SGLT2i: Σε ποιόν ασθενή?

Α Κόλλιας
Καθηγητής Παθολογίας

Γ' Παθολογική Κλινική, ΕΚΠΑ
ΓΝΝΘΑ 'Η Σωτηρία', Αθήνα

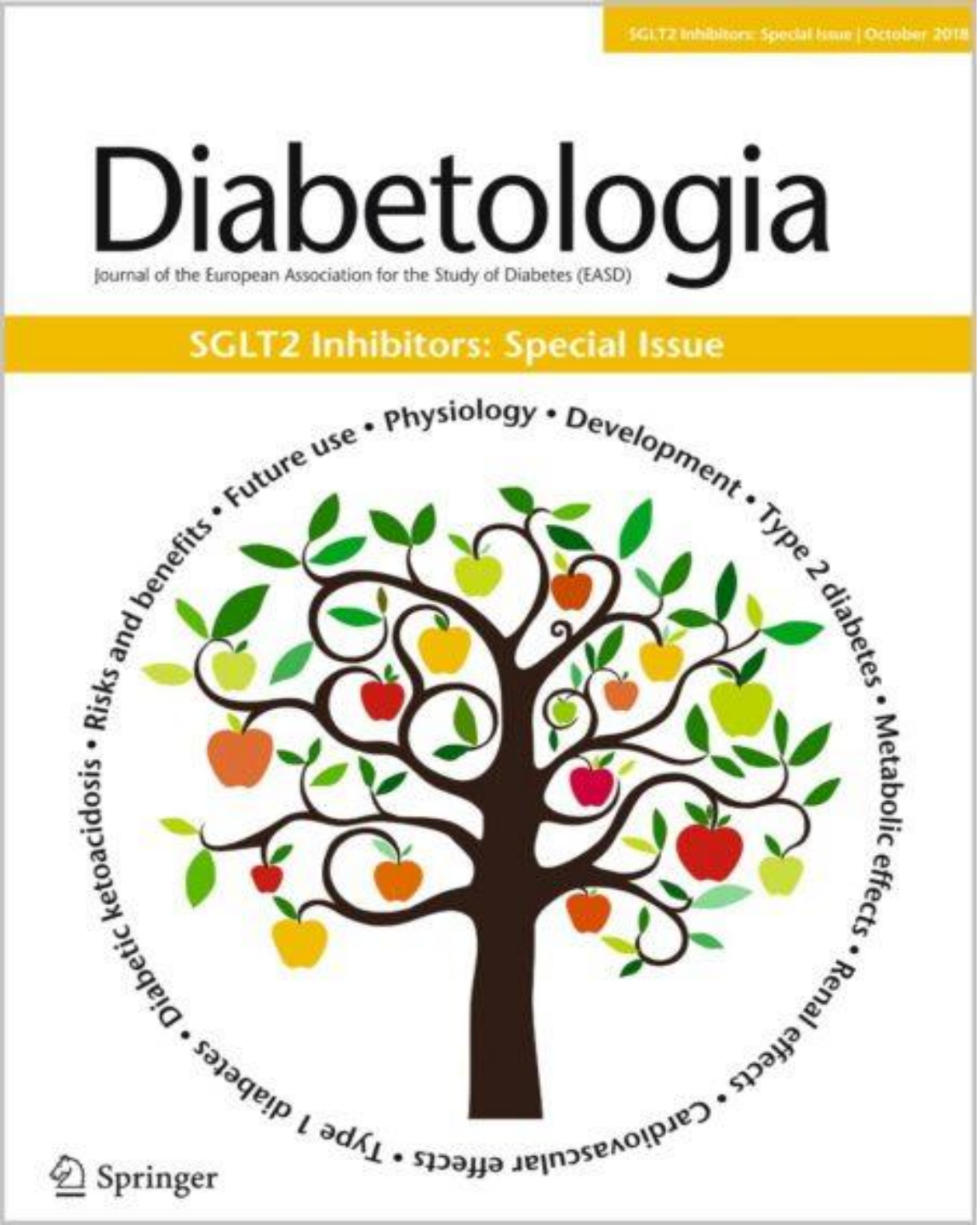
ΔΗΛΩΣΗ ΣΥΓΚΡΟΥΣΗΣ ΣΥΜΦΕΡΟΝΤΩΝ

Για την παρούσα παρουσίαση καμία

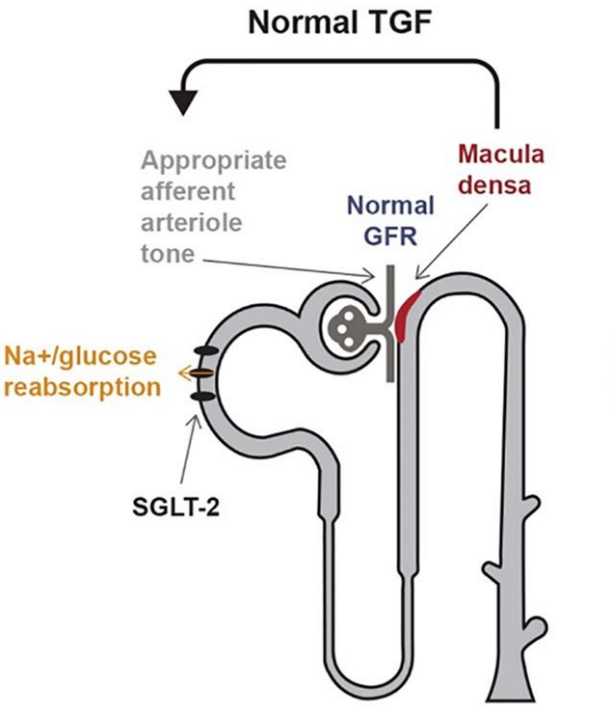
Ο ομιλητής στο παρελθόν έχει λάβει τιμητικές αμοιβές από
ELPEN, Libytec, Menarini, Rafarm, Sanofi, Servier, Uni-Pharma, Velka

SGLT2i: ΕΝΔΕΙΞΕΙΣ

- ✓ Εισαγωγή
- ✓ Σακχ. Διαβήτης 2
- ✓ Καρδιακή Ανεπάρκεια
- ✓ Χρόνια Νεφρική Ανεπάρκεια
- ✓ Πρακτικά Θέματα



- 1835 φλοριζίνη
- 1987 αντιδιαβητική δράση σε αρουραίους
- 1996 ανάπτυξη συνθετικών αναλόγων
- 2012-2017 εγκρίσεις για κανα-, νταπα-, εμπα-γλιφλοζίνη



Normal physiology

DiabetesObes Metab. 2020;22:16-29.

If you show two consecutive slides with the glomerulus, you risk to lose half your audience…

Barry M. Brenner, M.D. Professor Emeritus
Renal Division, Brigham and Women's Hospital, Boston, MA, USA

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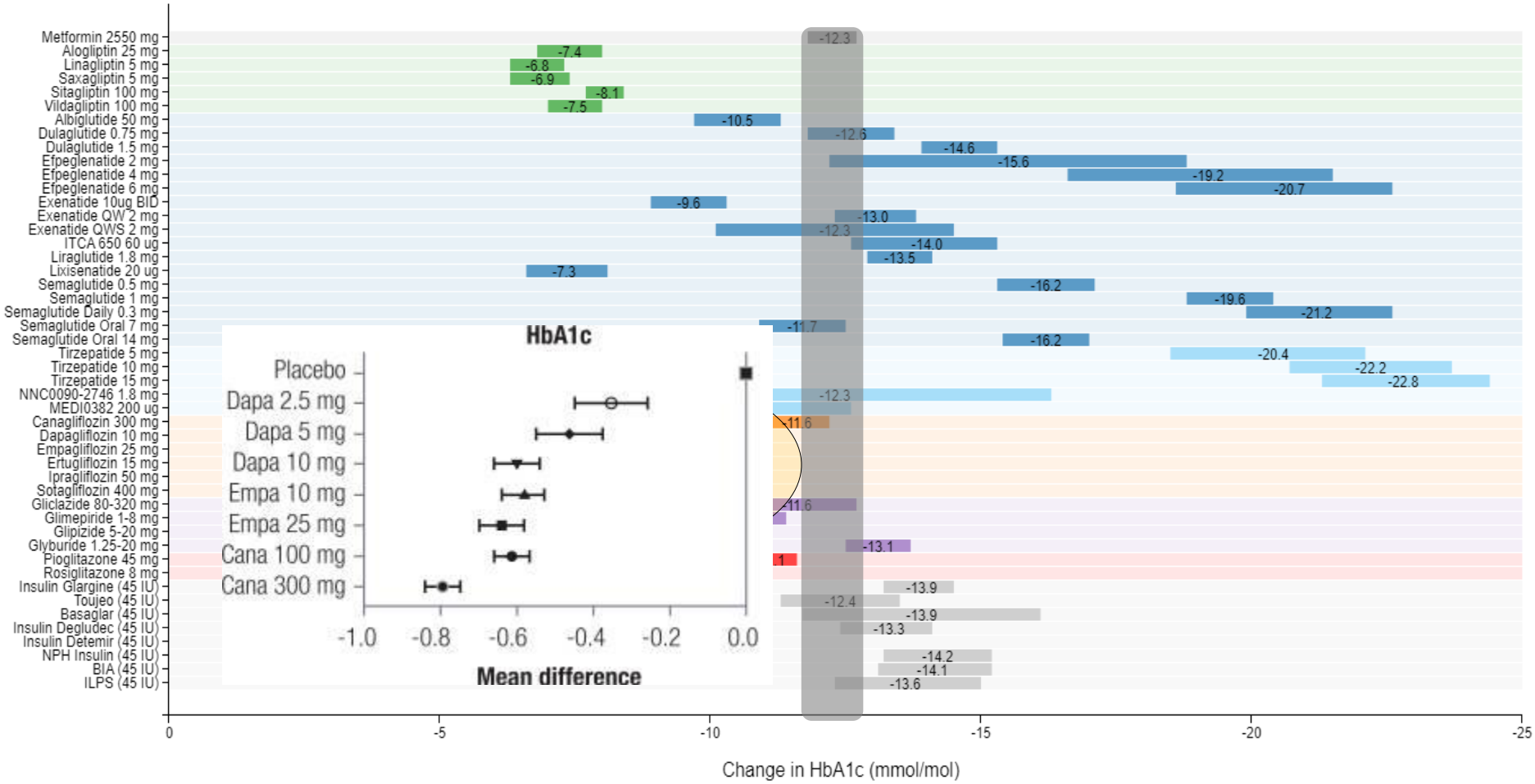
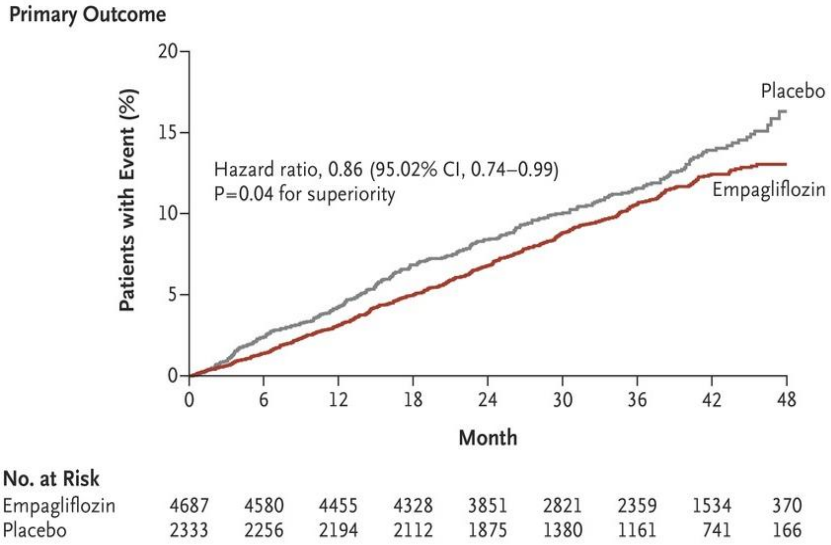
Αντιδιαβητική δράση SGLT2i



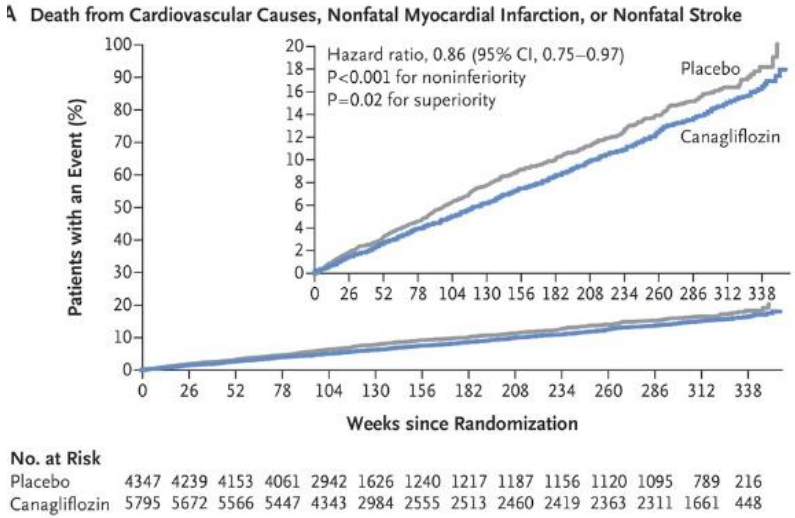
https://www.comparediabetesdrugs.com/cv/
Arch Endocrinol Metab 2022;66:68-76

EMPA-REG OUTCOME Trial



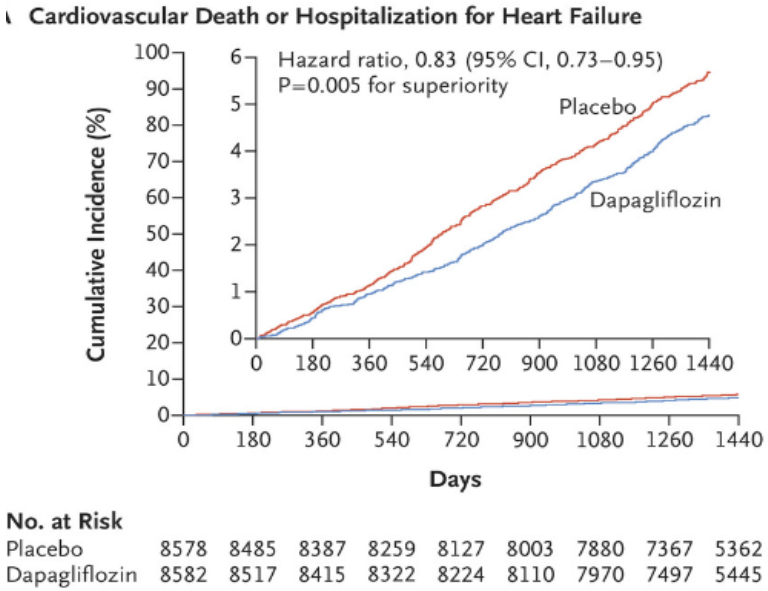
N Engl J Med 2015; 373:2117-2128

CANVAS Program



N Engl J Med 2017; 377:644-657

DECLARE-TIMI Trial



N Engl J Med 2019; 380:347-357

American Diabetes Association.

Management Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/OR** SGLT2i§ with proven CVD benefit

If HbA_{1c} above target

- For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m^2 OR albuminuria (ACR ≥3.0 mg/mmol [30mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If HbA_{1c} above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If HbA_{1c} above target

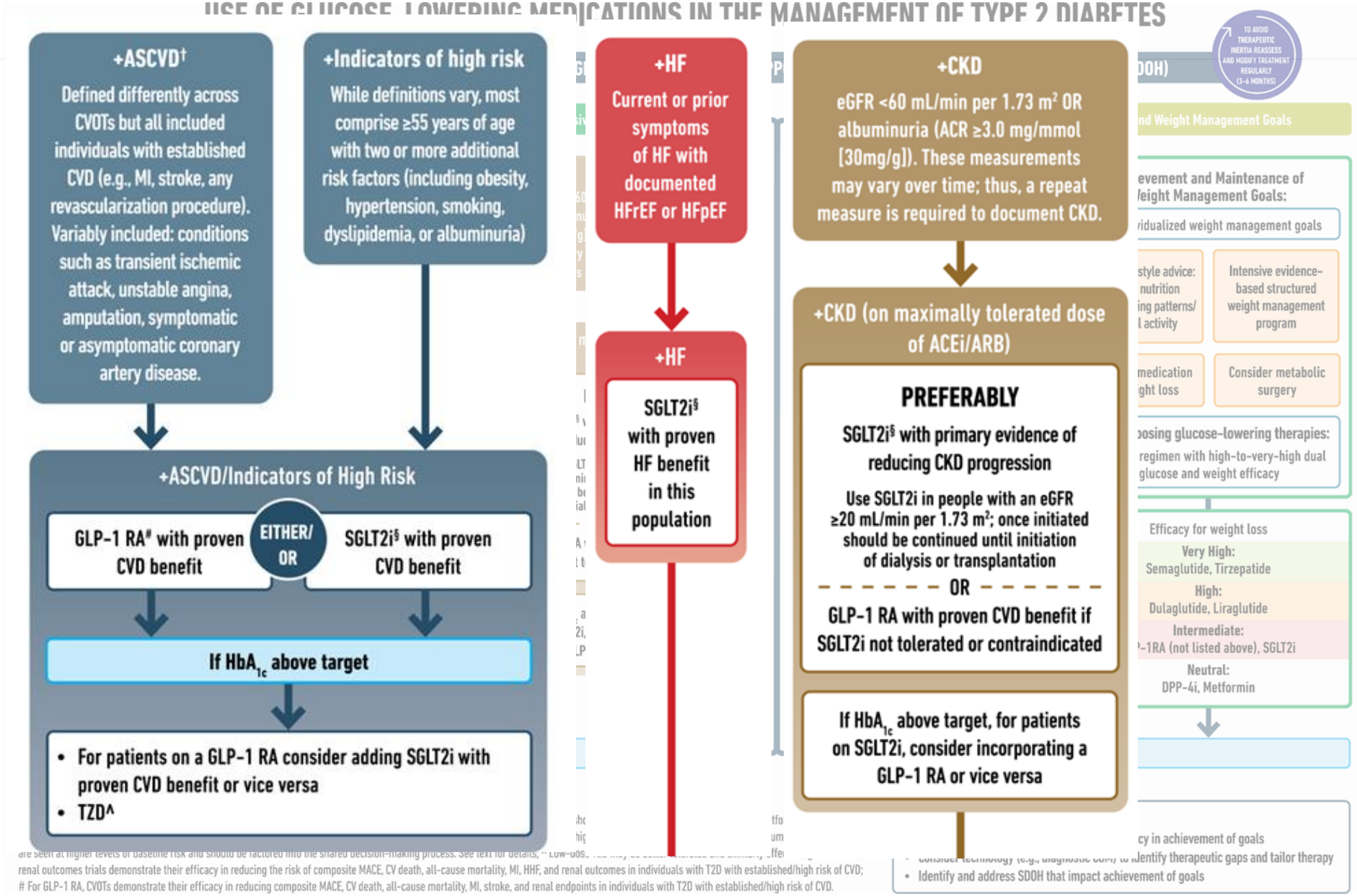
Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Diabetes Care. 2022;45:2753-2786.

Management Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

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- ✓ Εισαγωγή
- ✓ Σακχ. Διαβήτης 2
- ✓ **Καρδιακή Ανεπάρκεια**
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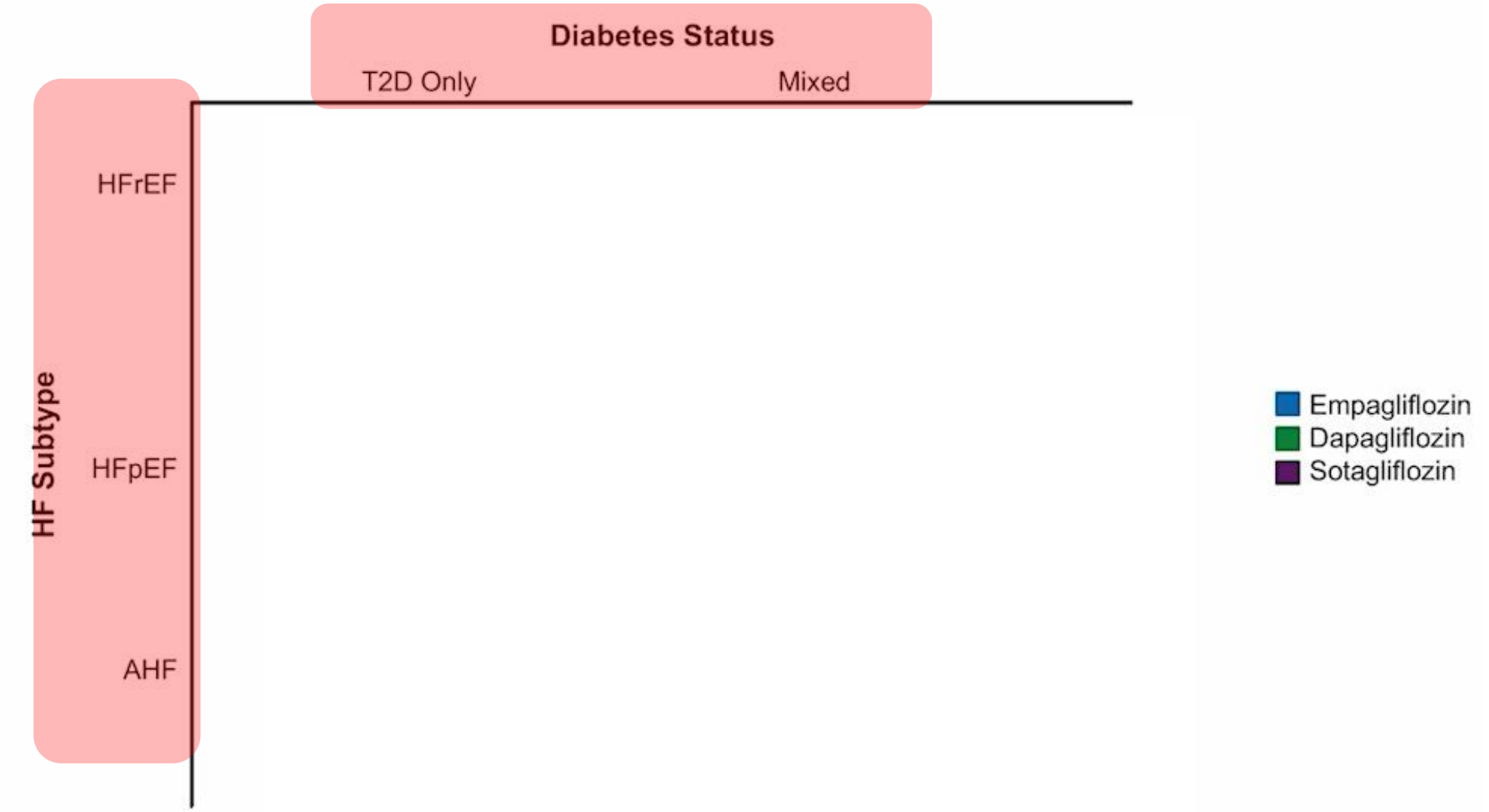
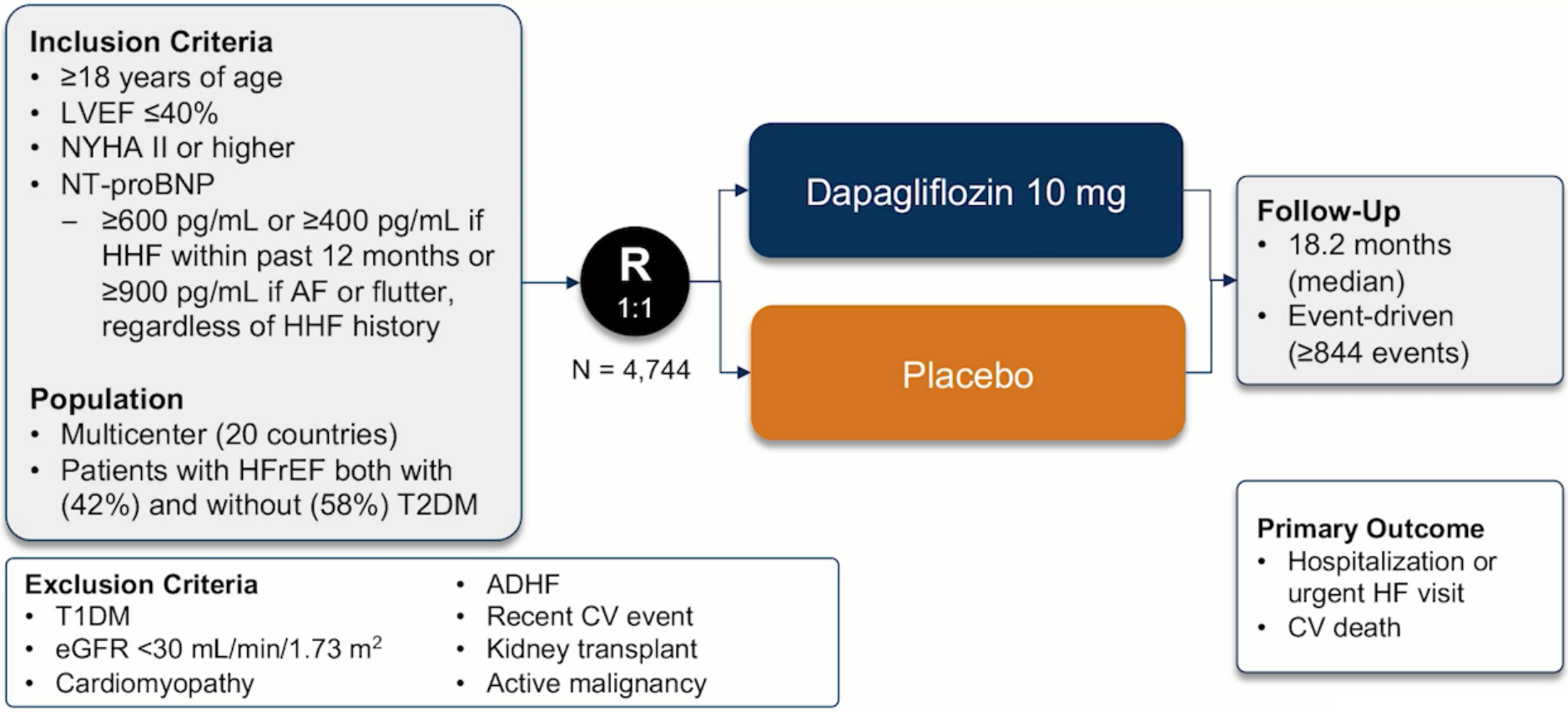
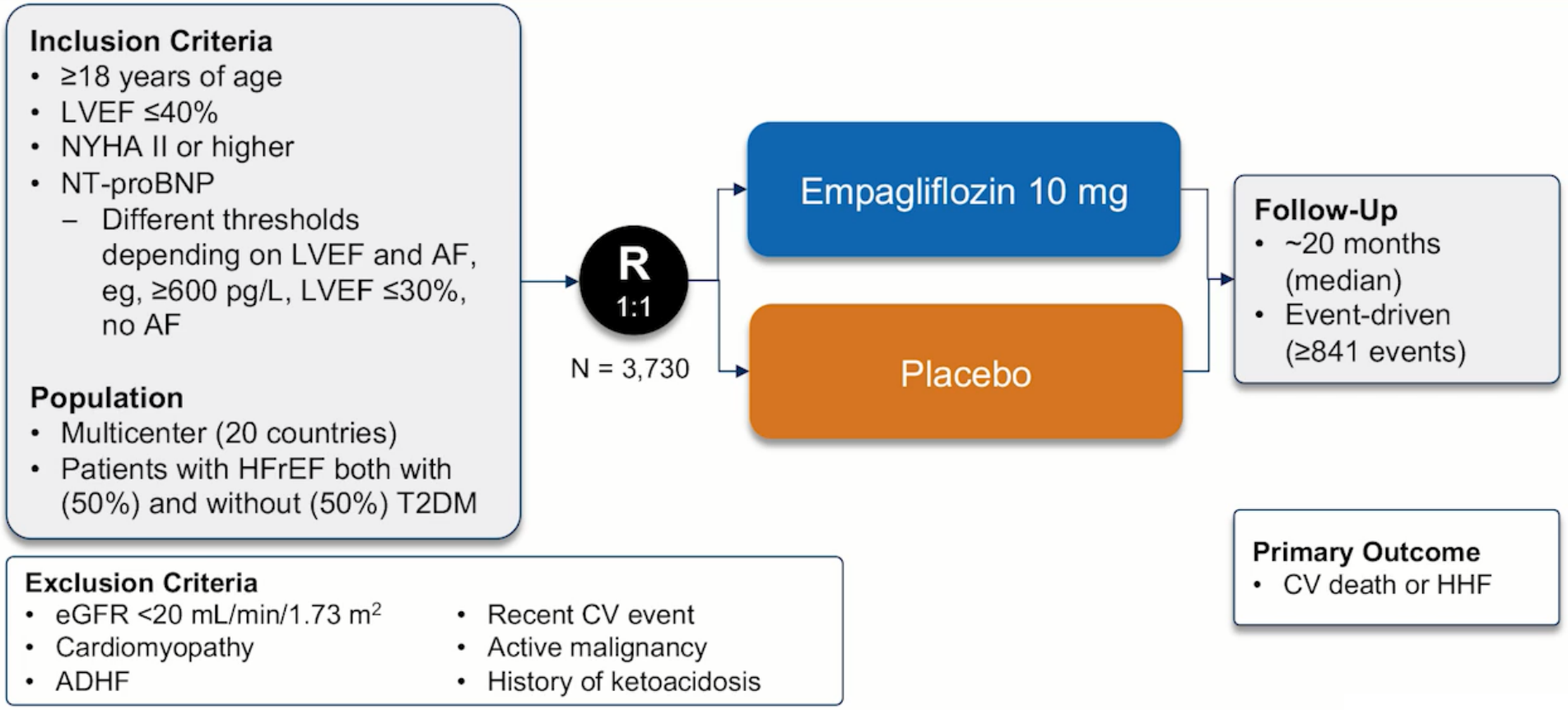

Diabetes Status
T2D Only
Mixed
HF Subtype
HFrEF
HFpEF
AHF
Empagliflozin
Dapagliflozin
Sotagliflozin

DAPA-HF



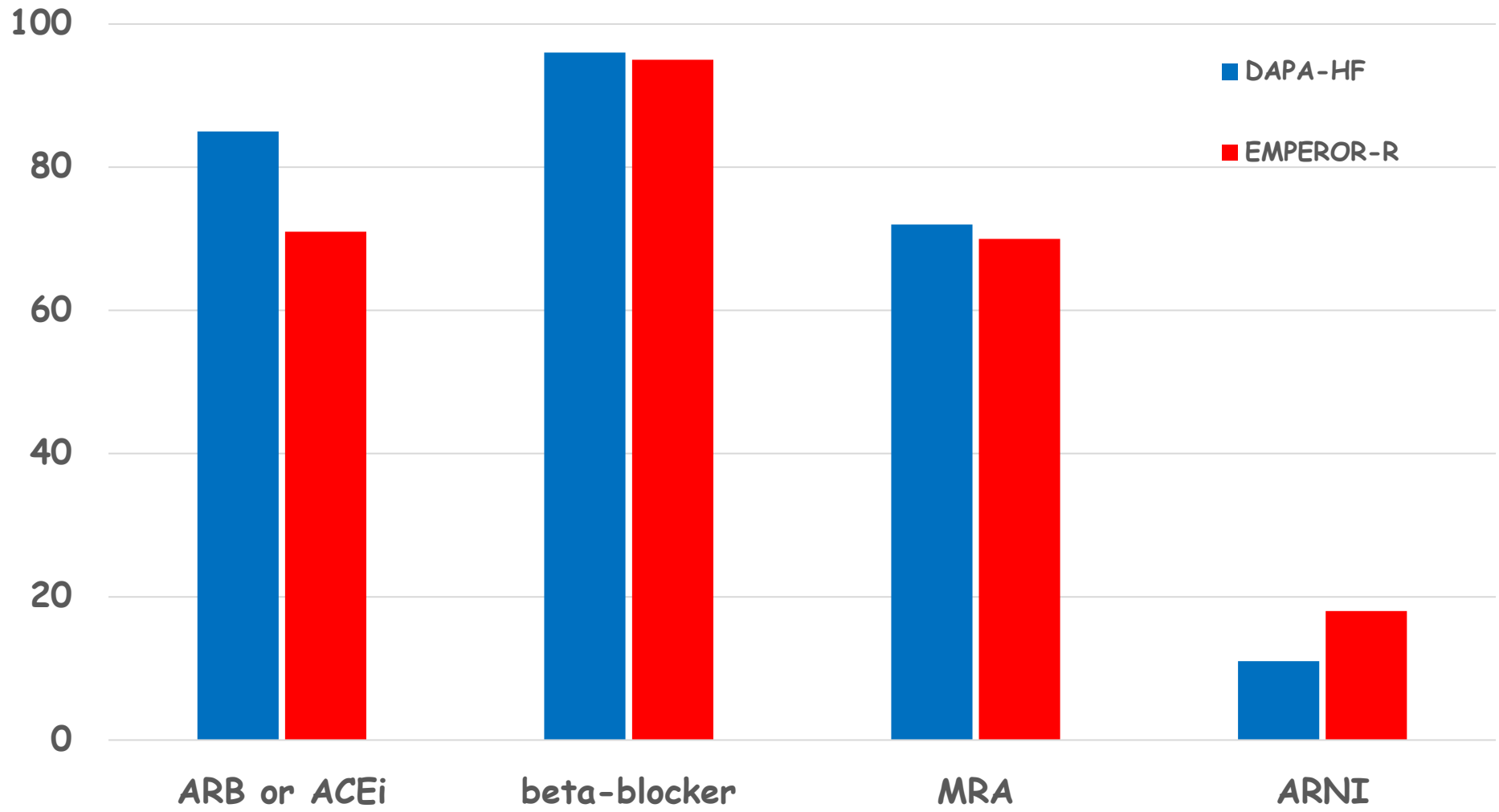
1. McMurray JJV et al. *Eur J Heart Fail*. 2019;21:665-675. 2. McMurray JJV et al. *Eur J Heart Fail*. 2019;21:1402-1411.
3. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008.

EMPEROR-Reduced



1. Packer M et al. *Eur J Heart Fail*. 2019;21:1270-1278. 2. Packer M et al. *N Engl J Med*. 2020;383:1413-1424.

HFrEF Υποκείμενη Θεραπεία



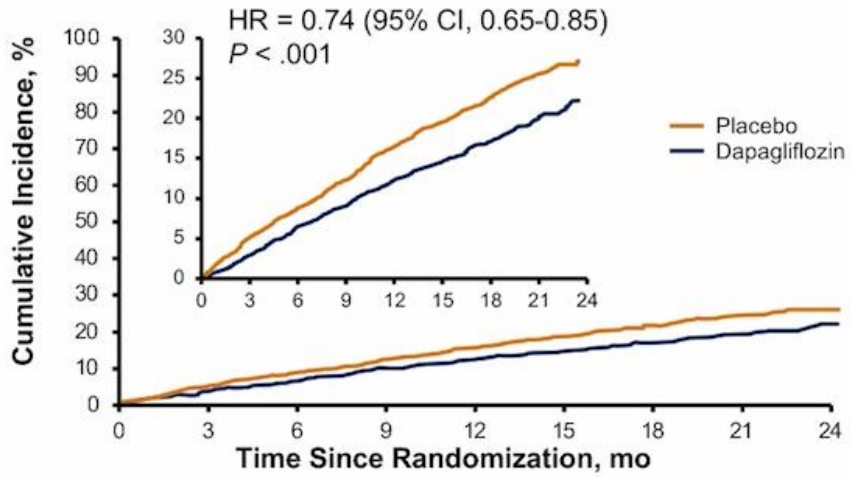
N Engl J Med 2019;381:1995-2008

N Engl J Med 2020;383:1413-1424

SGLT2i in HFrEF: Composite Endpoint

DAPA-HF

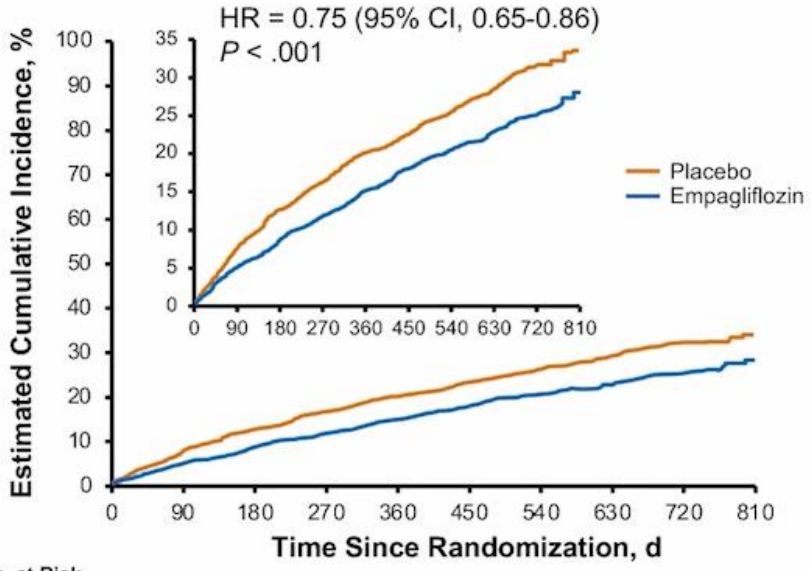
CV Death, HHF, Urgent HF Visit



No. at Risk									
Placebo	2,371	2,258	2,163	2,075	1,917	1,478	1,096	593	210
Dapagliflozin	2,373	2,305	2,221	2,147	2,002	1,560	1,146	612	210

EMPEROR-Reduced

CV Death, HHF



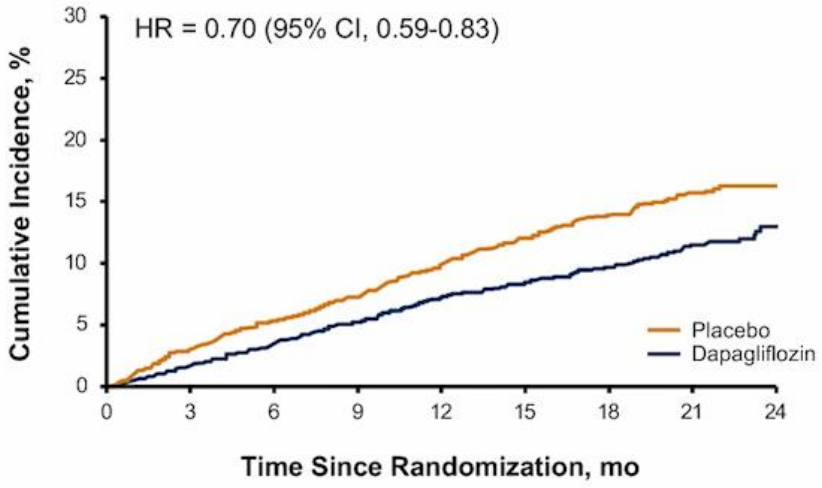
No. at Risk										
Placebo	1,867	1,715	1,612	1,345	1,108	854	611	410	224	109
Empagliflozin	1,863	1,763	1,677	1,424	1,172	909	645	423	231	101

N Engl J Med 2019;381:1995-2008

N Engl J Med 2020;383:1413-1424

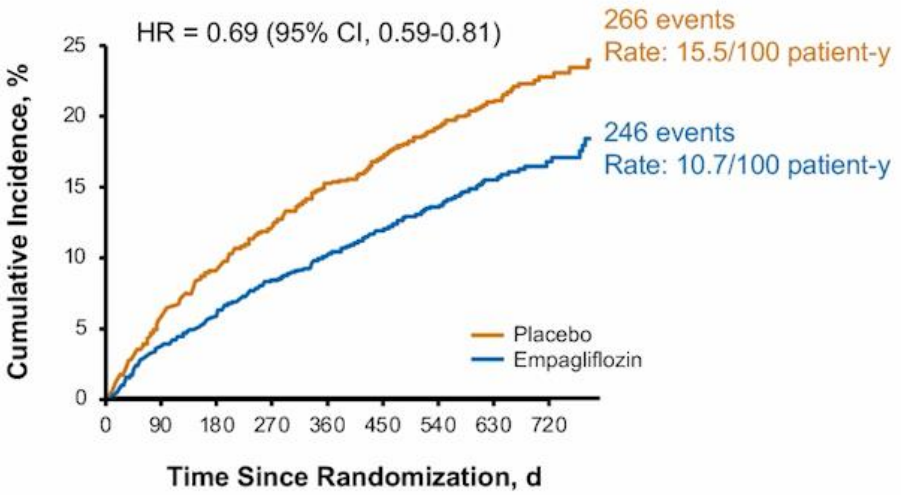
SGLT2i in HFrEF: Hospitalization for HF

DAPA-HF



No. at Risk									
Placebo	2,371	2,330	2,279	2,231	2,092	1,638	1,221	665	235
Dapagliflozin	2,373	2,342	2,296	2,251	2,130	1,666	1,243	672	233

EMPEROR-Reduced



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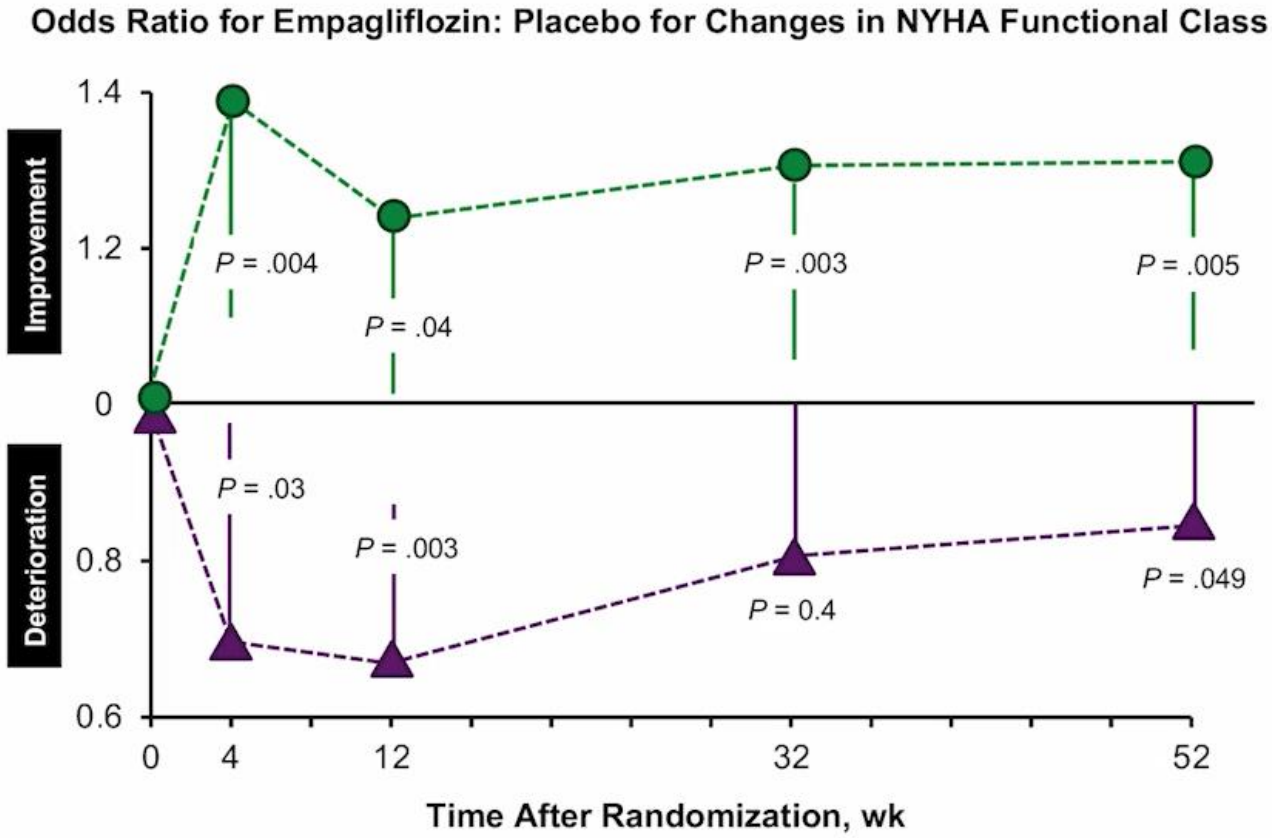
N Engl J Med 2019;381:1995-2008

N Engl J Med 2020;383:1413-1424

EMPEROR-Reduced: Empagliflozin Significantly Improved NYHA Functional Class in HFrEF[1]



Packer M et al. *Circulation*. 2021;143:326-336.

Επιδημιολογία HF

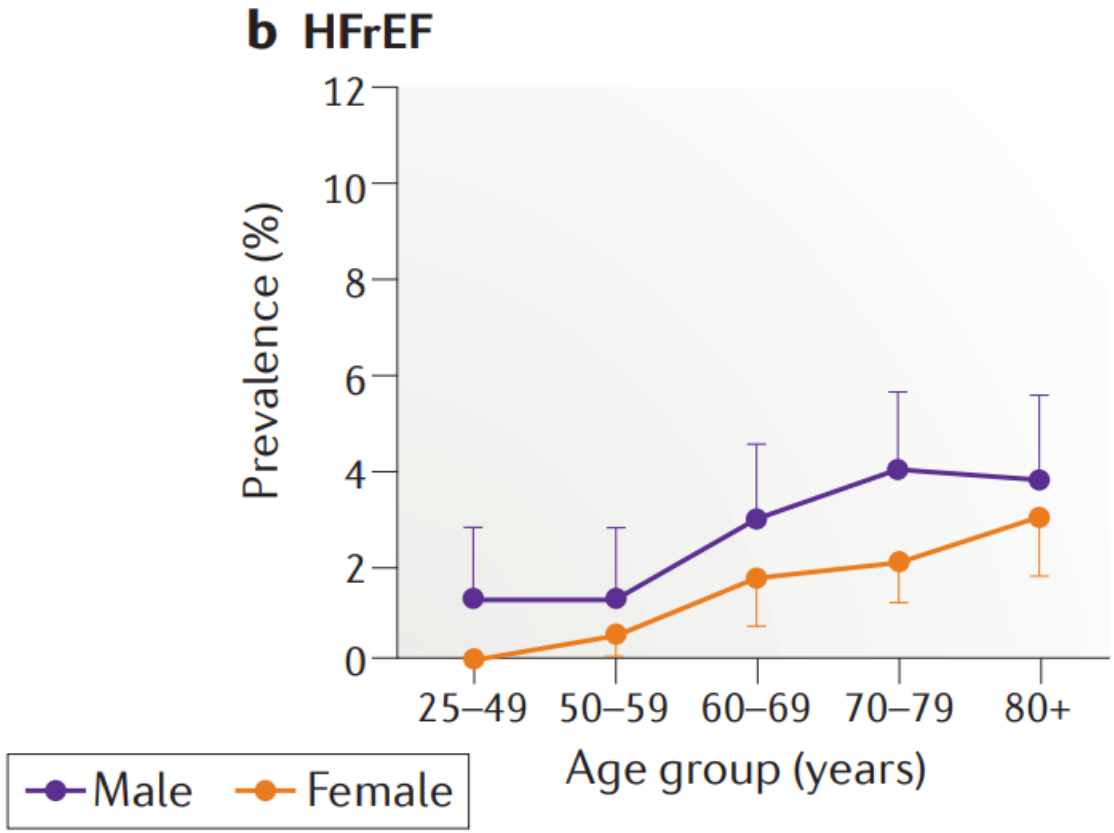
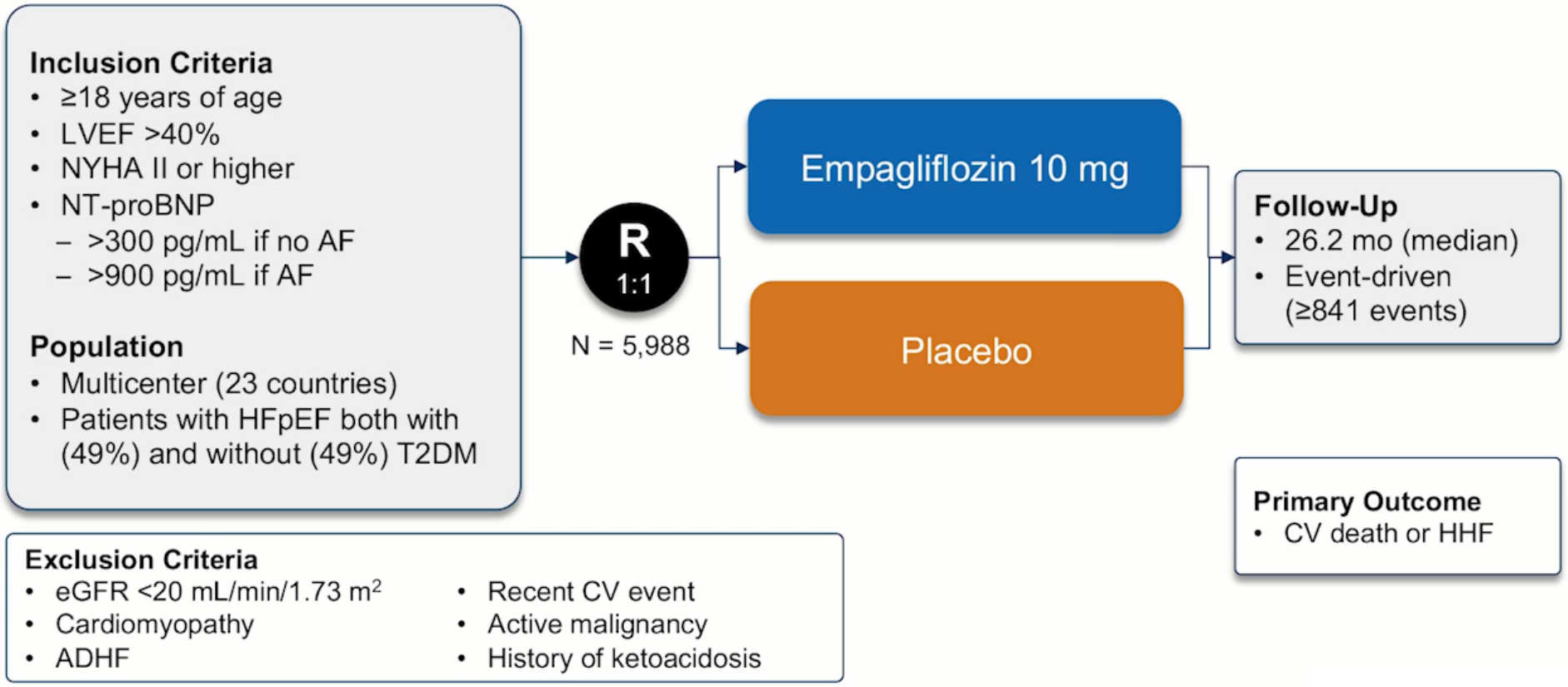


Figure 4 | **Prevalence of HFpEF and HFrEF by age and sex in a southwest European community-based cohort. a** | The prevalence of heart failure with preserved ejection

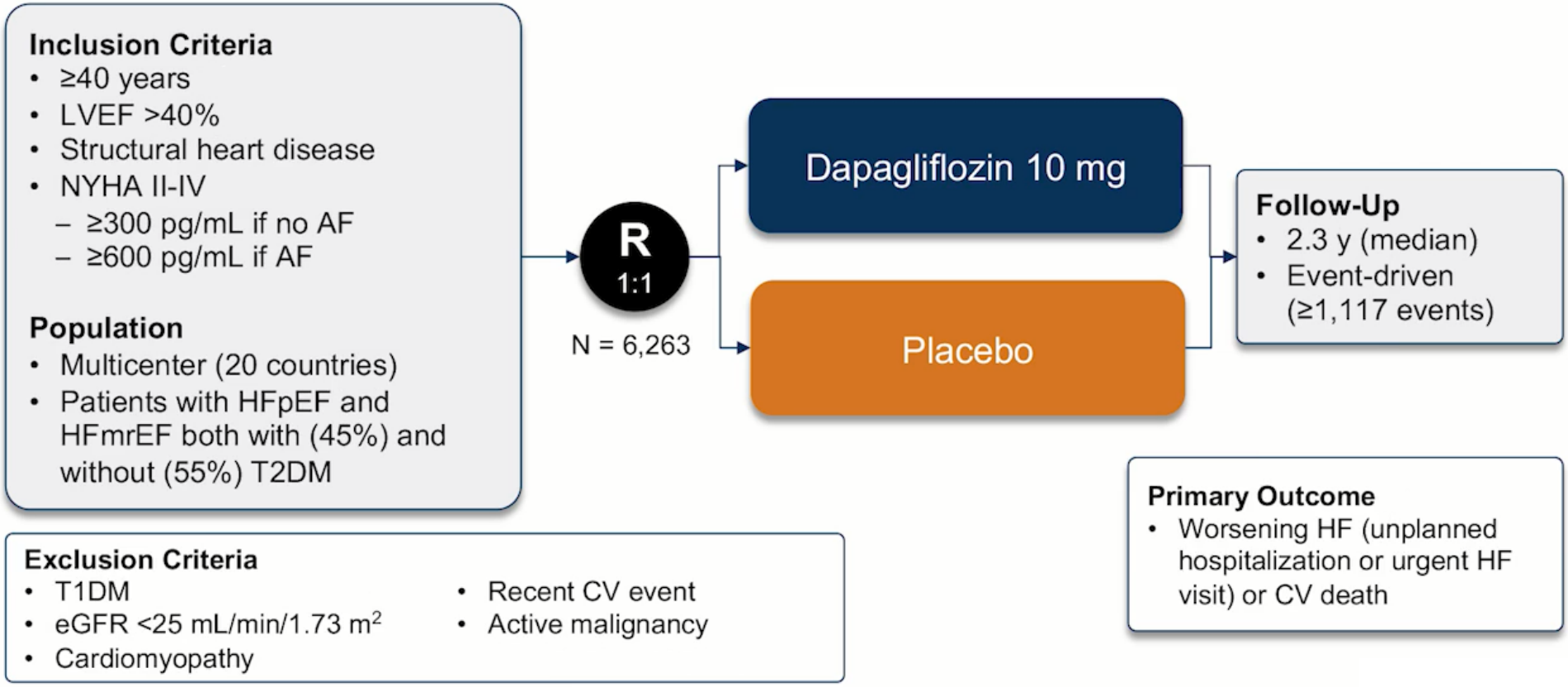
Nat Rev Cardiol. 2017;14:591-602.

EMPEROR-Preserved



1. Anker SD et al. *Eur J Heart Fail*. 2019;21:1279-1287. 2. Anker SD et al. *N Engl J Med*. 2021;385:1451-1461.

DELIVER

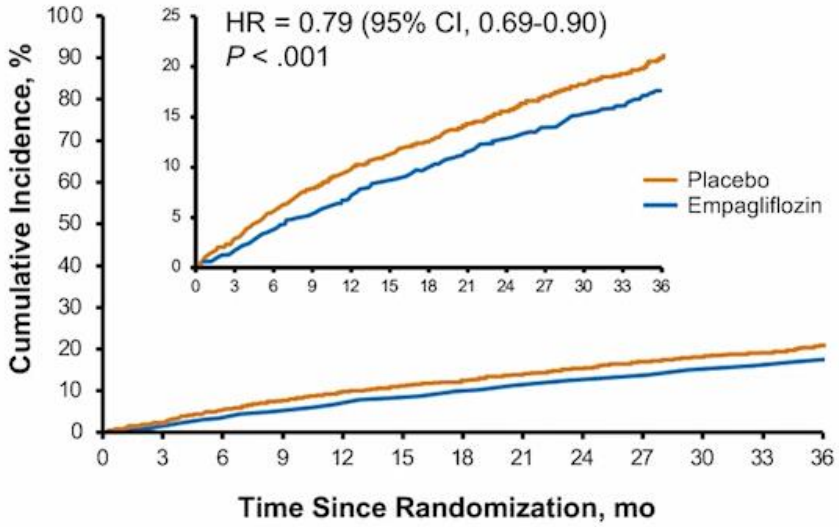


1. Solomon SD et al. *Eur J Heart Fail*. 2021;23:1217-1225. 2. Solomon S et al. *N Engl J Med*. 2022;387:1089-1098.

SGLT2i in HFpEF: Composite Endpoint

EMPEROR-Preserved

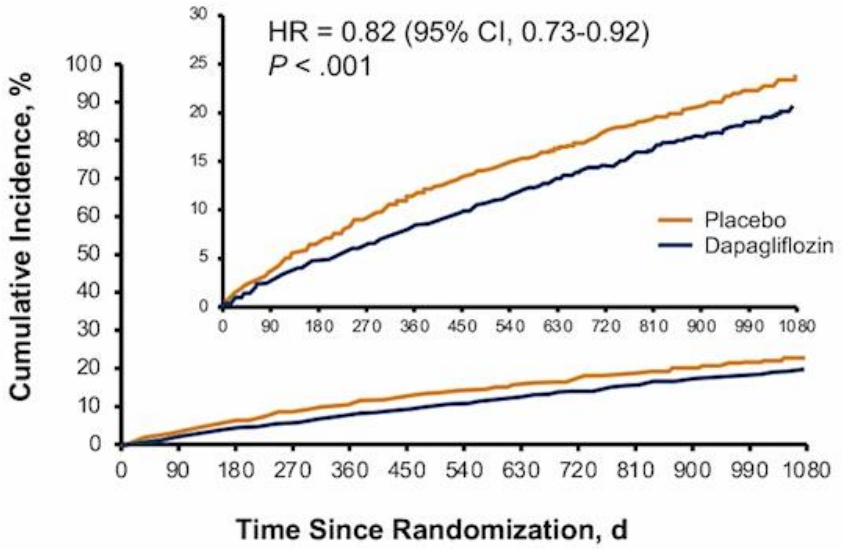
CV Death or HHF



No. at Risk													
Placebo	2,991	2,888	2,786	2,706	2,627	2,424	2,066	1,821	1,534	1,278	961	681	400
Empagliflozin	2,997	2,928	2,843	2,780	2,708	2,491	2,134	1,858	1,578	1,332	1,005	709	402

DELIVER

CV Death, HHF, or Urgent HF Visit

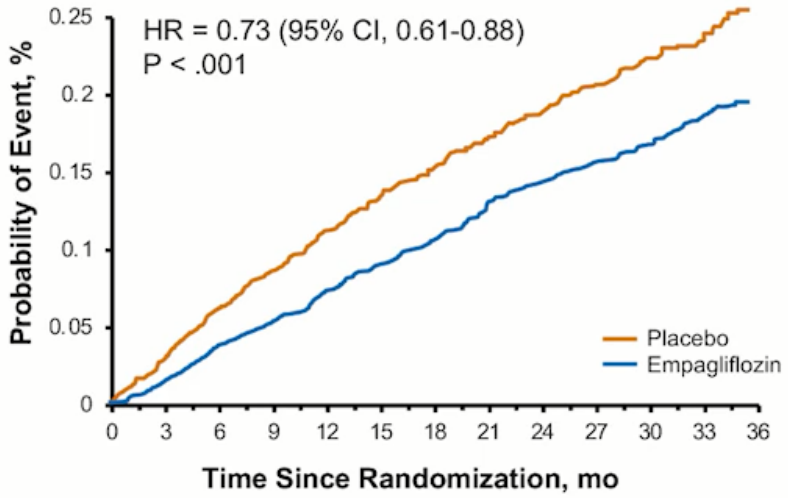


No. at Risk													
Placebo	3,132	3,007	2,896	2,799	2,710	2,608	2,318	2,080	1,923	1,554	1,140	772	383
Dapagliflozin	3,131	3,040	2,949	2,885	2,807	2,716	2,401	2,147	1,982	1,603	1,181	801	389

1. Anker SD et al. *N Engl J Med*. 2021;385:1451-1461. 2. Solomon S et al. *N Engl J Med*. 2022;387:1089-1098.

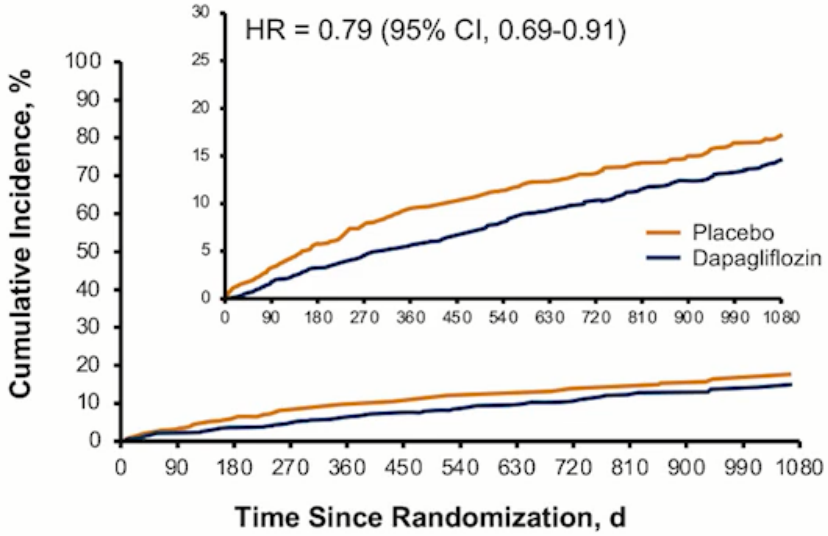
SGLT2i in HFpEF: Hospitalization for HF

EMPEROR-Preserved



No. at Risk													
Placebo	2,991	2,945	2,901	2,855	2,816	2,618	2,258	1,998	1,695	1,414	1,061	747	448
Empagliflozin	2,997	2,962	2,913	2,869	2,817	2,604	2,247	1,977	1,684	1,429	1,081	765	446

DELIVER



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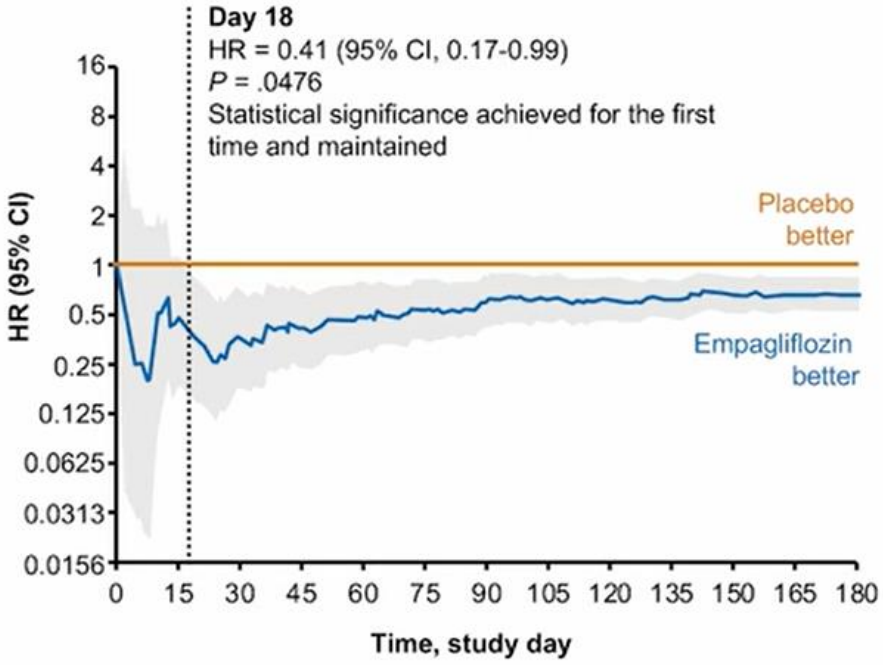
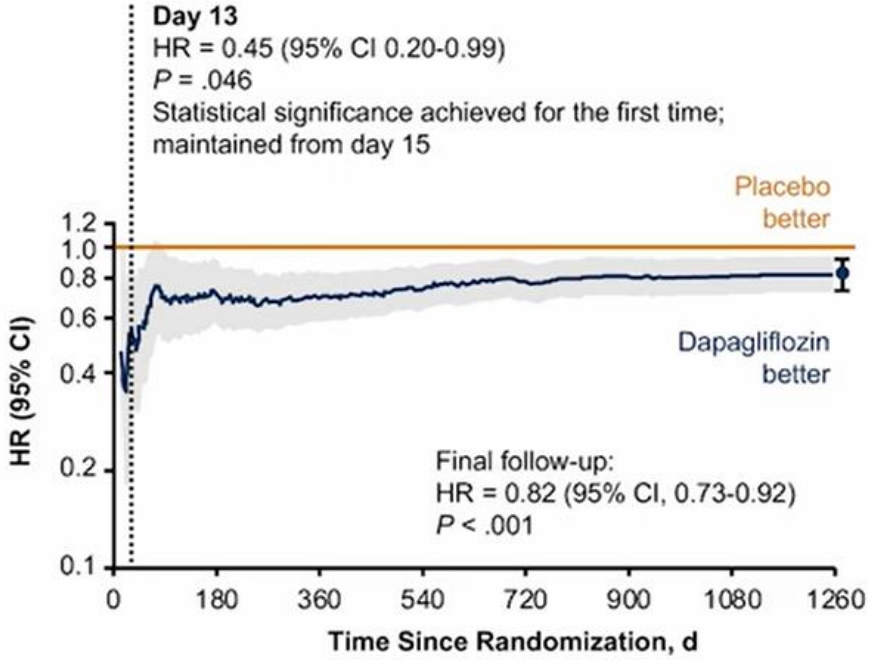
Time to CV Death or HF Hospitalization

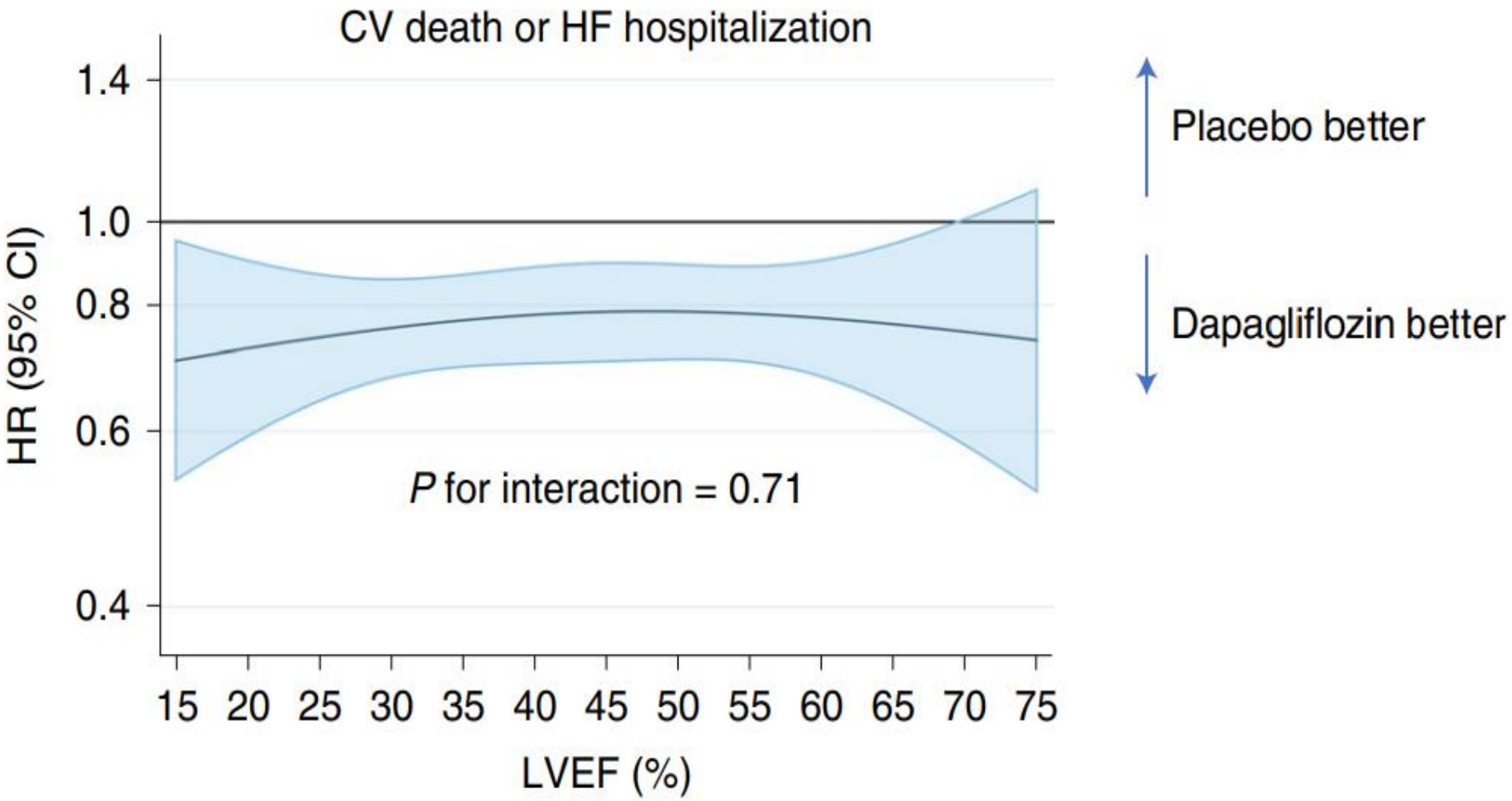
EMPEROR-Preserved



DELIVER



1. Butler J et al. *Eur J Heart Fail.* 2022;24:245-248. 2. Vaduganathan M et al. *JAMA Cardiol.* 2022 Oct 3. Online ahead of print.



Nat Med 2022;28:1956-1964

Empagliflozin and Dapagliflozin: Safe as Placebo in HFpEF Except for Increase in Minor Genital Mycotic Infections[1,2,a]

EMPEROR-Preserved

Events, %	Empagliflozin (n = 2,996)	Placebo (n = 2,989)
Patients with any AE	85.9	86.5
Patients with any serious AE	47.9	51.6
Acute renal failure	12.1	12.8
Any hypotension	10.4	8.6
Any UTI	9.9	8.1
Symptomatic hypotension	6.6	5.2
Hepatic injury	3.8	5.2

DELIVER

Events, %	Dapagliflozin (n = 3,131)	Placebo (n = 3,132)
Patients with any serious AE	43.5	45.5
Any AE increasing risk for LLA	6.0	6.4
Cardiac failure	8.4	11.0
COVID-19	5.3	4.2

Genital infections occurred in 2.2% of patients in the empagliflozin group and 0.7% of patients in the placebo group, with equal numbers of complicated infections in each group (0.3% vs 0.3%)

[a] Selected adverse events affecting ≥5% of patients in either treatment group.

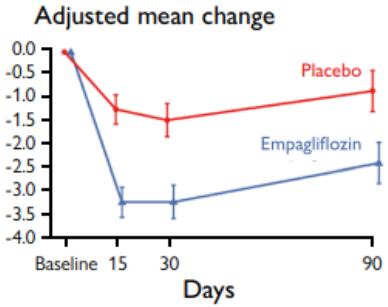
1. Anker SD et al. *N Engl J Med*. 2021;385:1451-1461. 2. Solomon S et al. *N Engl J Med*. 2022;387:1089-1098.

ESC European Society of Cardiology
European Heart Journal (2023) **44**, 41–50
https://doi.org/10.1093/eurheartj/ehac530

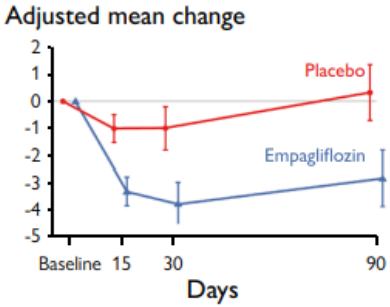
Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial

Treatment effect

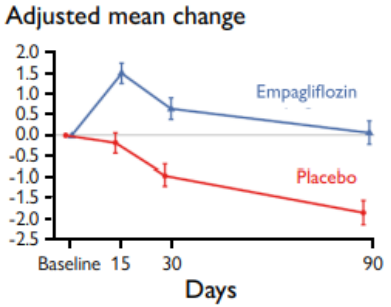
Body weight (kg)



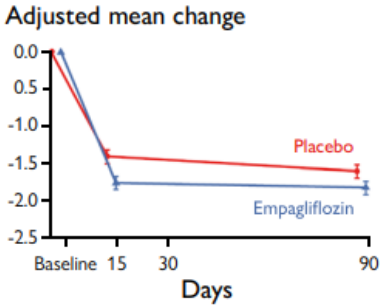
Body weight per mean daily loop diuretic dose*



Haemoconcentration†



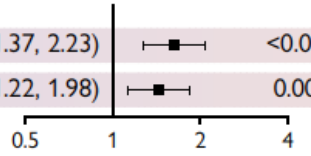
Clinical congestion score‡



Clinical benefit at day 90§

Body weight change

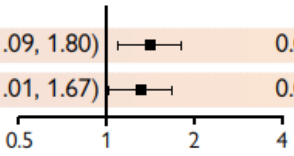
	N analysed: Weight reduction ≤ overall median	N analysed: Weight reduction > overall median	Win ratio (95% CI)	2-sided *p*-value
At day 15	234	220	1.75 (1.37, 2.23)	<0.0001
At day 30	228	223	1.55 (1.22, 1.98)	0.0004



Favours weight reduction ≤ overall median
Favours weight reduction > overall median

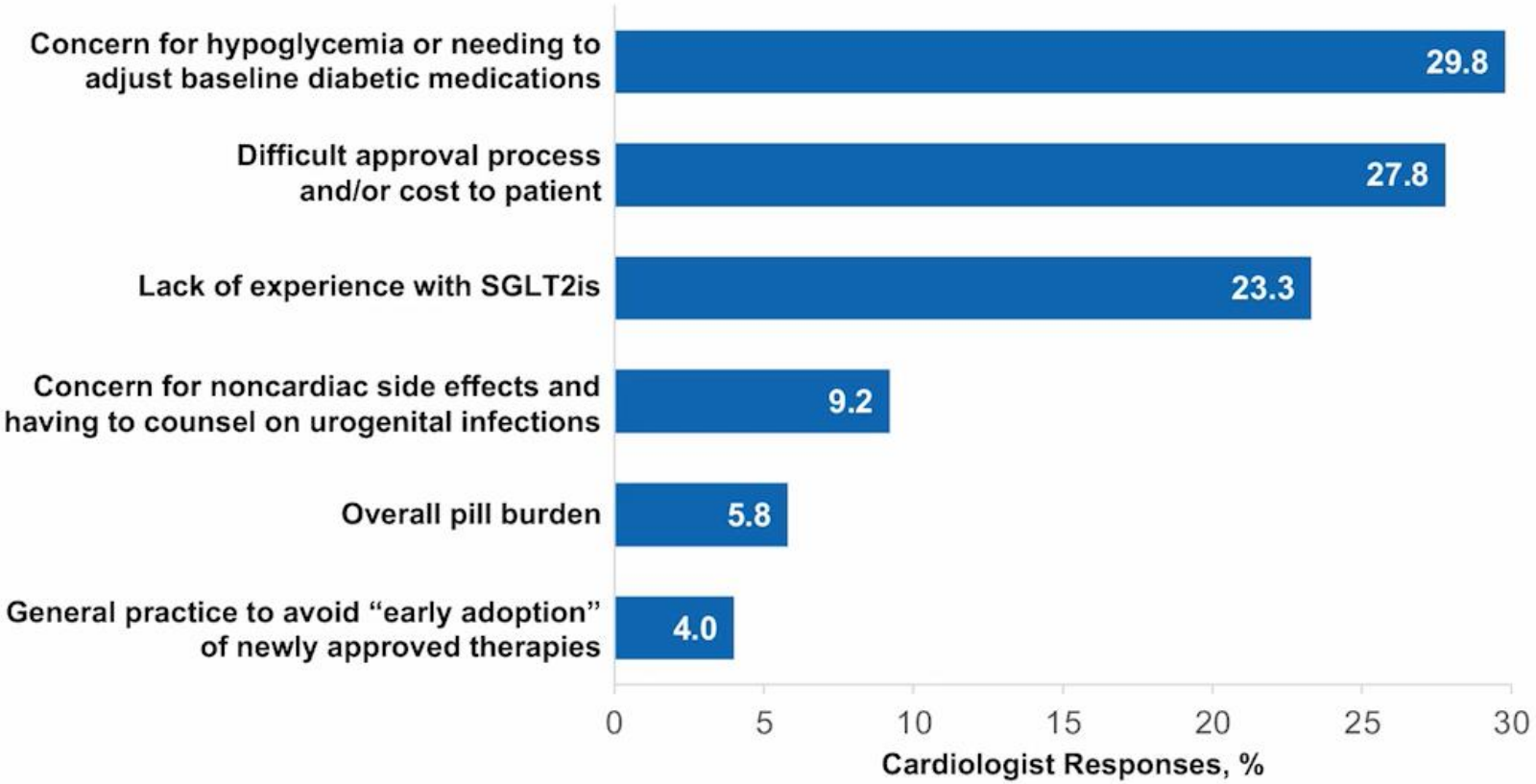
Haematocrit change

	N analysed: Haematocrit change < overall median	N analysed: Haematocrit change ≥ overall median	Win ratio (95% CI)	2-sided *p*-value
At day 15	188	204	1.40 (1.09, 1.80)	0.0082
At day 30	180	218	1.30 (1.01, 1.67)	0.0419



Favours haematocrit change < overall median
Favours haematocrit change ≥ overall median

Barriers to SGLT2i Prescribing Cited by Cardiologists[1,a]



[a] ACC online poll of ~500 cardiologists, 87.3% from the US; patient population described as HFrEF with T2DM.

1. Cheng RK et al. *J Am Coll Cardiol*. 2021;77:1375-1377.

SGLT2i: ΕΝΔΕΙΞΕΙΣ

- ✓ Εισαγωγή
- ✓ Σακχ. Διαβήτης 2
- ✓ Καρδιακή Ανεπάρκεια
- ✓ Χρόνια Νεφρική Ανεπάρκεια
- ✓ Πρακτικά Θέματα

Kidney outcomes in previous SGLT2i trials

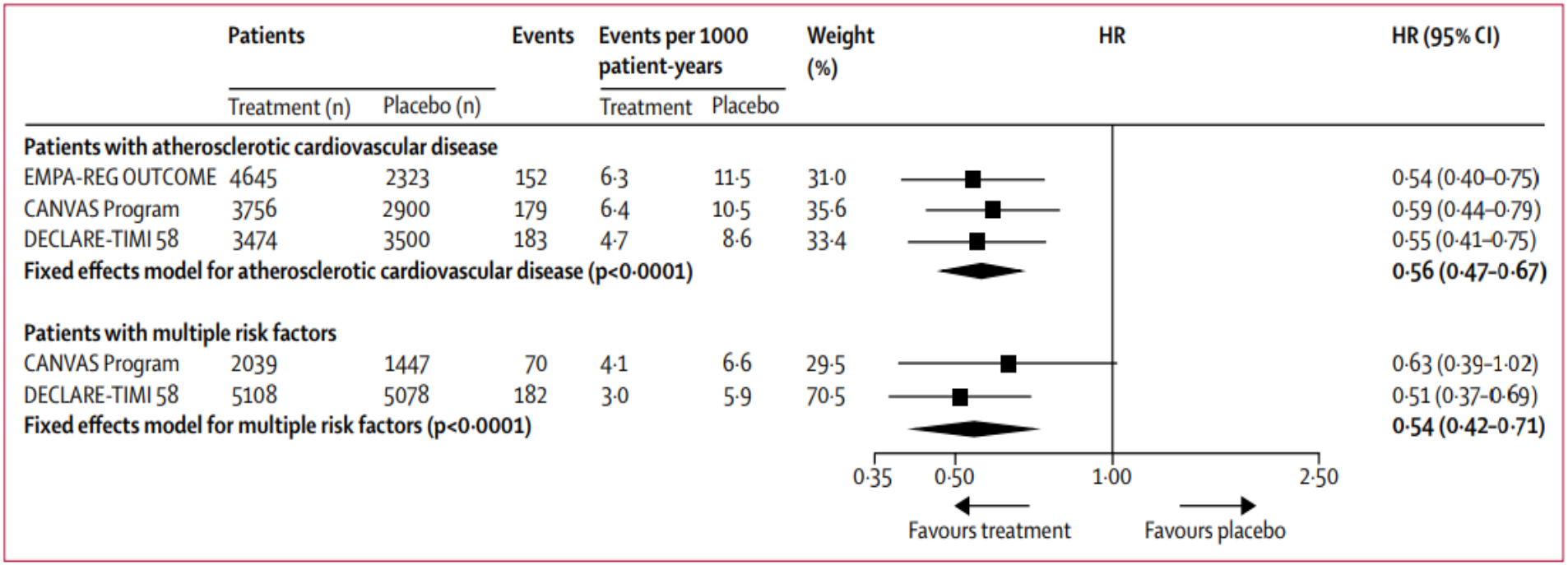
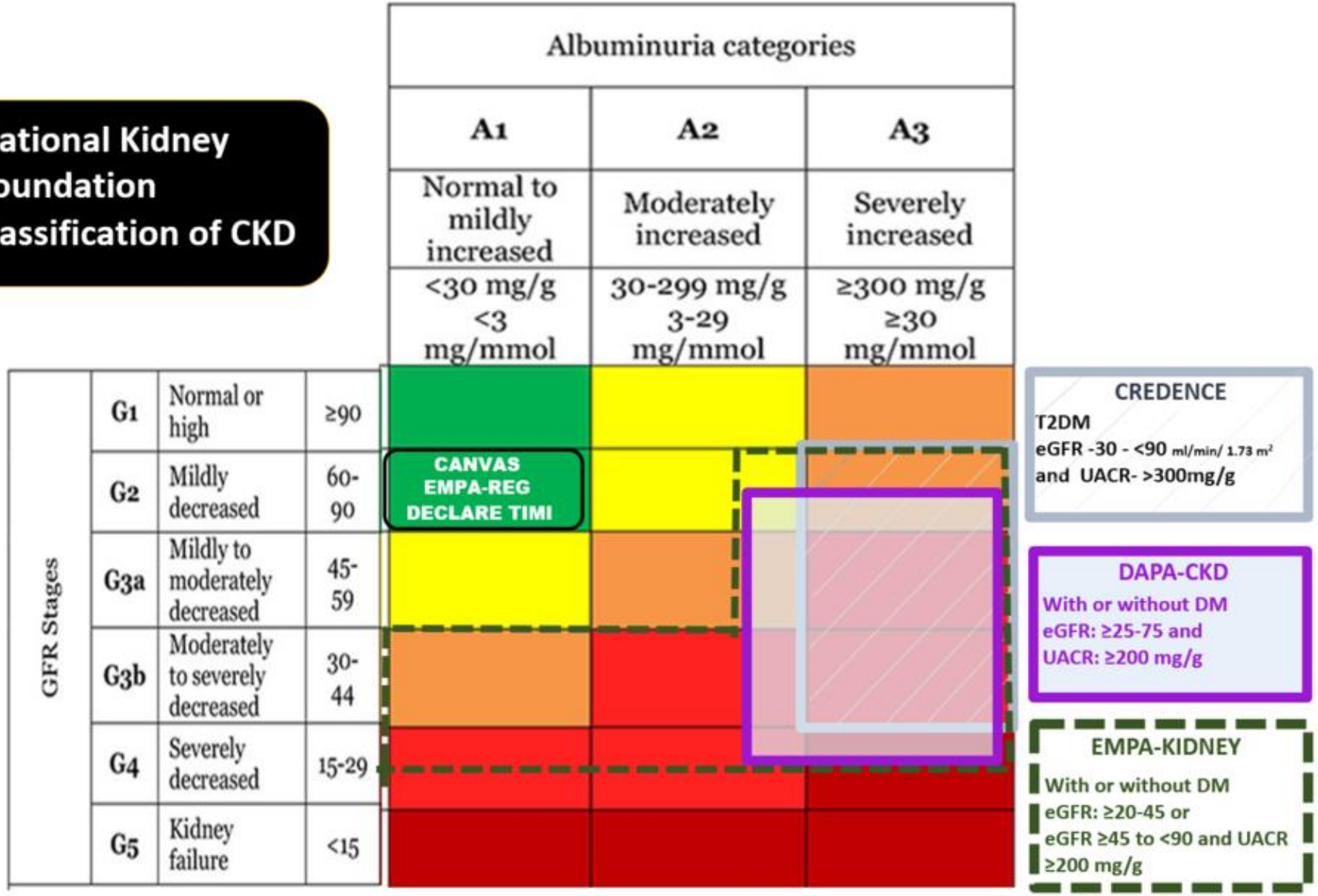


Figure 4: Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease

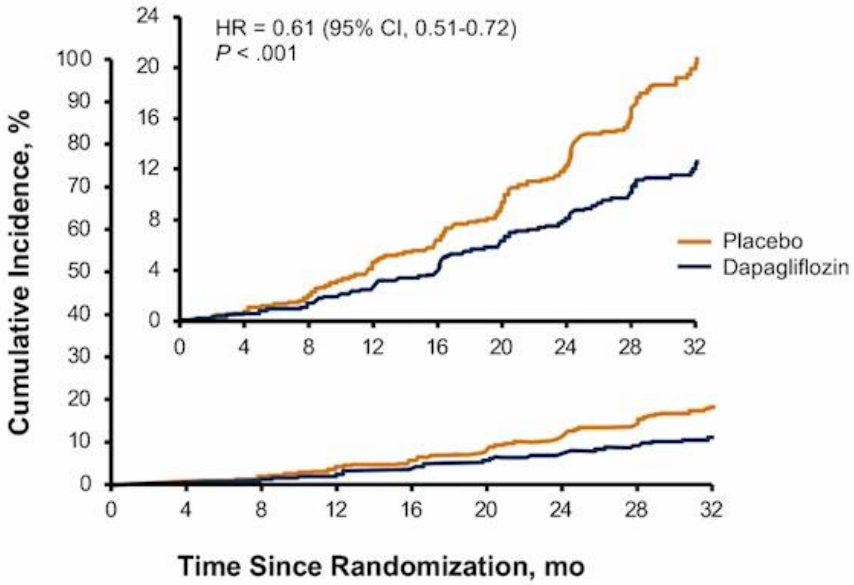
Lancet. 2019 ;393:31-39.

National Kidney Foundation classification of CKD



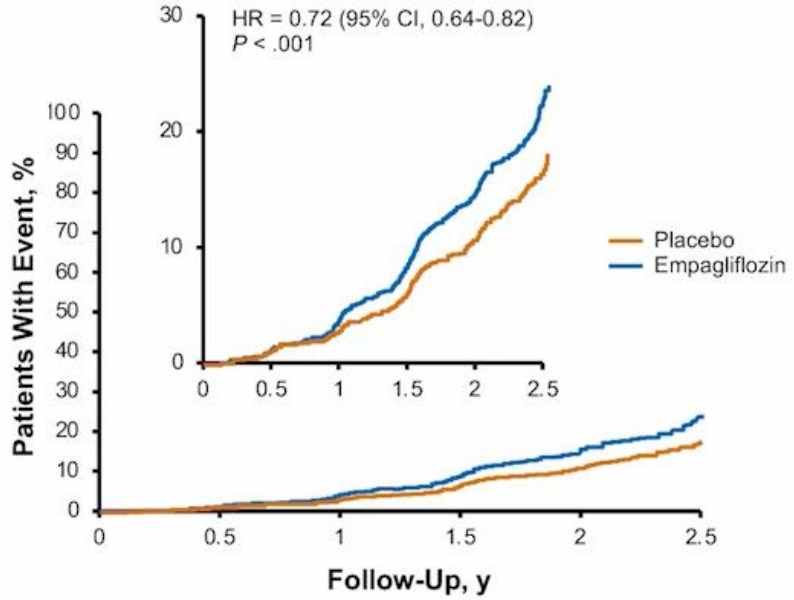
Empagliflozin and Dapagliflozin Slow Kidney Disease Progression and Reduce Death: Primary Composite Outcome[1,2]

DAPA-CKD



No. at Risk									
Placebo	2,152	1,993	1,936	1,858	1,791	1,664	1,231	774	270
Dapagliflozin	2,152	2,001	1,955	1,898	1,841	1,701	1,288	831	309

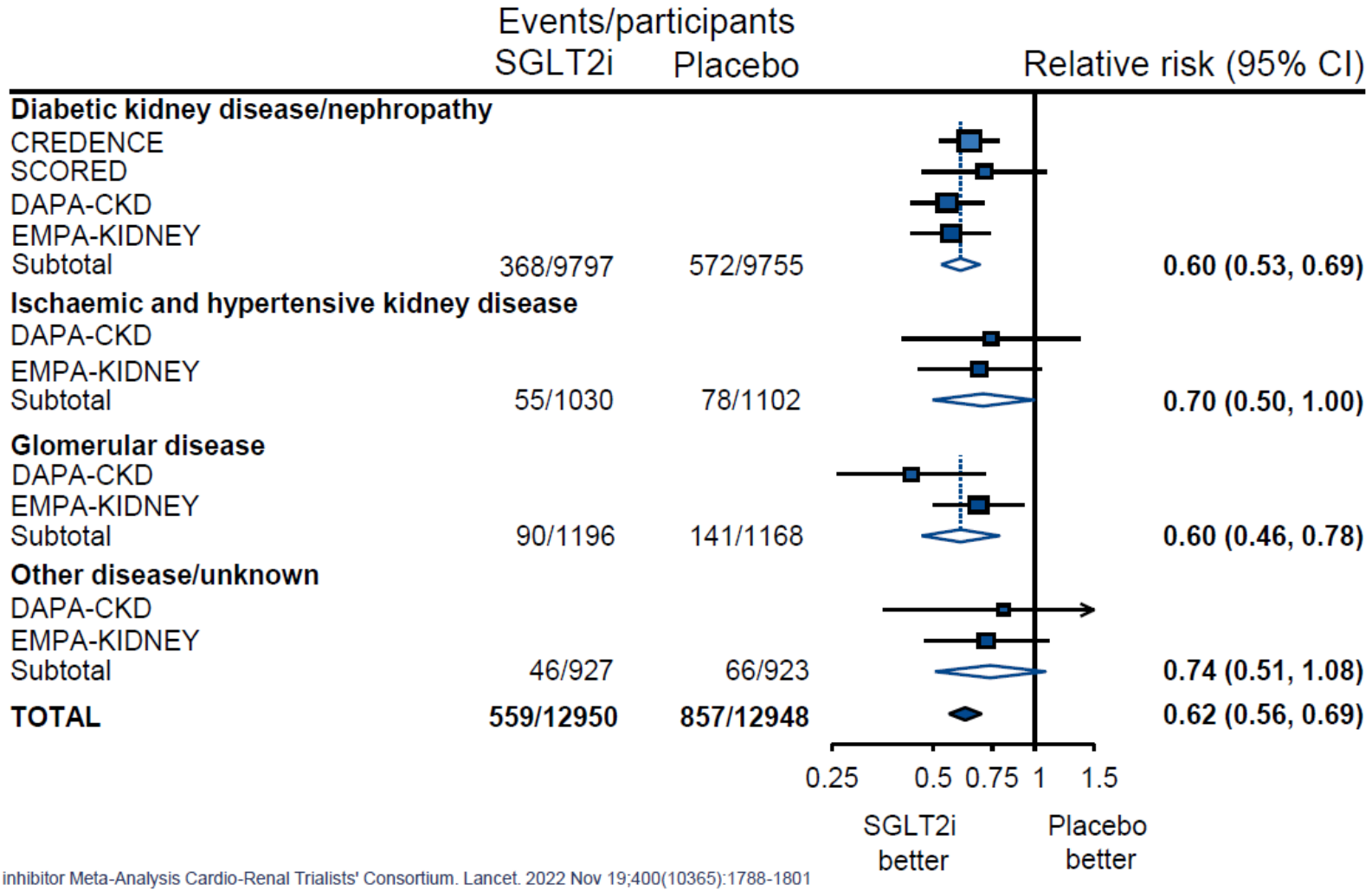
EMPA-KIDNEY



No. at Risk						
Placebo	3,305	3,250	3,129	2,243	1,496	592
Empagliflozin	3,304	3,252	3,163	2,275	1,538	624

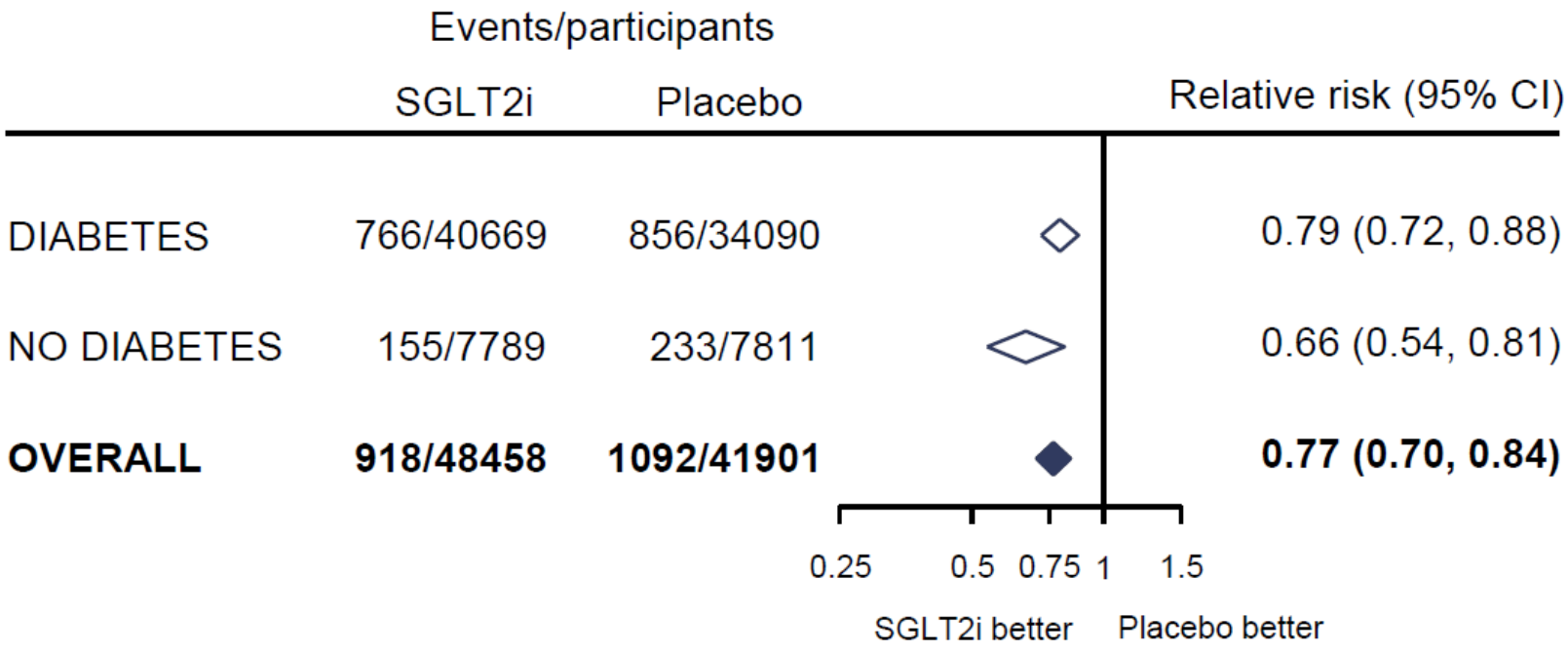
1. Heerspink HJL et al. *N Engl J Med*. 2020;383:1436-1446. 2. Herrington WG et al. *N Engl J Med*. 2022

The Benefit of SGLT2 Inhibitors to Delay CKD Progression are Consistent Regardless of the Type of Kidney Disease



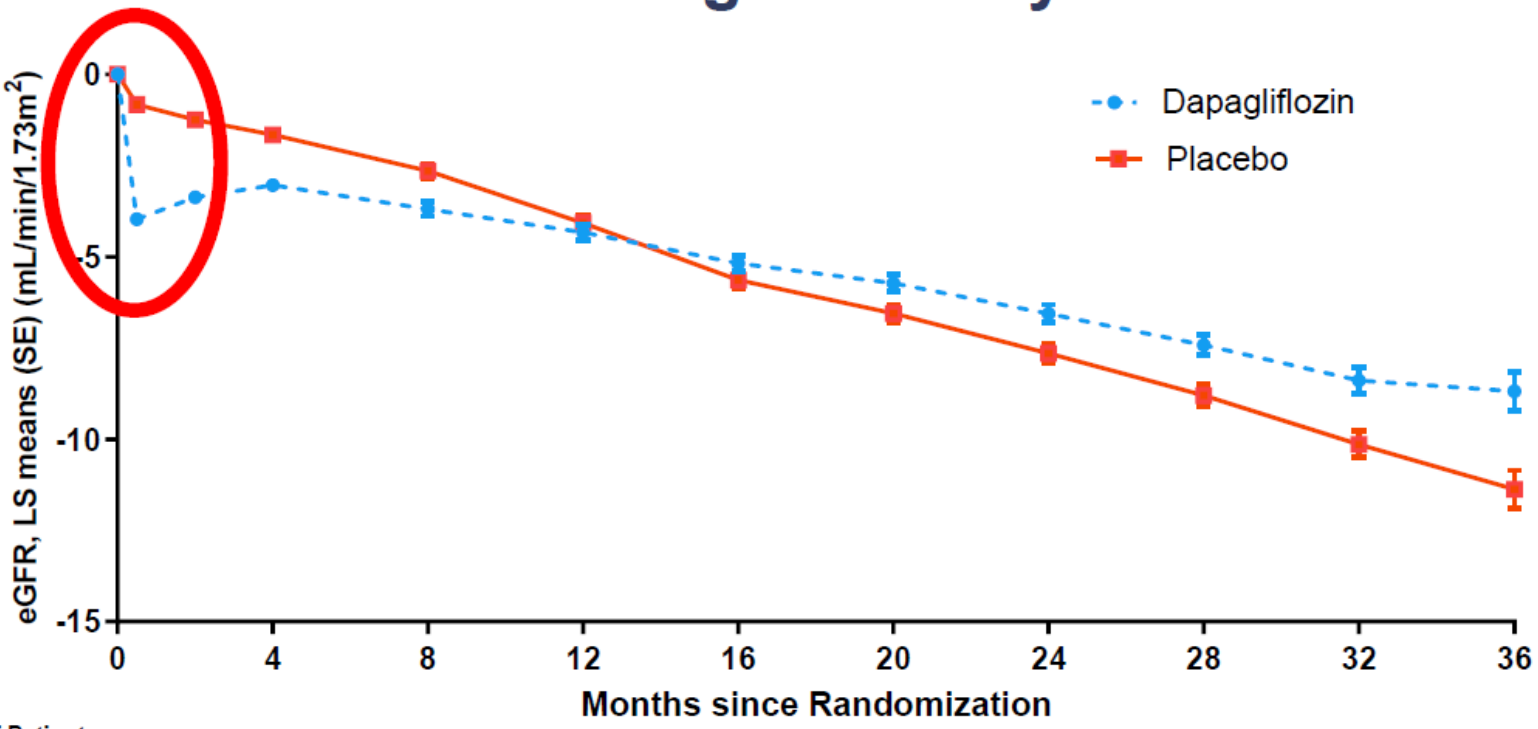
SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Lancet. 2022 Nov 19;400(10365):1788-1801

SGLT2 inhibitors Reduce the Risk of Acute Kidney Injury



SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Lancet. 2022 Nov 19;400(10365):1788-1801

DAPA-CKD: eGFR decline during the study



No. of Patients

Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157
Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157

LS means eGFR slope (SE)	Dapagliflozin	Placebo	Between group difference (95% CI)
Acute, mL/min/1.73m²/2 weeks	−3.97 (0.15)	−0.82 (0.15)	
Chronic, mL/min/1.73m²/year	−2.86 (0.11)	−3.79 (0.11)	0.93 (0.61, 1.25)

CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares; SE, standard error.
Heerspink HJL. et.al. *N Engl J Med* 2020;383:1436-1446.

SGLT2i: ΕΝΔΕΙΞΕΙΣ

- ✓ Εισαγωγή
- ✓ Σακχ. Διαβήτης 2
- ✓ Καρδιακή Ανεπάρκεια
- ✓ Χρόνια Νεφρική Ανεπάρκεια
- ✓ Πρακτικά Θέματα

What About eGFR to Initiate? Synthesis of Findings From 10 CV and Kidney Outcomes Trials[1,a]

Depends on *why* you are using the SGLT2 inhibitor!

Reason	eGFR, mL/min/1.73 m^2
HFrEF	**≥20** (empagliflozin) **≥30** (dapagliflozin)
HFpEF	**≥20** (empagliflozin) **≥25** (dapagliflozin)

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Cardiorenal effects in T2DM	**≥30**

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HFpEF	**≥20** (empagliflozin) **≥25** (dapagliflozin)
CKD	**≥30** (canagliflozin) **≥25** (dapagliflozin) **≥20** (empagliflozin)
Cardiorenal effects in T2DM	**≥30**
Glycemic control	**≥45** (continue to get A1C lowering)

Ανεπιθύμητες Ενέργειες με βάση την παρουσία ΣΔ

Adverse Effect	T2DM	No T2DM
Genital mycotic infections	Yes	
Volume-related AEs	Yes	
Diabetic ketoacidosis	Yes	
Hypoglycemia	Yes	
Urinary tract infections		
Acute kidney injury		
Amputations		
Fractures		

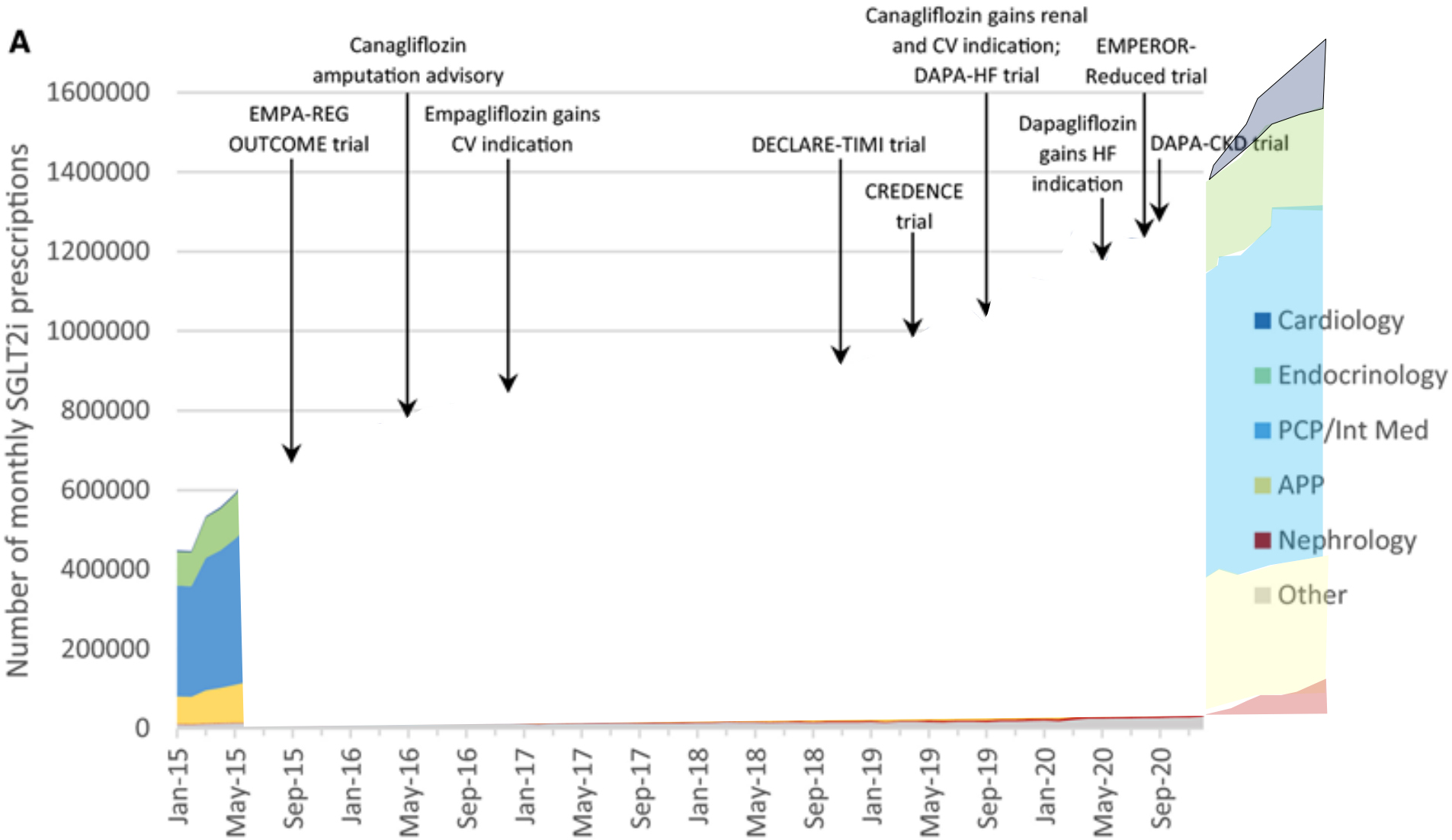
Ανεπιθύμητες Ενέργειες με βάση την παρουσία ΣΔ

Adverse Effect	T2DM	No T2DM
Genital mycotic infections	Yes	Yes
Volume-related AEs	Yes	Yes
Diabetic ketoacidosis	Yes	No risk
Hypoglycemia	Yes	No risk
Urinary tract infections		
Acute kidney injury		
Amputations		
Fractures		

Ανεπιθύμητες Ενέργειες με βάση την παρουσία ΣΔ

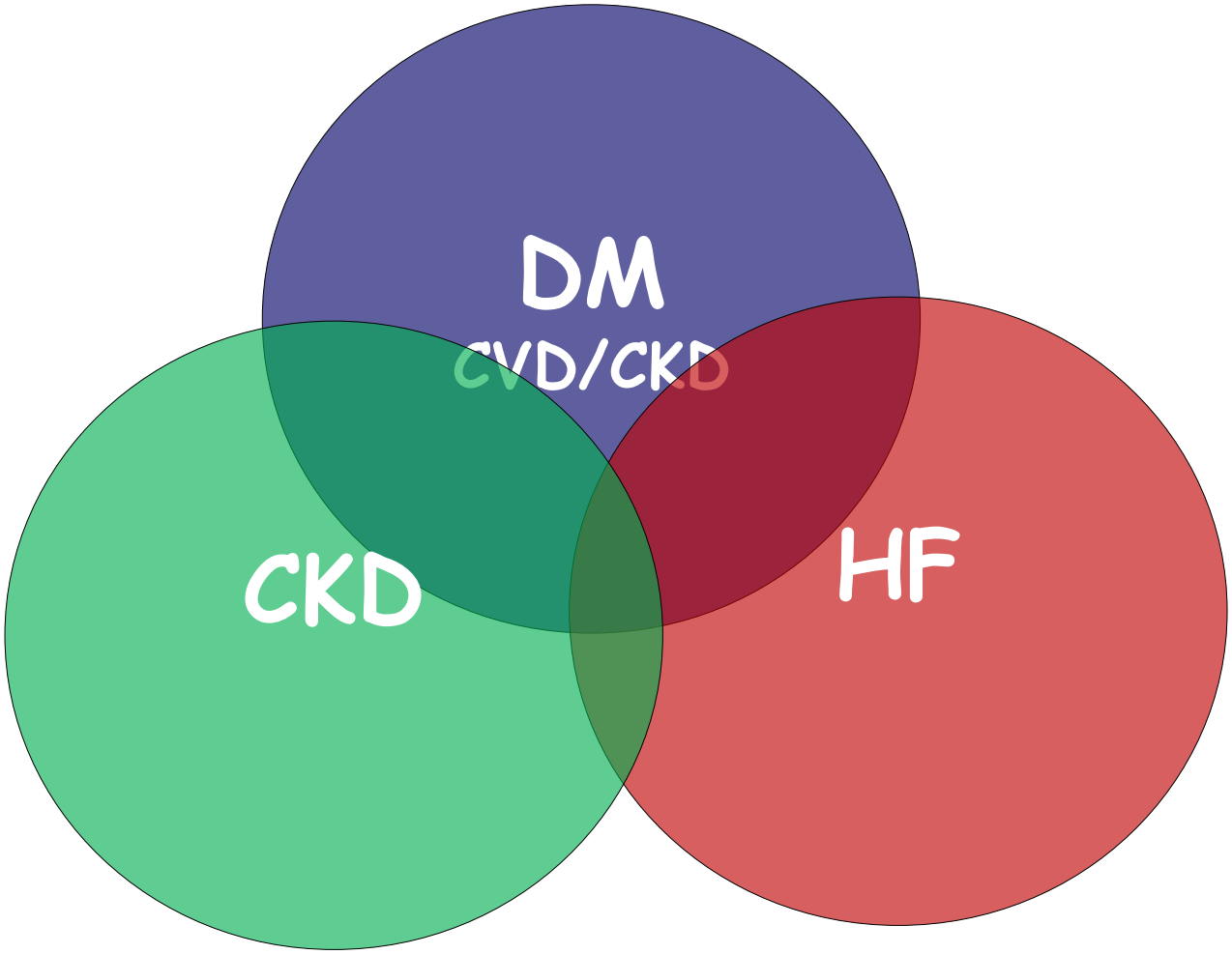
Adverse Effect	T2DM	No T2DM
Genital mycotic infections	Yes	Yes
Volume-related AEs	Yes	Yes
Diabetic ketoacidosis	Yes	No risk
Hypoglycemia	Yes	No risk
Urinary tract infections	No difference in risk	
Acute kidney injury	No difference in risk	
Amputations	No difference in risk	
Fractures	No difference in risk	

Συνταγές SGLT2i US 2015-2020

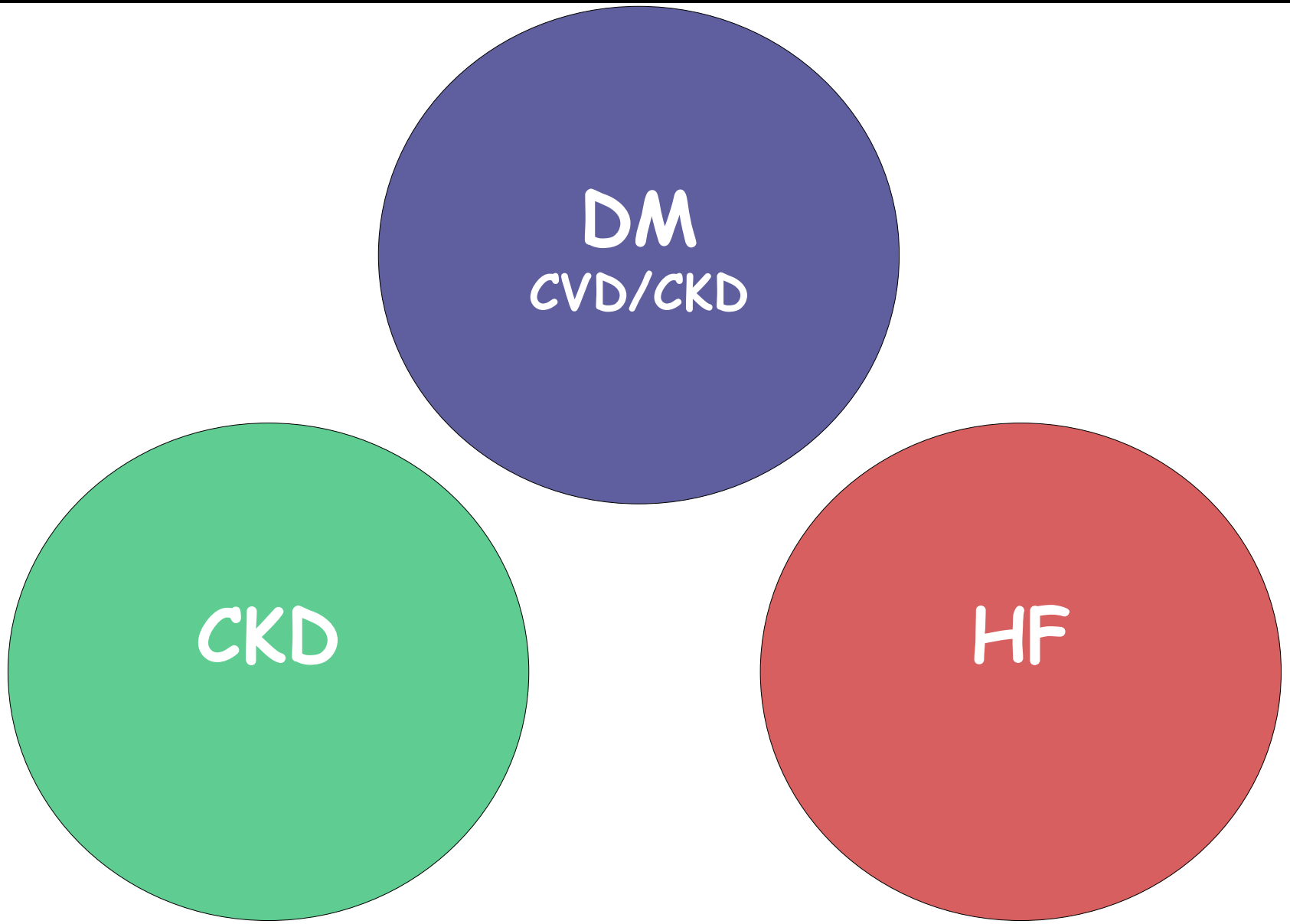


J Am Heart Assoc 2022 May;11:e023811.

SGLT2i ΕΝΔΕΙΞΕΙΣ



SGLT2i ΕΝΔΕΙΞΕΙΣ



Agent	T2DM	Any HF	CKD
Dapagliflozin	√	√	√
Empagliflozin	√	√	pending