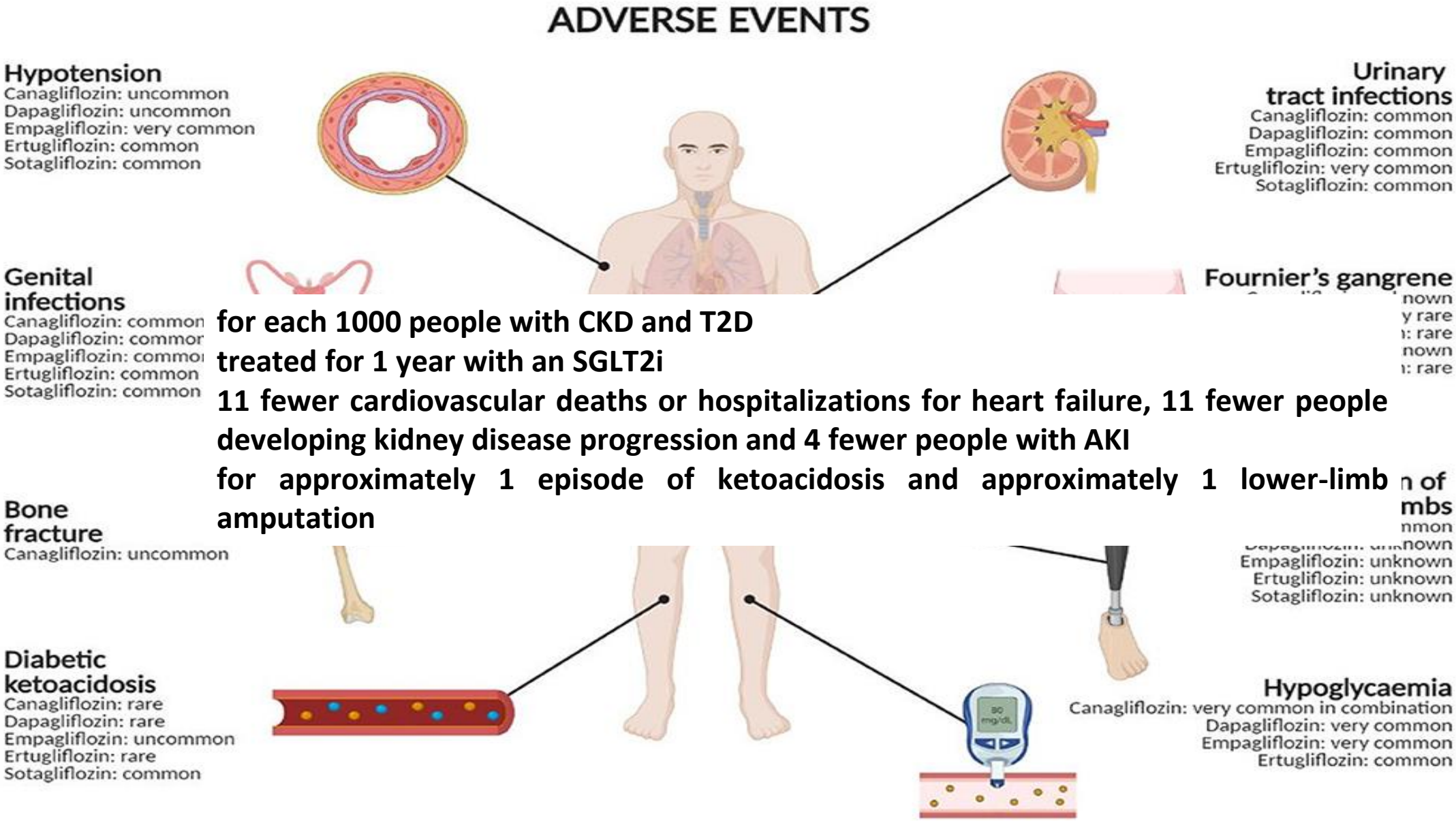
EMPEROR-Preserved: empagliflozin slowed the rate of decline in kidney function in people with HFpEF with or without T2D

Incidence of the composite kidney outcome in people treated with empagliflozin was similar to placebo

HR 0.95
(95% CI 0.73, 1.24)

time to first occurrence of (1) chronic dialysis (2) renal transplantation (3) sustained reduction of ≥40% in e GFR; or (4) sustained eGFR <15 mL/min/1.73 m2

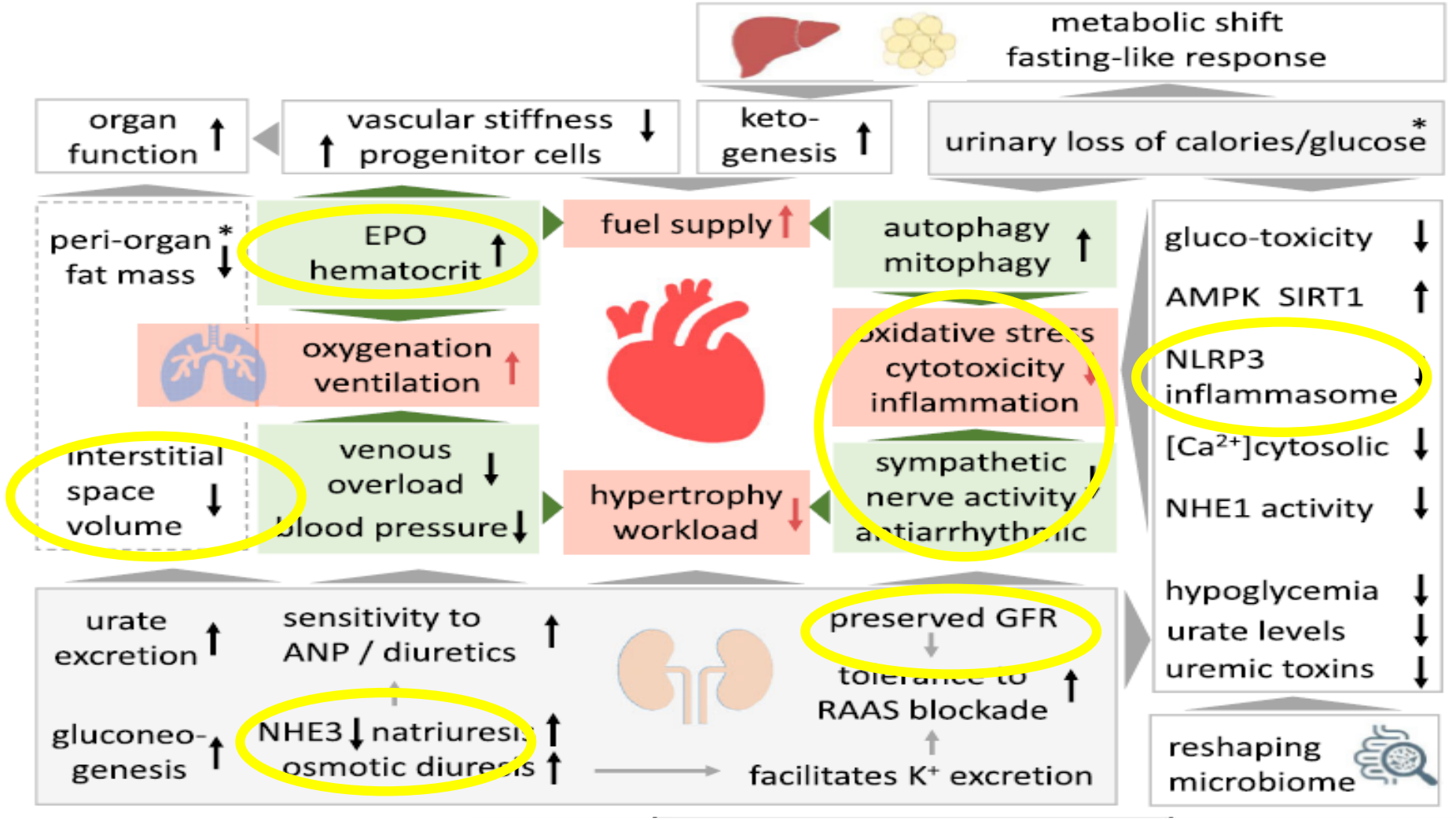
Incidence of acute kidney failure was similar between treatment arms



Massolo A et al. Front Card Med, 2023

How can inhibition of glucose and sodium transport in the early proximal tubule protect the cardiorenal system?

Volker Vallon , 2024



EMPOWER program kidney outcomes

	EMPA-REG OUTCOME[1–4] N=7020	EMPEROR-R[5,6] N=3730	EMPEROR-P[7] N=5988
Patient population	**T2D + high CV risk** 32% kidney disease	**HFrEF** 53% CKD	**HFpEF** 50% eGFR <60 ml/min/1.73 m^2
eGFR Mean, ml/min/1.73 m^2	74	62	61
UACR Median, mg/g	18	36/15 CKD/no CKD	NR
Kidney composite outcomes	Incident or worsening nephropathy, RRR vs Pbo ↓39%	Kidney composite†, RRR vs Pbo ↓50%	Kidney composite†, similar (HR vs Pbo 0.95)
eGFR Long-term kidney function, slope diff. to placebo ml/min/1.73 m^2	+1.68[11]	+1.73	+1.36
Kidney safety	AKI/acute kidney failure, reduced	Acute kidney failure, similar rate	Acute kidney failure, similar rate

Trials (ref)	Year of completion	SGLT2i	Patient population									SGLT2i vs. placebo group	HR (95%CI)
EMPA-REG OUTCOME [48]	2015	empagliflozin (10 or 25 mg)	T2DM and CVD									16.2% vs. 23.6%12.7% vs 18.8%1.5% vs. 2.6%0.3% vs. 0.6%	0.61 (0.55–0.69)0.6 (0.53–0.7)0.56 (0.3 0.79)0.45 (0.21–0.9
CANVAS [17]	2017	canagliflozin(100 or 300 mg)	T2D andhigh CVD risk									89.4 vs. 128.7per 1000 patient-years5.5 vs. 9.0	0.73 (0.67–0.79)0.6 (0.47–0.77)
DECLARE-TIMI58 [20]	2018	Dapagliflozin(10 mg)	T2DMand ≥ 1 CVDrisk factor									4.3% vs. 5.6%	0.76 (0.67–0.87)
CREDENCE [18]	2019	canagliflozin(100 mg)	T2DM and CKD									11.1% vs. 15.4%	0.70 (0.59–0.82)
VERTIS CV [80]	2019	ertugliflozin(5 or 15 mg)	T2D and established CVD									3.2% vs. 3.9%	0.81 (0.63–1.04)
EMPEROR reduced [50]	2020	empagliflozin(10 mg)	HF with reduced EF									1.6% s 3.1%–0.93 vs. –4.21 ml perminute per 1.73 m^2	0.50 (0.32–0.77) (95%CI –1.97–0.11) and(95% CI, –5.26 t –3.17)
EMPEROR – preserved [51]	2021	empagliflozin(10 mg)	HF with preserved EF										(–1.25 vs. –2.62 ml per minute per 1.73 m^2 per year
DAPA-CKD [35]	2020	dapagliflozin(10 mg)	CKD (T2D and non-diabetics									9.2% vs. 14.5%6.6% vs. 11.3%	0.61 (0.51 –0.72)0.5 (0.45–0.68)
EMPA-KIDNEY [58]	2022	Empagliflozin(10 mg)	CKD (T2D and non-diabetics)	6609	2.0 years	37.5 ± 14.8	412 (94–1190)	hospitalization for HF or cardiovascular death	4.0% vs. 4.6%	0.84 (0.67–1.07)	ESKD, a sustained decline in eGFR to < 10 mL/min/1.73m^2, renal death, or a sustained decline of ≥ 40% in eGFR from randomization) or (ii) Cardiovascular death	13.1% vs. 16.9%	0.72 (0.64–0.82)

Table 2. Primary and Secondary Outcomes and Adverse Events of Special Interest.*

Outcome	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no./total no. (%)	*events/100 patient-yr*	*no./total no. (%)*	*events/100 patient-yr*		
Primary outcome						
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	7.5	0.61 (0.51–0.72)	<0.001
Decline in estimated GFR of ≥50%	112/2152 (5.2)	2.6	201/2152 (9.3)	4.8	0.53 (0.42–0.67)	NA
End-stage kidney disease	109/2152 (5.1)	2.5	161/2152 (7.5)	3.8	0.64 (0.50–0.82)	NA
Estimated GFR of <15 ml/min/1.73 m^2	84/2152 (3.9)	1.9	120/2152 (5.6)	2.8	0.67 (0.51–0.88)	NA
Long-term dialysis†	68/2152 (3.2)	1.5	99/2152 (4.6)	2.2	0.66 (0.48–0.90)	NA
Kidney transplantation†	3/2152 (0.1)	0.1	8/2152 (0.4)	0.2	—	NA
Death from renal causes	2/2152 (<0.1)	0.0	6/2152 (0.3)	0.1	—	NA
Death from cardiovascular causes	65/2152 (3.0)	1.4	80/2152 (3.7)	1.7	0.81 (0.58–1.12)	NA
Secondary outcomes						
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal causes	142/2152 (6.6)	3.3	243/2152 (11.3)	5.8	0.56 (0.45–0.68)	<0.001
Composite of death from cardiovascular causes or hospitalization for heart failure	100/2152 (4.6)	2.2	138/2152 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any cause	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	0.69 (0.53–0.88)	0.004
Safety outcomes‡						
Discontinuation of regimen due to adverse event	118/2149 (5.5)	—	123/2149 (5.7)	—	—	0.79
Any serious adverse event	633/2149 (29.5)	—	729/2149 (33.9)	—	—	0.002
Adverse events of interest						
Amputation§	35/2149 (1.6)	—	39/2149 (1.8)	—	—	0.73
Any definite or probable diabetic ketoacidosis	0/2149	—	2/2149 (<0.1)	—	—	0.50
Fracture¶	85/2149 (4.0)	—	69/2149 (3.2)	—	—	0.22
Renal-related adverse event¶	155/2149 (7.2)	—	188/2149 (8.7)	—	—	0.07
Major hypoglycemia‖	14/2149 (0.7)	—	28/2149 (1.3)	—	—	0.04
Volume depletion¶	127/2149 (5.9)	—	90/2149 (4.2)	—	—	0.01

Kidney Medicine

Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors and CKD: Are You a #Flozinator?

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