Protezione Cardionefro-metabolica degli SGLT2i nello Scompenso Cardiaco

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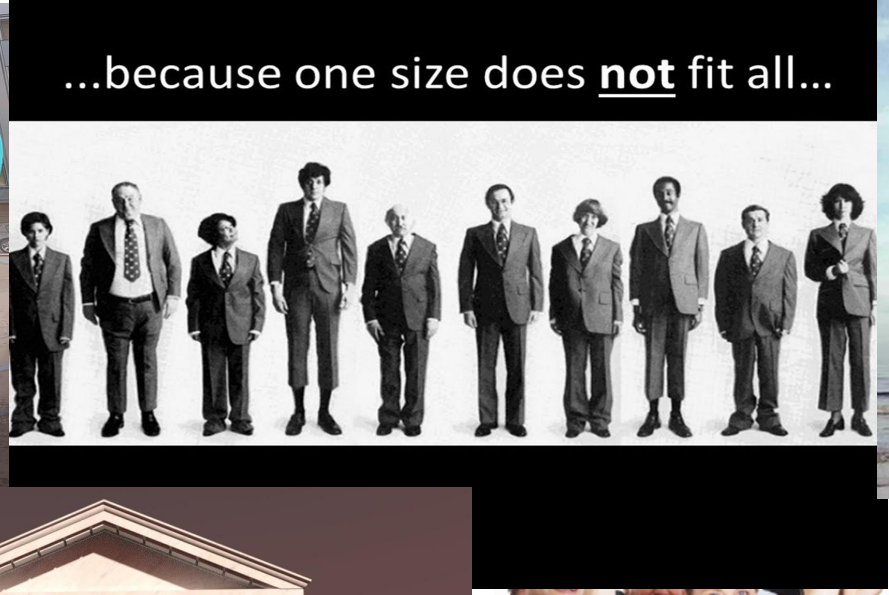
DISCLOSURES

Steering Committe Member : Amgen, Merck, Novartis
Advisory Board & Speaker's Fee: Amgen, Sanofi, Amarin, UCB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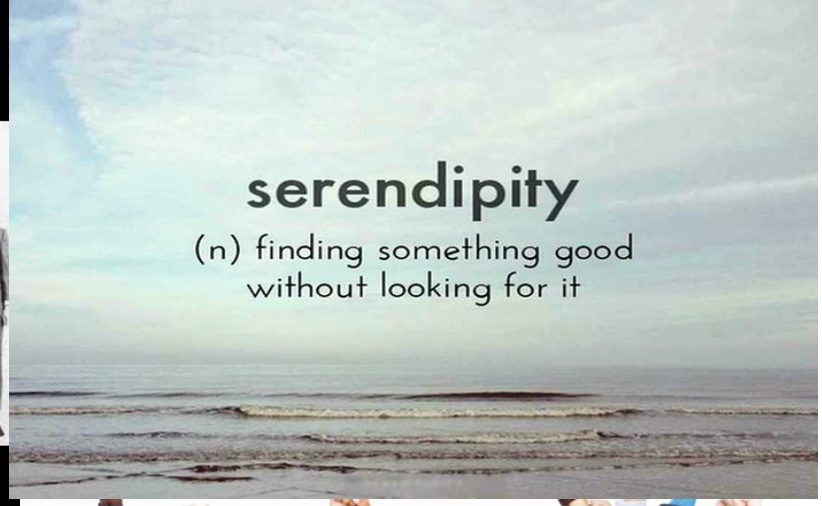
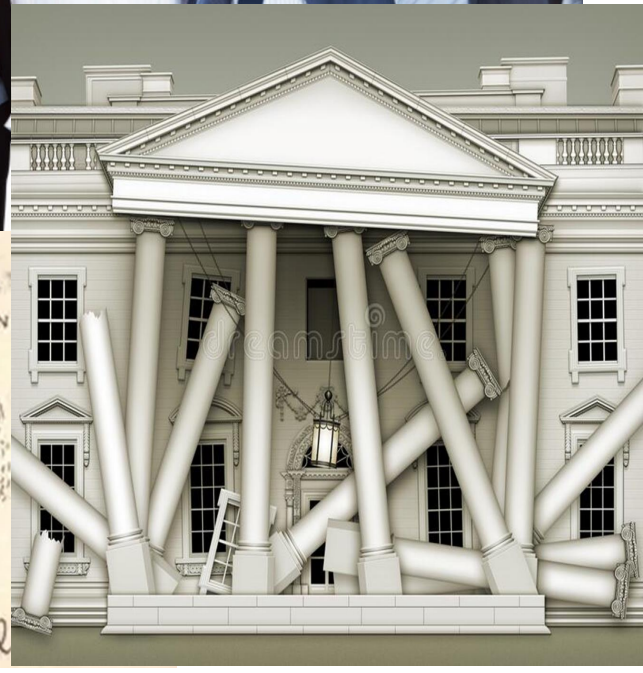
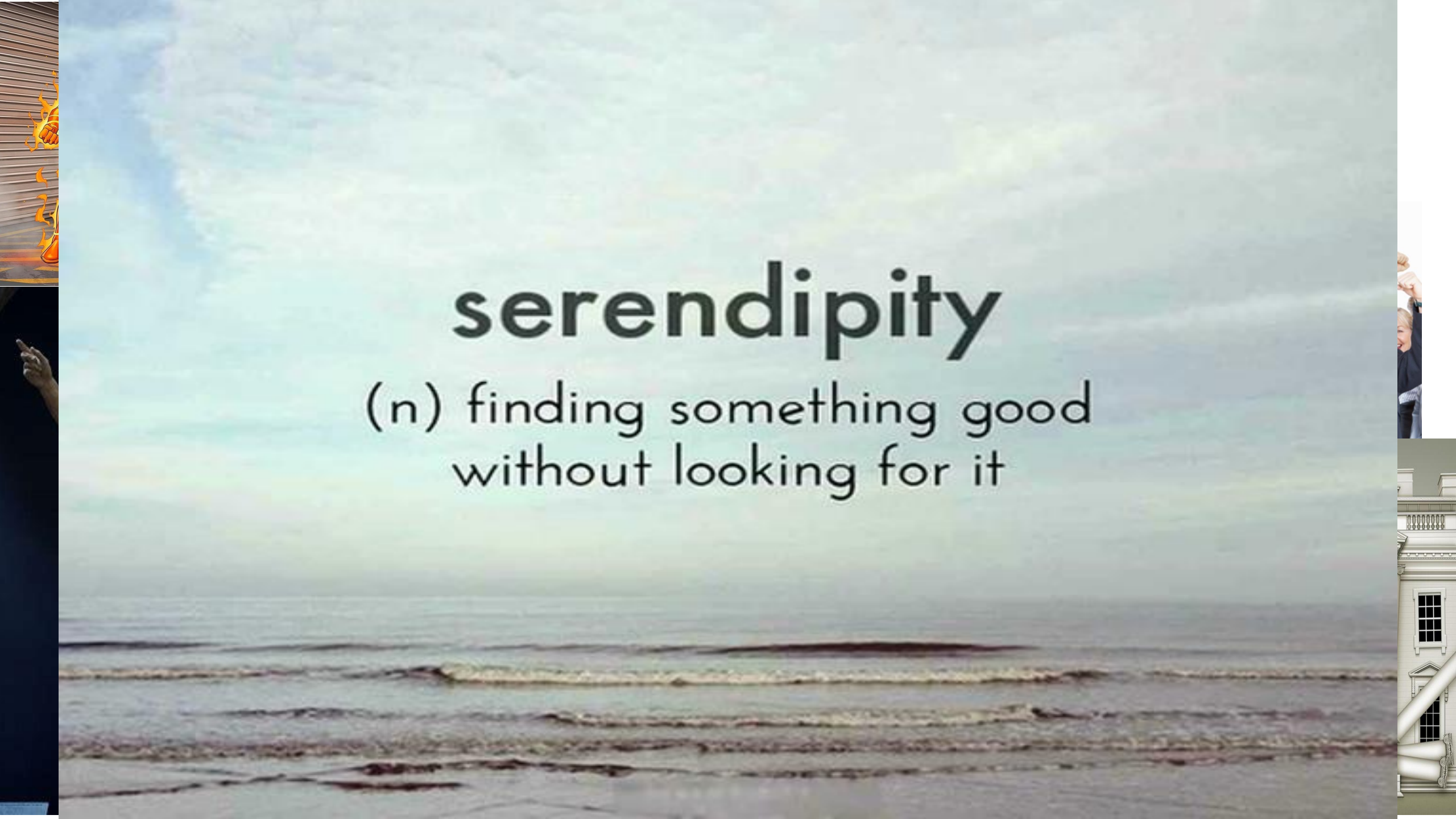

serendipity
(n) finding something good
without looking for it




GIN RUMMY


PRENDERE DUE PICCIONI CON UNA
" GET TWO PIGEONS WITH ONE FAVA BEAN
catching two birds with one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Safety of antihyperglycemic medications: the case of the rosiglitazone

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

Nissen et al. *N Engl J Med* 2007; 356:2457-2471

FDA Cardiovascular safety issue

FDA issues safety on Avandia

"The U.S. Food and Drug Administration (FDA) is aware of a **potential safety issue** related to Avandia (rosiglitazone), a drug approved to treat type 2 diabetes. Safety data from controlled clinical trials have shown that there is a **potentially significant increase in the risk of heart attack and heart-related deaths** in patients taking Avandia".

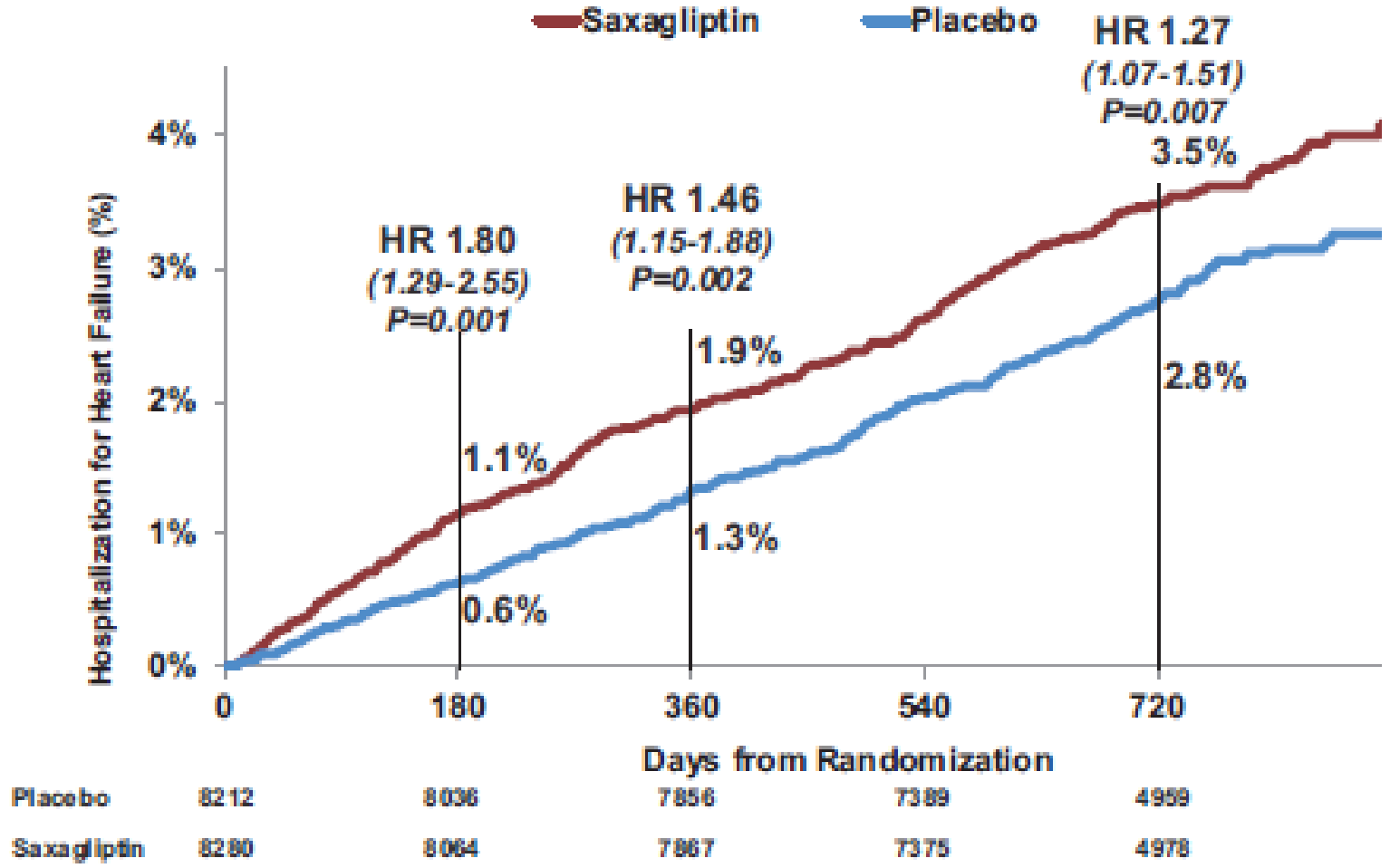
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108917.htm

FDA guidance for industry to evaluate CV risk in new antihyperglycemic medications

- **Effects on CV risk** to be more thoroughly addressed during antihyperglycemic medication development; recommendation to demonstrate that therapy **will not result** in unacceptable **increase in CV risk**;
- Inclusion of **patients with a higher risk of CV events** e.g. patients with advanced CV disease, elderly patients, and patients with impaired renal function;
- A **minimum of 2 years**' CV safety data must be provided;
- All phase 2 and 3 studies should include a **prospective, independent adjudication of CV events**. Adjudicated events should include CV **mortality, myocardial infarction, and stroke** and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other end points.

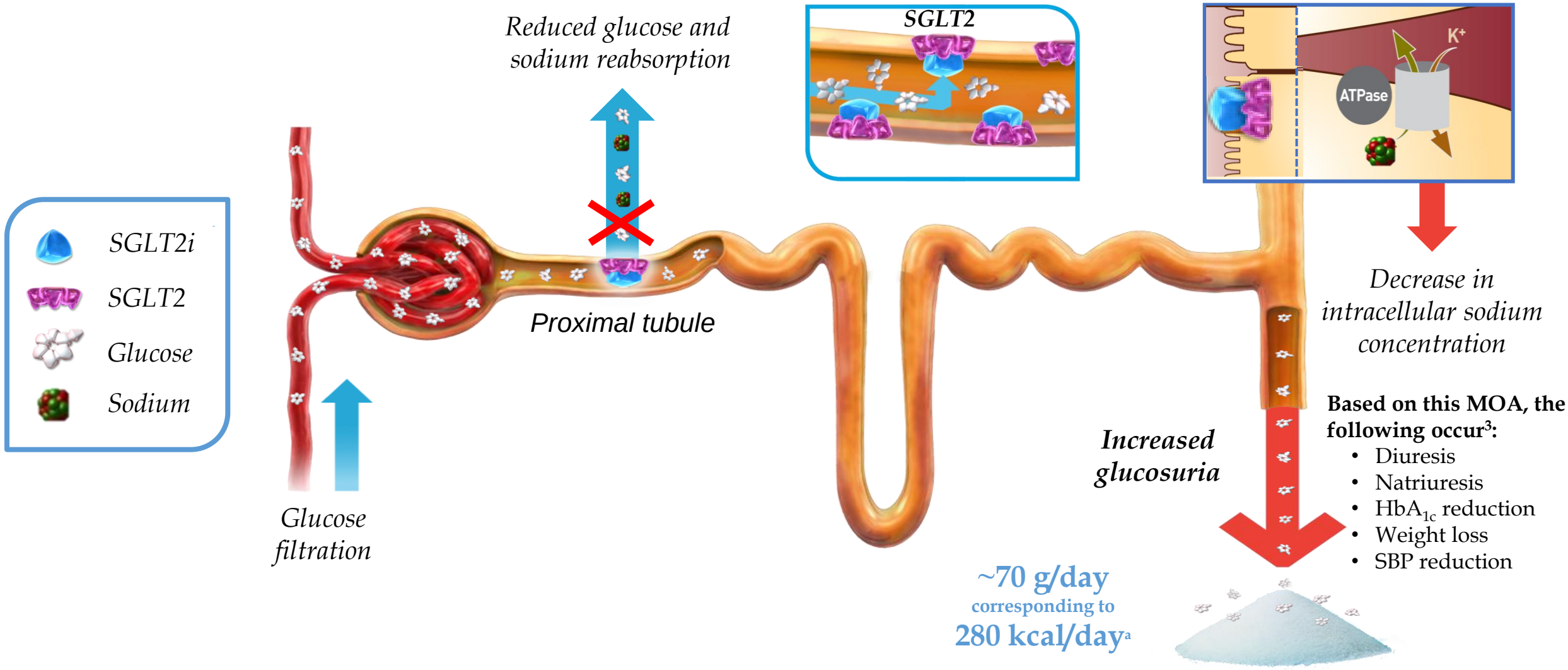
July 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

SAVOR-TIMI 53: excess of hospitalizations for heart failure in saxagliptin group



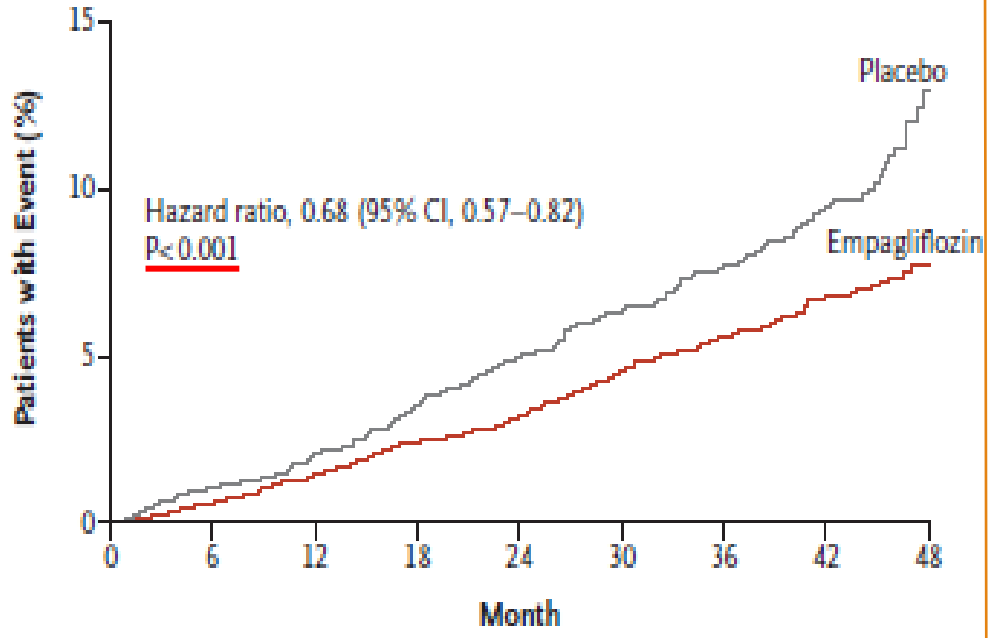
Scirica B.M. et al. *Circulation*. 2014;130:1579-1588.

SGLT2 inhibition: An insulin-independent approach to remove excess glucose by reducing the renal threshold



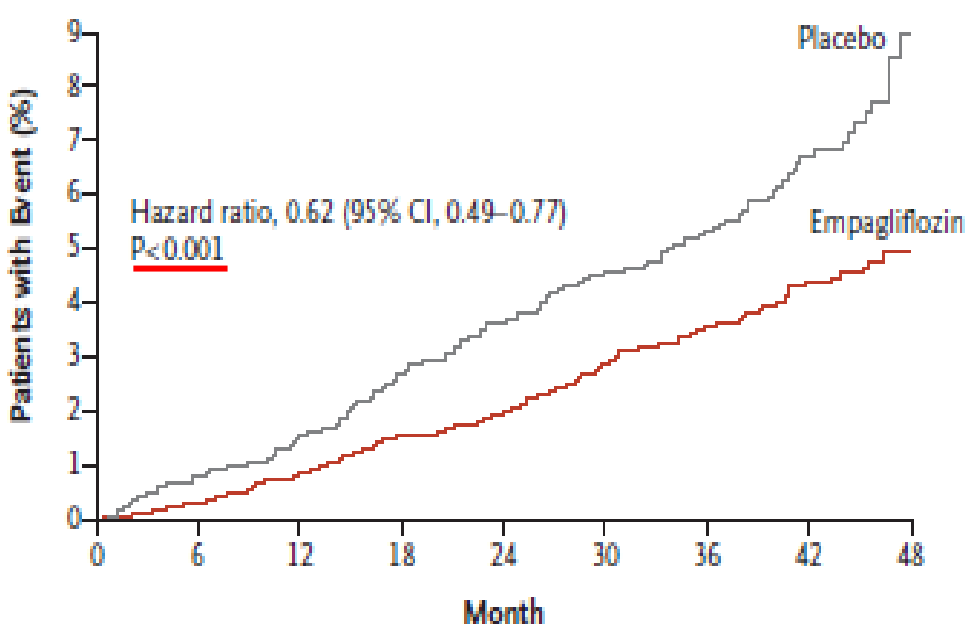
EMPA-REG Outcome Results

Death from any cause



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Death from CV causes



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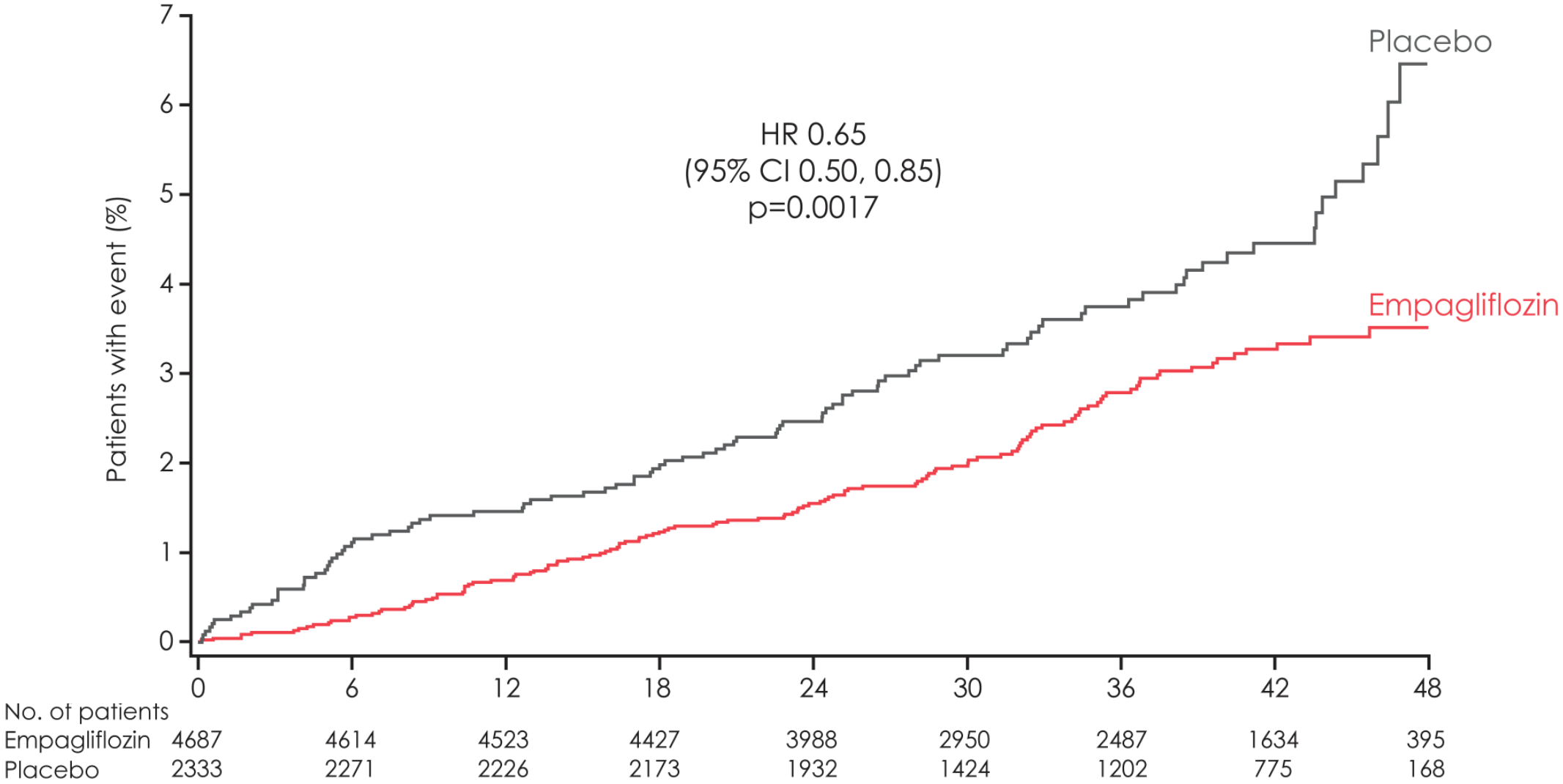
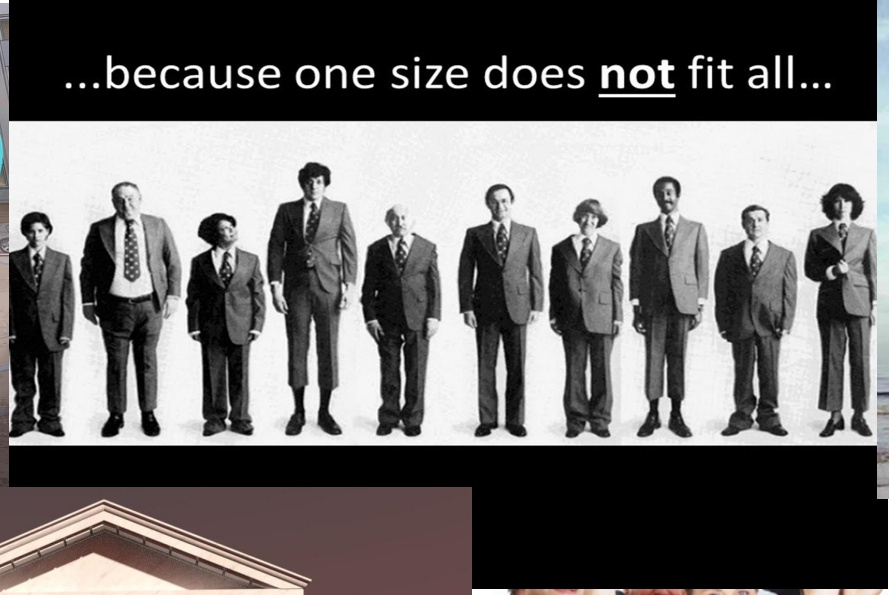
Zinman et al. *N Engl J Med* 2015; 373:2117-2128

Hospitalisation for heart failure



Zinman et al. *N Engl J Med* 2015; 373:2117-2128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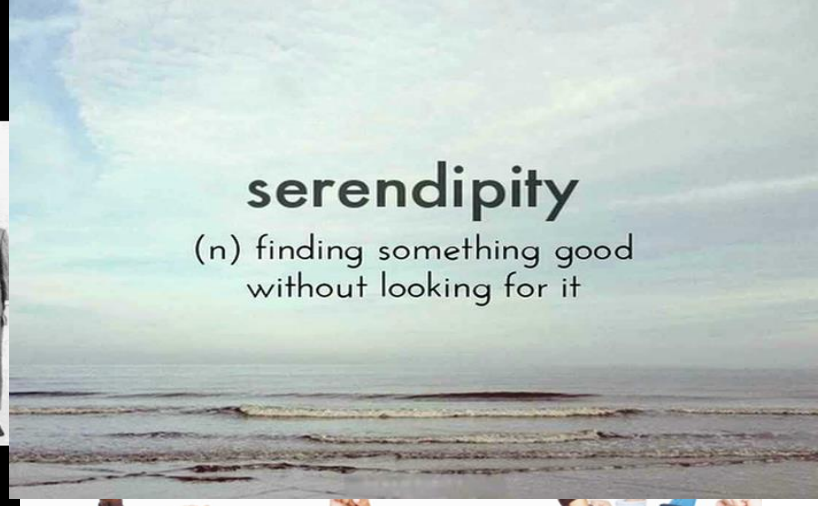
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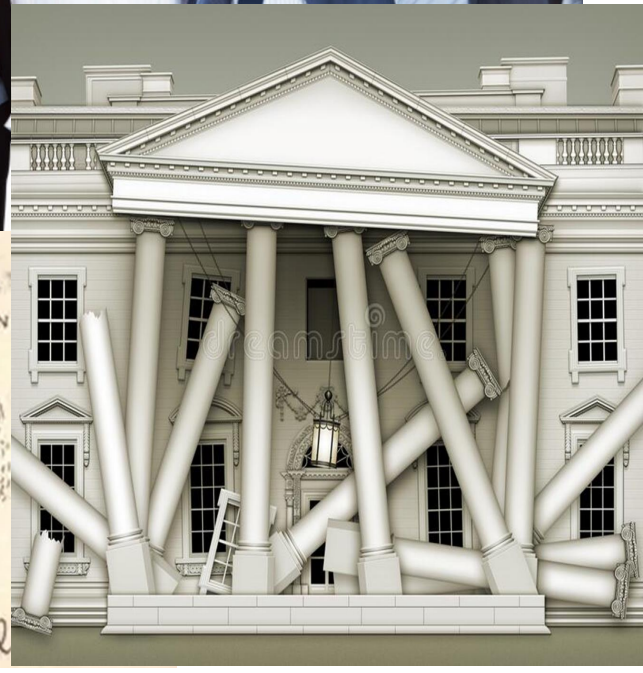


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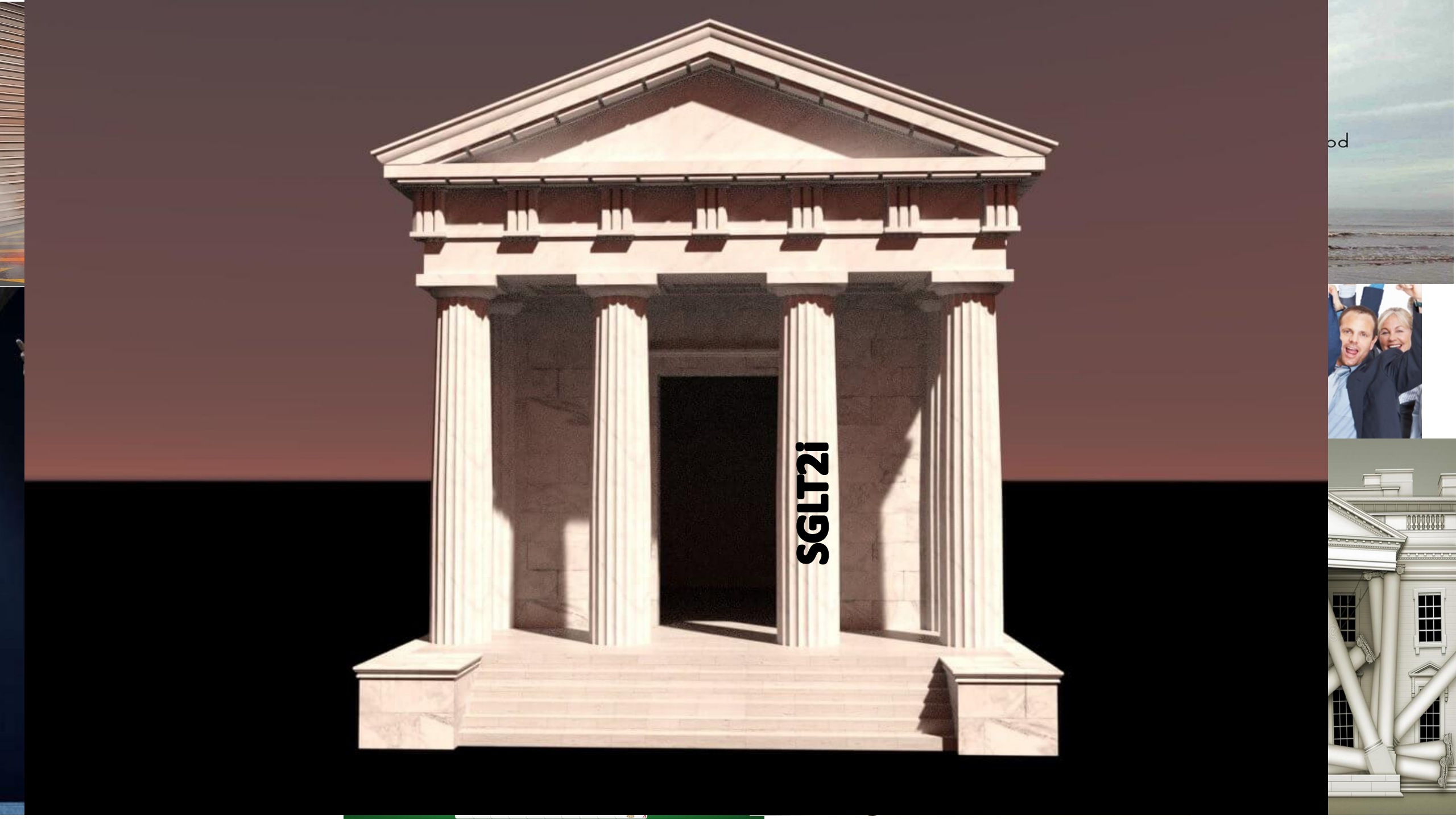
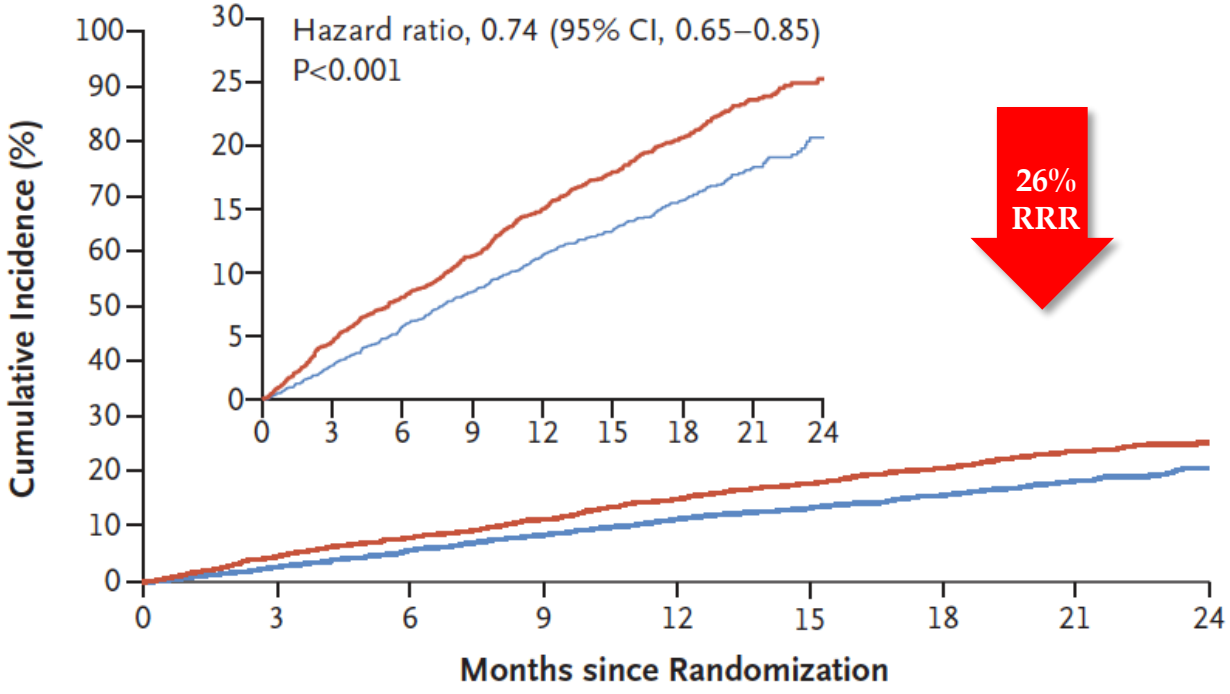

SGLT2i

SGLT2i in ambulatory patients with HFrEF

DAPA-HF

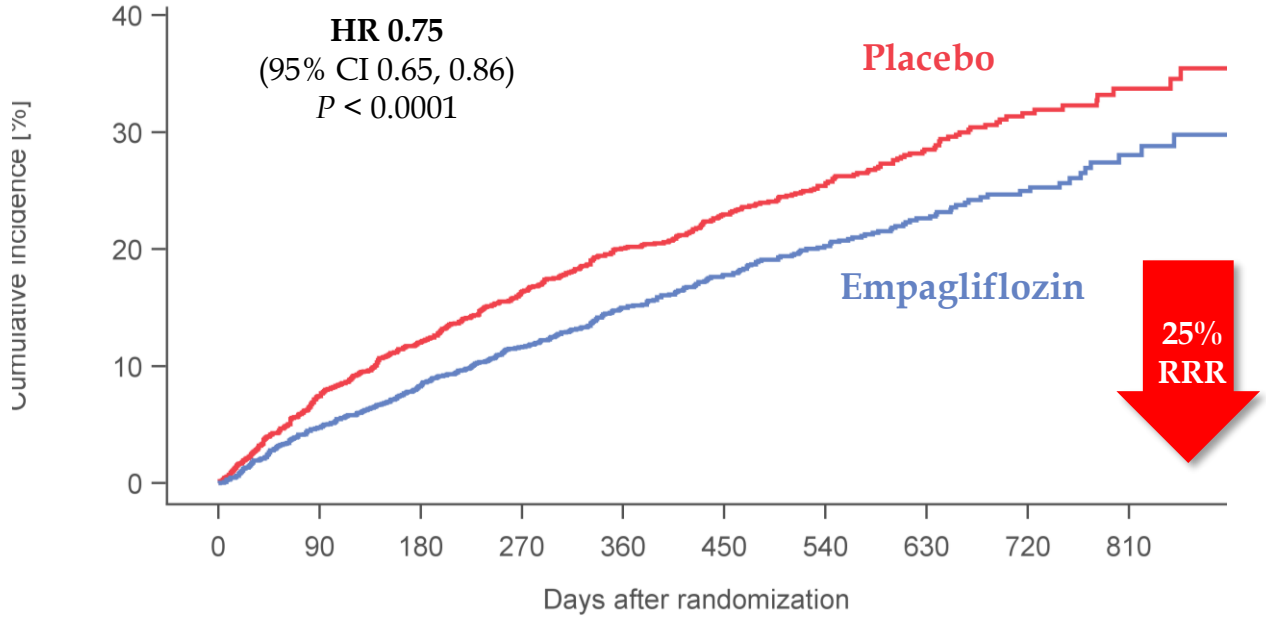
Worsening heart failure or Cardiovascular Death



N Engl J Med. 2019;381:1995-2008

EMPEROR-Reduced

Cardiovascular Death or Hospitalization for Heart Failure



N Engl J Med 2020;383:1413-24.

ESC European Society of Cardiology
European Heart Journal (2021) 42, 3599–3726
doi:10.1093/eurheartj/ehab368
ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

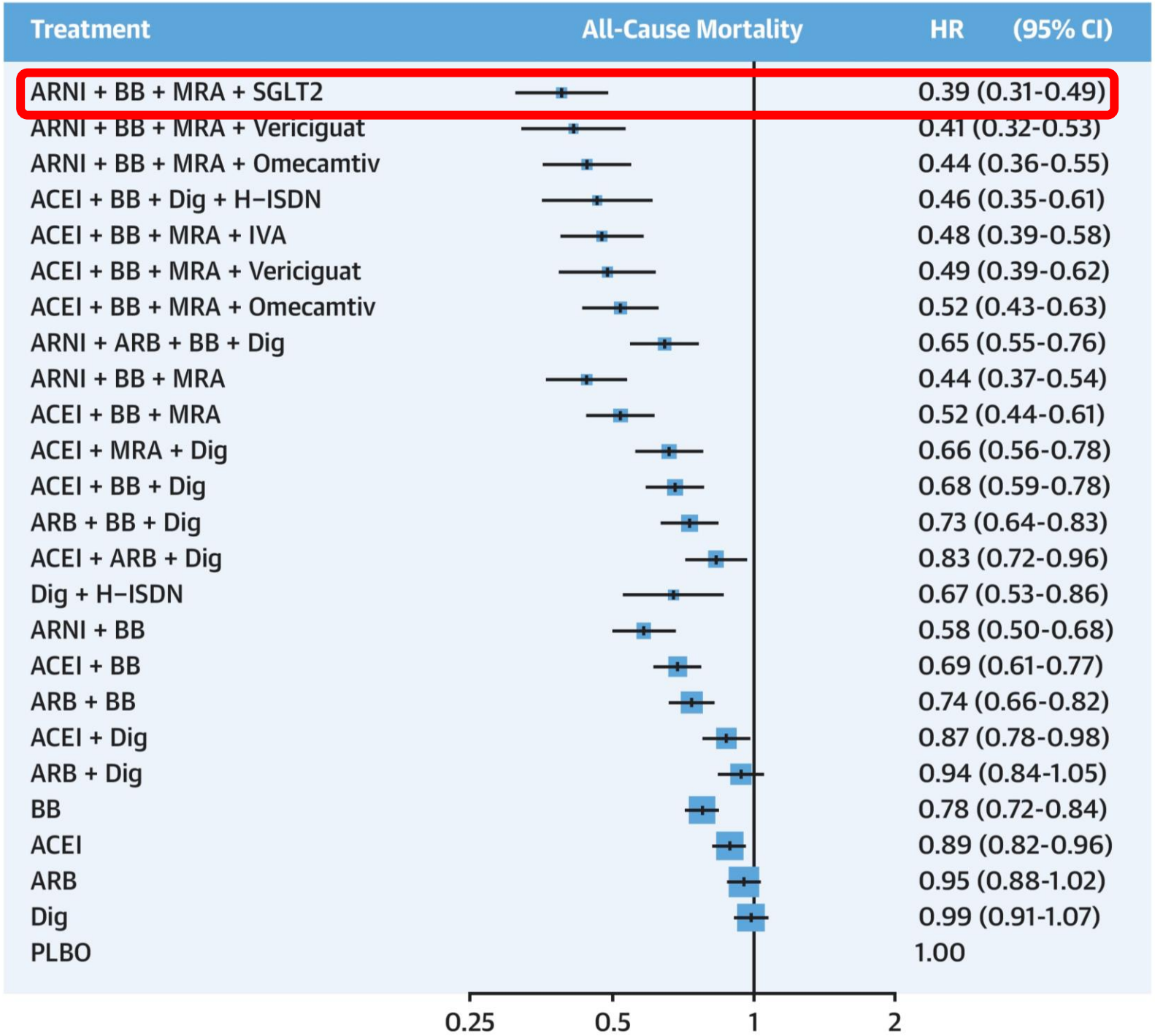
With the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Celutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

Drugs recommended for HFrEF

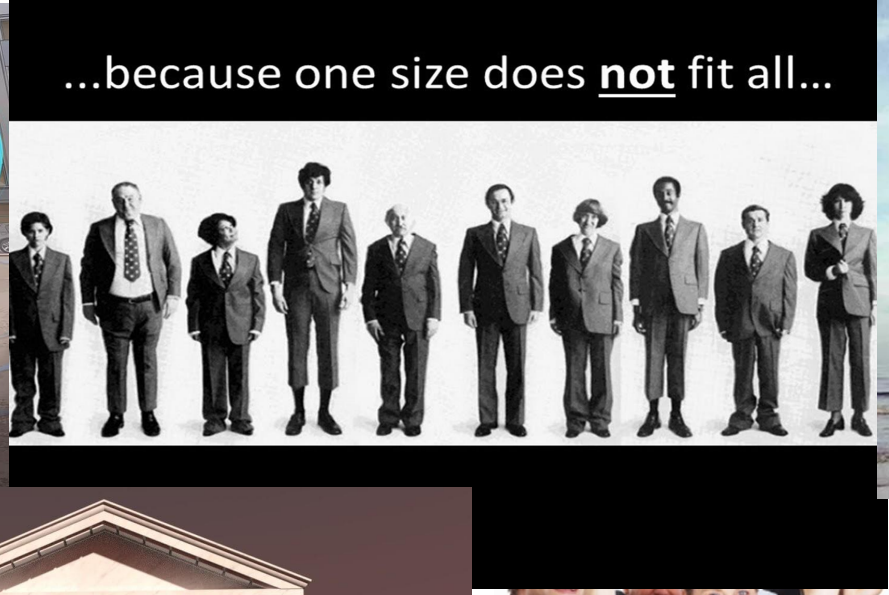
Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B



Additive Benefits of Using all 4 Pillars

JACC heart Failure 2022; 10(2); 10:73-84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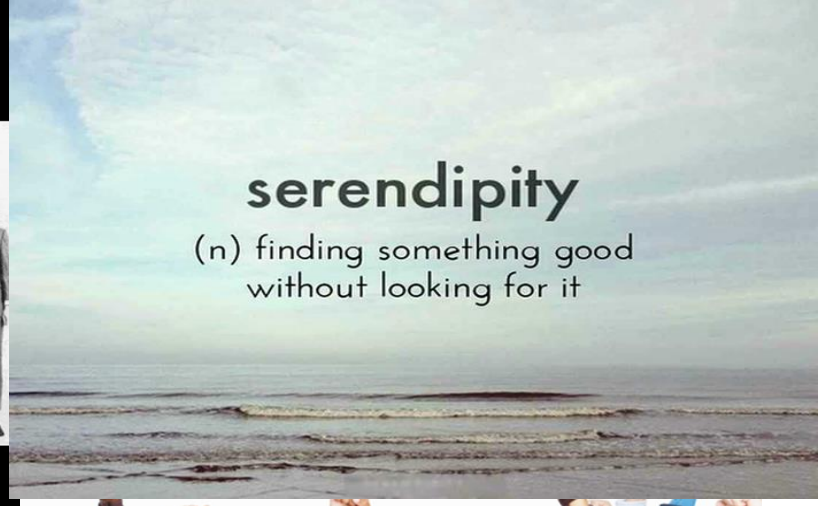
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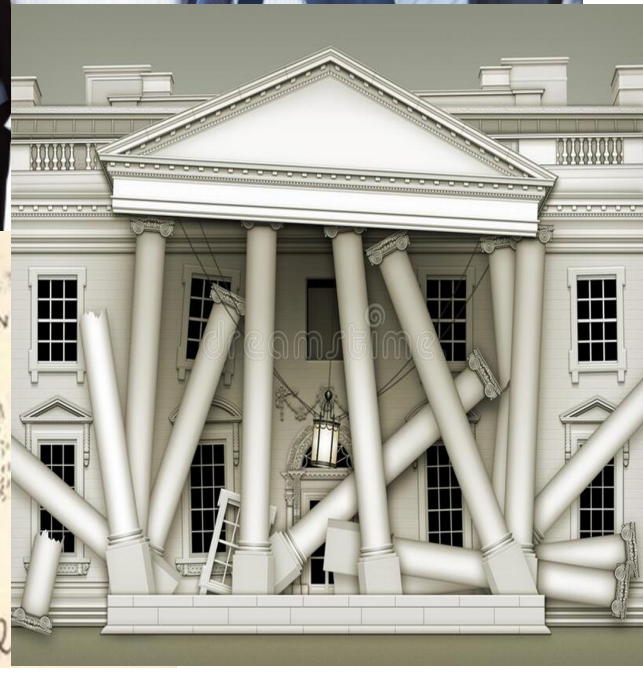


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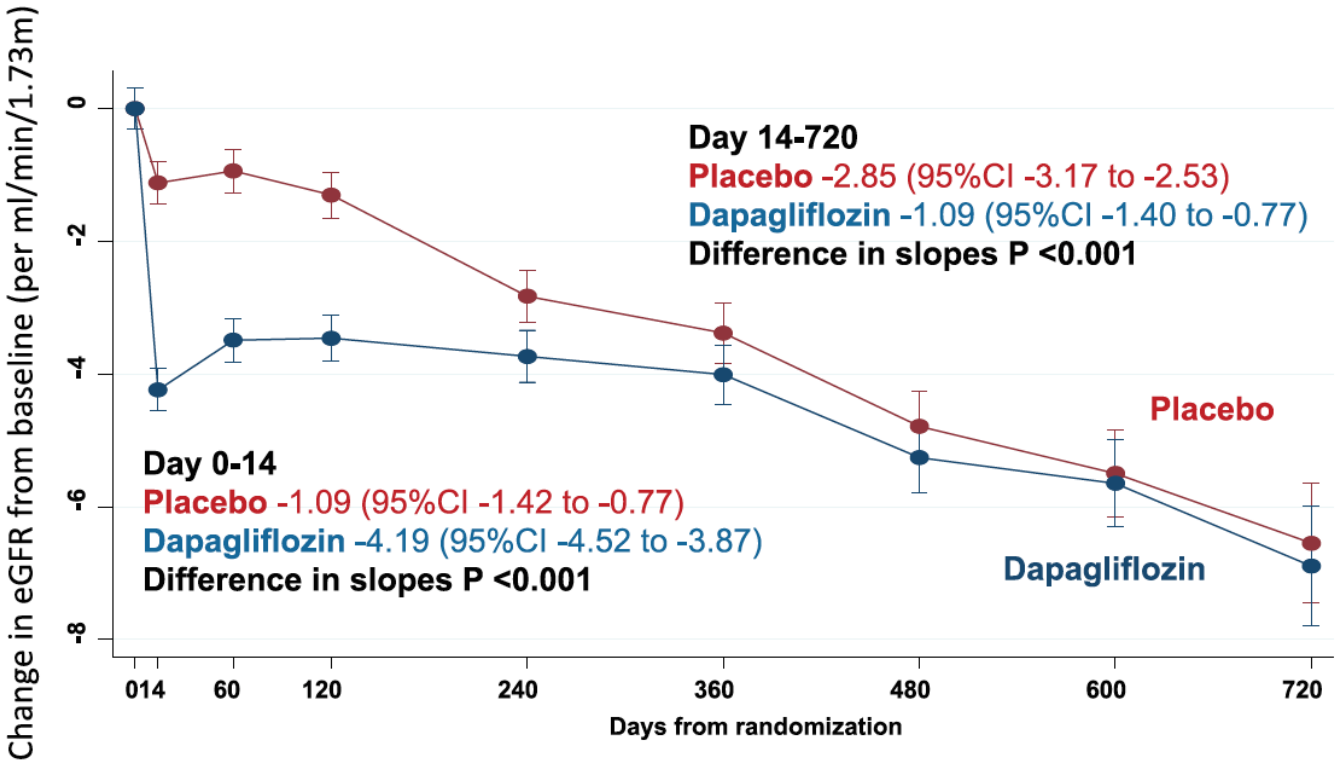
Mr Fantastic


SGLT2i

Slowing rate of decline in eGFR

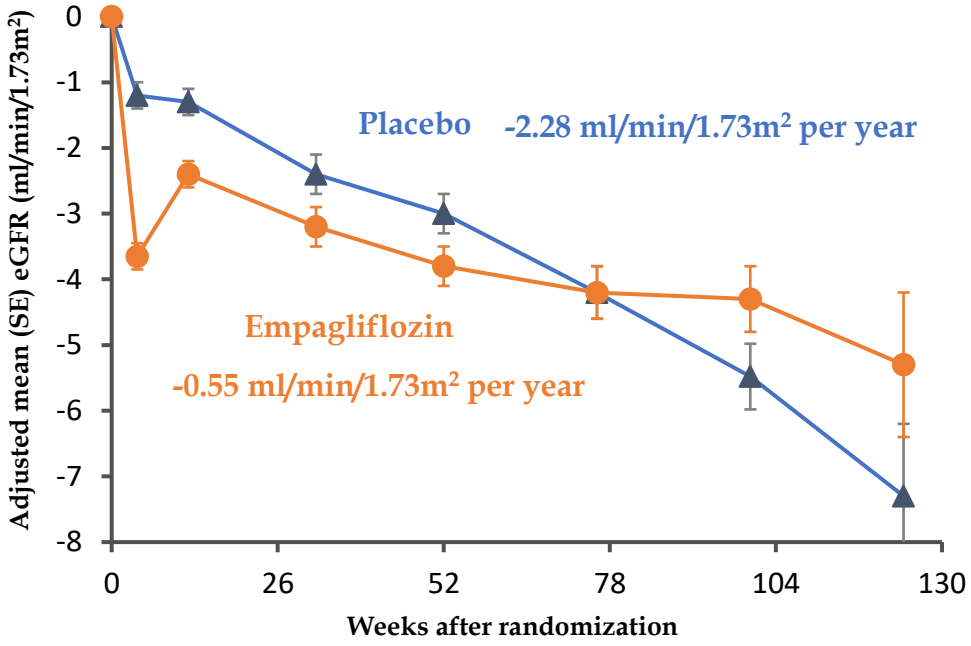
DAPA-HF



Difference = 1.78 ml/min/yr

Circulation. 2021;143:298–309

EMPEROR-Reduced

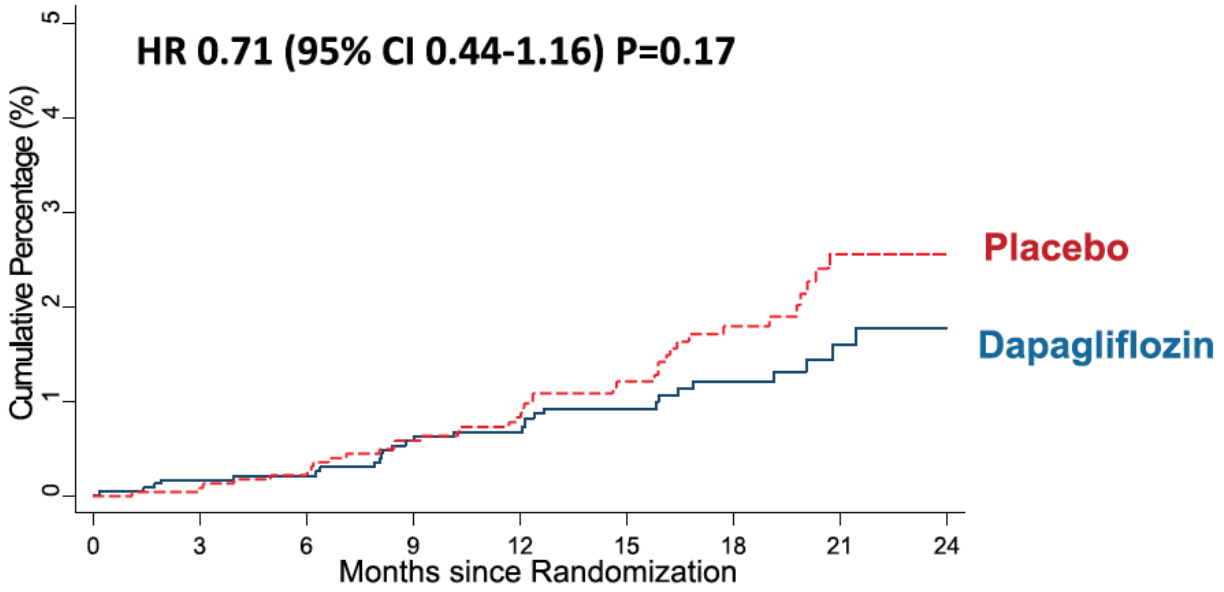


Difference = 1.73 ml/min/yr

N Engl J Med 2020;383:1413-24.

Effect of SGLTi on renal composite outcome

DAPA-HF



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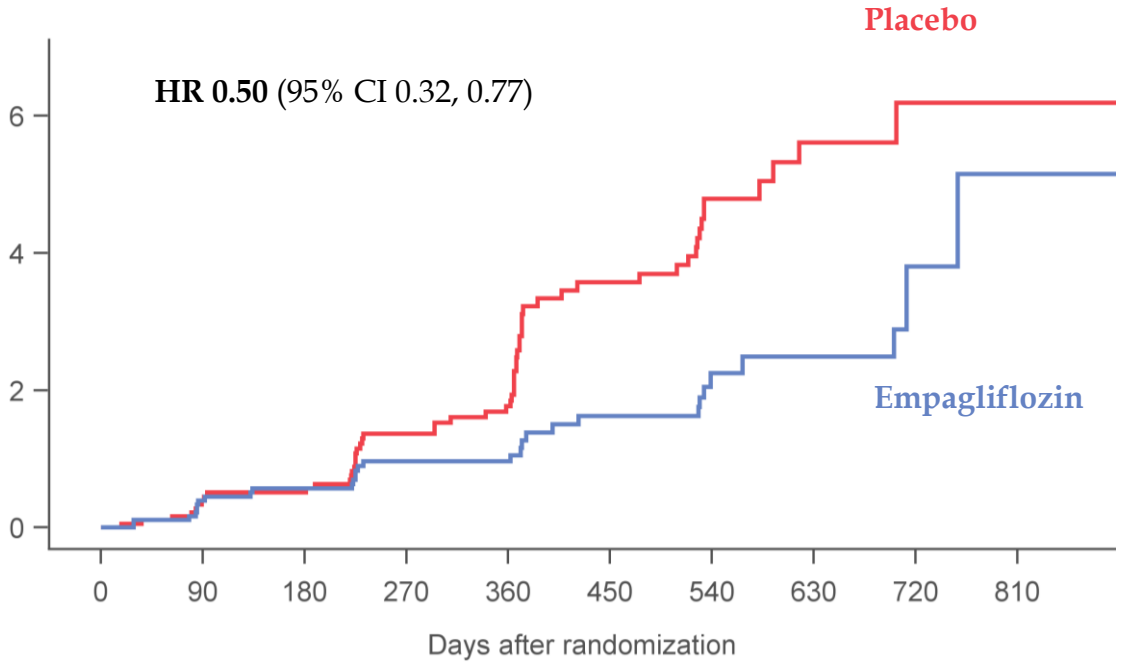
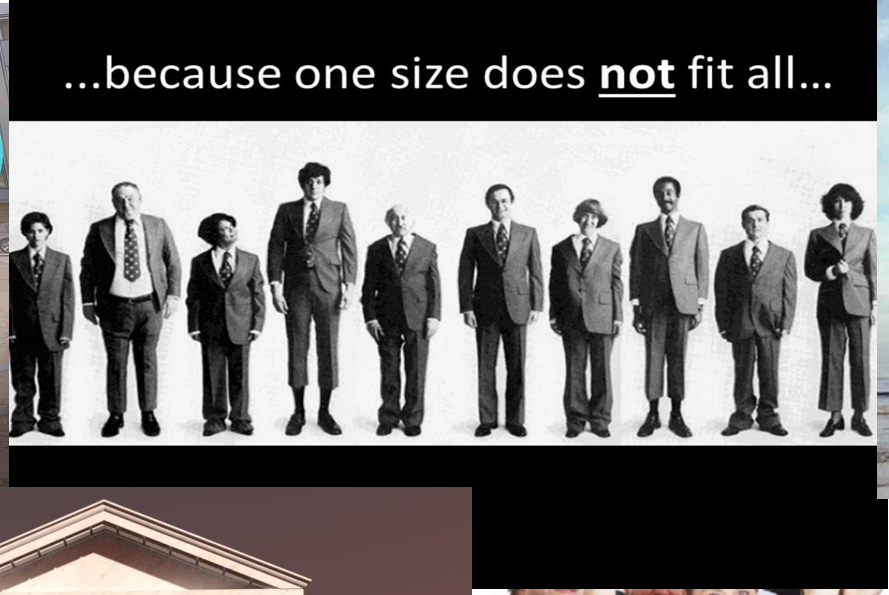


N Engl J Med 2020;383:1413-24.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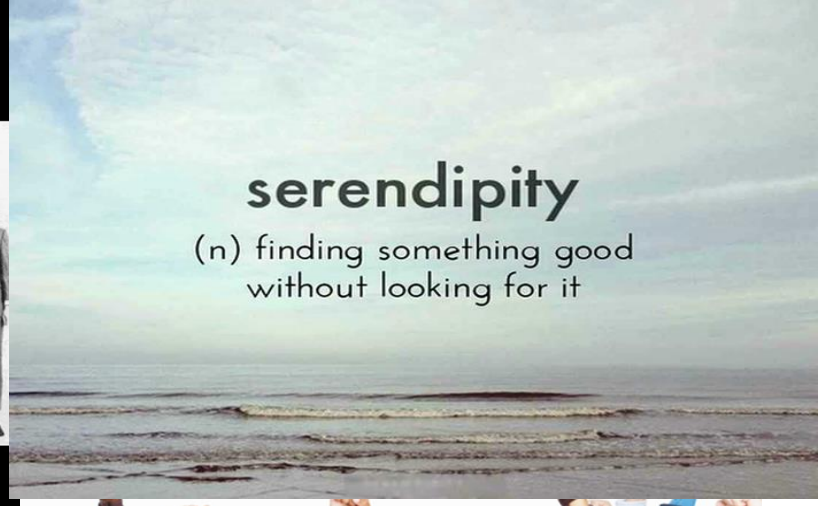
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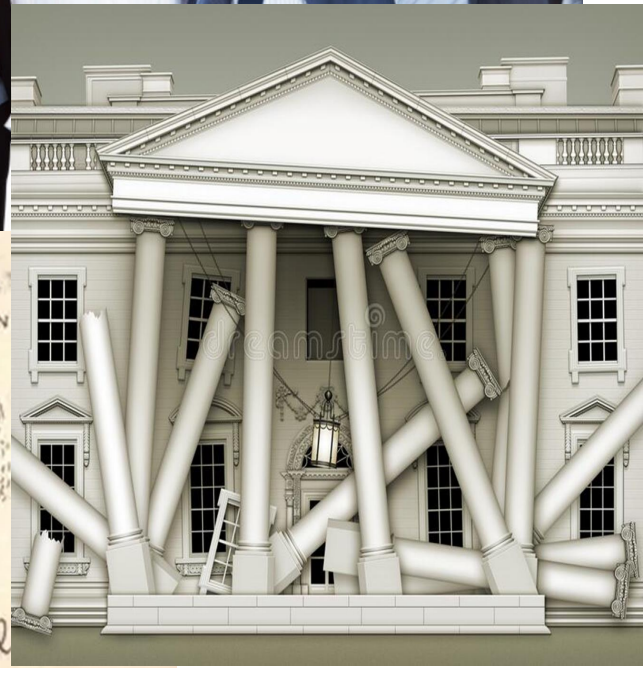


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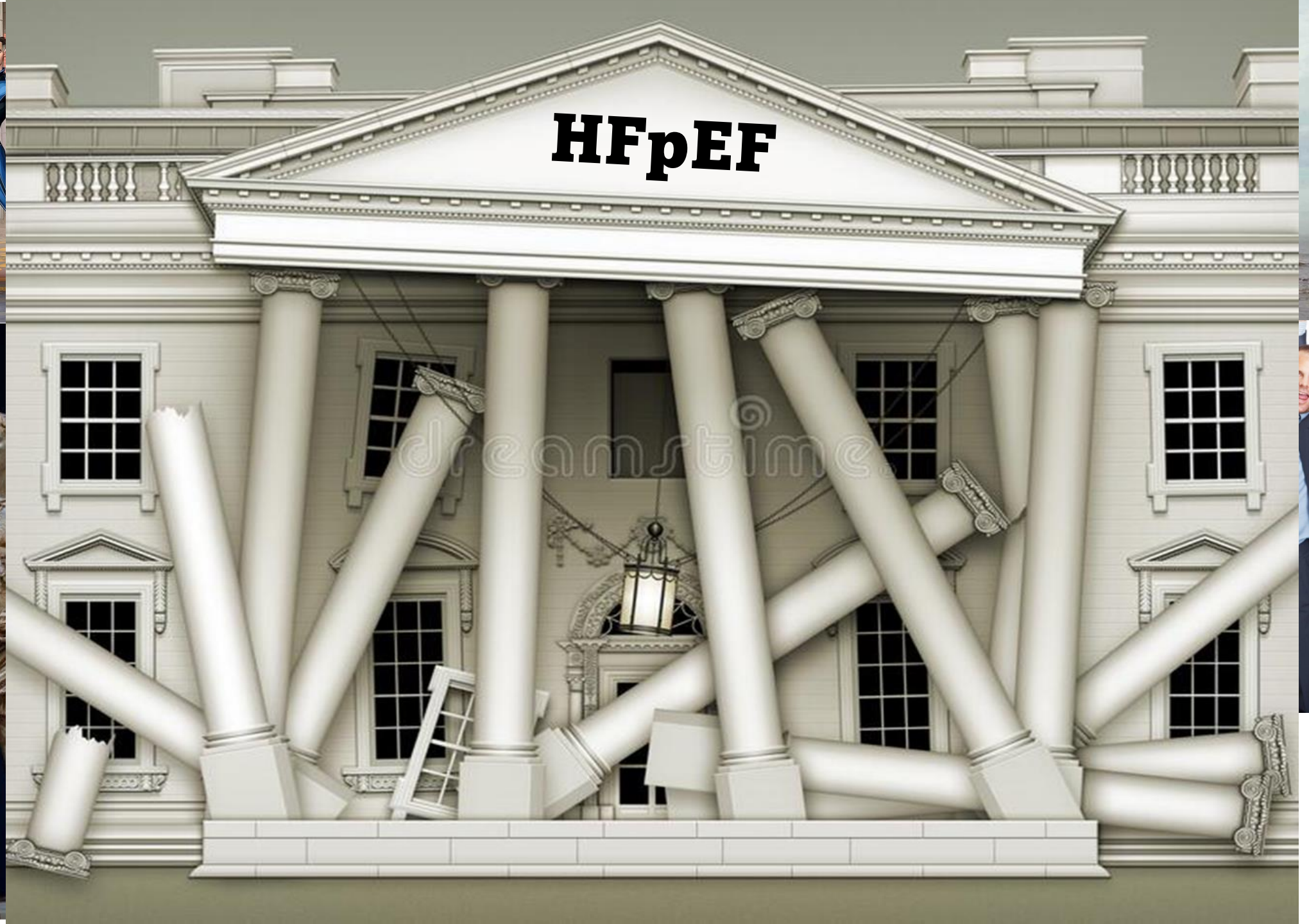
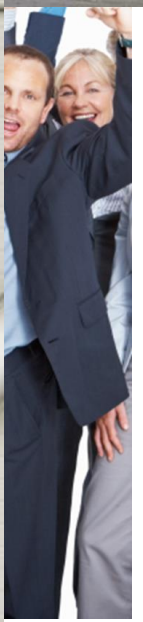
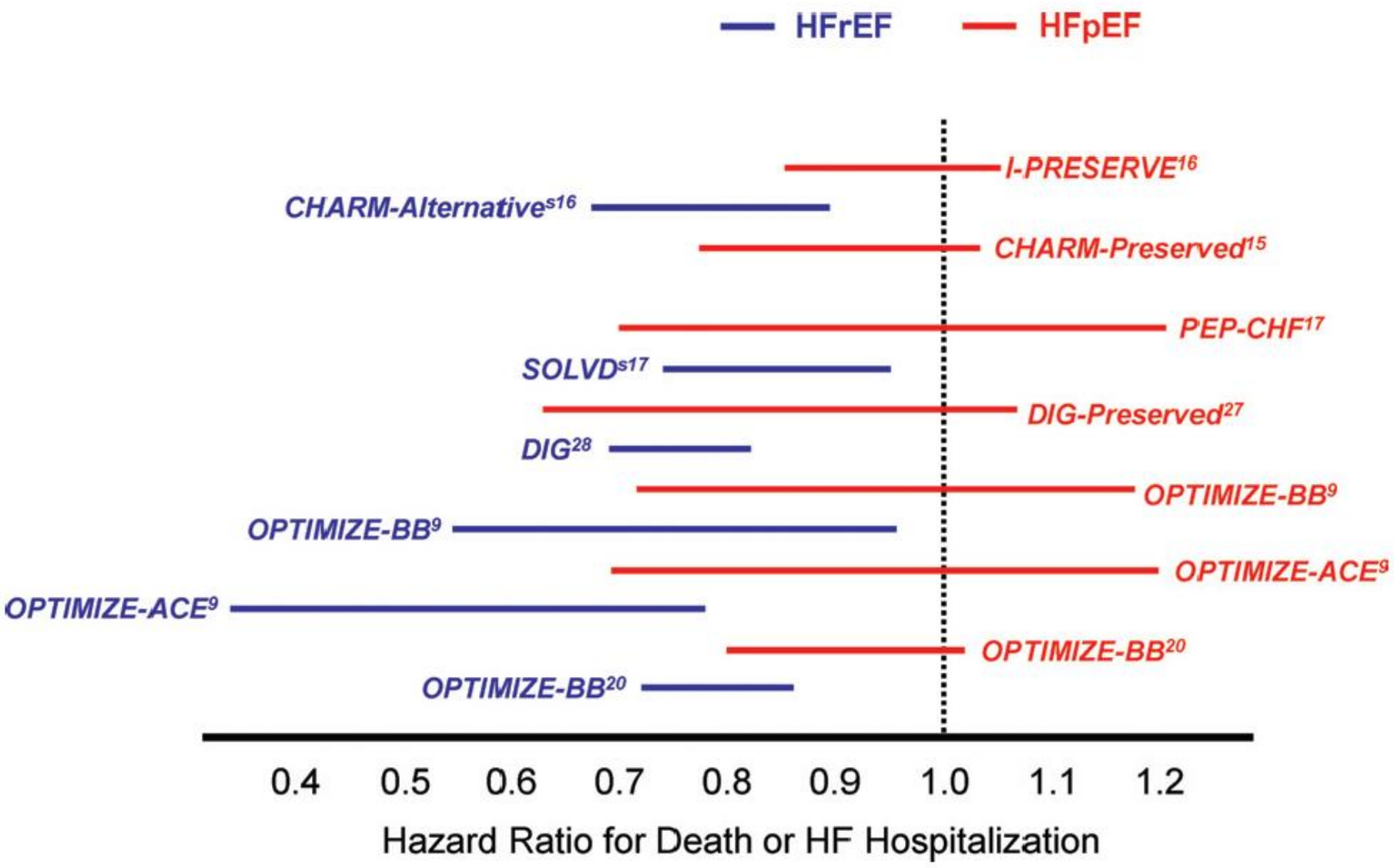
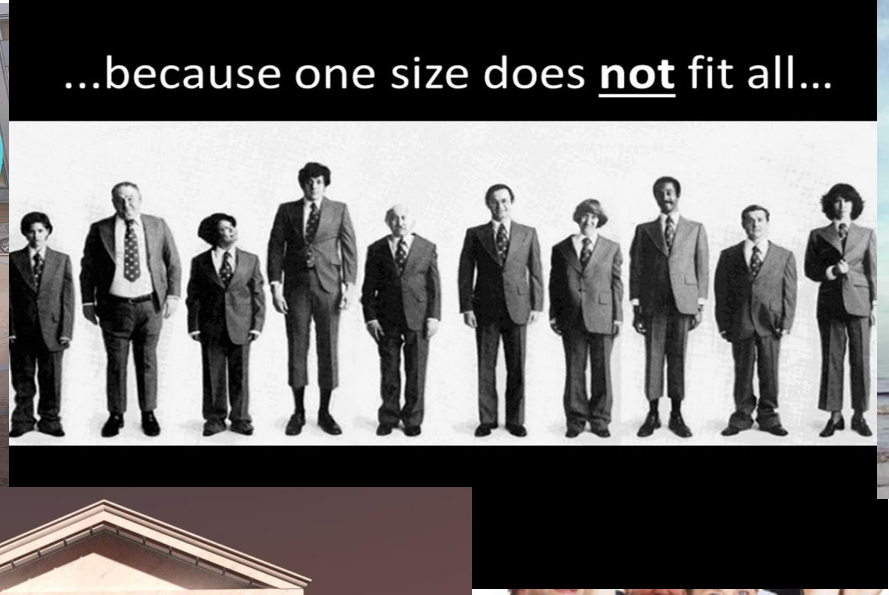

HFpEF



Benefit of Treatments in HFrEF vs HFpEF

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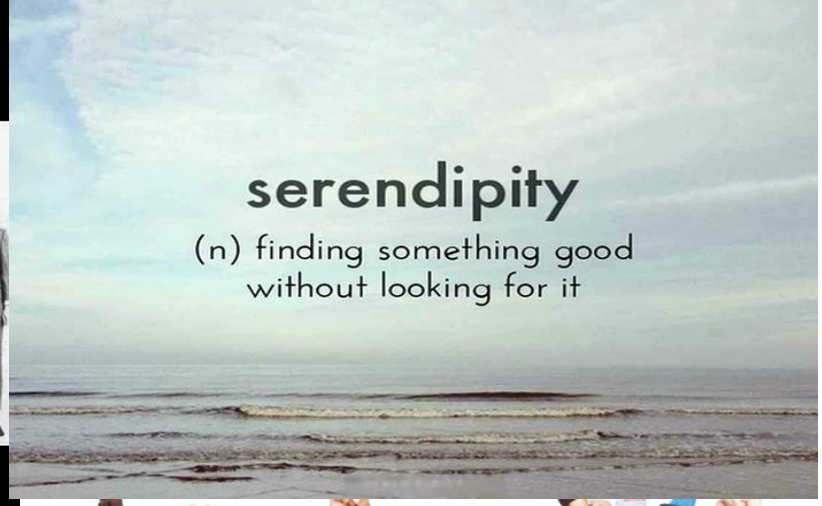
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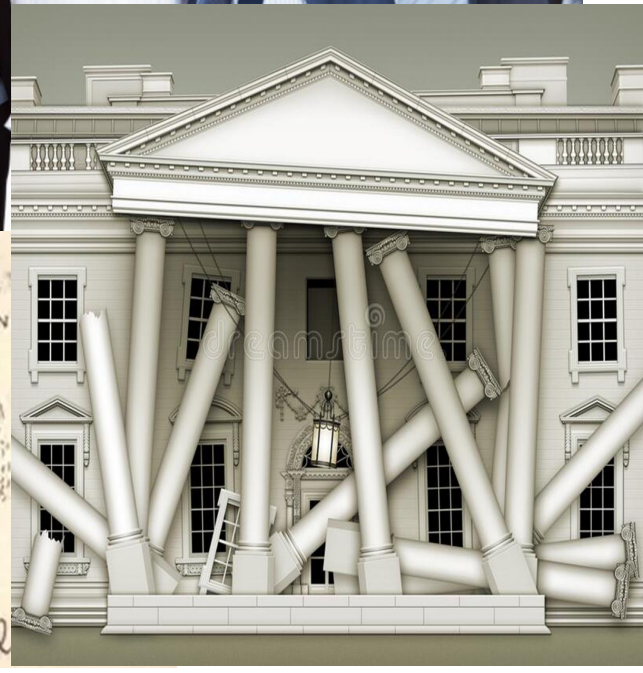


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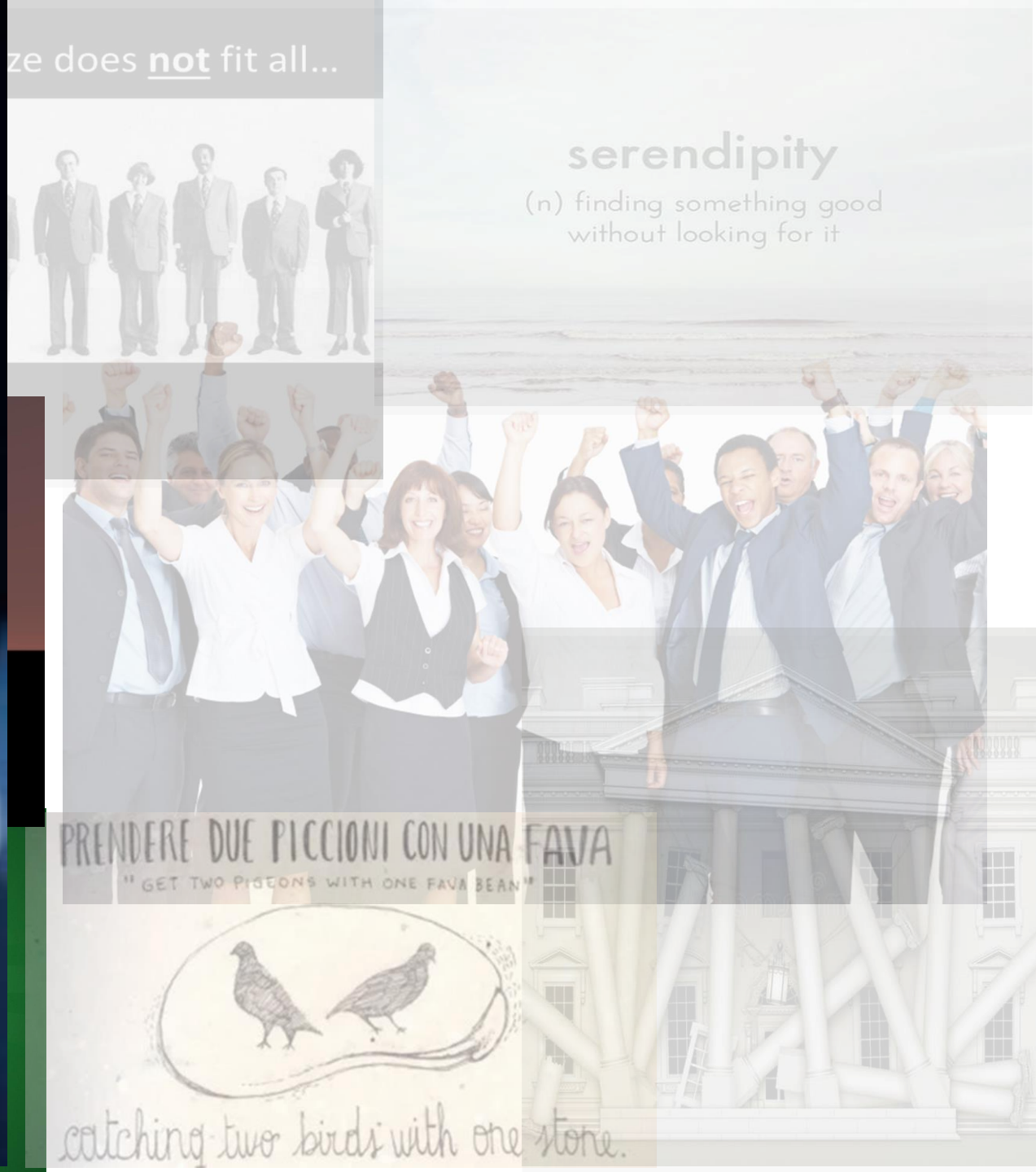
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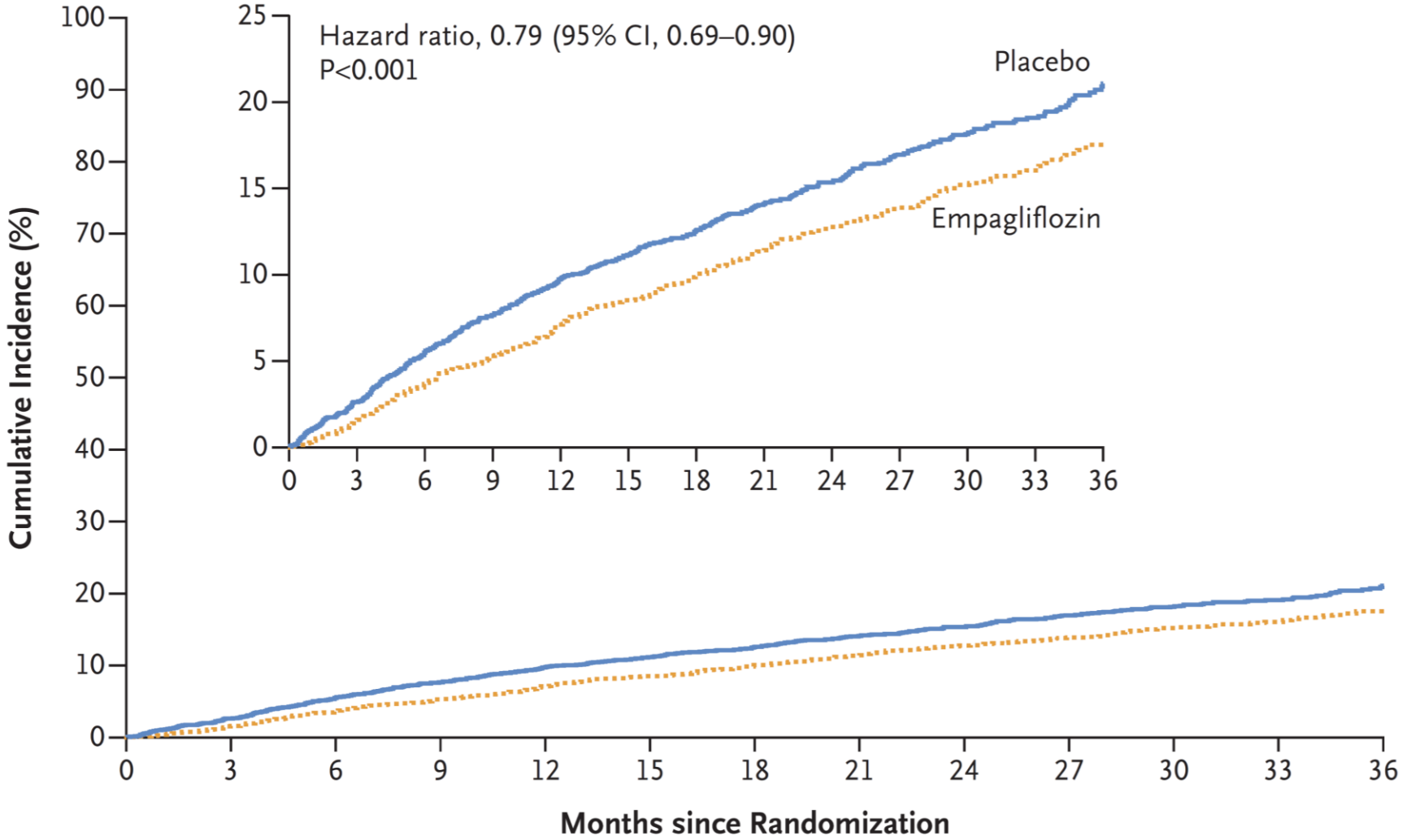
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 14, 2021 VOL. 385 NO. 16

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

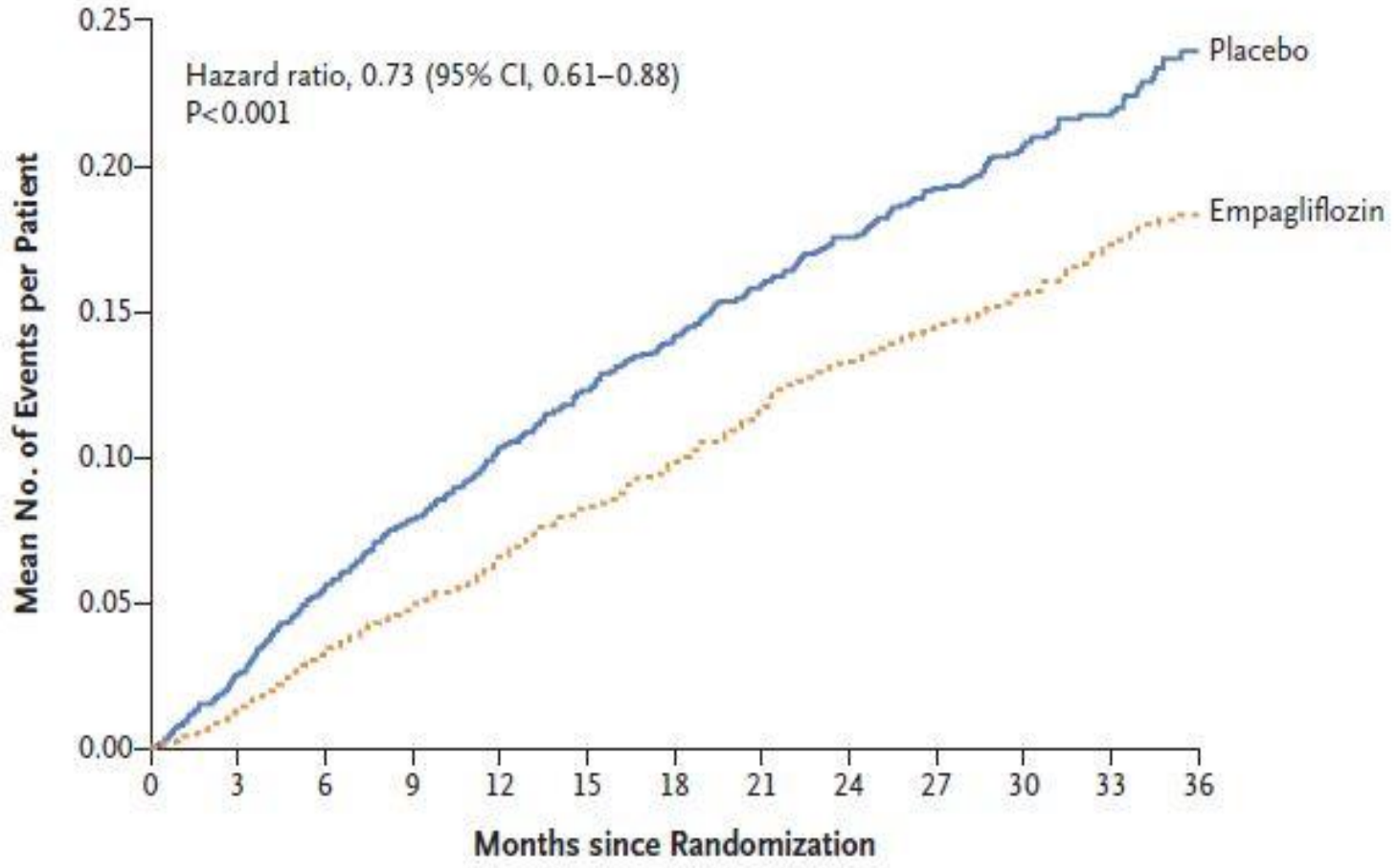
S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, I.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

Primary EP: CV Death or HF Hospitalization



Anker S.D. et al, N Eng J Med 2021 385:1451-1461

Hospitalizations for Heart Failure



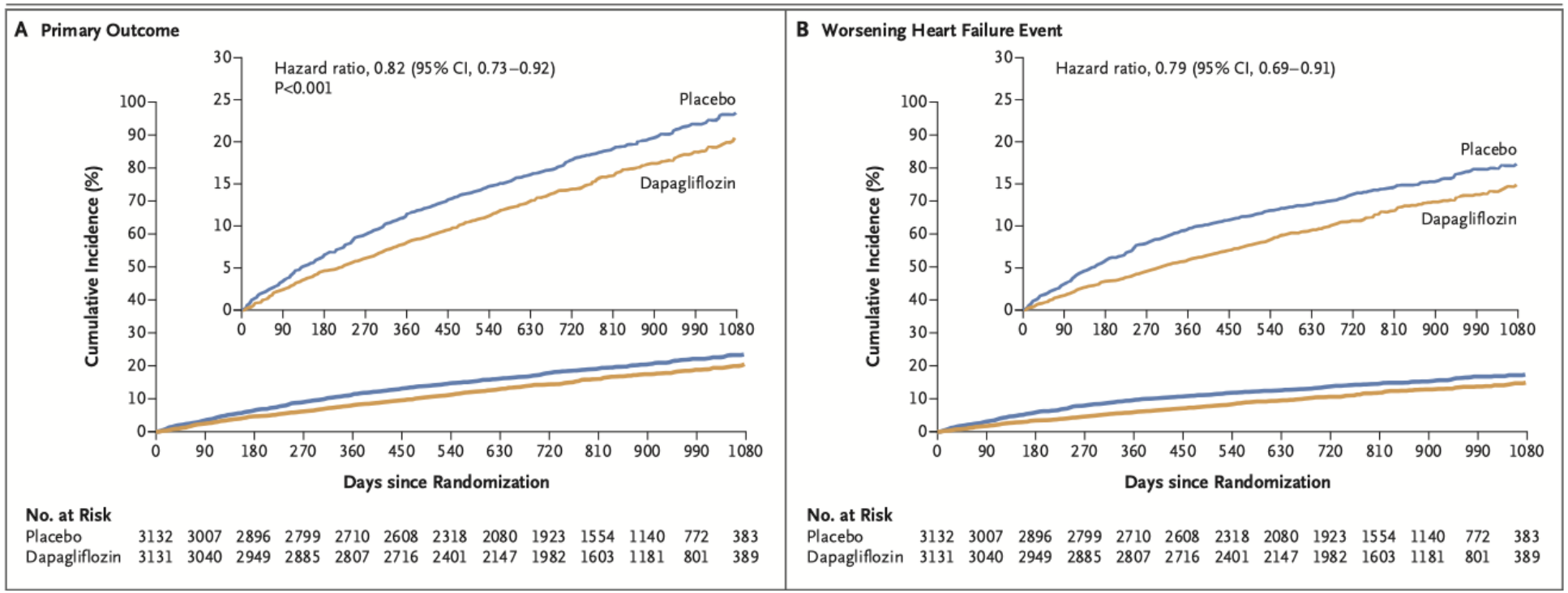
No. at Risk													
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

Anker S.D. et al, N Eng J Med 2021 385:1451-1461

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

6263 pt
LVEF >40%;
elevated NT-proBNP;
NYHA II–IV
ambulatory or hospitalised patients



Solomon SD, et al. DELIVER trial. N Engl J Med. 2022

ESC European Society of Cardiology

European Heart Journal (2023) **44**, 3627–3639
https://doi.org/10.1093/eurheartj/ehad195

ESC GUIDELINES

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

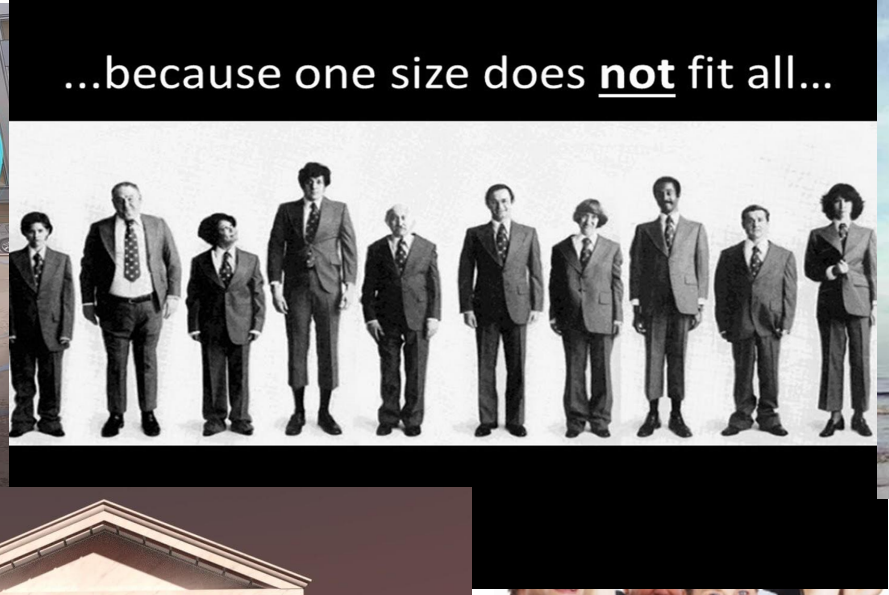
Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A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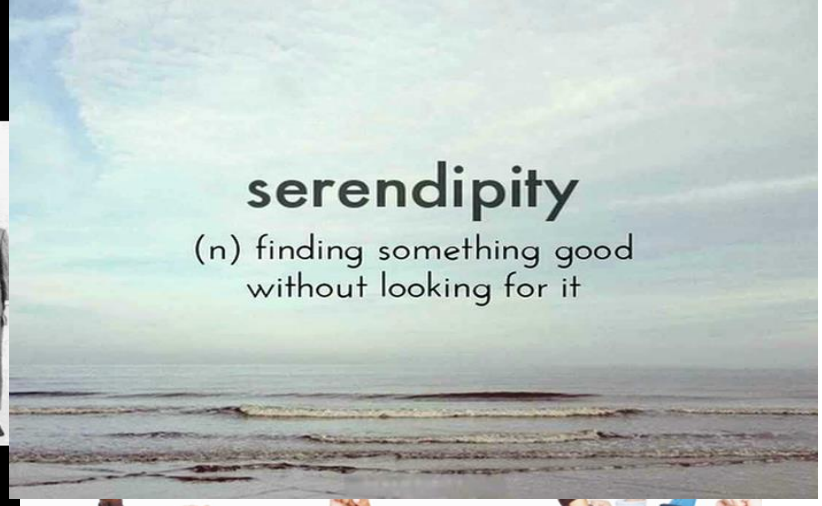
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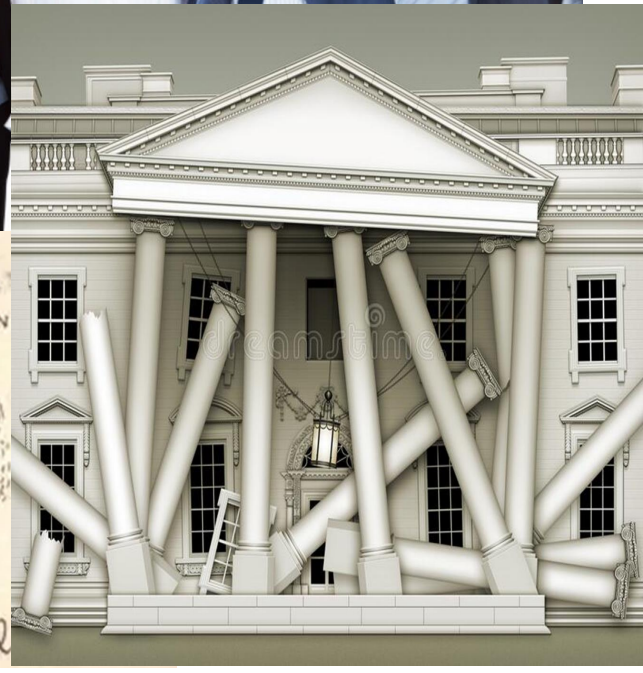


GIN RUMMY


PRENDERE DUE PICCIONI CON UNA
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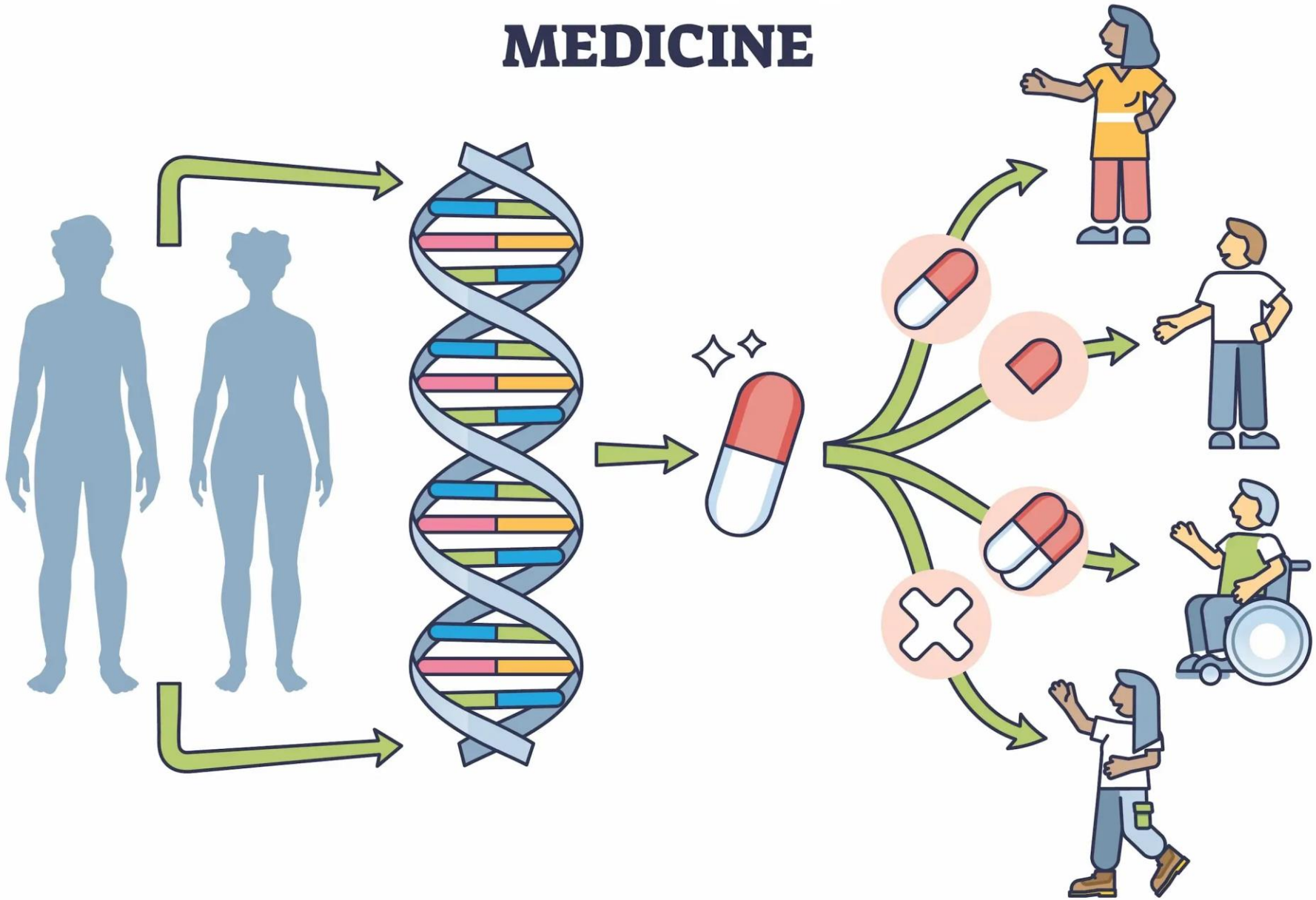
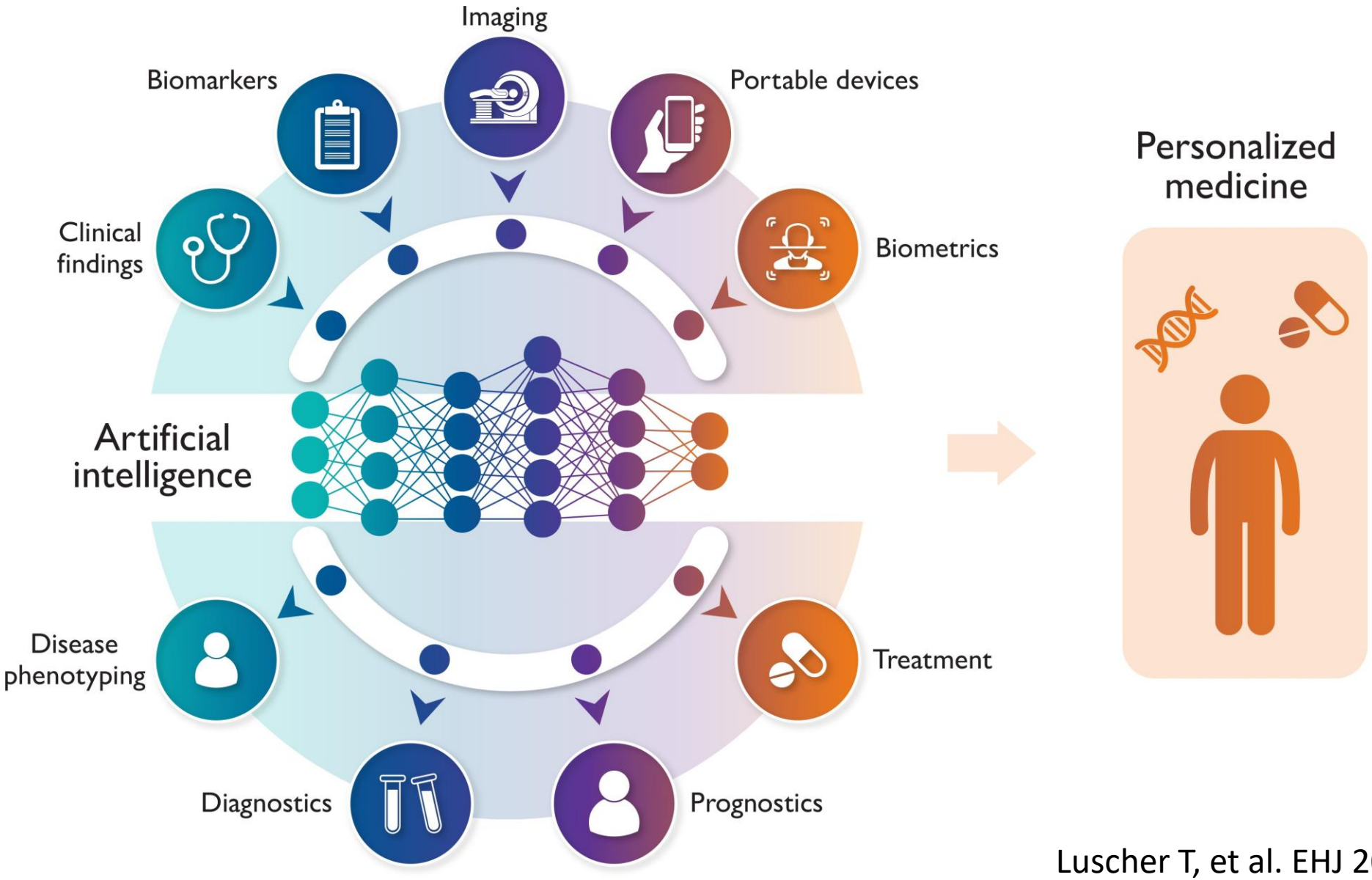
catching two birds with one

...because one size does **not** fit all...

PERSONALIZED MEDICINE



AI-based Revolution in CV Medicine



Luscher T, et al. EHJ 2024

How Appropriate is SGLT2i for Diverse Patient Phenotypes?

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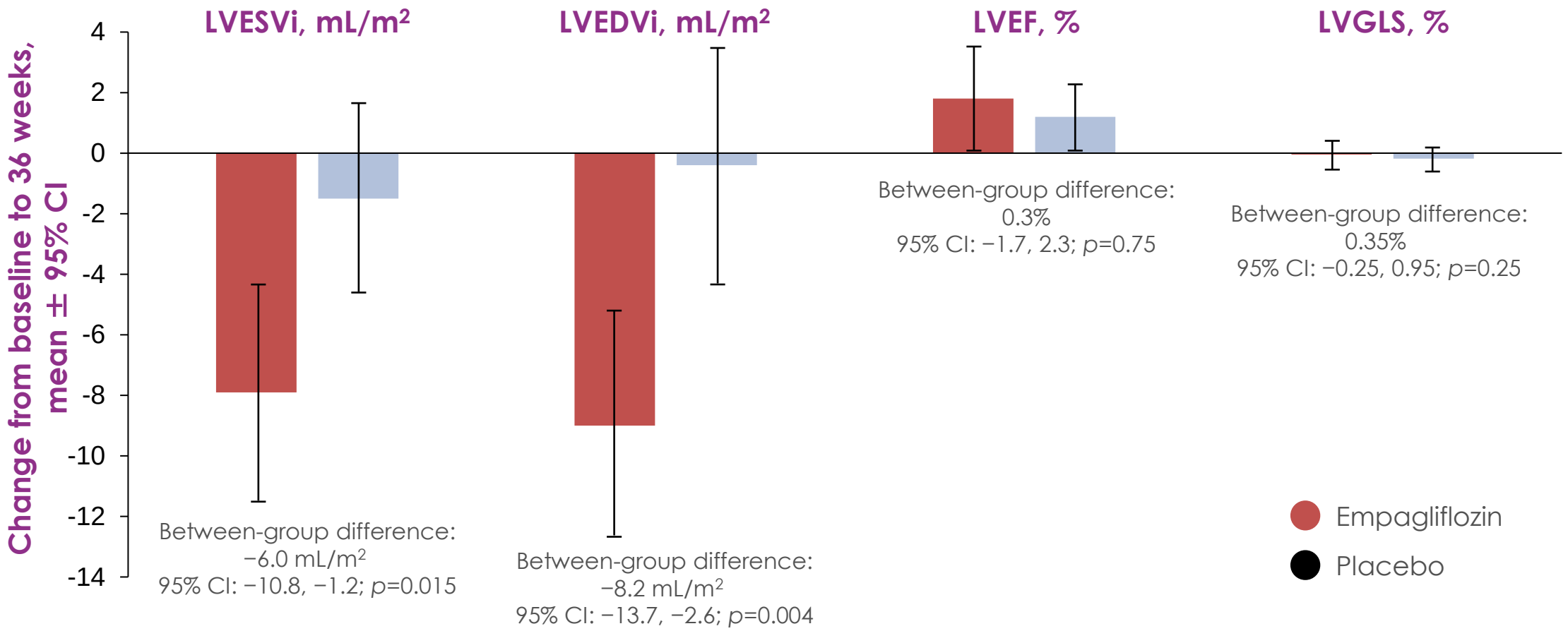
SUGAR-DM: reverse LV remodelling in HFrEF with T2D or pre-diabetes

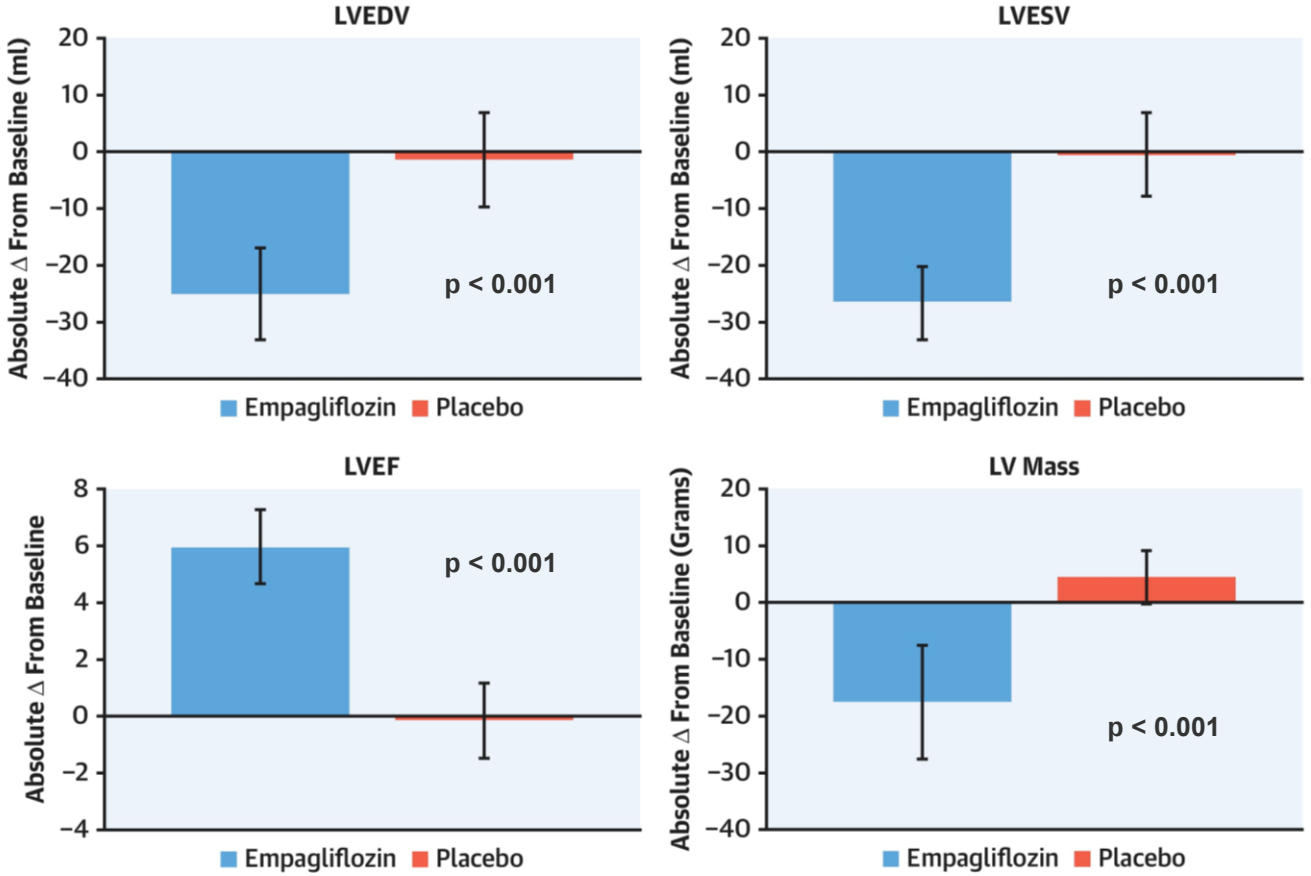


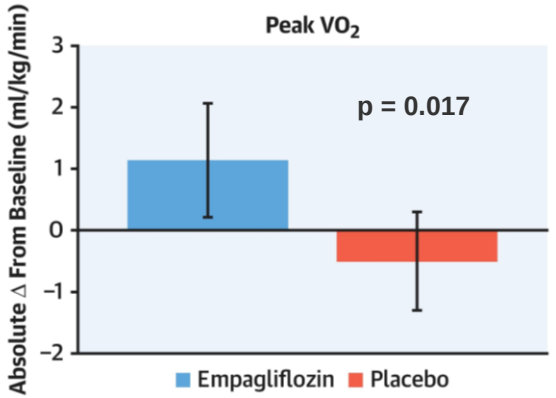
Lee MY *et al. Circulation.* 2021;143:516.

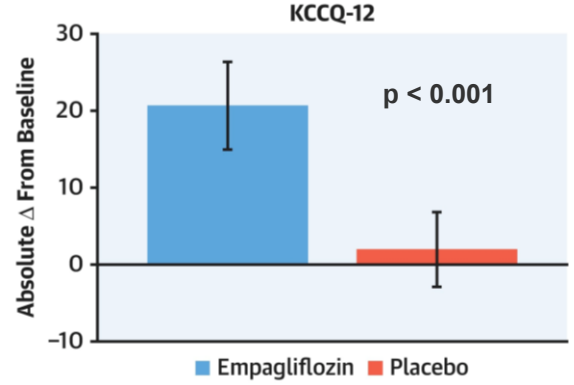
Empagliflozin in Non-diabetic Heart Failure Patients With Reduced Ejection Fraction – EMPA- TROPISM

Double-blind, placebo-controlled trial, nondiabetic HFrEF pts (n = 84) randomized to empagliflozin or placebo for 6 months

Primary endpoint: change in LV end-diastolic and -systolic volume assessed by CMR







J Am Coll Cardiol 2021;77:243–55

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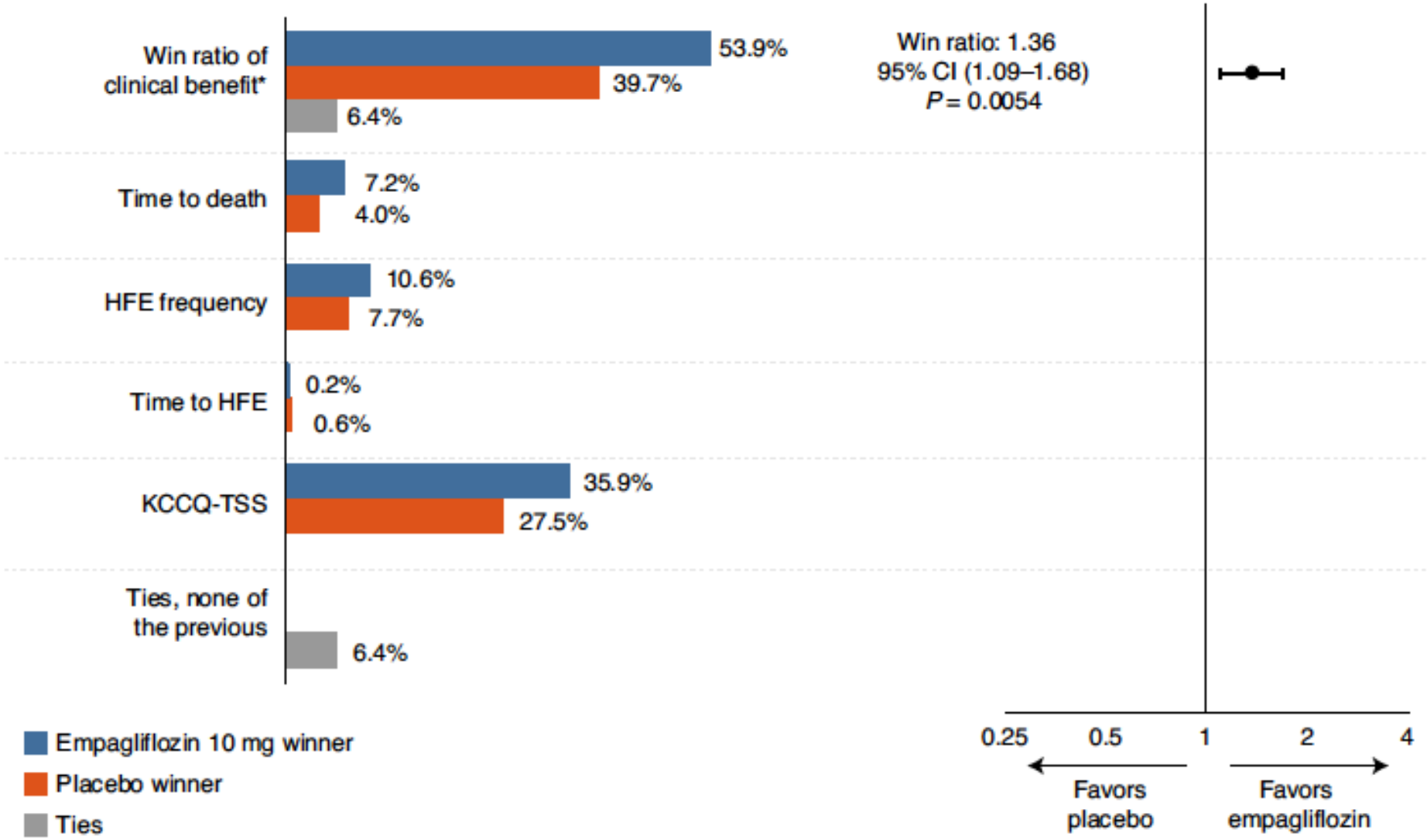
EMPULSE: empagliflozin in patients hospitalized for acute HF

The primary outcome of the trial was clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5 point or greater difference in change from baseline in the KCCQ Symptom Score at 90 days, as assessed using a win ratio



Voors AA et al. Nat Med. 2022

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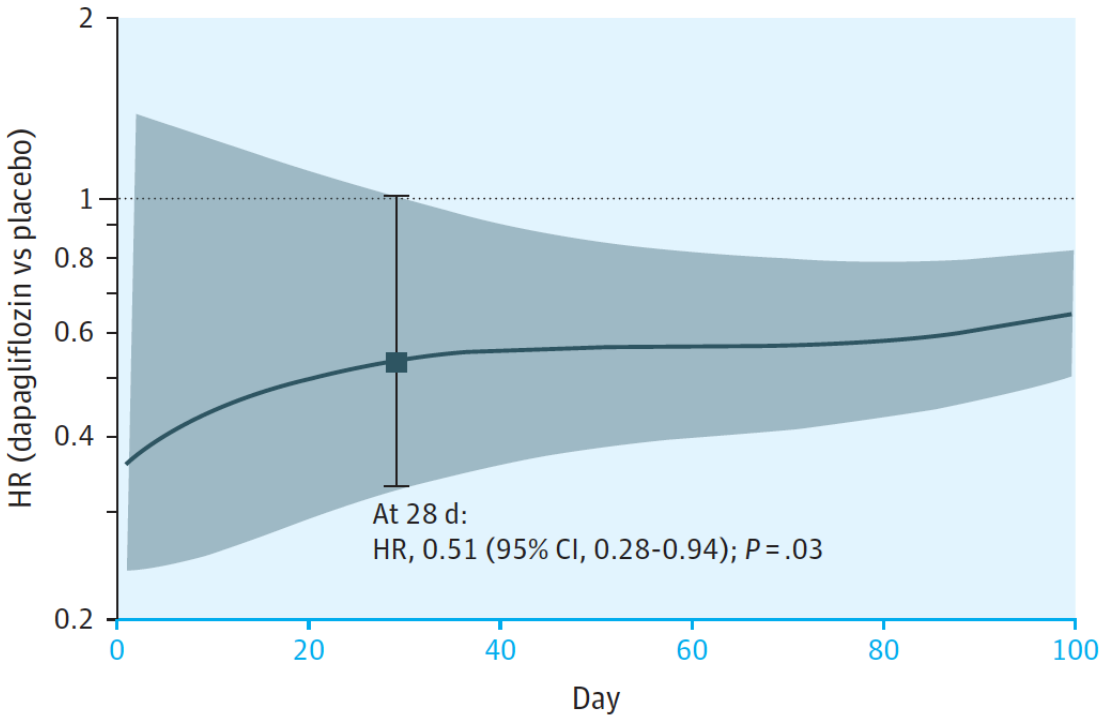
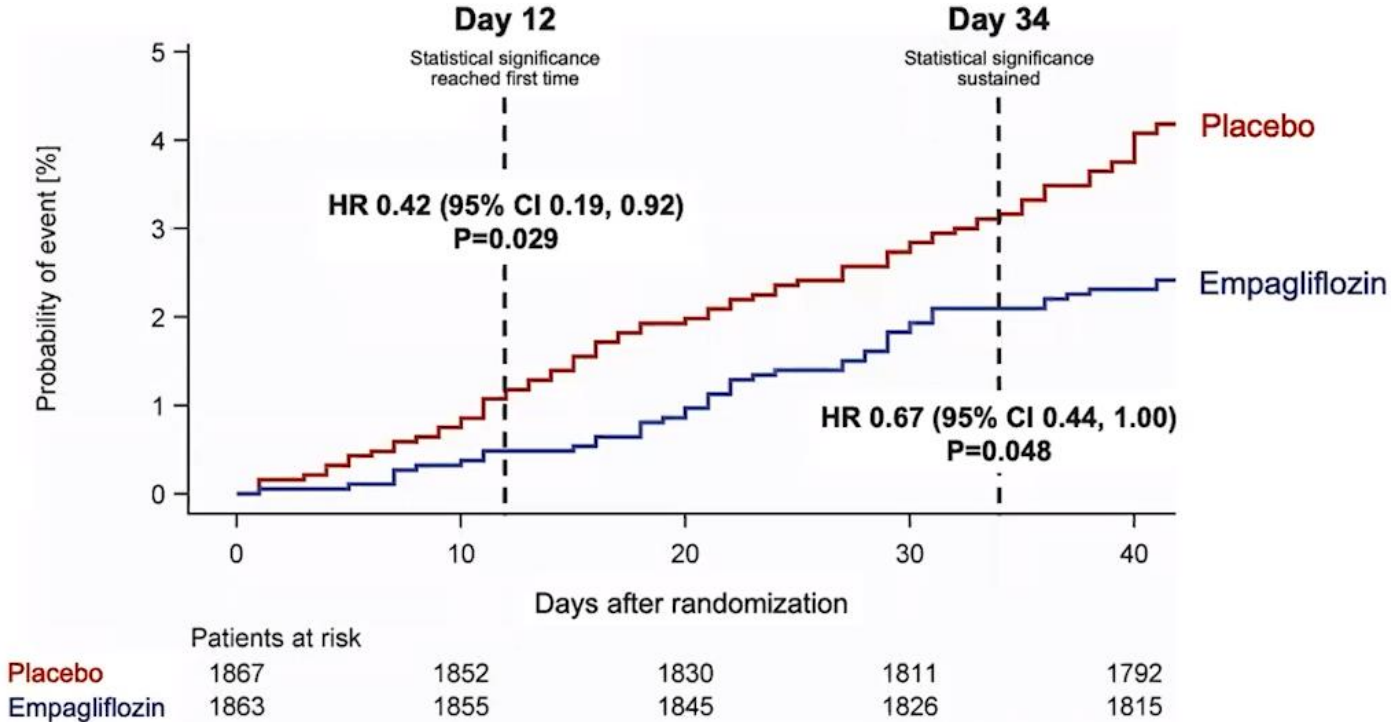
Early Clinical Benefit of SGLT2 i





JAMA Cardiol. 2021;6(5):499-507

Adapted from Packer et al., Presented during e-space 1st Cardio-renal-metabolic Global Web Conference, January 22 – 24, 2021

Empagliflozin and hypotension in different SBP subgroup

	Baseline SBP (mmHg)					
	<110 (n=927)		110–130 (n=1752)		>130 (n=1047)	
	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin
Any adverse event – number	489	438	875	877	499	548
Hypotension*						
Number (%)	62 (12.7)	58 (13.2)	66 (7.5)	88 (10.0)	35 (7.0)	30 (5.5)
Incidence rate/100 patient-years	11.8	12.4	6.6	8.6	5.9	4.6
Symptomatic hypotension†						
Number (%)	44 (9.0)	35 (8.0)	41 (4.7)	51 (5.8)	18 (3.6)	20 (3.6)
Incidence rate/100 patient-years	8.2	7.3	4.0	4.9	2.9	3.0

*Based on preselected adverse events. †Investigator defined.

Böhm M *et al. J Am Coll Cardiol.* 2021;78:1337.

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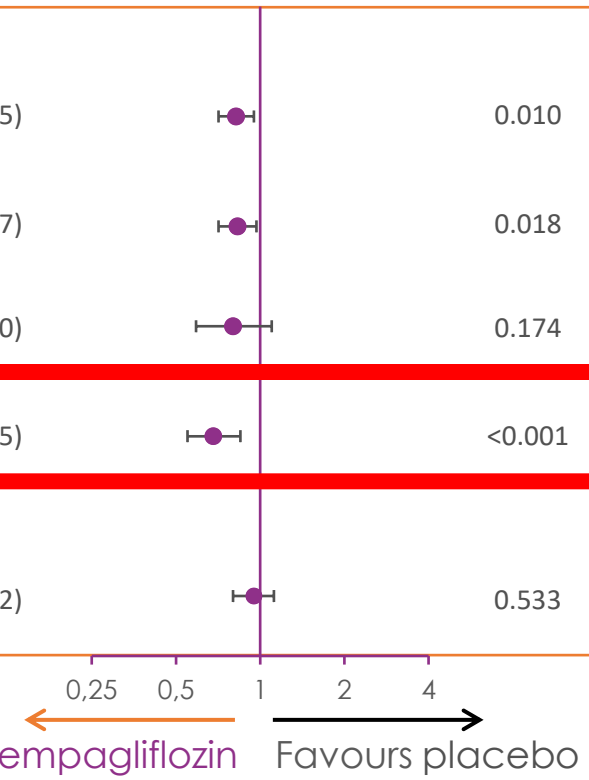
EMPEROR-Pooled: Effect of Empa on hyper/hypokalaemia

	Empagliflozin		Placebo				
	n/N (%)	Event rate/100 patient-years	n/N (%)	Event rate/100 patient-years	HR (95% CI)	HR (95% CI)	Interaction *p*-value
Hyperkalaemia							
Investigator-reported hyperkalaemia or initiation of potassium binders*	313/4837 (6.5)	4.1	371/4837 (7.7)	5.0	0.82 (0.71, 0.95)		0.010
Investigator-reported hyperkalaemia	295/4859 (6.1)	3.9	347/4852 (7.2)	4.6	0.83 (0.71, 0.97)		0.018
Initiation of potassium binders*	73/4837 (1.5)	0.9	85/4837 (1.8)	1.1	0.80 (0.59, 1.10)		0.174
Potassium >6.0 mmol/L or new initiation of potassium binders†	145/4718 (3.1)	2.1	204/4746 (4.3)	3.0	0.68 (0.55, 0.85)		<0.001
Hypokalaemia							
Investigator-reported hypokalaemia or initiation of potassium supplement‡	273/4257 (6.4)	4.1	285/4241 (6.7)	4.3	0.95 (0.80, 1.12)		0.533



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Böhm M *et al. J Am Coll Cardiol.* 2021;78:1337.

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SGLT2i HTx Study RESULTS Baseline characteristics

	Overall (n=71)	SGLT2i treated pts (n=37)	Controls (n=34)	p value
Age (years)	55 ± 9	54 ± 9		0.3
Male sex	47 (85.5)	26 (89.7)		0.35
Systolic BP (mmHg)	108 ± 13			0.7
Cardiac index (l/min/m^2)	2.0 ± 0.4		± 0.4	0.13
Mean PAP (mmHg)			27 ± 9	0.5
Wedge Pressure (mmHg)		18 ± 8	18 ± 7	0.9
Ejection fraction (%)		25 ±7	25 ± 8	0.7
LV End-diastolic volume (ml)	± 110	256 ± 122	217 ± 91	0.15
RV FAC(%)	33 ± 9	34 ± 9	32 ± 10	0.6
NT-proBNP (pg/ml)	2028 [1245-3007]	2374 [1130-3578]	1951 [1252-2753]	0.6
Furosemide (mg/die)	88 ± 64	88 ± 75	88 ± 52	0.3

71 patients (37 cases, 34 controls) with no difference in baseline characteristics

RESULTS - Haemodynamics

	SGLT2i treated pts (n=26)		
	Baseline RHC	**6-month RHC**	**p value**
CI ($l/min/m^2$)	2.0 ± 0.5	2.3 ± 0.4	**0.04**
PAPs (mmHg)	44 ± 17	36 ± 17	**<0.01**
PAPm (mmHg)	28 ± 12	24 ± 12	0.05
Wedge (mmHg)	18 ± 9	16 ± 10	0.06
RAP (mmHg)	8 ± 5	7 ± 4	0.1
PVR (UW)	2.9 ± 1.7	2.4 ± 1.3	0.14

RESULTS - SGLT2i tolerability and specific effects

- All patients started on study drug
- One (2.7%) early drug interruption
- No reported collateral effects

EXCELLENT TOLERABILITY

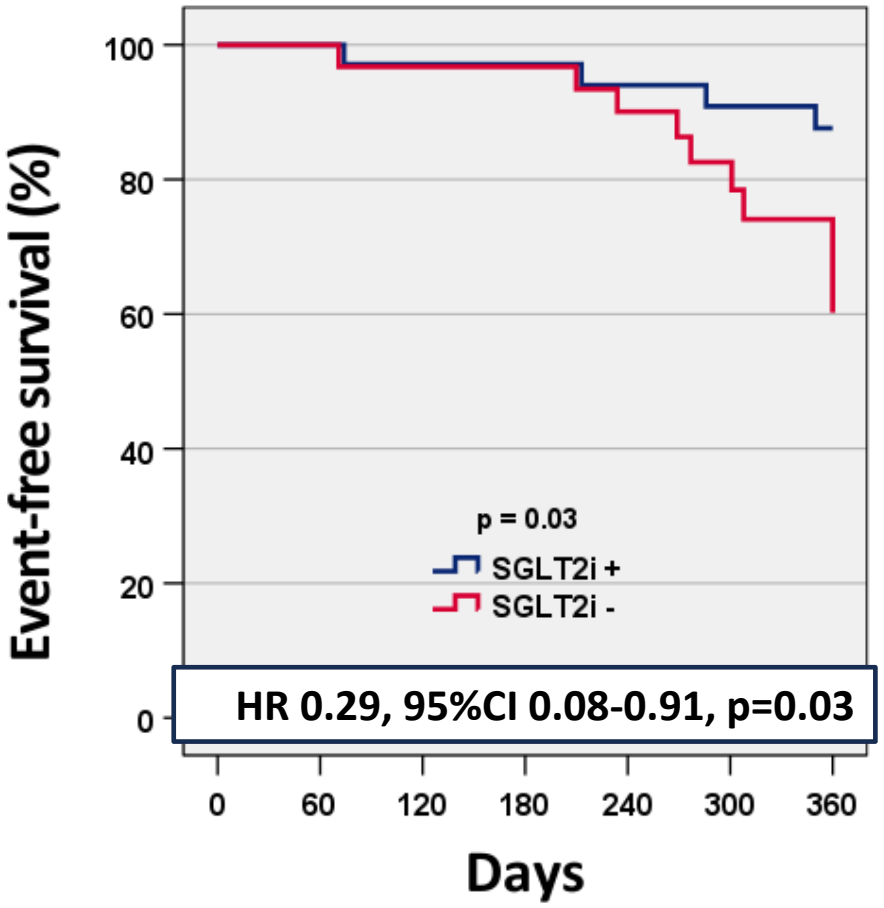
	BASELINE	6-month	p value
NYHA CLASS	2.47 ± 0.6	2.27 ± 0.58	**0.03**
Systolic BP (mmHg)	110 ± 10	103 ± 11	**<0.01**
NT-proBNP [IQR]	2374[1130-3578]	2039 [719-3867]	1.0
Creatinine (mg/dl)	1.28 ± 0.40	1.31 ± 0.32	0.3
Hb (g/dl)	13.3 ± 1.9	13.9 ± 2.1	0.06
Hct (%)	40.4 ± 5.6	41.2 ± 4.7	**0.02**

RESULTS

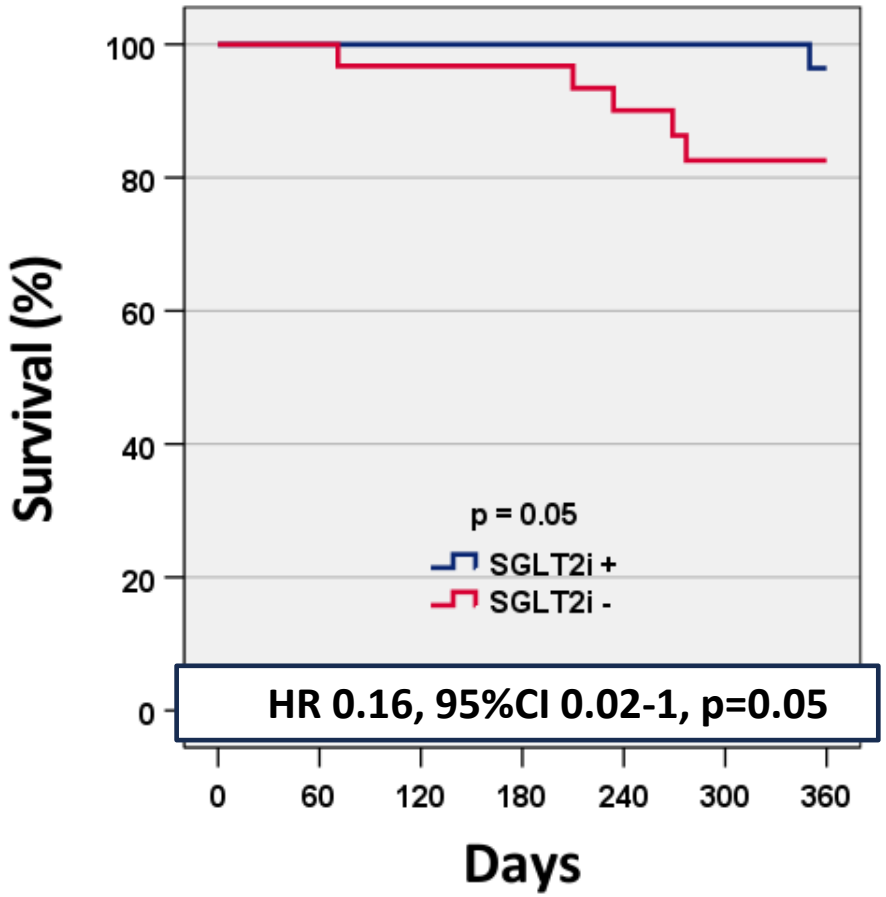
Clinical endpoints

Primary endpoint

(all-cause death, urgent HT, LVAD)



All-cause death



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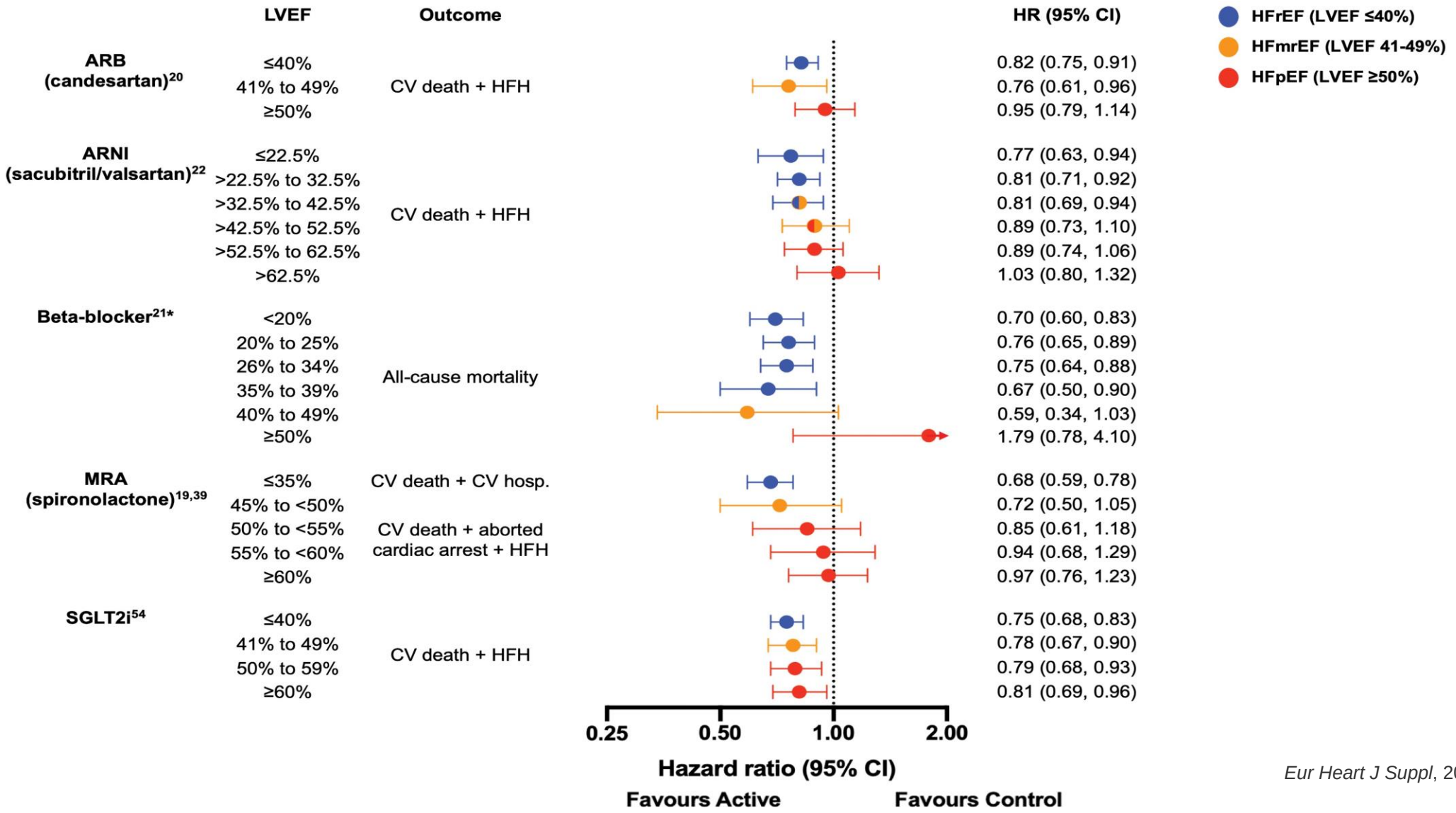
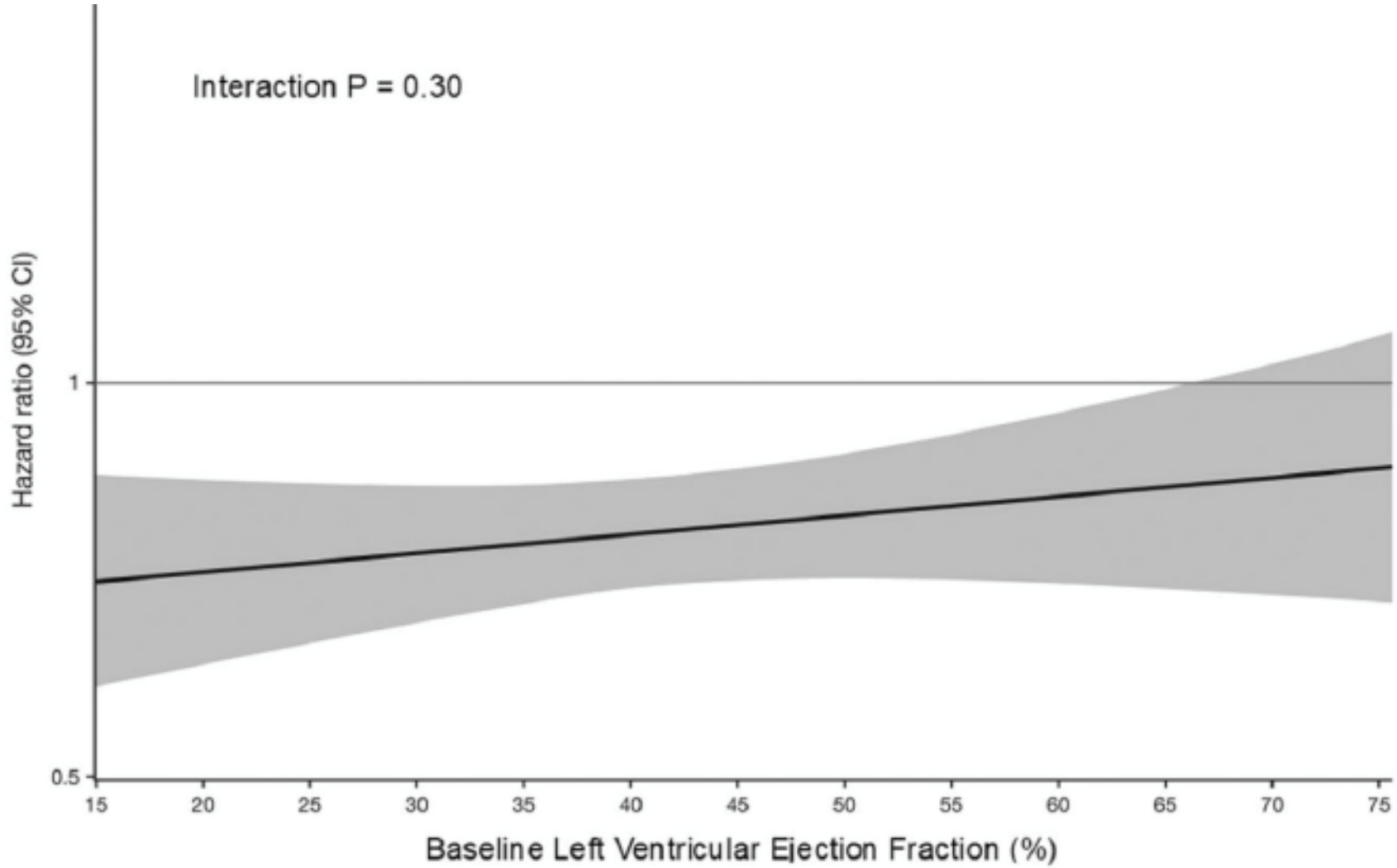
Fab 4 Effects across the full spectrum of LVEF

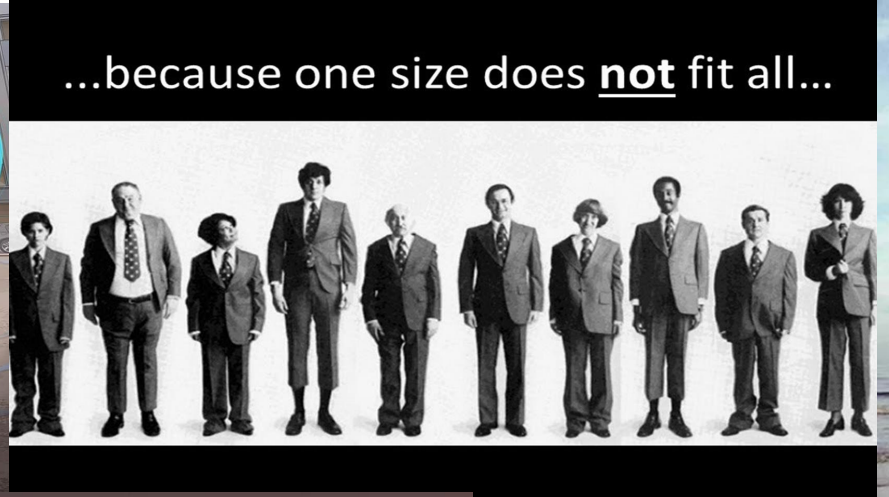


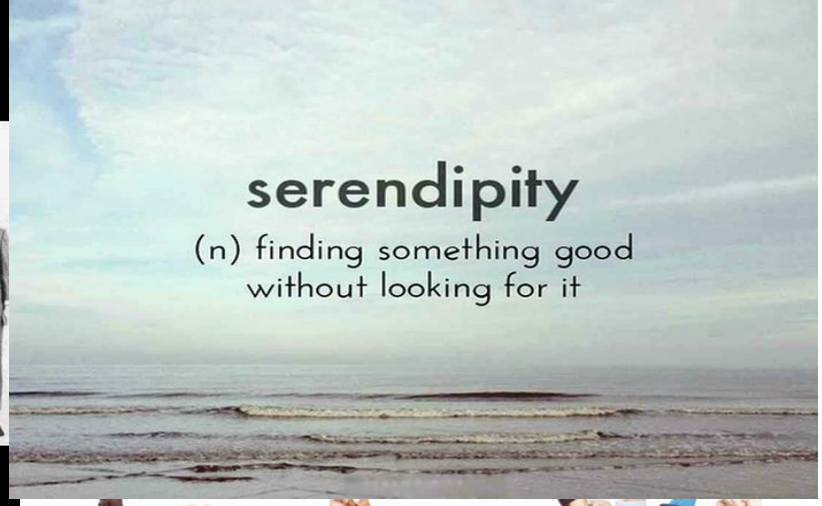
Eur Heart J Suppl, 202;24: L10–L19,

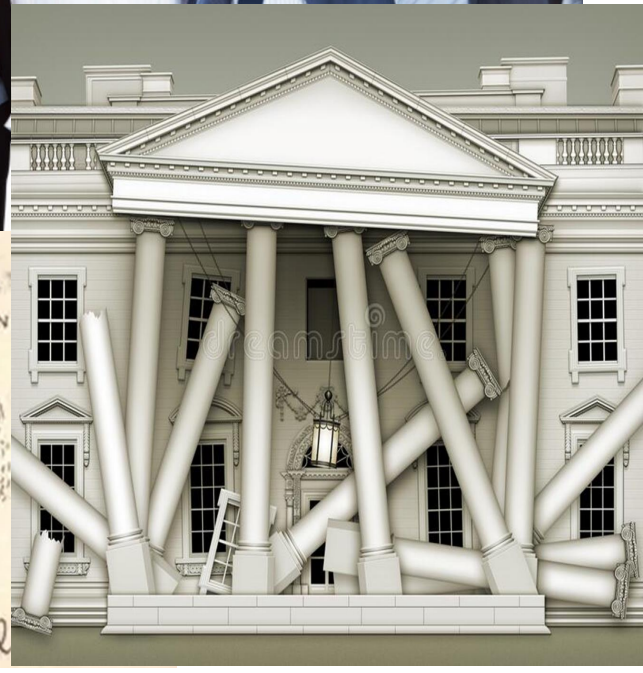
SGLT2i across the full spectrum of LVEF



Butler J et al. Eur Heart J. 2021 Dec 8;ehab798. doi: 10.1093/eurheartj/ehab798


...because one size does not fit all...


serendipity
(n) finding something good
without looking for it




GIN RUMMY

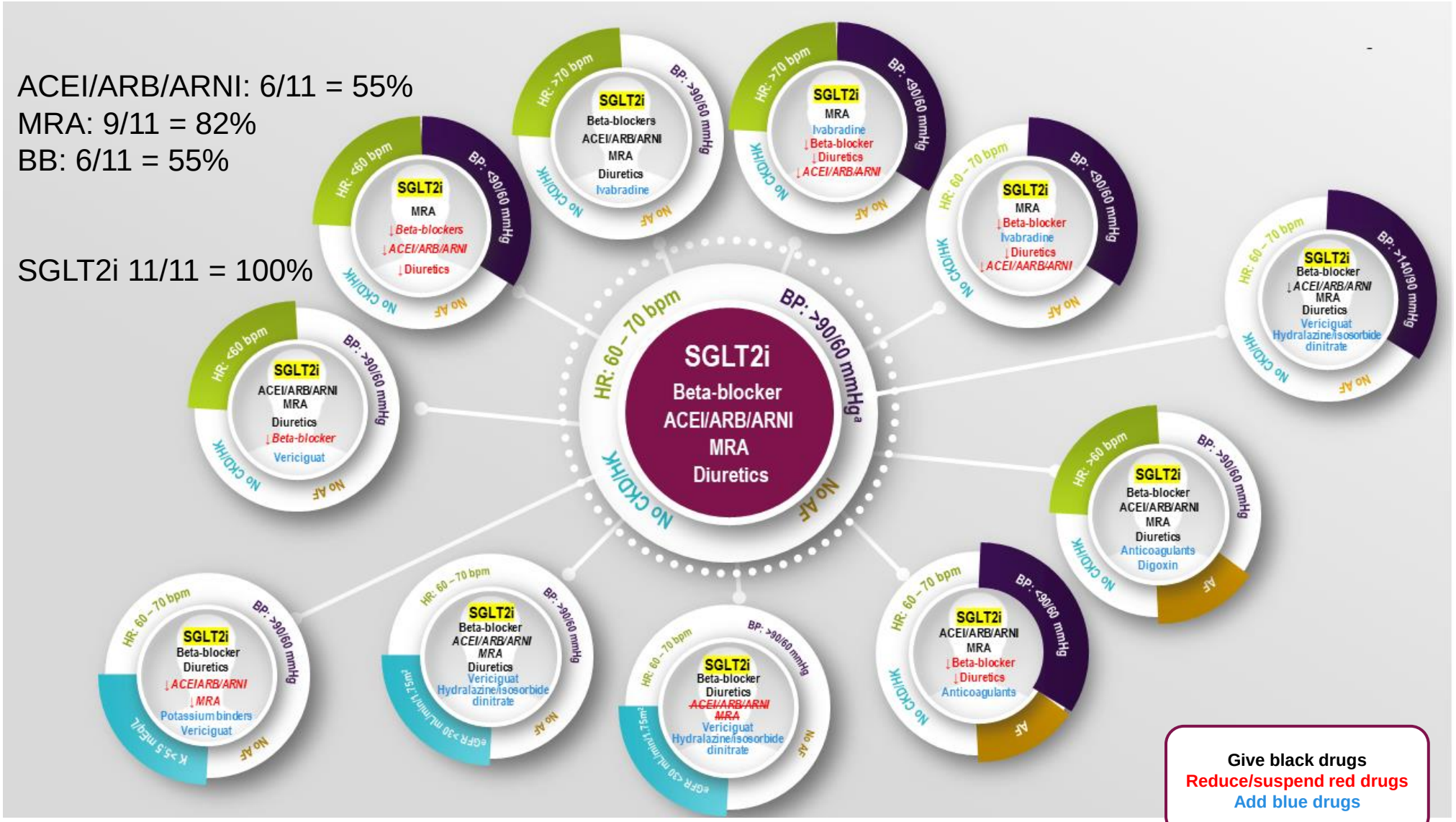

PRENDERE DUE PICCIONI CON UNA
" GET TWO PIGEONS WITH ONE FAVA BEAN
catching two birds with one

EMPOWERMENT AND DEMOCRACY

2021 HFA-ESC Consensus for HFrEF Patient Phenotypes

ACEI/ARB/ARNI: 6/11 = 55%
MRA: 9/11 = 82%
BB: 6/11 = 55%

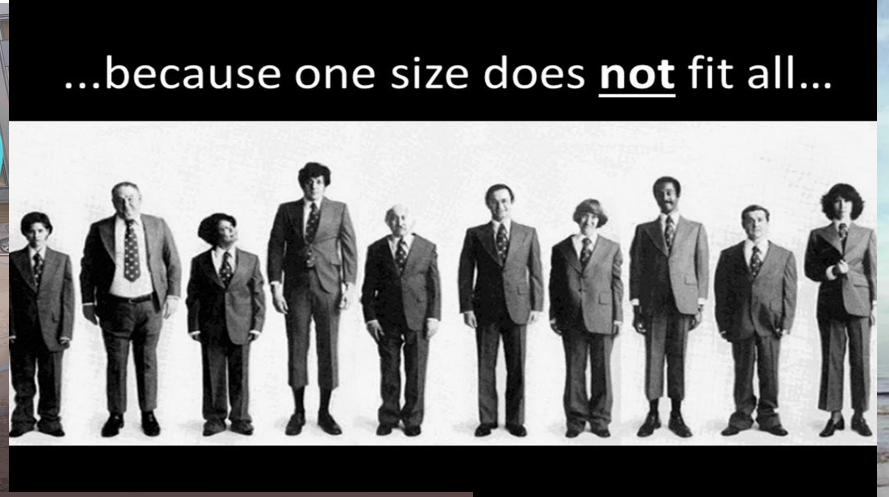
SGLT2i 11/11 = 100%



Give black drugs
Reduce/suspend red drugs
Add blue drugs

[a]In patients with predominant chronic coronary syndrome, BP threshold is 120/80 mmHg.

Rosano GMC et al. Online ahead of print. *Eur J Heart Fail.* 2021;10.1002/ejhf.2206.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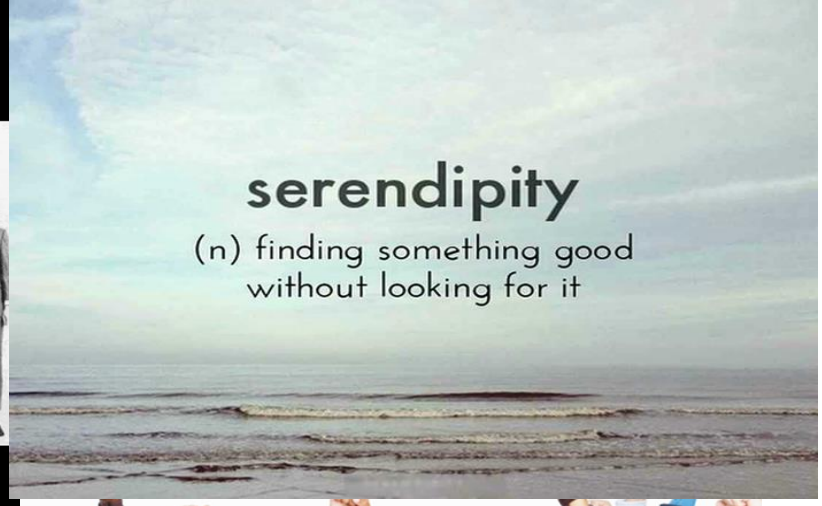
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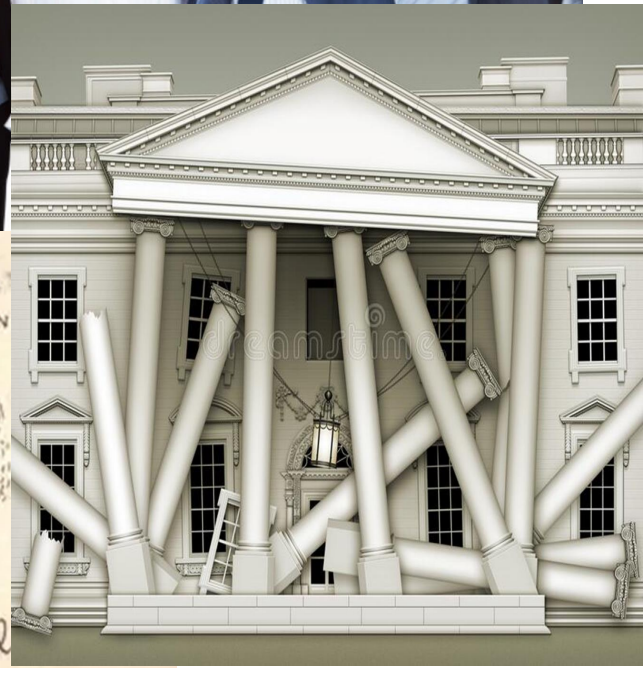



GIN RUMMY


PRENDERE DUE PICCIONI CON UNA
" GET TWO PIGEONS WITH ONE FAVA BEAN
catching two birds with one


I pass
Charlie (0)
GIN RUMMY
Melds
Deadwood (44)
You (0)

THE BERRYS


HEART
FAILURE?

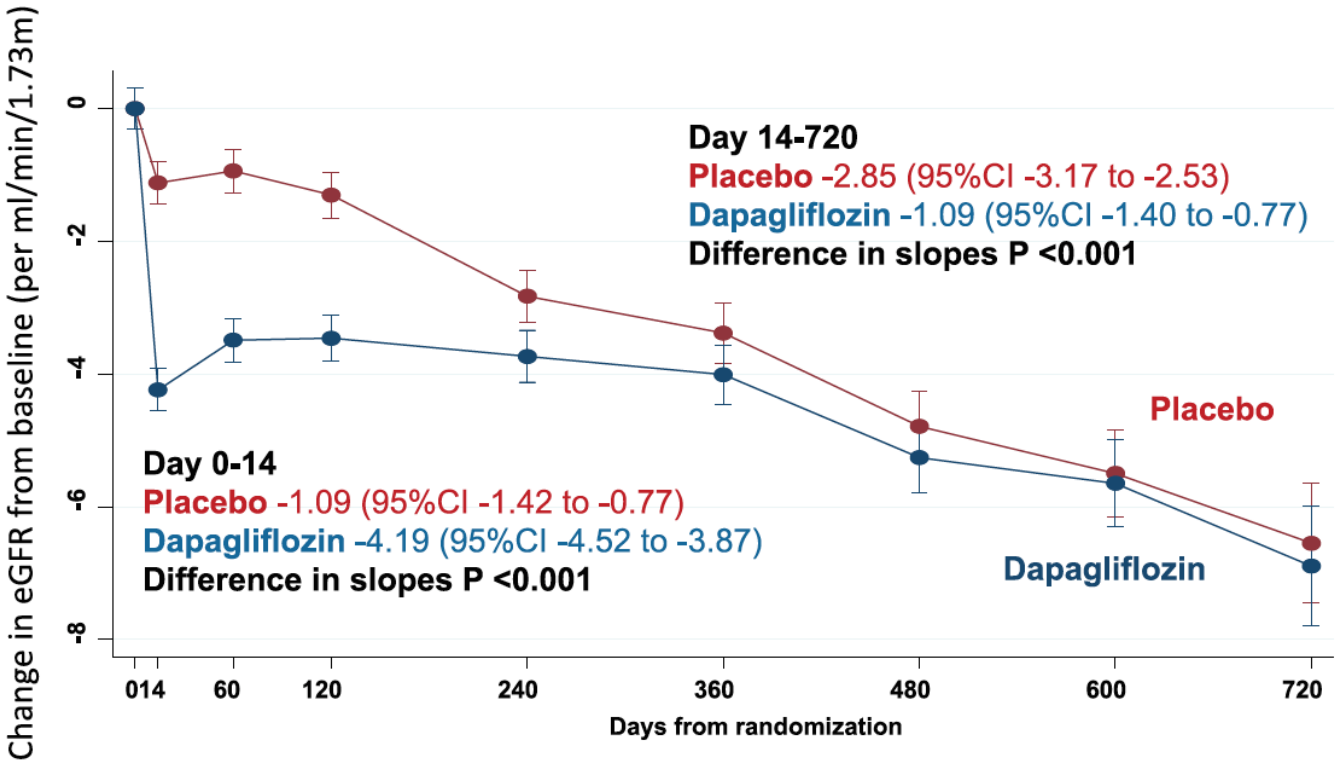

SGLT2
INHIBITOR !


IT'S A
NO BRAINER

EMPOWERMENT AND DEMOCRACY

Slowing rate of decline in eGFR

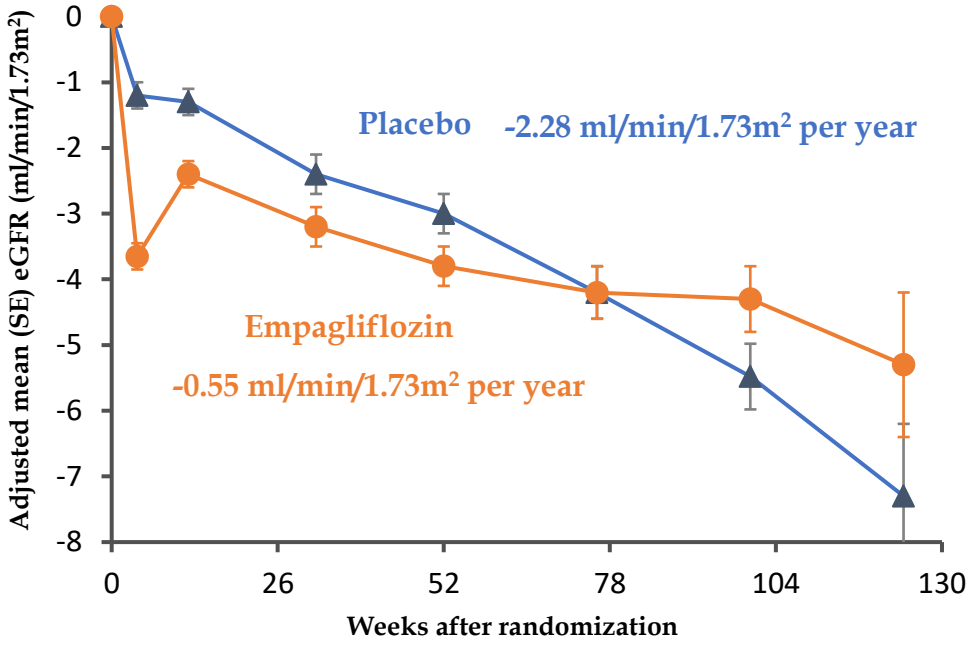
DAPA-HF



Difference = 1.78 ml/min/yr

Circulation. 2021;143:298–309

EMPEROR-Reduced

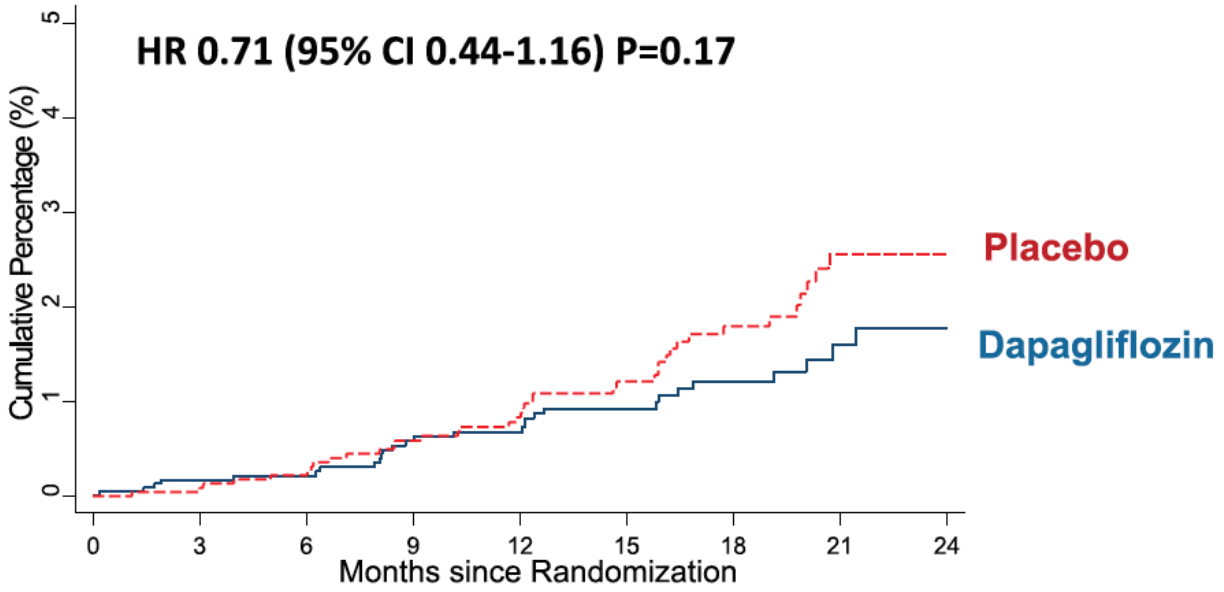


Difference = 1.73 ml/min/yr

N Engl J Med 2020;383:1413-24.

Effect of SGLTi on renal composite outcome

DAPA-HF



Circulation. 2021;143:298–309

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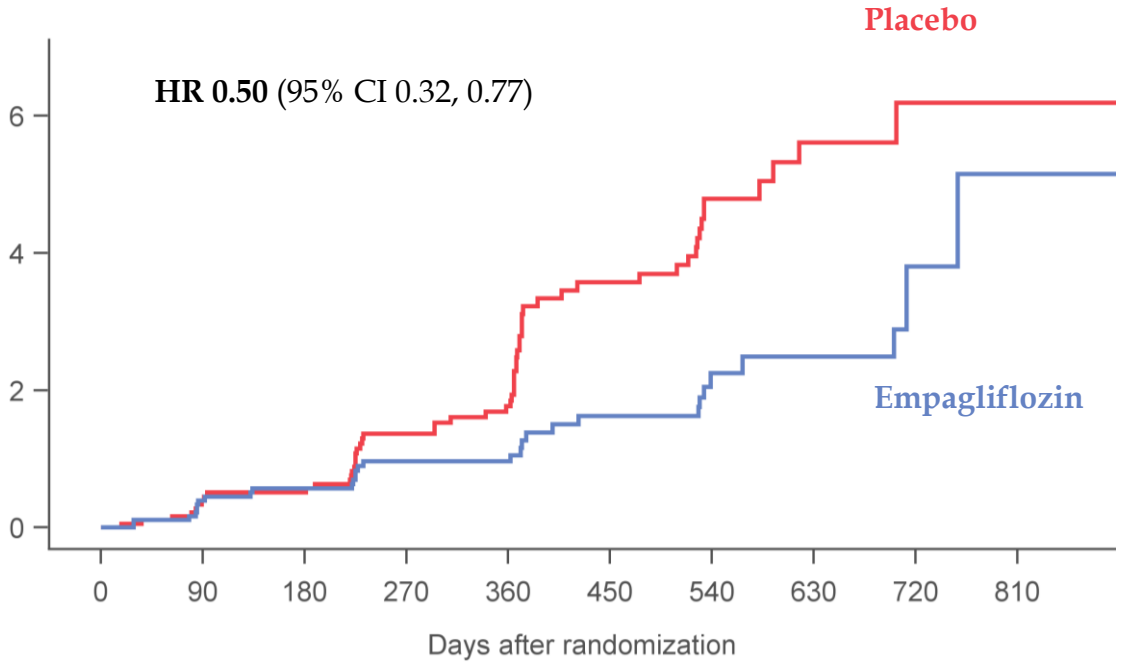


N Engl J Med 2020;383:1413-24.

SGLT2i and renal protection

Mechanism of action

Reduction in Intraglomerular pressure
↑ Afferent vasoconstriction
↓ Glomerular Hyperfiltration

Neurohormonal Improvement
↓ Intrarenal RAAS activity
↓ SNS activity

Reduction in Inflammation/Fibrosis
↓ Inflammation biomarkers
↓ Fibrosis biomarkers

Renal metabolism Hypoxia reduction
↓ Solute transport
↓ Oxygen demand

CLINICAL EFFECT

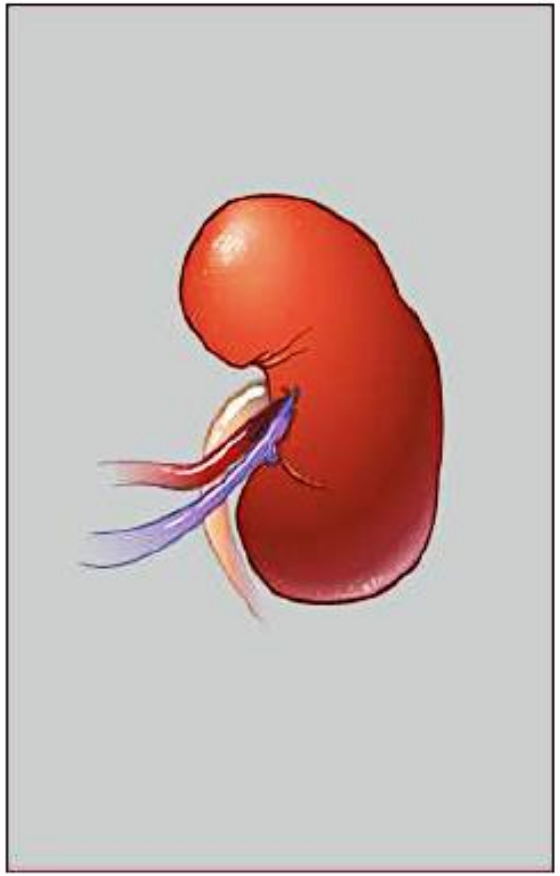
GFR preservation

↓Blood Pressure

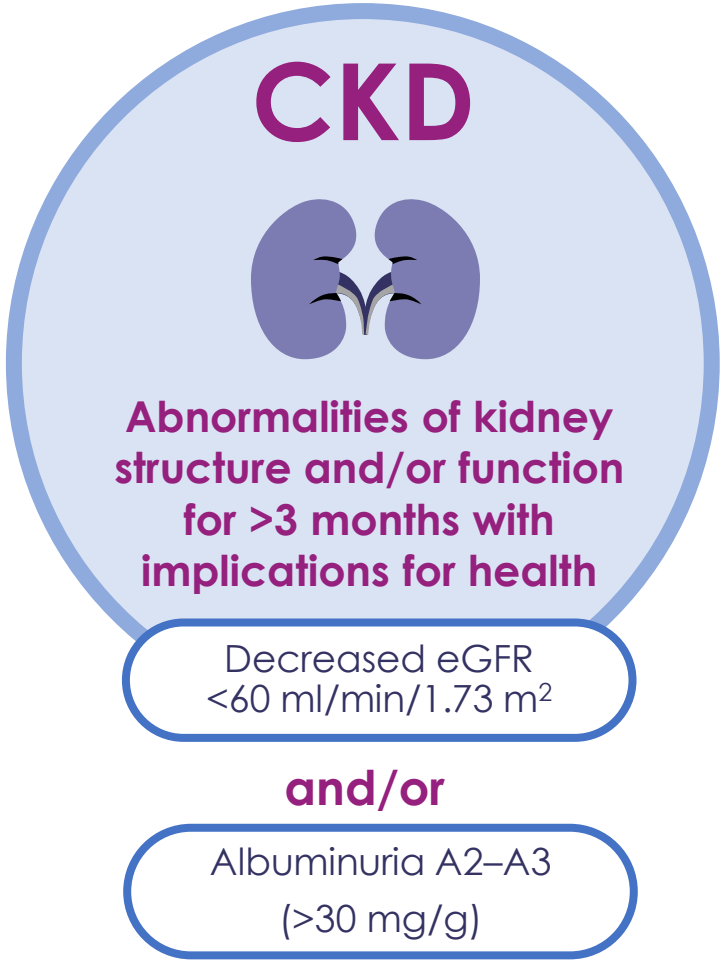
↓ Tubular / Glomerular damage
↓ Albuminuria

↓ Ischemic Renal damage
↑ Hb/Hematocrit

RENAL PROTECTION



Diagnosis and risk stratification of CKD with eGFR and UACR



KDIGO: classification and prognosis of CKD

eGFR categories (ml/min/1.73 m²) description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	Low*	Moderately increased	High
	G2	Mildly decreased	60–89	Low*	Moderately increased	High
	G3a	Mildly to moderately decreased	45–59	Moderately increased	High	Very high
	G3b	Moderately to severely decreased	30–44	High	Very high	Very high
	G4	Severely decreased	15–29	Very high	Very high	Very high
	G5	Kidney failure	<15	Very high	Very high	Very high

Risk of progression

Risk of progression

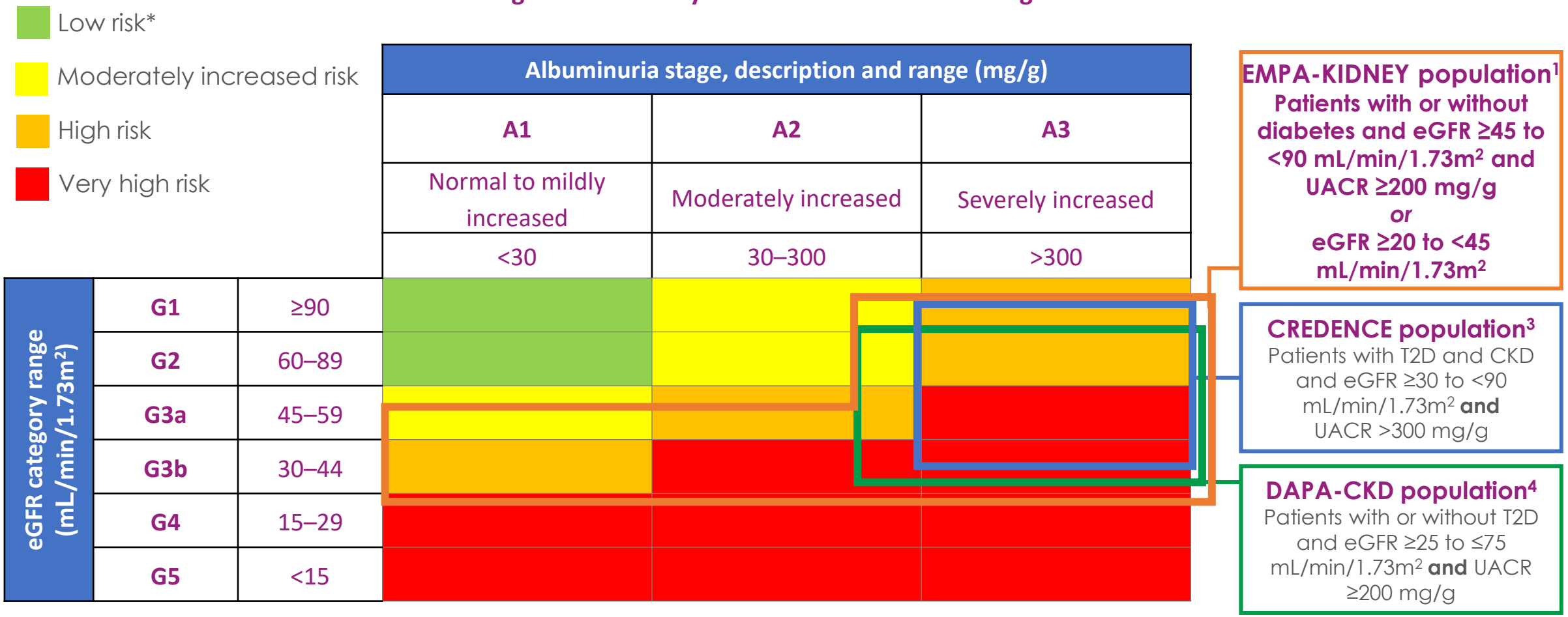
*If no other markers of kidney disease, no CKD

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio

Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int*. 2020;98(suppl):S1-S115

EMPA-KIDNEY vs CREDENCE vs DAPA-CKD

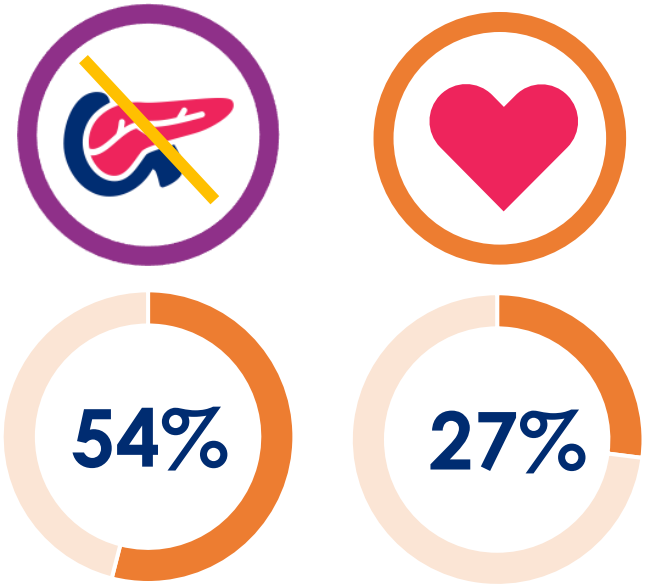
Prognosis of CKD by eGFR and albuminuria categories[2]



*If no other markers of kidney disease, no CKD.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; T2D, type 2 diabetes.

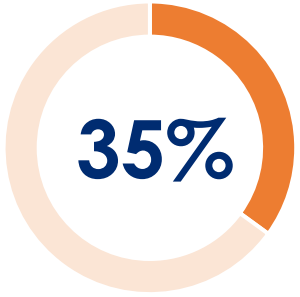
1. The EMPA-KIDNEY Collaborative Group. *N Engl J Med*. 2023 Jan 12;388(2):117-127. 2. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1):1–150. 3. Perkovic V, *et al. N Engl J Med*. 2019; 380:2295-2306 4. Wheeler DC, *et al. Nephrol Dial Transplant* 2020;35:1700.

Patients Enrolled in EMPA-KIDNEY (n=6609)

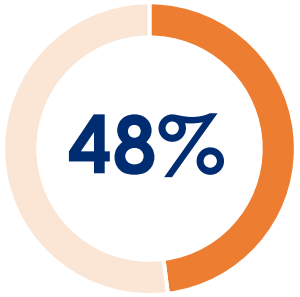


had **no prior history of diabetes**

had **CV disease***

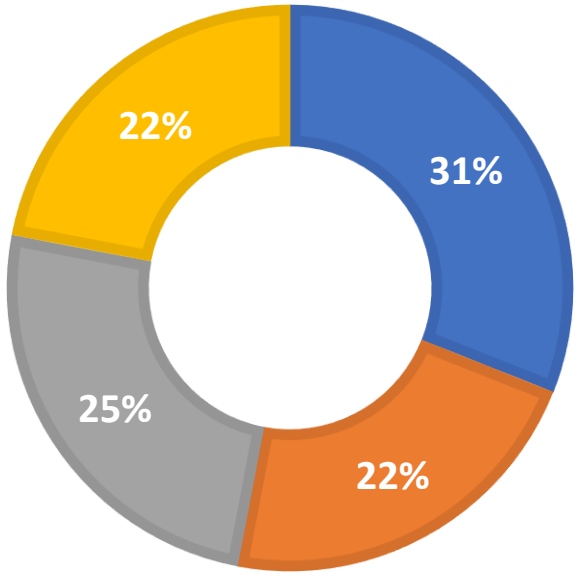


had an **eGFR <30 ml/min/1.73 m²**

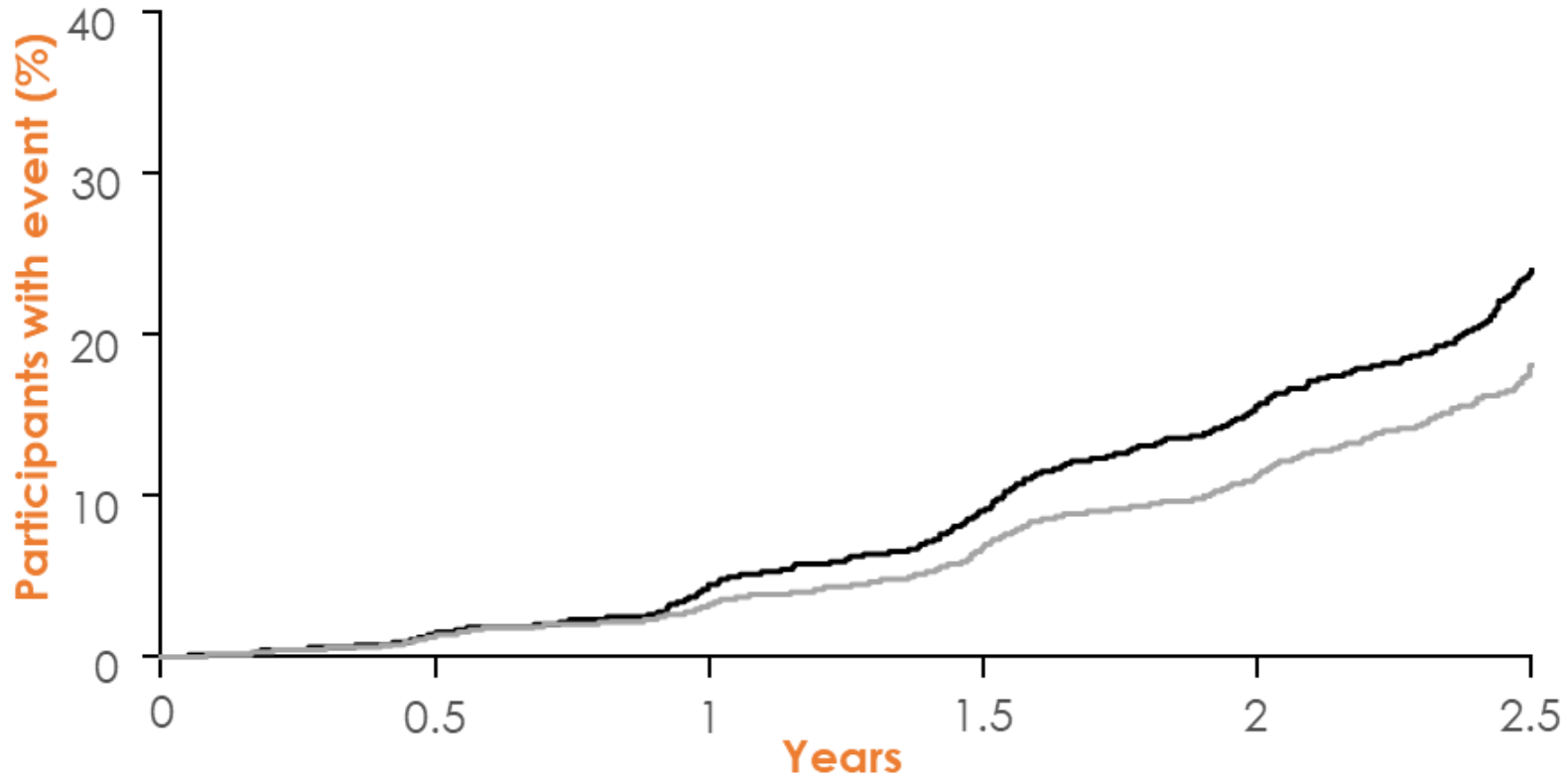


had a **UACR <300 mg/g**

PRIMARY KIDNEY DIAGNOSIS



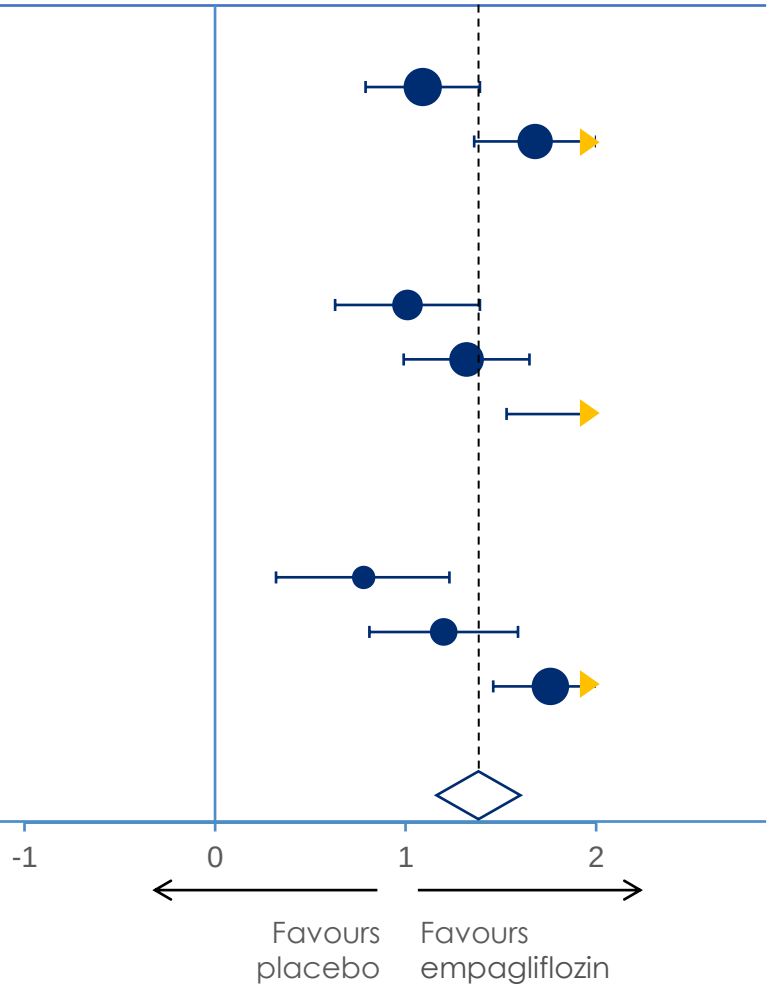
EMPA-KIDNEY – Primary Endpoint



No. at risk						
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

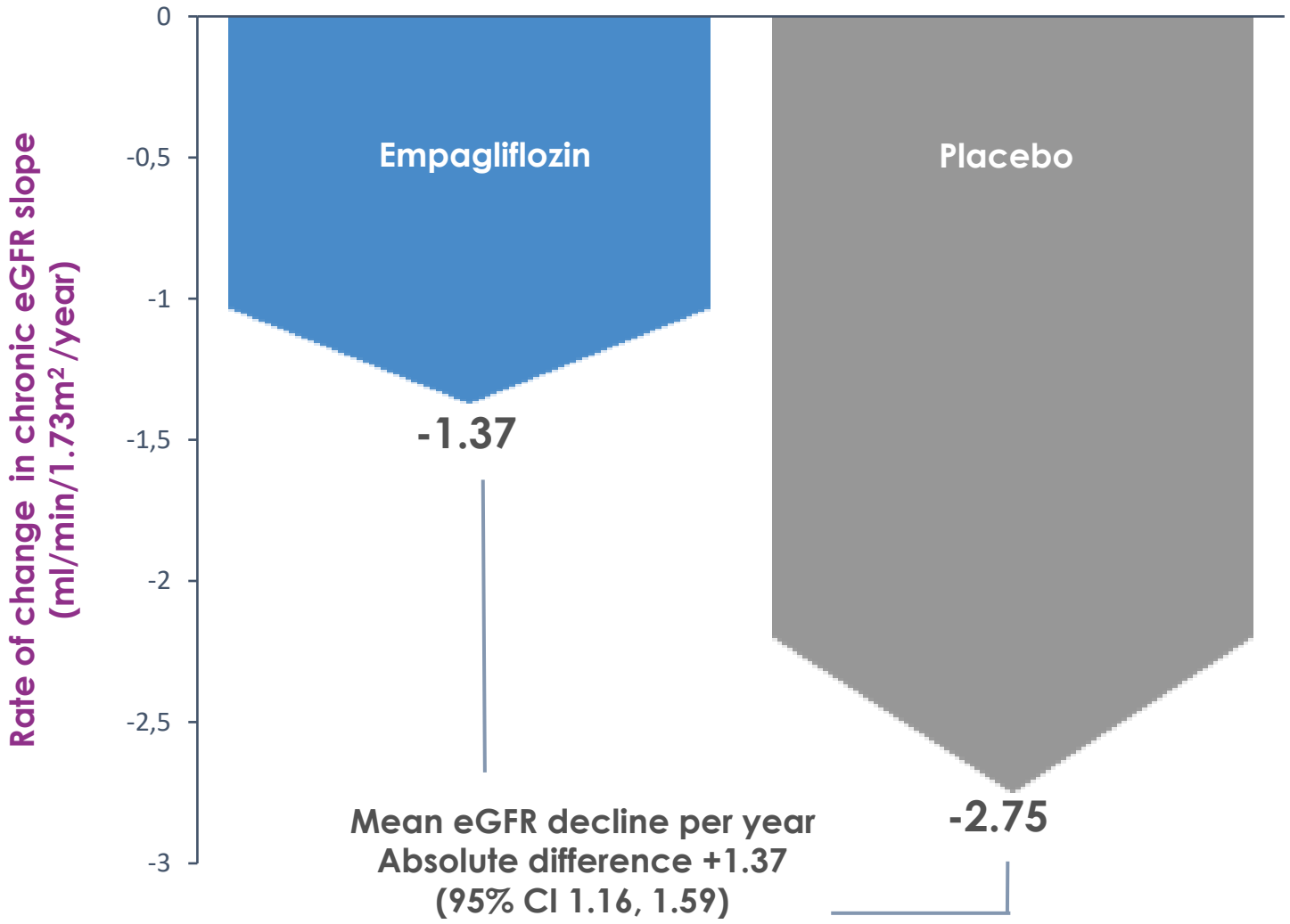
Annual rate of change in eGFR by key subgroups

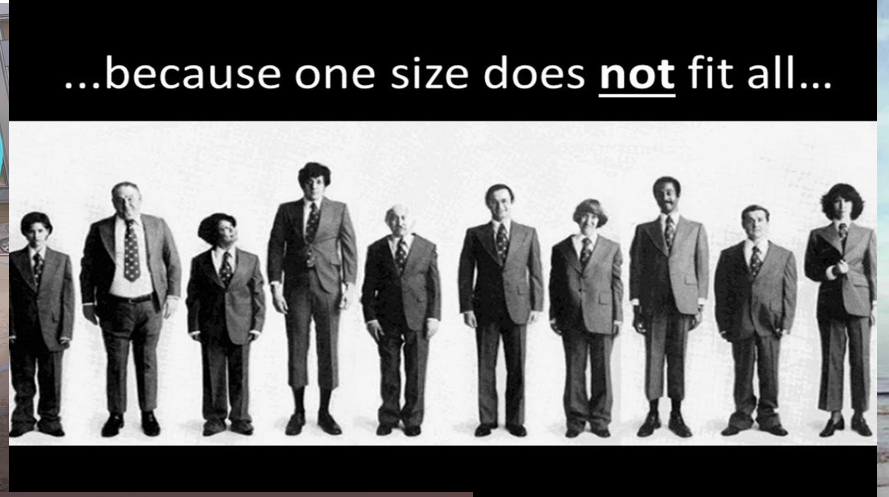
Subgroup	Empagliflozin	Placebo	Absolute difference (95% CI)
	Annual rate of change in eGFR, ml/min/1.73 m^2, mean (SE)		
Diabetes			
No	-1.66 (0.11)	-2.75 (0.11)	1.09 (0.79, 1.39)
Yes	-1.05 (0.12)	-2.73 (0.12)	1.68 (1.36, 2.00)
eGFR, ml/min/1.73 m^2			
<30	-1.84 (0.14)	-2.85 (0.14)	1.01 (0.63, 1.39)
≥30 to <45	-1.18 (0.12)	-2.50 (0.12)	1.32 (0.99, 1.65)
≥45	-1.58 (0.17)	-3.60 (0.17)	2.01 (1.53, 2.49)
UACR, mg/g			
A1 (<30) normal to mildly increased	-0.11 (0.17)	-0.89 (0.16)	0.78 (0.32, 1.23)
A2 (≥30 to ≤300) moderately increased	-0.49 (0.14)	-1.69 (0.14)	1.20 (0.81, 1.59)
A3 (>300) severely increased	-2.35 (0.11)	-4.11 (0.11)	1.76 (1.46, 2.05)
All participants	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**

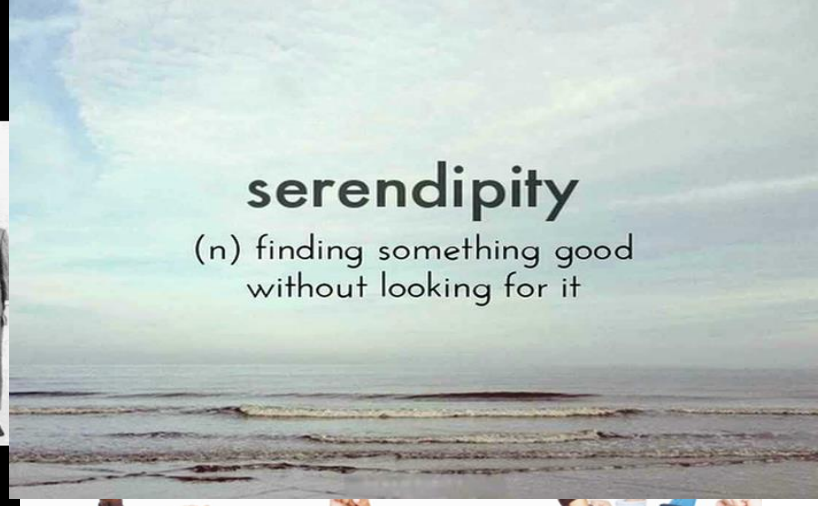


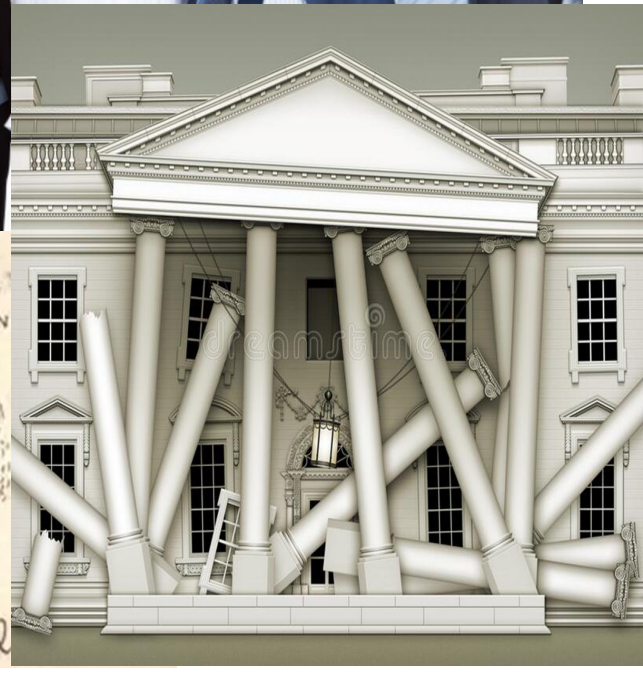
*Mean annual rates of change in eGFR from 2 months to the final follow-up visit ('chronic slopes') by treatment allocation were estimated using shared parameter models eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117

eGFR decline with Placebo and Empagliflozin




...because one size does not fit all...


serendipity
(n) finding something good
without looking for it




GIN RUMMY


PRENDERE DUE PICCIONI CON UNA
" GET TWO PIGEONS WITH ONE FAVA BEAN
catching two birds with one

PRENDERE DUE PICCIONI CON UNA FAVA

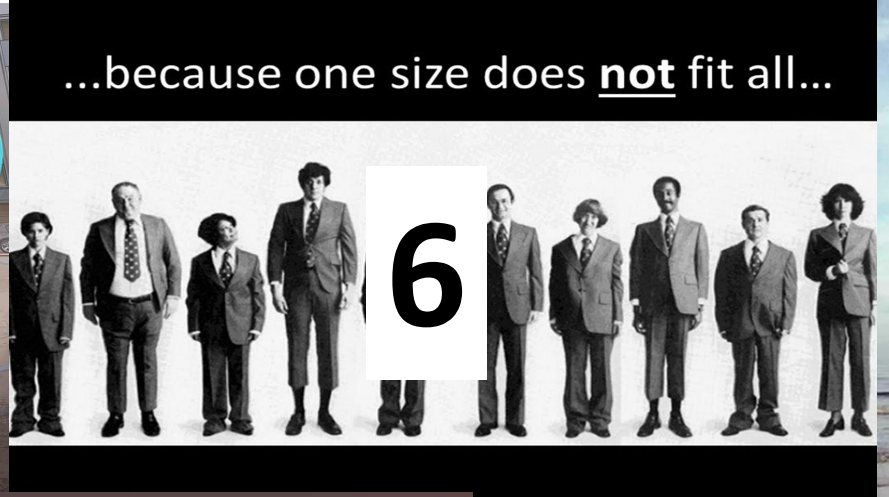
"GET TWO PIGEONS WITH ONE FAVA BEAN"

catching two birds with one stone.

SCOMPENSO

DIABETE


3


...because one size does not fit all...
6

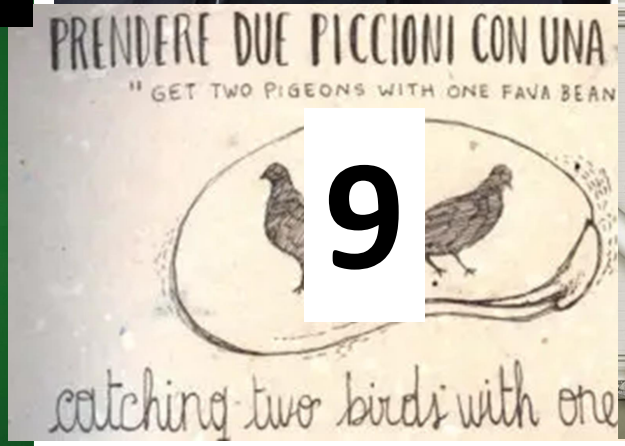

1


5


2

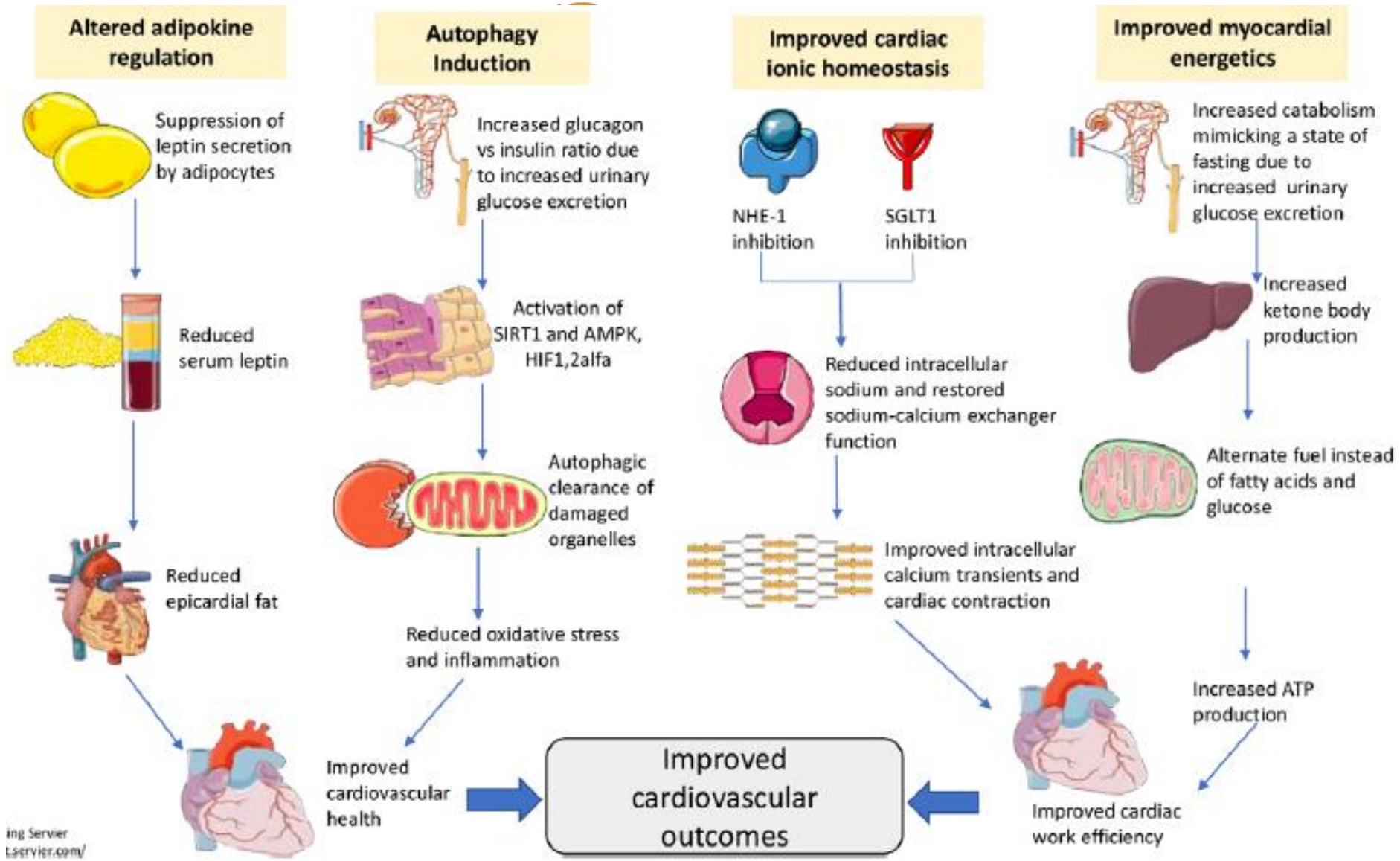

7


8

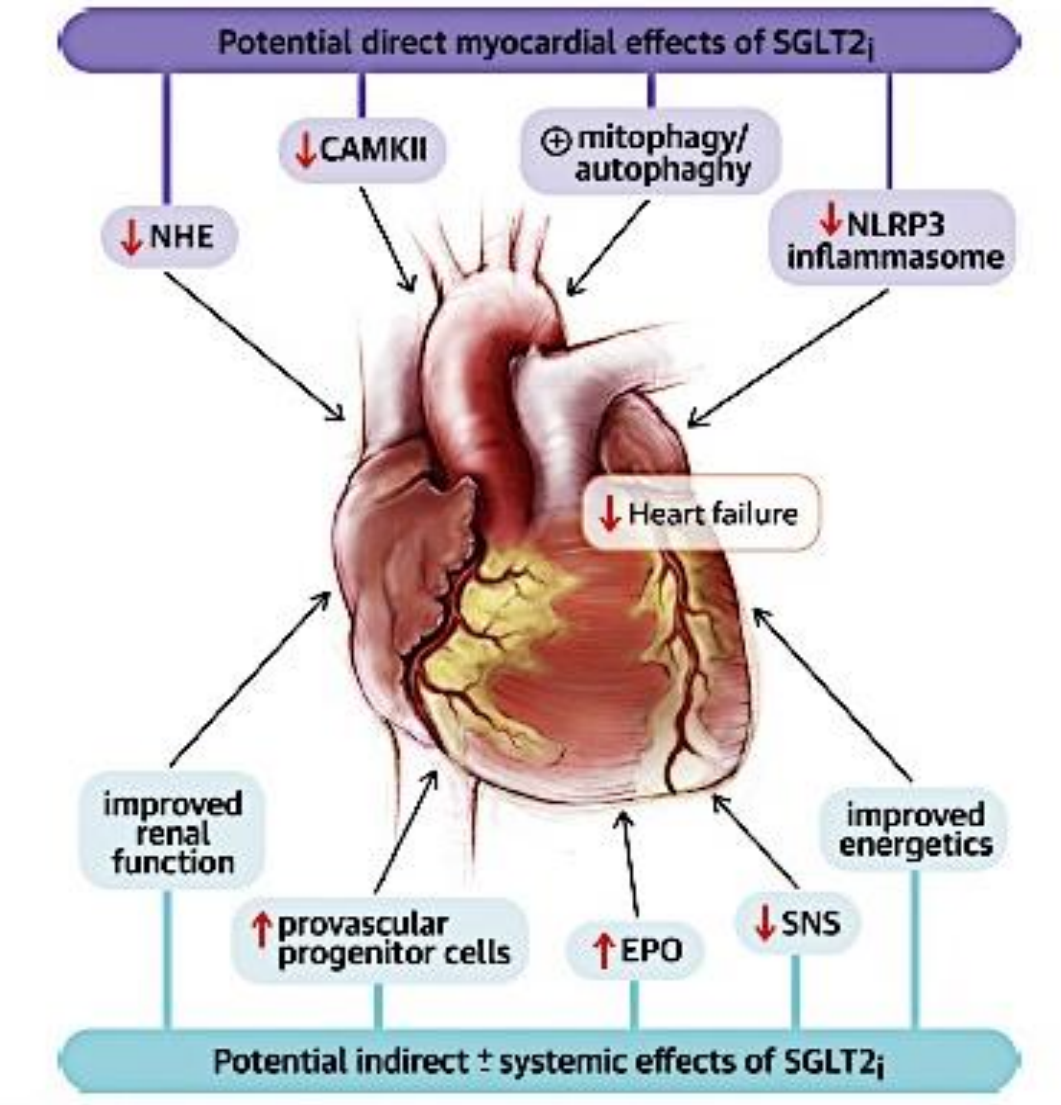

PRENDERE DUE PICCIONI CON UNA
" GET TWO PIGEONS WITH ONE FAVA BEAN
9
catching two birds with one


4

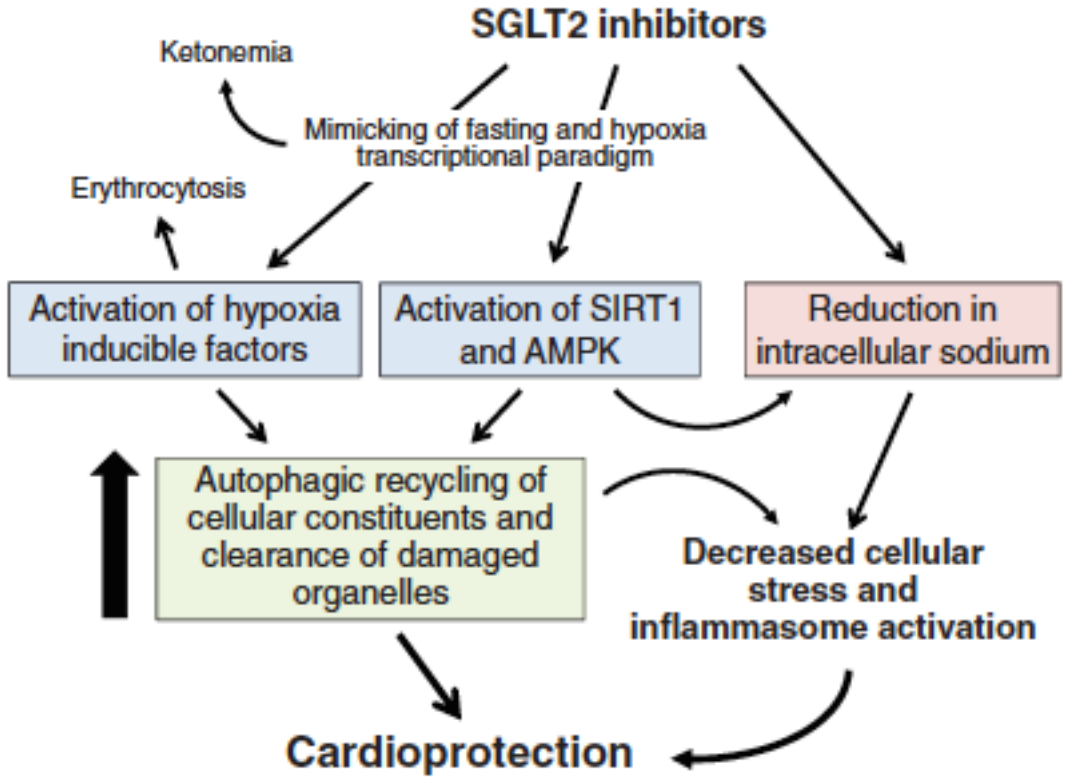
SGLT2i mechanisms of action in Heart Failure



Potential Direct Myocardial and Indirect Systemic Effect of SGLT2i

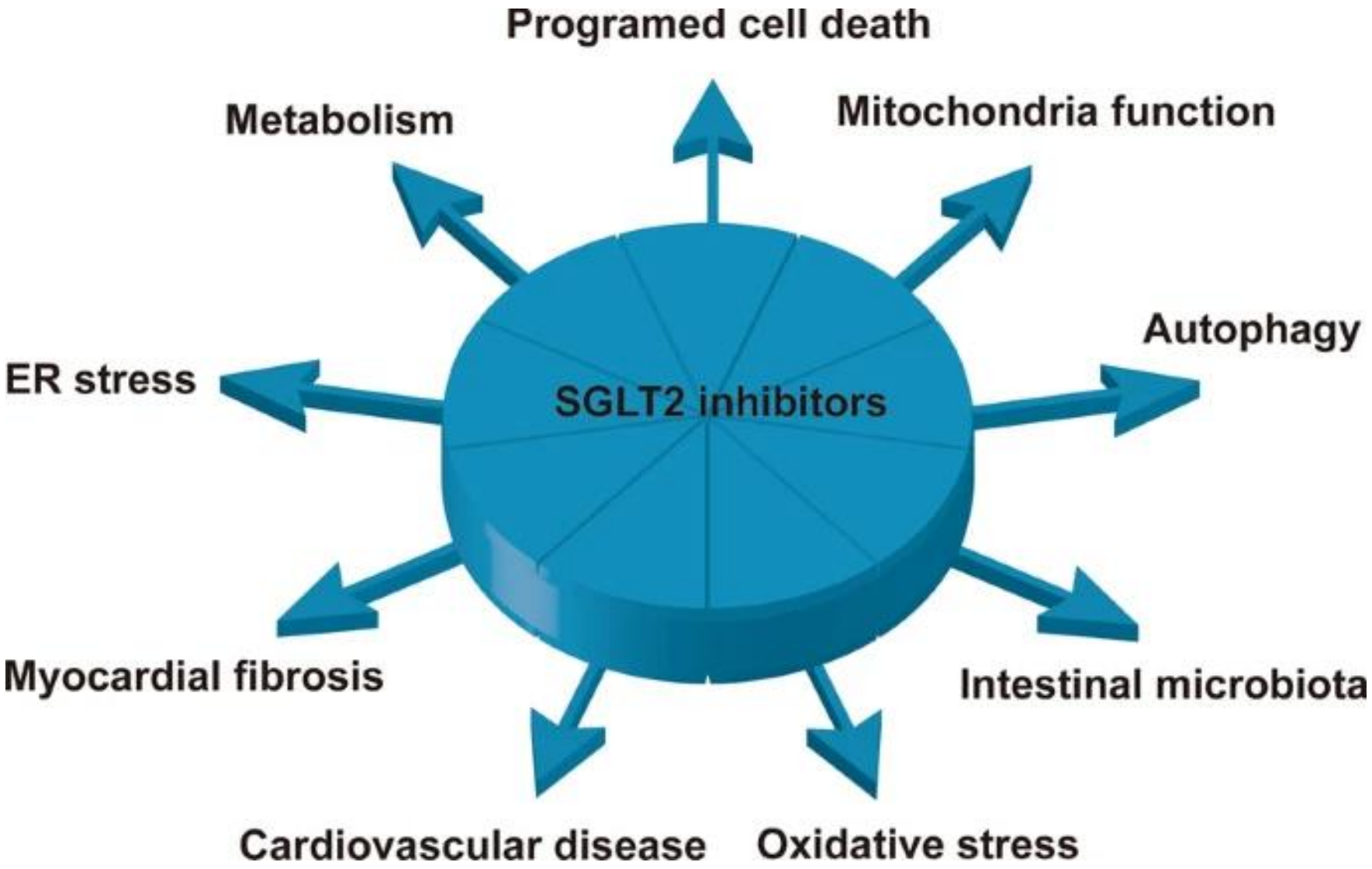


Lopachuck et al. JACC basic Trans Science 2020; 5(6):632-44

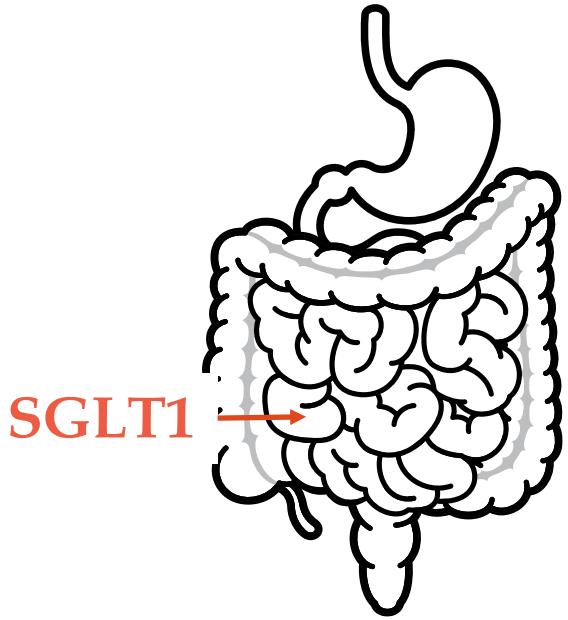


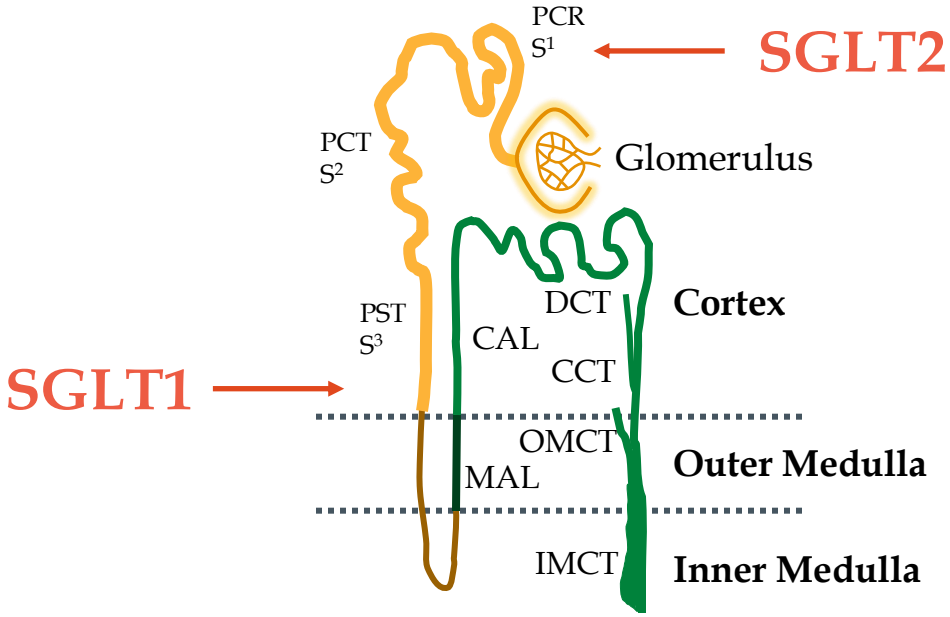
Packer European Journal of Heart Failure 2020; 22: 618–628

Potential Direct Myocardial and Indirect Systemic Effect of SGLT2i



Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor





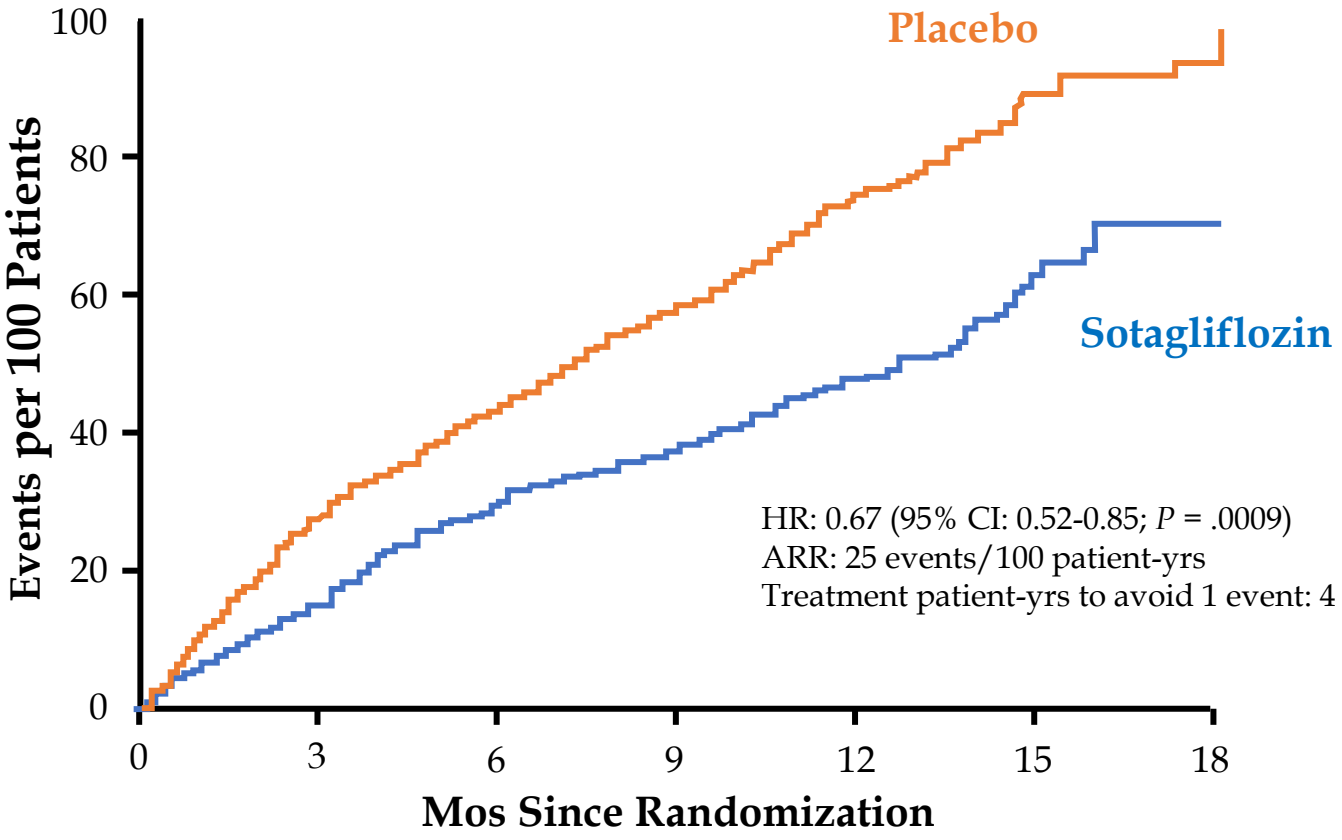
- SGLT1: primary transporter for intestinal absorption of glucose and galactose[1]
- Sotagliflozin inhibits SGLT1 independent of insulin[2]
  - **Does not depend** on renal function[1]

- SGLT2: expressed in kidney; reabsorbs 90% of filtered glucose[3]
- Sotagliflozin inhibits SGLT2 independent of insulin[2]
  - **Does depend** on renal function[1]

1. Sands. Diabetes Care. 2015;38:1181. 2. Cefalo. Cardiovasc Diabetol. 2019;18:20. 3. Mather. Kidney Int Suppl. 2011;S1.

SOLOIST-WHF: Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

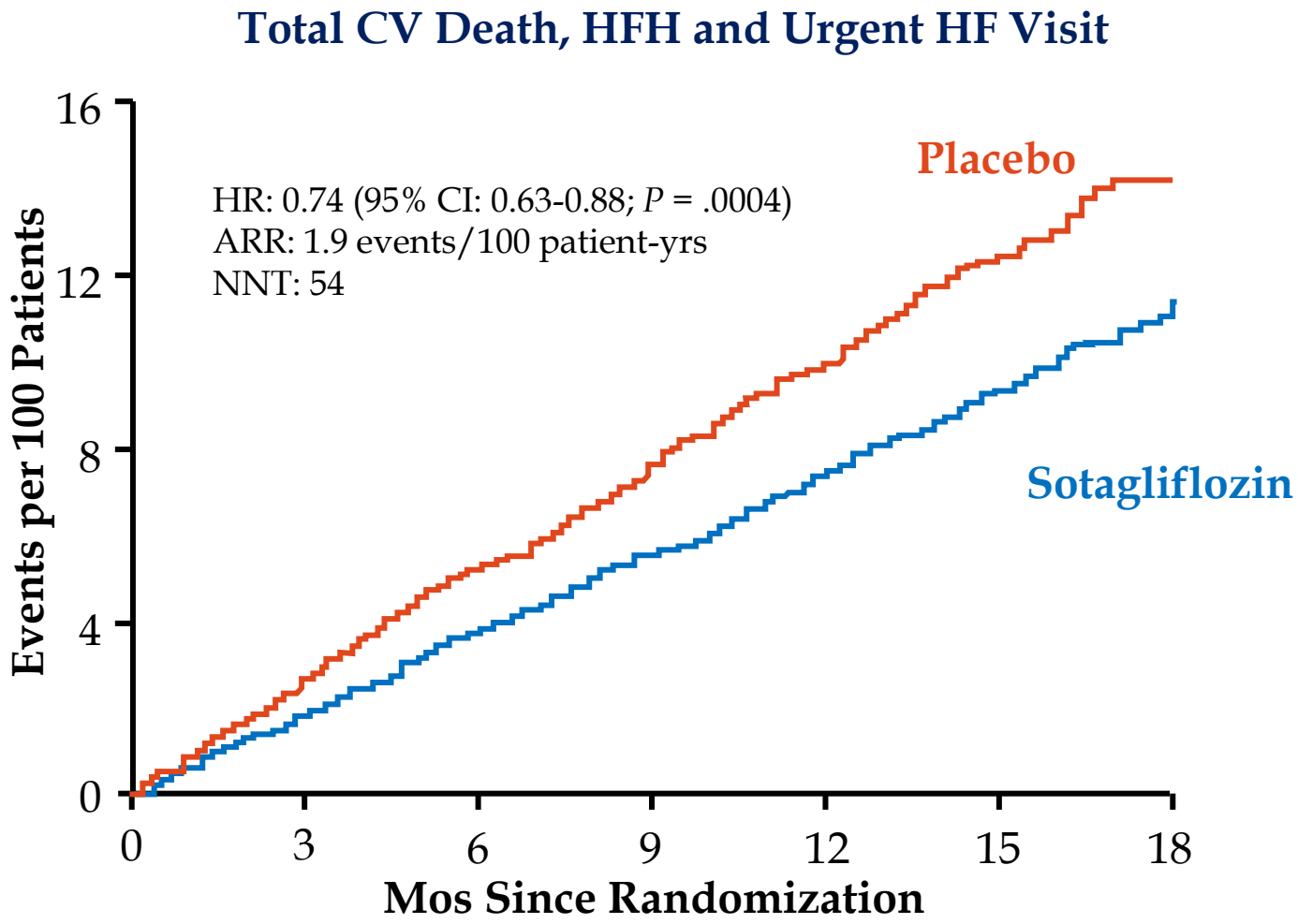
CV Death, HF Hospedalization and Urgent HF Visit



- Admission with signs and symptoms of heart failure
- Treatment with intravenous diuretics
- Stabilized, off oxygen, transitioning to oral diuretics
- BNP ≥150 pg/mL (≥450 pg/mL if atrial fibrillation) or NT- proBNP ≥600 pg/mL (≥1800 pg/mL if atrial fibrillation)
- Type 2 diabetes

N Engl J Med 2021;384:117-28

SCORED: Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease



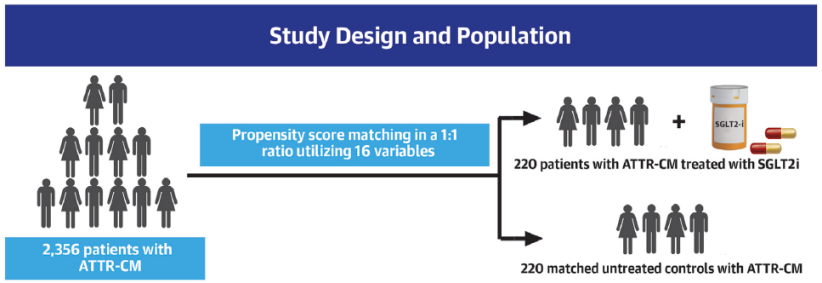
- Type 2 diabetes mellitus with a glycated hemoglobin level of 7% or higher
- Chronic kidney disease (eGFR, 25 to 60 ml per minute per 1.73 mq)

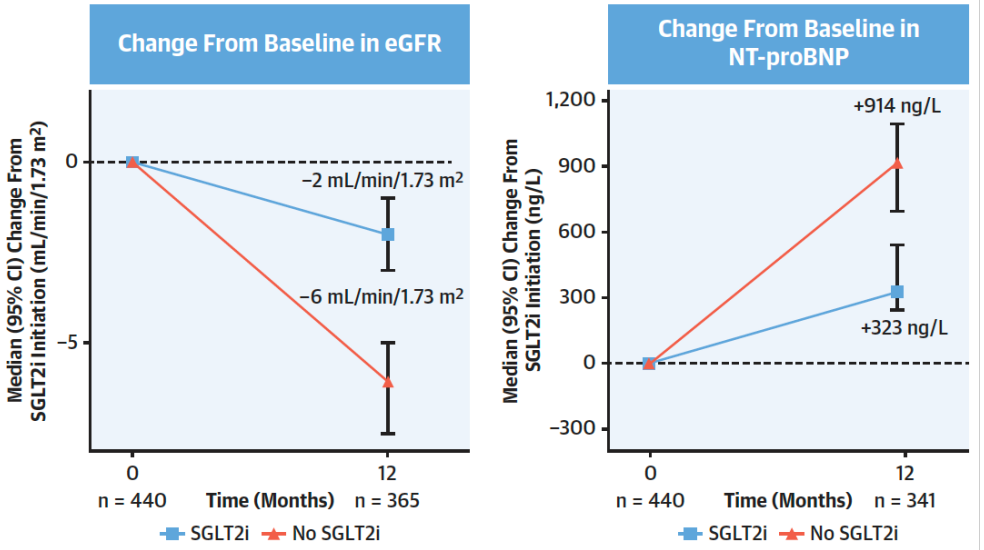
and

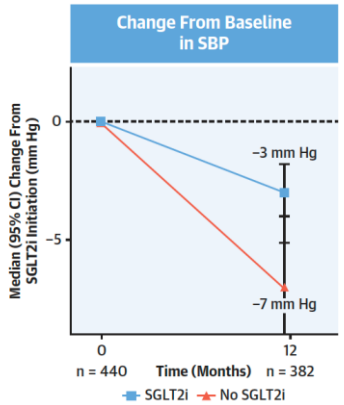
- Additional cardiovascular risk factors

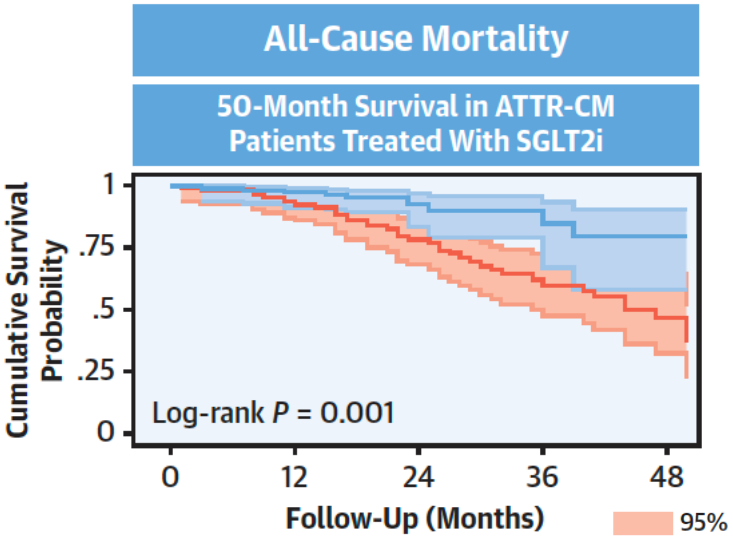
N Engl J Med 2021;384:129-39

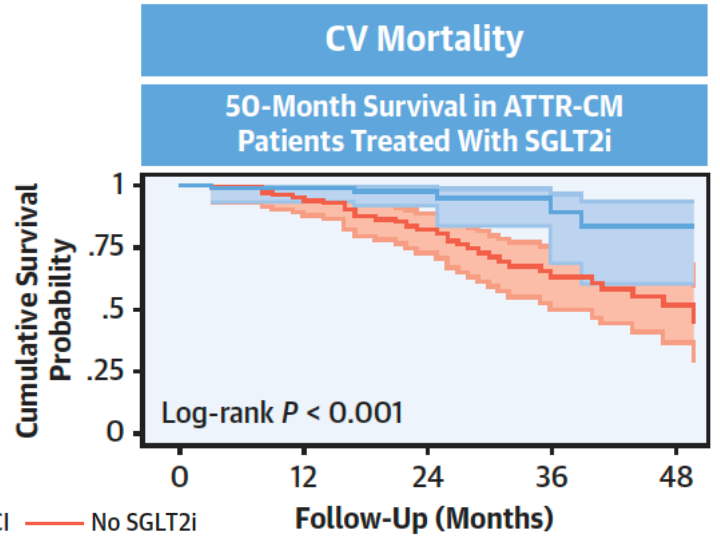
SGLT2i in Patients With ATTR Cardiomyopathy

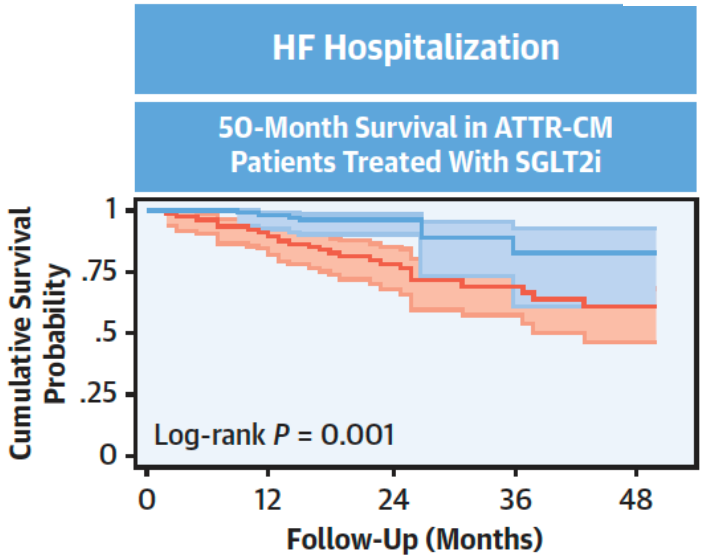


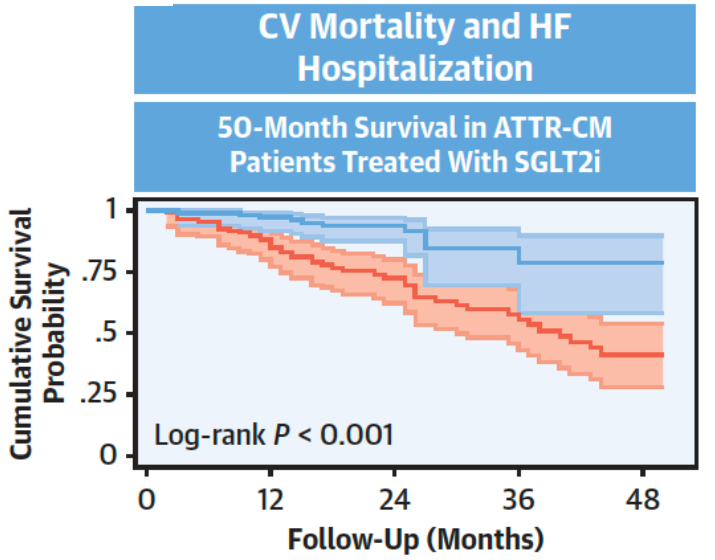












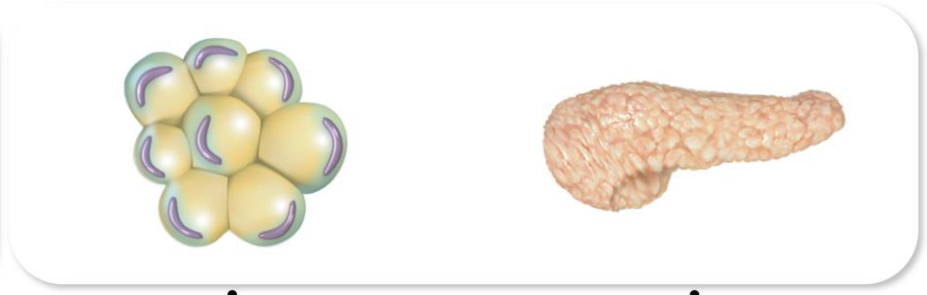
JACC 2024;83:2411–2422

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–98
https://doi.org/10.1093/eurheartj/ehad192

Type 2 diabetes mellitus



Patient presentation

Evaluation

- Cardiovascular disease? (Class I)
- Chronic kidney disease? (Class I)
- Confirmed
- Confirmed
- CVD and type 2 diabetes mellitus

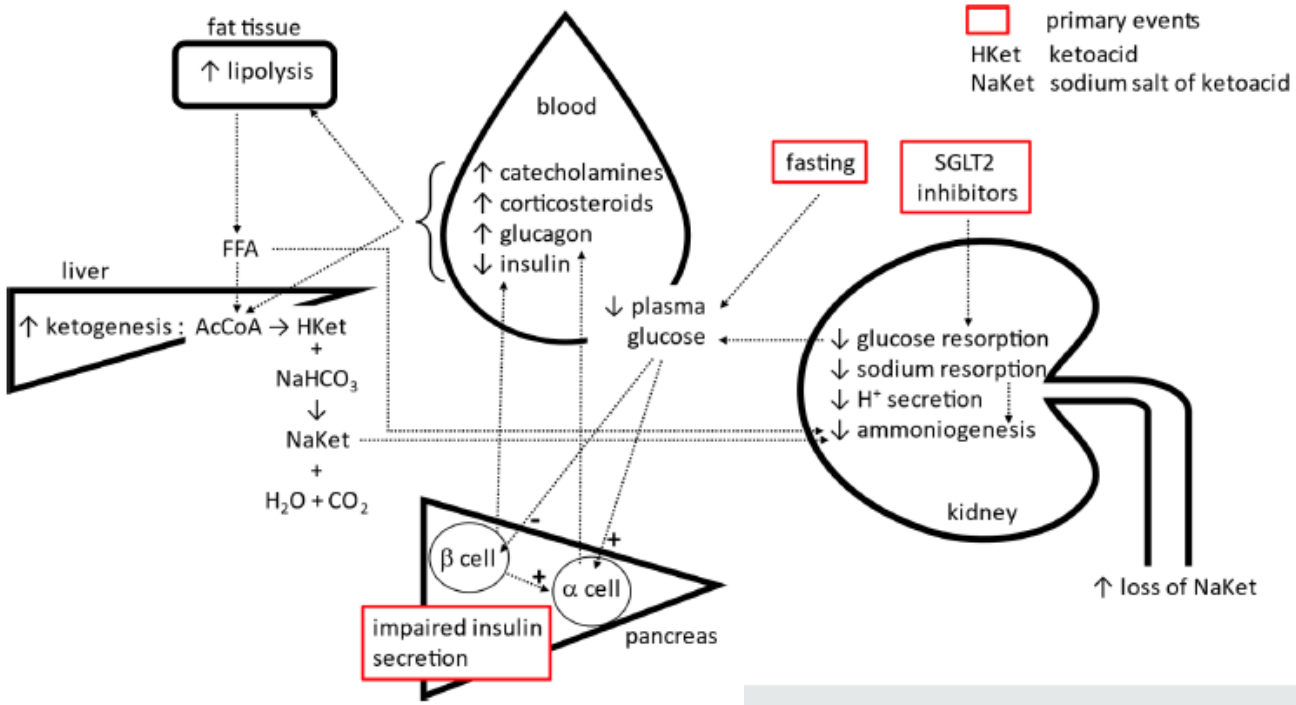
Diagnosis

- Type 2 diabetes mellitus and ASCVD
- Type 2 diabetes mellitus and HF
- Type 2 diabetes mellitus and CKD

Treatment

- To reduce cardiovascular risk independent of glucose control
  - GLP-1 RA[a] (Class I)
  - SGLT2 inhibitor[b] (Class I)
- To reduce heart failure hospitalization in all patients with T2DM and HF (HFpEF, HFmrEF, HFrEF)
  - SGLT2 inhibitor[c] (Class I)
- To reduce cardiovascular and kidney failure risk
  - SGLT2 inhibitor[d] (Class I)
  - Finerenone (Class I)

Euglycemic Ketoacidosis



Factor	Sodium-Glucose Cotransporter-2 Inhibitor–Induced Diabetic Ketoacidosis	Diabetic Ketoacidosis
Endogenous glucose production	↑	↑↑
Insulin release	↓	↓↓
Insulin resistance	↑	↑↑
Tissue glucose disposal	↓	↓↓
Kidney glucose clearance	↑↑	↑
Plasma glucose levels	Normal or increased, often <250 mg/dl[a]	Typically 350–800 mg/dl
Extracellular fluid volume	↓	↓↓
Presenting symptoms	More nonspecific to include malaise, nausea, anorexia, abdominal pain	Polyuria and polydipsia due to osmotic diuresis, nausea, vomiting, shortness of breath

Euglycemic Ketoacidosis

Risk factors for sSGLT2i –associated ketoacidosis

Restriction in dietary carbohydrate availability as seen with the use of ketogenic diets	Glycosuric effect of SGLT2i combined with decreased dietary carbohydrate intake leads to decreased insulin levels Increased lipolysis due to reductions in carbohydrate intake leads to an increased glucagon-insulin ratio, which predisposes to ketogenesis	Avoid very low–carbohydrate diets
Surgical stress, trauma, intercurrent illness such as gastroenteritis where there is an inability to eat or drink	Decreased food intake leads to reduced insulin levels, thereby increasing likelihood of ketogenesis Nonspecific symptoms, such as malaise and nausea, along with mild or absent glycemia may cause patient to decrease insulin dose, thus increasing risk of ketosis Increased levels of counter-regulatory hormones (catecholamines and cortisol) accelerate lipolysis and increase insulin demand	Discontinue SGLT2i 3 d prior to elective surgery Discontinue SGLT2i with acute illness Educate patient to monitor for ketonuria, in addition to glucose, and contact provider with any symptoms or detectable ketonuria Supplemental doses of rapid-acting insulin, along with fluids and ingestion of carbohydrates
Lean body habitus	Carbohydrate deficit is greater in lean versus obese individuals because the degree of glycosuria relative to filtered load is independent of body size following SGLT2i	Educate lean/muscle-bound patients as to their increased risk and symptoms
Alcohol use disorder and salicylate toxicity	Alcohol withdrawal and salicylate toxicity are both associated with increased lipolysis and decreased insulin-glucagon ratio, thereby increasing risk of ketogenesis, conditions	Discontinue SGLT2i Be aware of patients with chronic salicylate toxicity

Recommendations
Maintain appropriate fluid intake
Ensure adequate carbohydrate intake and avoid low-carbohydrate diets
Avoid skipping insulin doses and skipping meals
In situations of acute illness, vomiting, diarrhea, or inability to eat or drink
Discontinue SGLT2i
Contact provider even if blood glucose levels are not elevated
Continue to monitor glucose levels and monitor for presence of urinary ketones
If on insulin therapy, contact provider for dose adjustments; do not stop insulin
Ketoacidosis symptoms are nonspecific (malaise, nausea, anorexia, vomiting) and can occur despite normal or minimally elevated blood glucose level
If ketonuria detected, patient may be advised to administer dose of rapid-acting insulin and consume 30 g carbohydrate
Restart SGLT2i when eating and drinking normally, usually after 24–48 h as directed by medical provider

CJASN 2021; 16: 1284–1291