BIELLA CUORE
12-13 SETTEMBRE 2025

SGLT2i nel paziente con patologia cardiovascolare pregressa: benefici cardio renali metabolici

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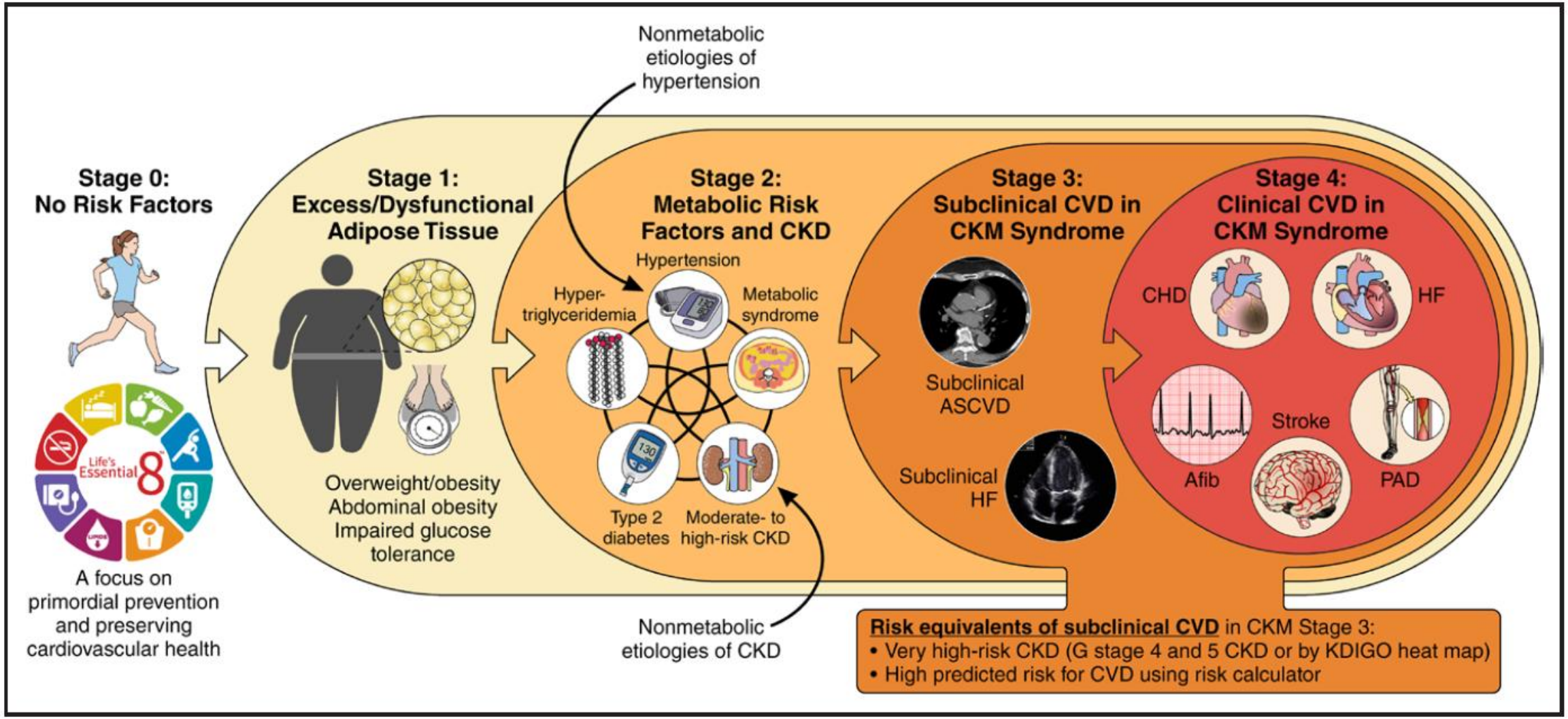
Cardiovascular-Kidney-Metabolic (CKM) Syndrome



Disorders of the Cardio-Renal-Metabolic systems affect more than 1 billion people worldwide and often co-exist[1,2]

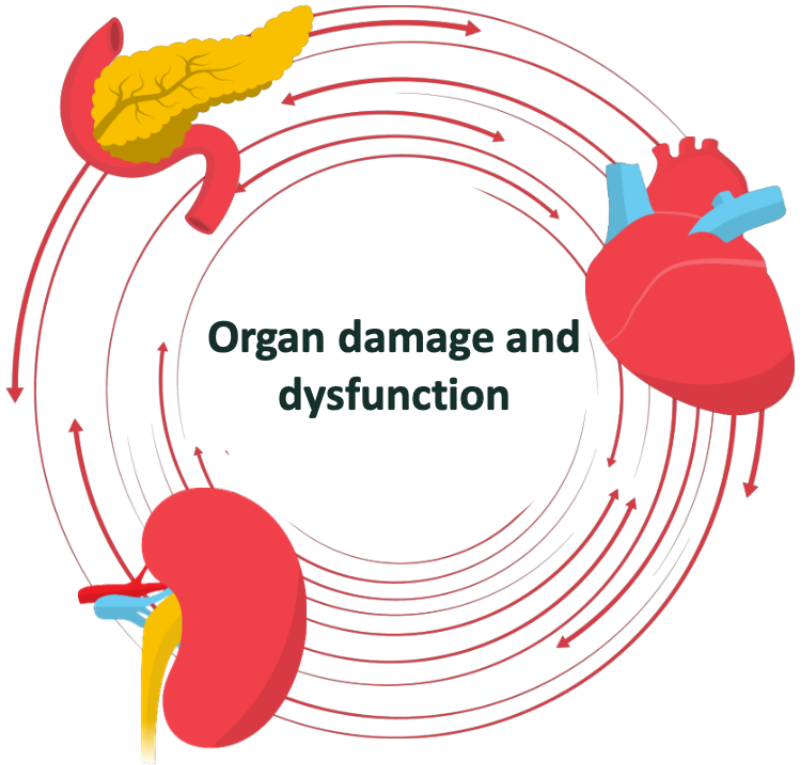
T2D + CVD

~One-third of patients with T2D have CV disease[1,2]

T2D + CKD/ESKD

~37% of adults with diabetes have been diagnosed with CKD*[3]

Diabetes and/or hypertension are the primary causes of **~75% of ESKD** prevalent cases in the US[4]



T2D + CVD/HF

CV disease is the **leading cause of mortality** in patients with T2D[5,6]

Up to 40% of patients with HF have T2D[7]

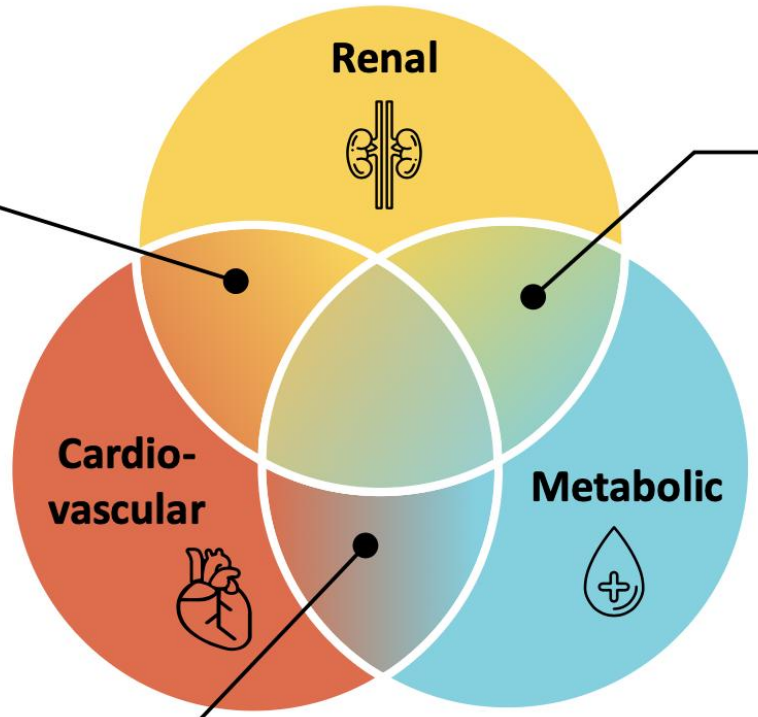
CKD + HF

20–67% of patients with HF are estimated to have CKD[8]

Cardiovascular, renal and metabolic conditions frequently coexist because they are interrelated

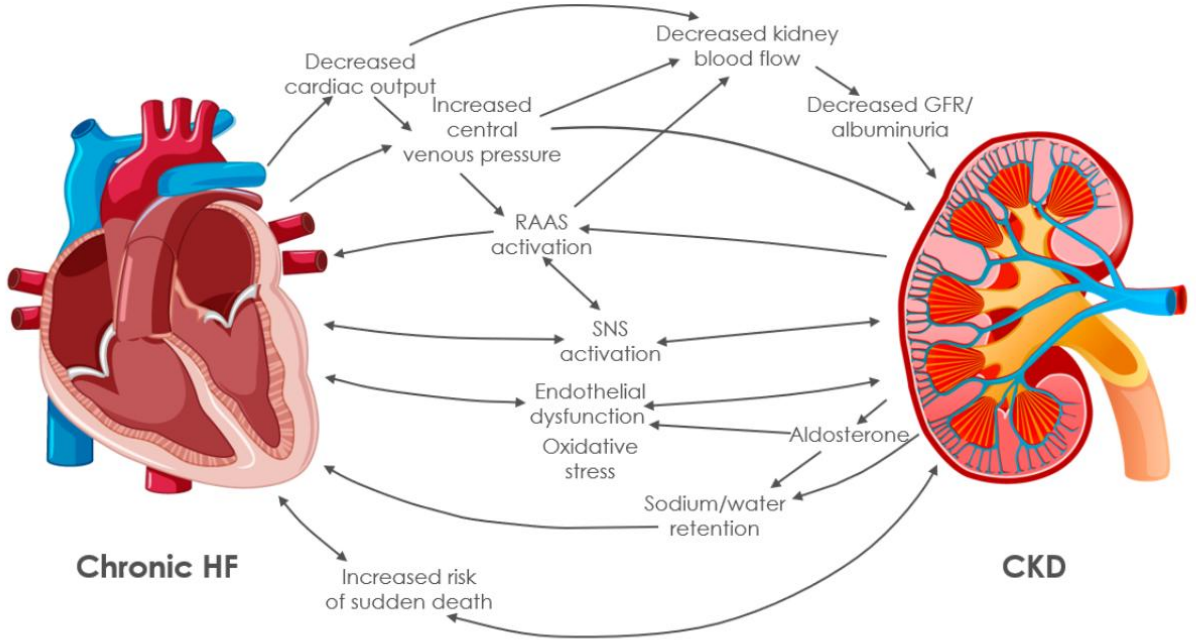
- Up to 60% of people with CKD have CV disease[1]
- 30–40% of people with HF have CKD[2]

- Approximately one in three people with T2D have CV disease[3]
- 20–40% of people with HF have T2D[4]



- Up to 40% of people with T2D have CKD[5,6]

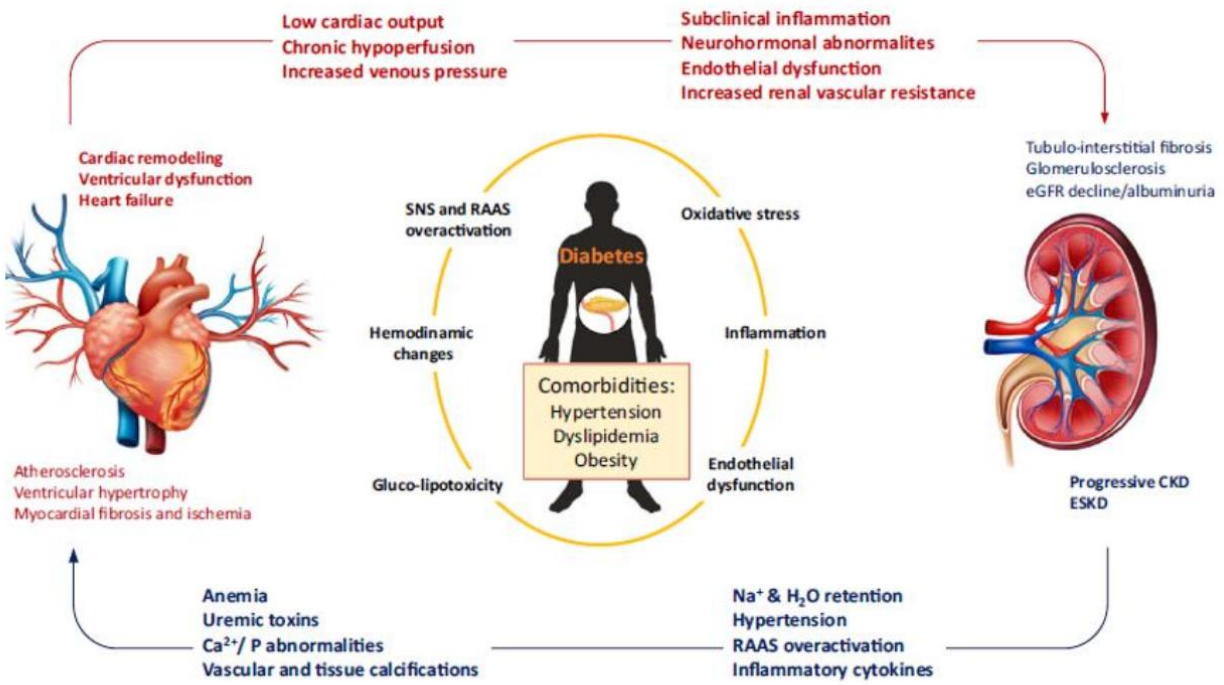
CKD as an amplifier of cardiovascular risk[2,3]



There is a close and specific **association between HF and CKD pathophysiology**[1]

- **Low glomerular filtration rate and albuminuria independently increase the risk of MACE and CV death**
- **CKD and diabetes precipitate peripheral artery disease below the knee**
- **Vascular calcification is common in CKD and increases CVD risk**
- **Pro-inflammatory state which potentiates CVD risk**
- **Development of HF and/or progressive CKD n increase bidirectional organ damage, in tandem with neurohormonal activation and inflammation**
- **Anemia is common in CKD and exacerbates CVD**

HF is an amplifier of CKD



There is a close and specific **association between HF and CKD pathophysiology**[1]

- Cardiac remodeling/HF or ventricular disfunction CV death lead to a Chronic hypoperfusion of kidney
- Elevated systolic blood pressure, Obesity and Dyslipidemia are predictors of fast CKD progression
- Controlling hypertension can slow the progression of kidney damage and reduce CV disease risk
- Pro-inflammatory state and oxidative stress lead to organ fibrosis and sclerosis
- Development of HF and/or progressive CKD n increase bidirectional organ damage, in tandem with neurohormonal activation and inflammation
- lemodynamic, mechanical, and structural processes contributing to the decline in kidney function

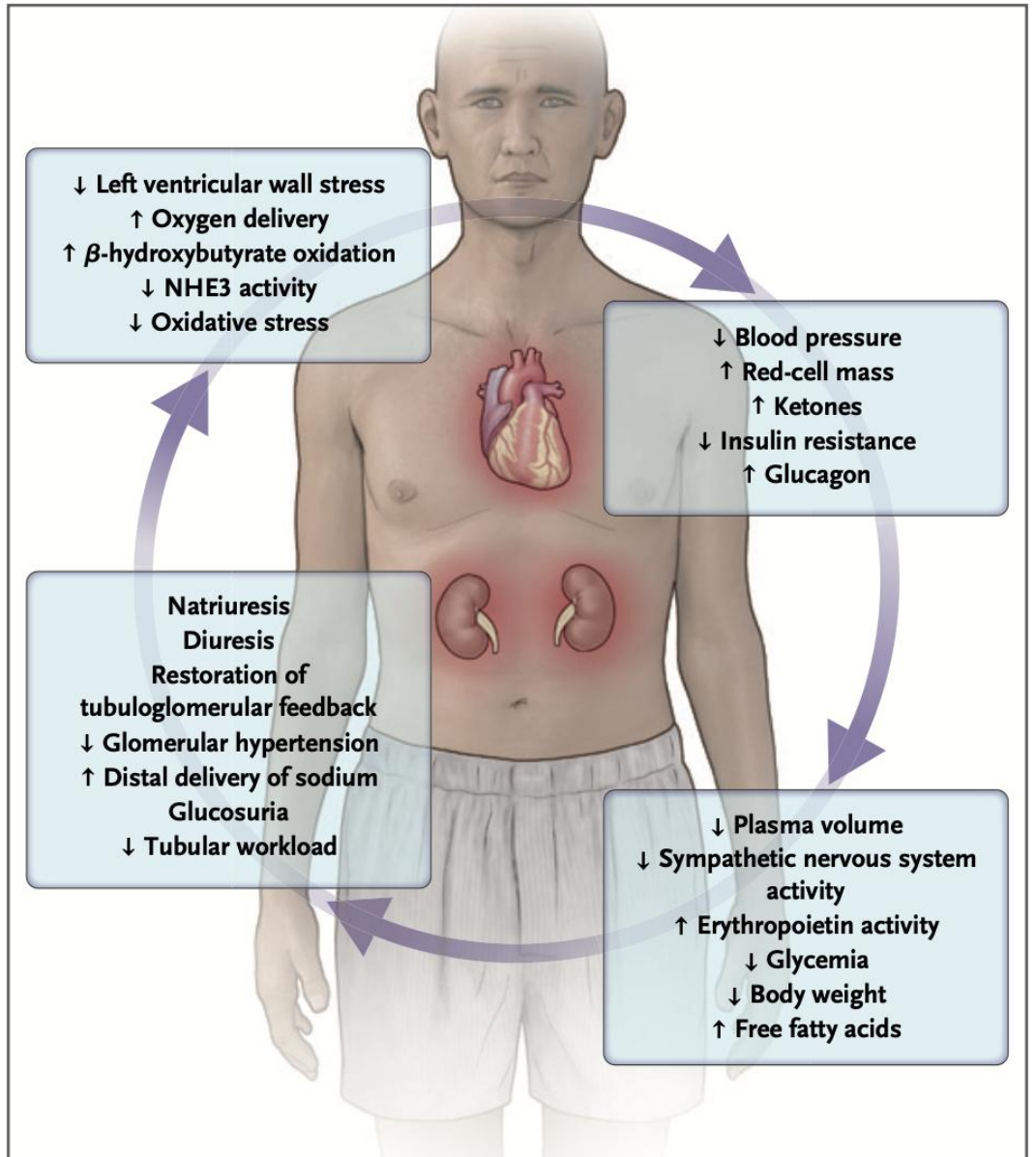
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

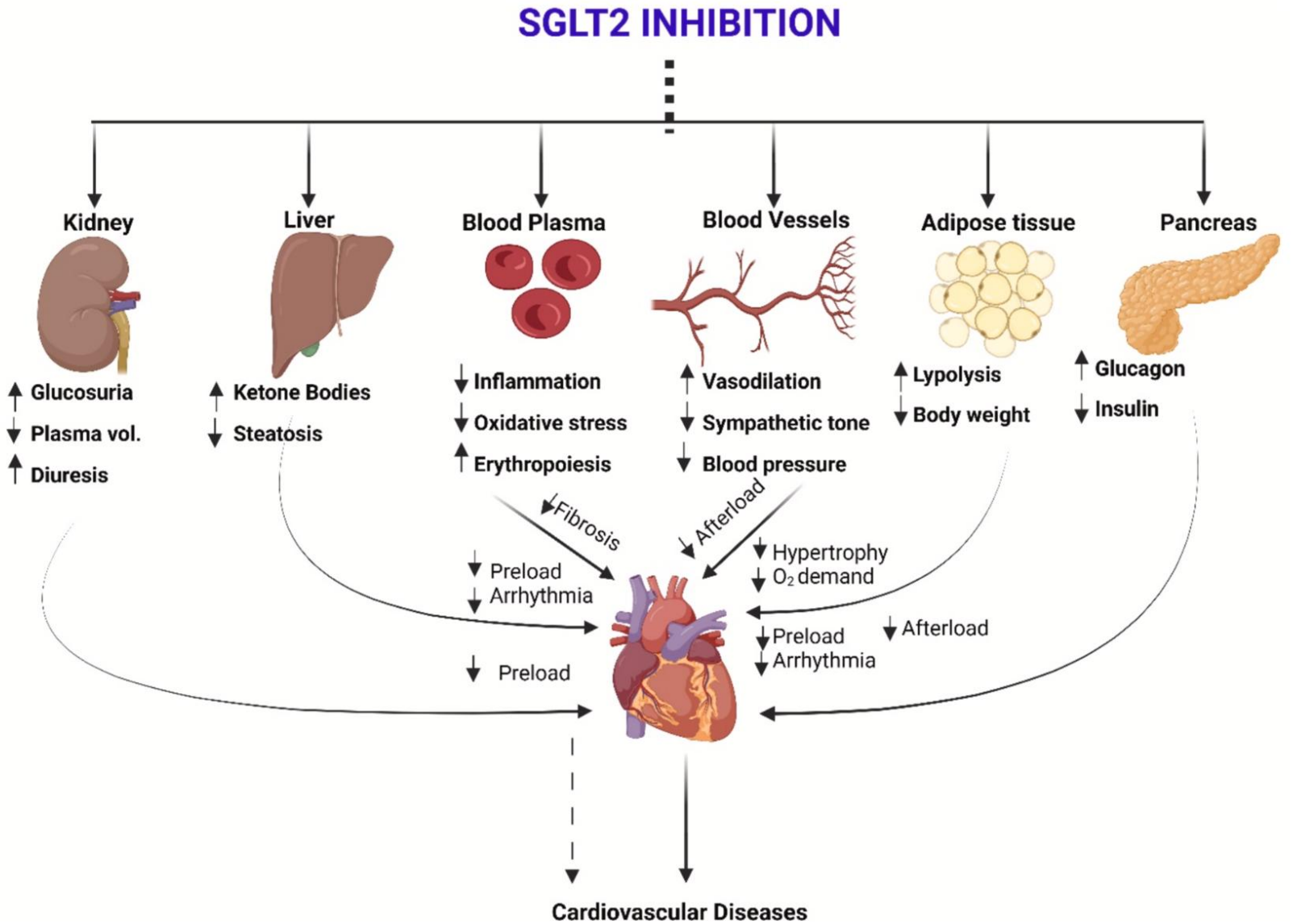
Dan L. Longo, M.D., *Editor*

Gliflozins in the Management of Cardiovascular Disease

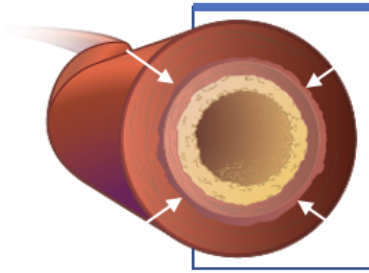
Eugene Braunwald, M.D.



Braunwald et al. New England Journal of Medicine 2022; 386:2024-2034

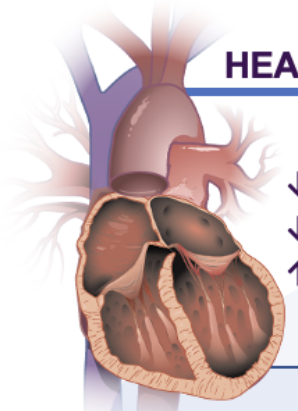


Diabet Research and Clinical Practice 2025



CIRCULATION[1,2]

↓Interstitial & plasma volume
↓Arterial stiffness
Improved endothelial function
↓Systolic blood pressure
↑Hematopoiesis & hematocrit



HEART[2]

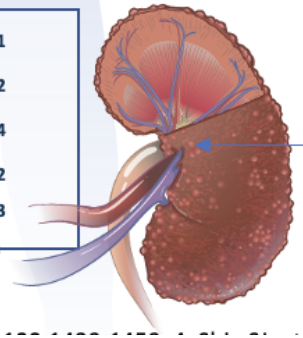
↓Cardiac preload/afterload
↓Cardiac wall stress
↑Cardiac efficiency/output

SGLT-2 INHIBITION

Glycosuria[2]
Diuresis[3]
Natriuresis[2,3]

↓Glucose/sodium reabsorption[1]
↓Intraglomerular pressure[2]
↓Intrarenal RAAS activity[4]
↓Hyperfiltration[2]
↓Inflammation/hypoxia[3]

KIDNEY



CARDIORENAL PROTECTION[2,3]

↑Cardiac function
↑Renal function

IMPROVED CLINICAL OUTCOMES[3,5]

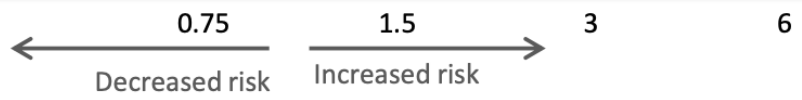
↓CV outcomes & death
↓HF hospitalization
Stabilization of eGFR
↓Albuminuria

Sattar N et al. *Diabetologia*. 2016;59(7):1333-1339. 2. Verma S et al. *JAMA Cardiol*. 2017;2(9):939-940. 3. Scheen RJ. *Circ Res*. 2018;122:1439-1459. 4. Shin SJ, et al. *PLoS One*. 2016;11:e0165703. 5. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32.

The presence of cardio-renal disease is associated with increased risk of mortality in patients with T2D

Pooled death risks associated with presence of CV or kidney disease compared to a CVRD-free T2D patient group (N=772,336)*

Outcomes	CVRD single presence vs CVRD-free group	HR† (95% CI)
All-cause death	Cardio-renal disease	2.02 (1.75, 2.33)
	HF	2.30 (2.14, 2.47)
	CKD	1.88 (1.59, 2.22)
	Cardio-renal syndrome	3.14 (2.90, 3.40)
	Stroke	1.59 (1.40, 1.81)
	Peripheral artery disease	1.72 (1.55, 1.92)
	MI	1.38 (1.21, 1.57)
CV disease death‡	Cardio-renal disease	2.05 (1.82, 2.32)
	HF	2.76 (2.12, 3.59)
	CKD	1.79 (1.59, 2.02)
	Cardio-renal syndrome	3.91 (3.02, 5.07)
	Stroke	2.31 (2.01, 2.65)
	Peripheral artery disease	2.24 (1.94, 2.58)
	MI	1.96 (1.80, 2.14)



AGENDA

- SGLT2i nei pazienti diabetici
- SGLT2i e scompenso cardiaco
- SGLT2i e nefroprotezione

AGENDA

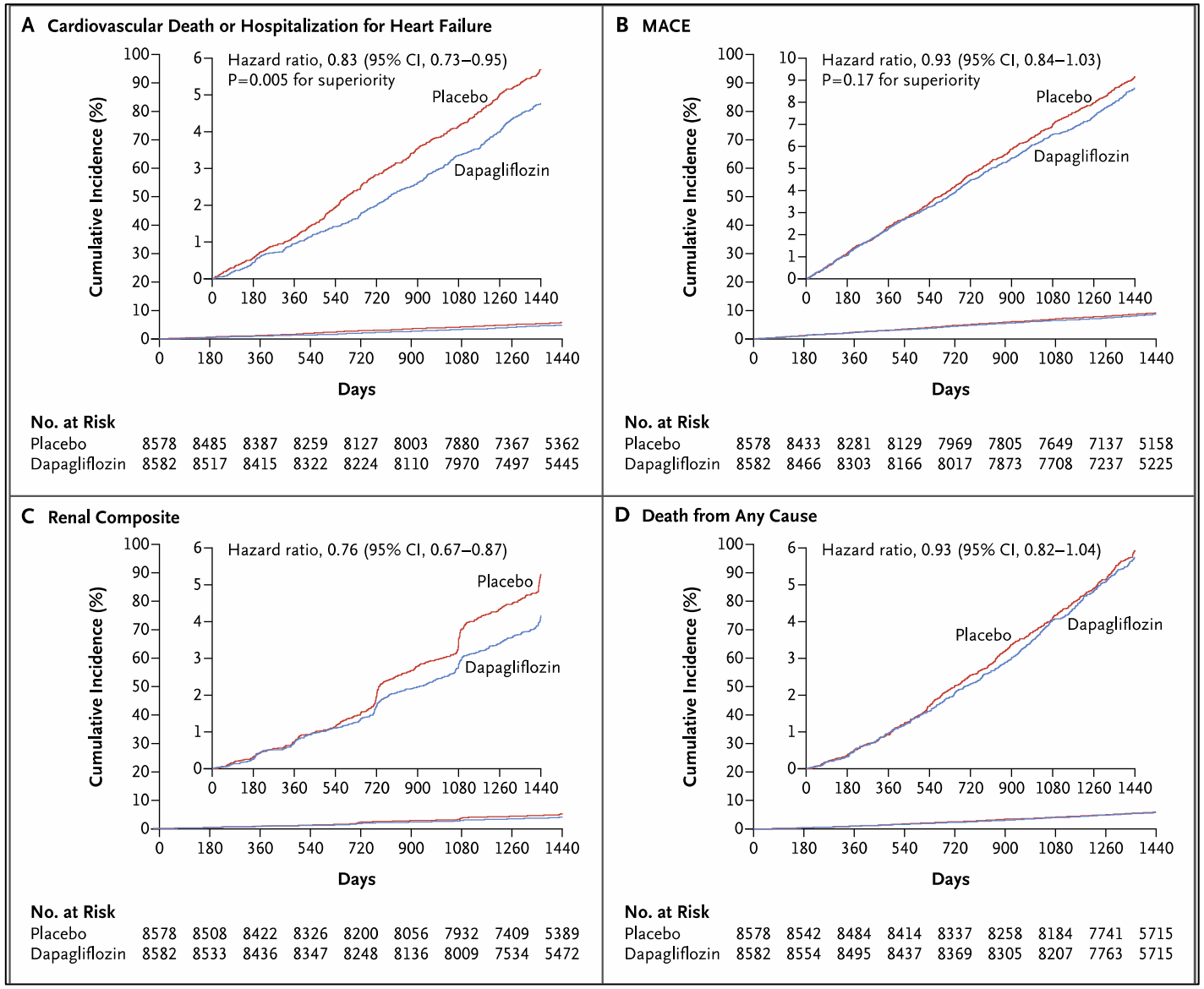
- SGLT2i nei pazienti diabetici

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

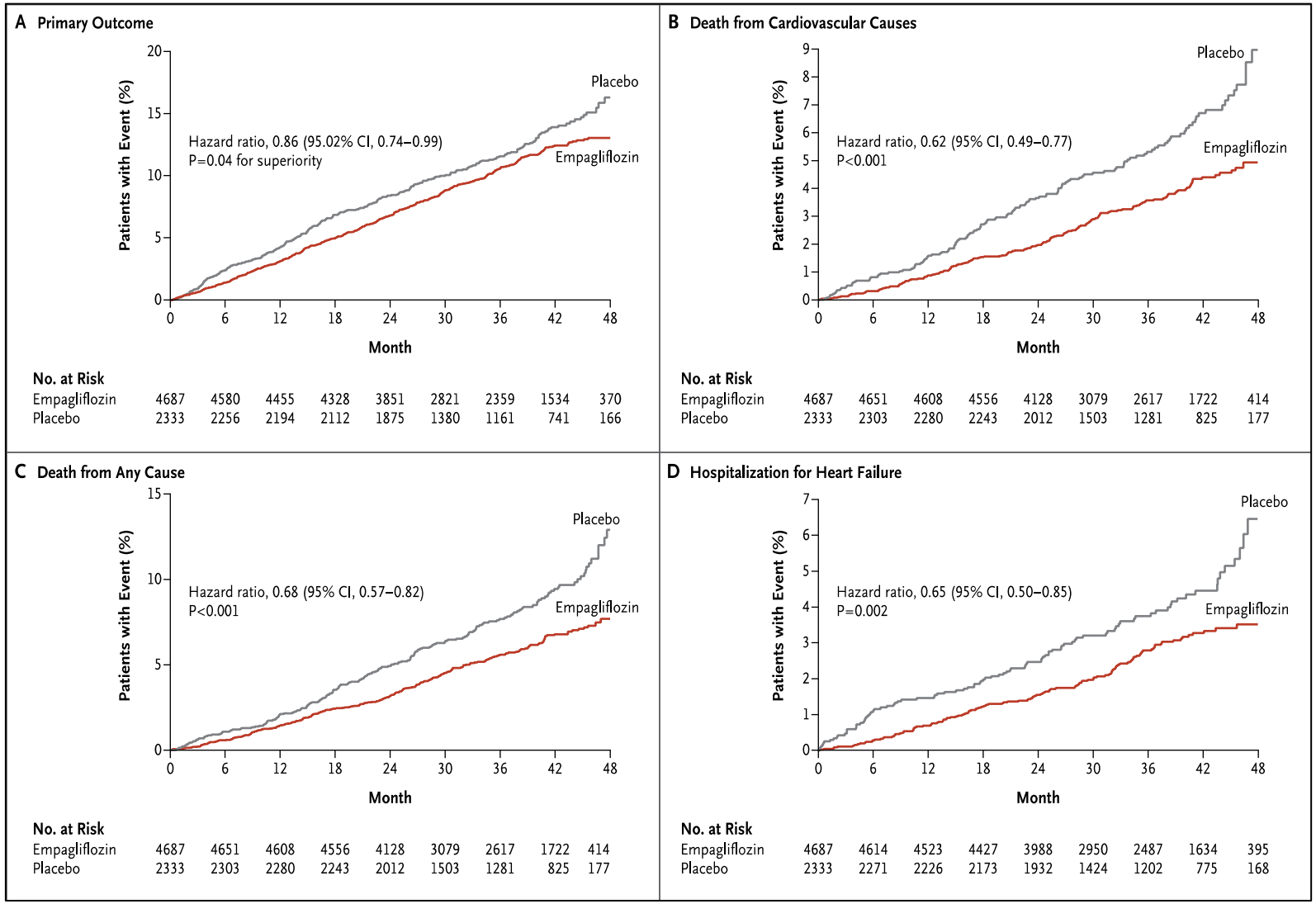


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators



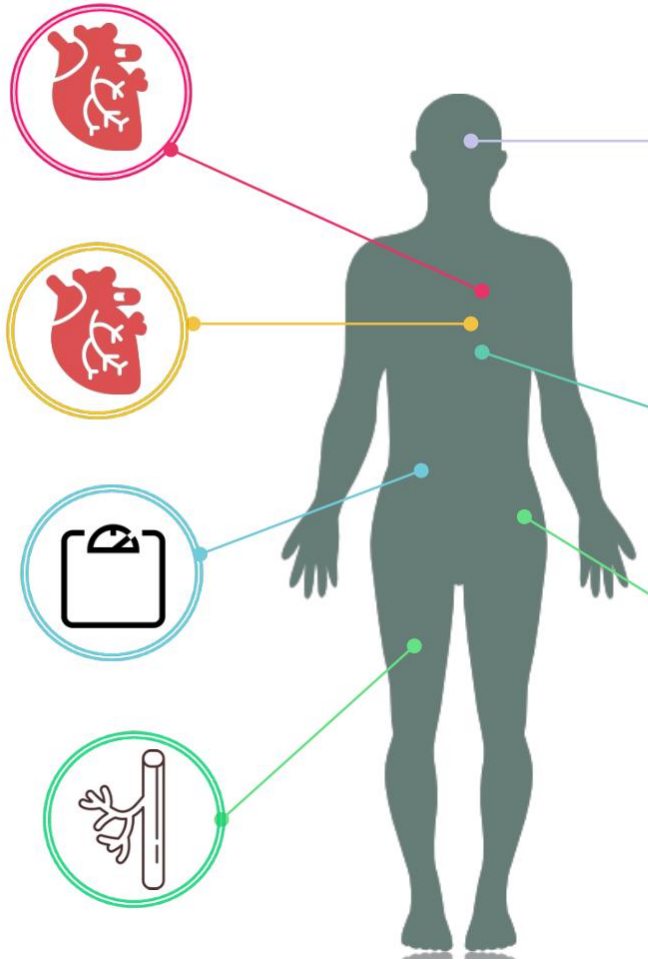
Trial definition of CV diseases and baseline characteristics[1,2,3]

Cardiac failure
~10%

Myocardial infarction
~47%

Body mass index > 30 kg/m²
~52%

Peripheral artery disease
~21%



Stroke
~23%

Coronary artery disease
~75%

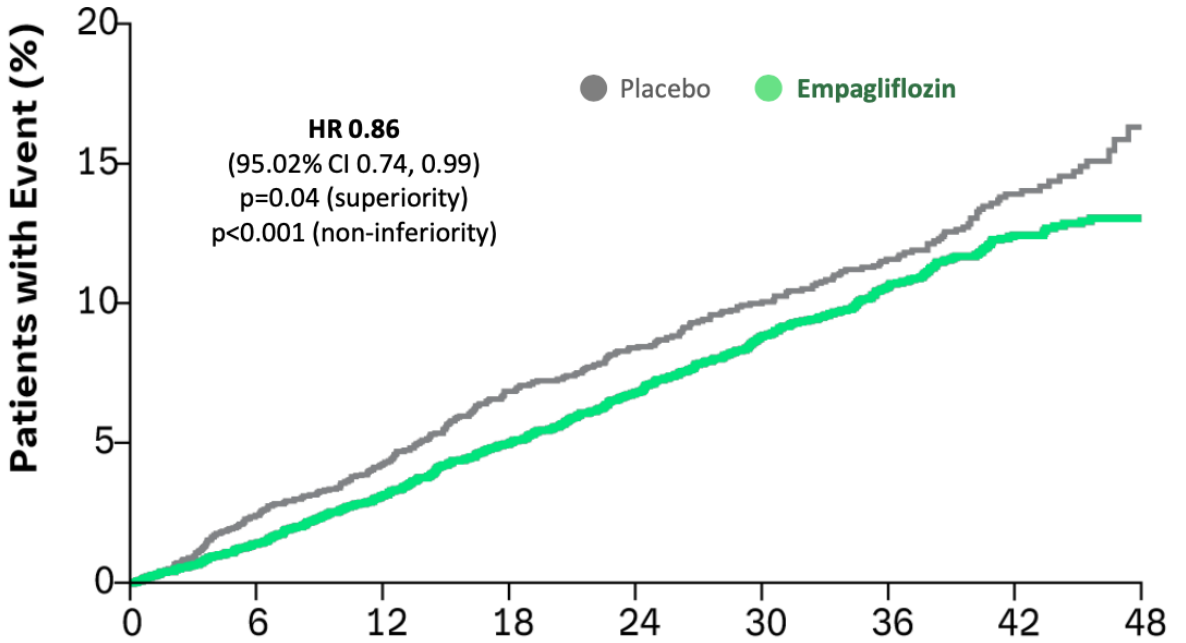
Prevalent Kidney disease
(eGFR [MDRD] <60 mL/min/1.73m² and/or macroalbuminuria [UACR >300 mg/g] at baseline)
~32%

Empagliflozin* reduced the risk of 3P-MACE in patients with T2D and CV disease

EMPA-REG OUTCOME

3P-MACE†

14% RRR



No. at Risk									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
Empagliflozin	**4687**	**4580**	**4455**	**4328**	**3851**	**2821**	**2359**	**1534**	**370**

Long-term cardio-renal outcomes: SGLT2 inhibitors show reductions in CV, HHF and kidney outcomes in patients with T2D

	EMPA-REG OUTCOME[5,6] (empagliflozin)	CANVAS Program[7] (canagliflozin)	DECLARE-TIMI 58[8,9] (dapagliflozin)	VERTIS CV[10] (ertugliflozin)
3P-MACE	**HR 0.86** (95% CI 0.74, 0.99) p=0.04	**HR 0.86** (95% CI 0.75, 0.97) p=0.02*	**HR 0.93** (95% CI 0.84, 1.03) p=0.17	**HR 0.97** (95.6% CI 0.85, 1.11) p<0.001 for non-inferiority
CV death	**HR 0.62** (95% CI 0.49, 0.77) p<0.001‡	**HR 0.87** (95% CI 0.72, 1.06)†	**HR 0.98** (95% CI 0.82, 1.17)†	**HR 0.92** (95.8% CI 0.77, 1.11)†
HHF	**HR 0.65** (95% CI 0.50, 0.85) p=0.002‡	**HR 0.67** (95% CI 0.52, 0.87)†	**HR 0.73** (95% CI 0.61, 0.88)†	**HR 0.70** (95% CI 0.54, 0.90)†
Kidney outcomes§	**HR 0.61** (95% CI 0.53, 0.70) p<0.001‡	**HR 0.60** (95% CI 0.47, 0.77)†	**HR 0.53** (95% CI 0.43, 0.66) p<0.0001‡	**HR 0.81** (95.8% CI 0.63, 1.04)†

AGENDA

- SGLT2i e scompenso cardiaco

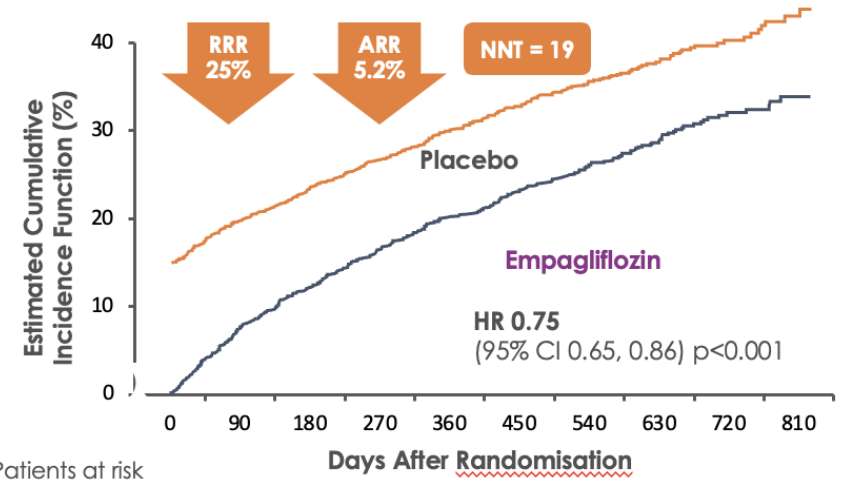
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

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

Primary Endpoint and 1st

First Adjudicated CV Death or Hospitalisation for Heart Failure

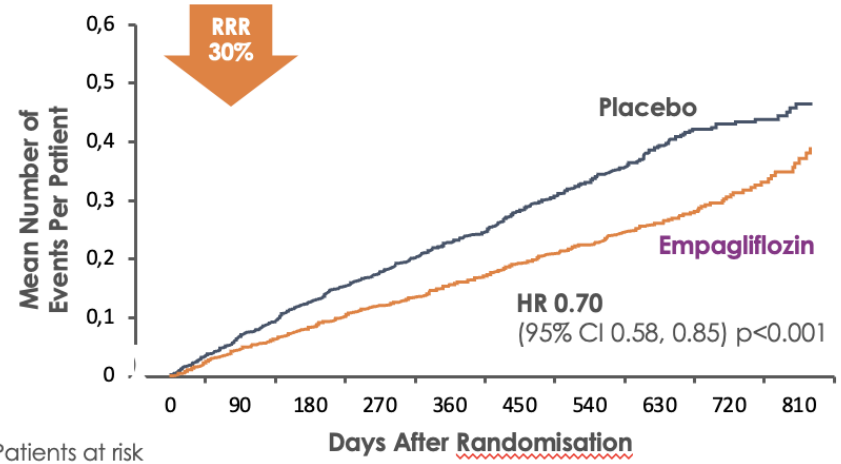


Patients at risk

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

Key Secondary Endpoint

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

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

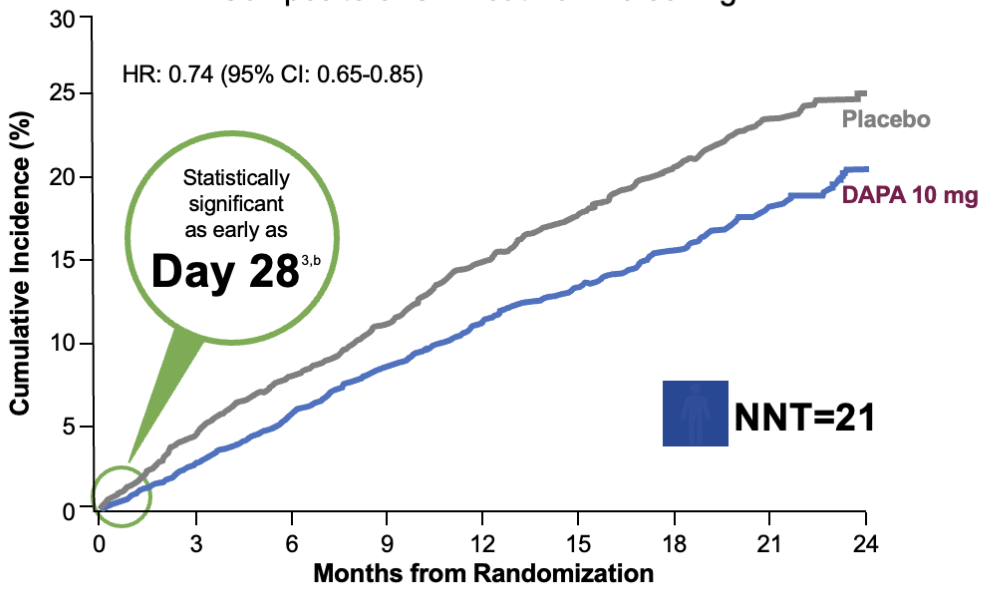
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

DAPAHF

Primary Endpoint

Composite of CV Death or Worsening HF[a]



CV Death or Worsening HF[a]
26 % RRR
4.9 % ARR
p=0.00001

CV death
18 % RRR
1.9% ARR
p=0.029

Worsening HF[a]
30 % RRR
3.7% ARR
p=0.00003

Consistent benefit in the primary endpoint across key subgroups

All-cause mortality was also reduced in the dapagliflozin group

All-cause mortality
17 % RRR
2.3% ARR
p=0.022[c]

Quality of life
18 % RRI
P<0.001

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, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

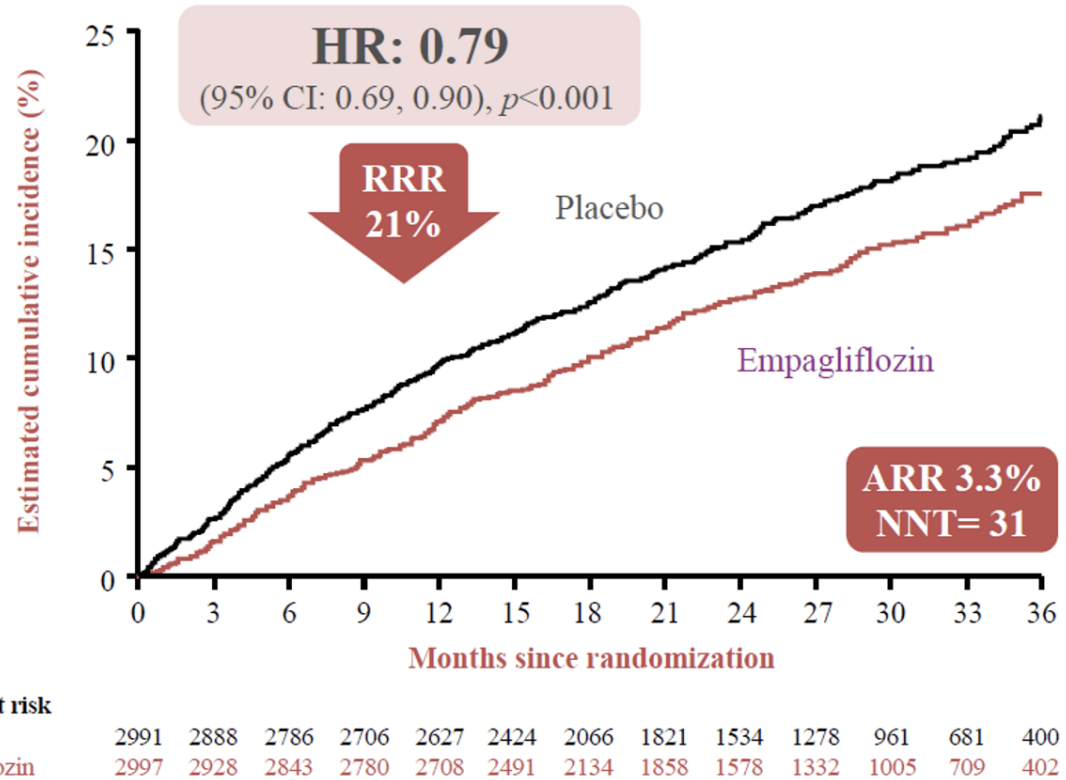
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*

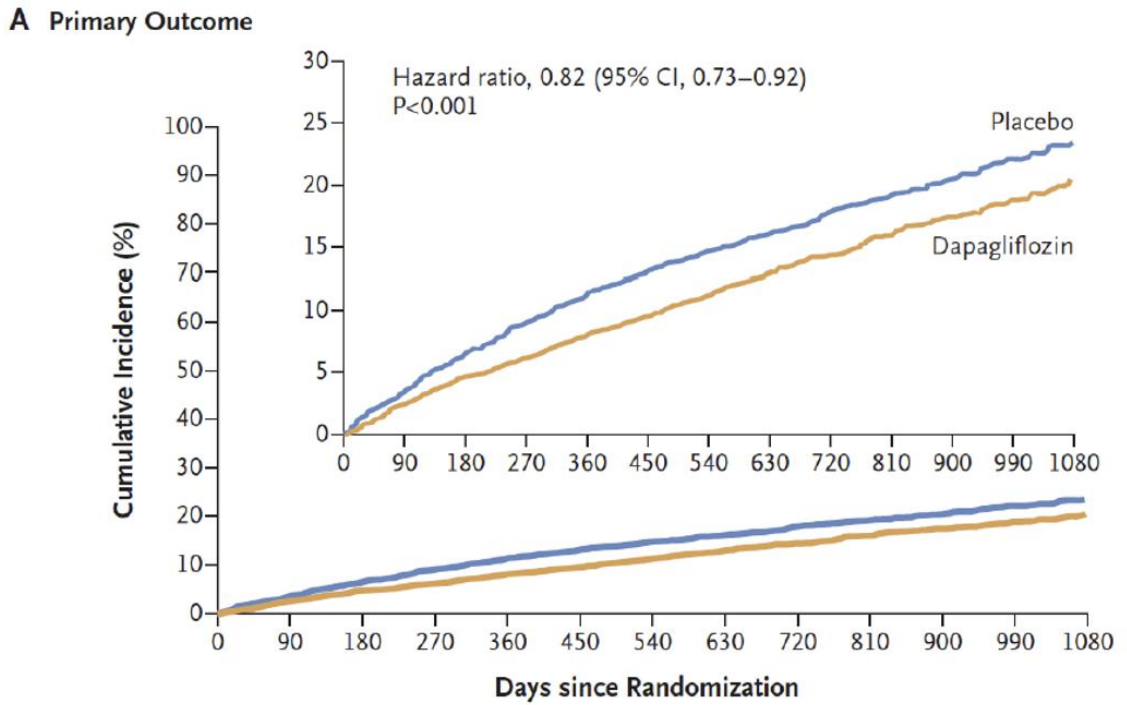
- Primary endpoint:
  - Time to first event of adj CV death or HF hospitalisation



Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

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



No. at Risk

Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

Solomon et al. NEJM Aug 2022

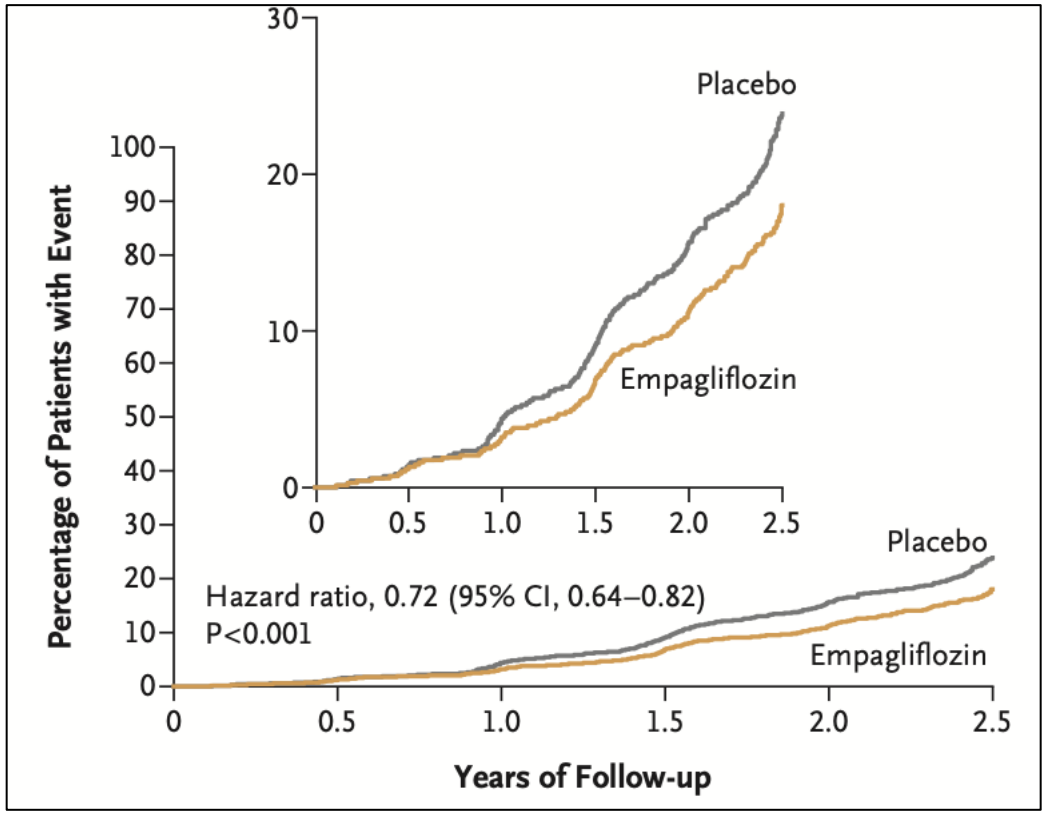
AGENDA

- SGLT2i e nefroprotezione

ORIGINAL ARTICLE

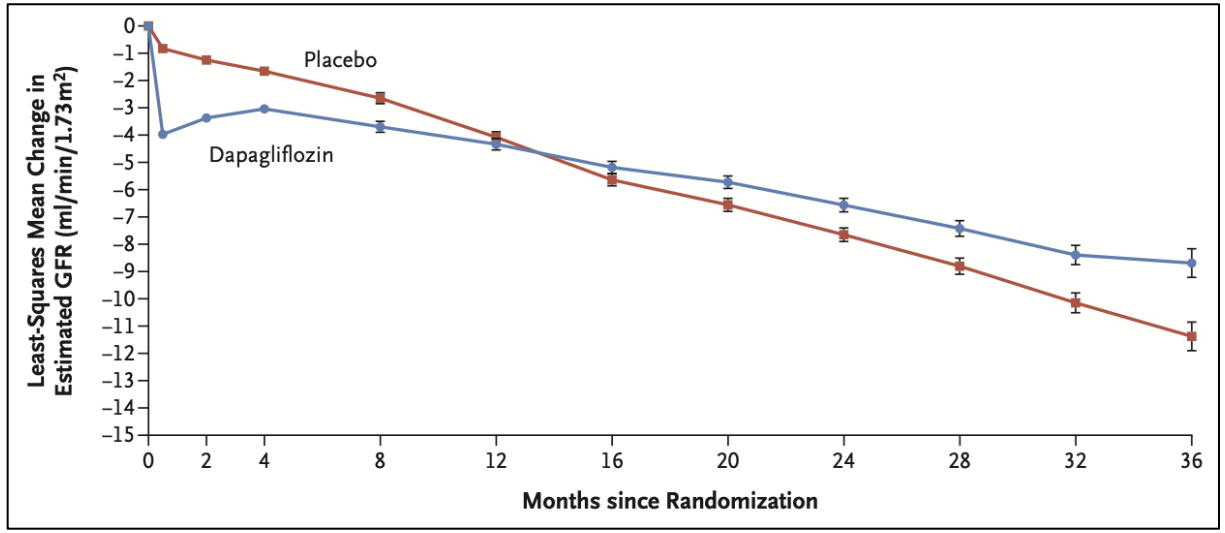
Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

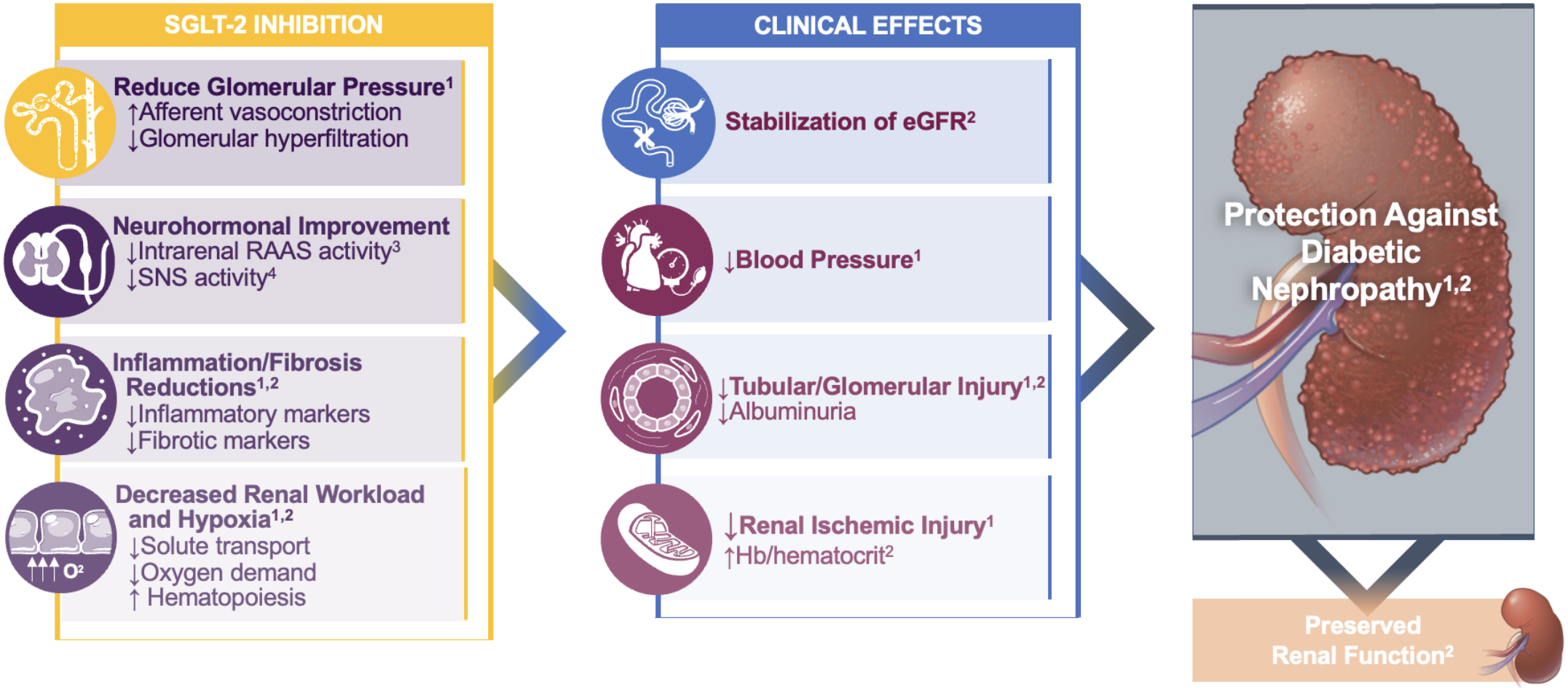


ORIGINAL ARTICLE

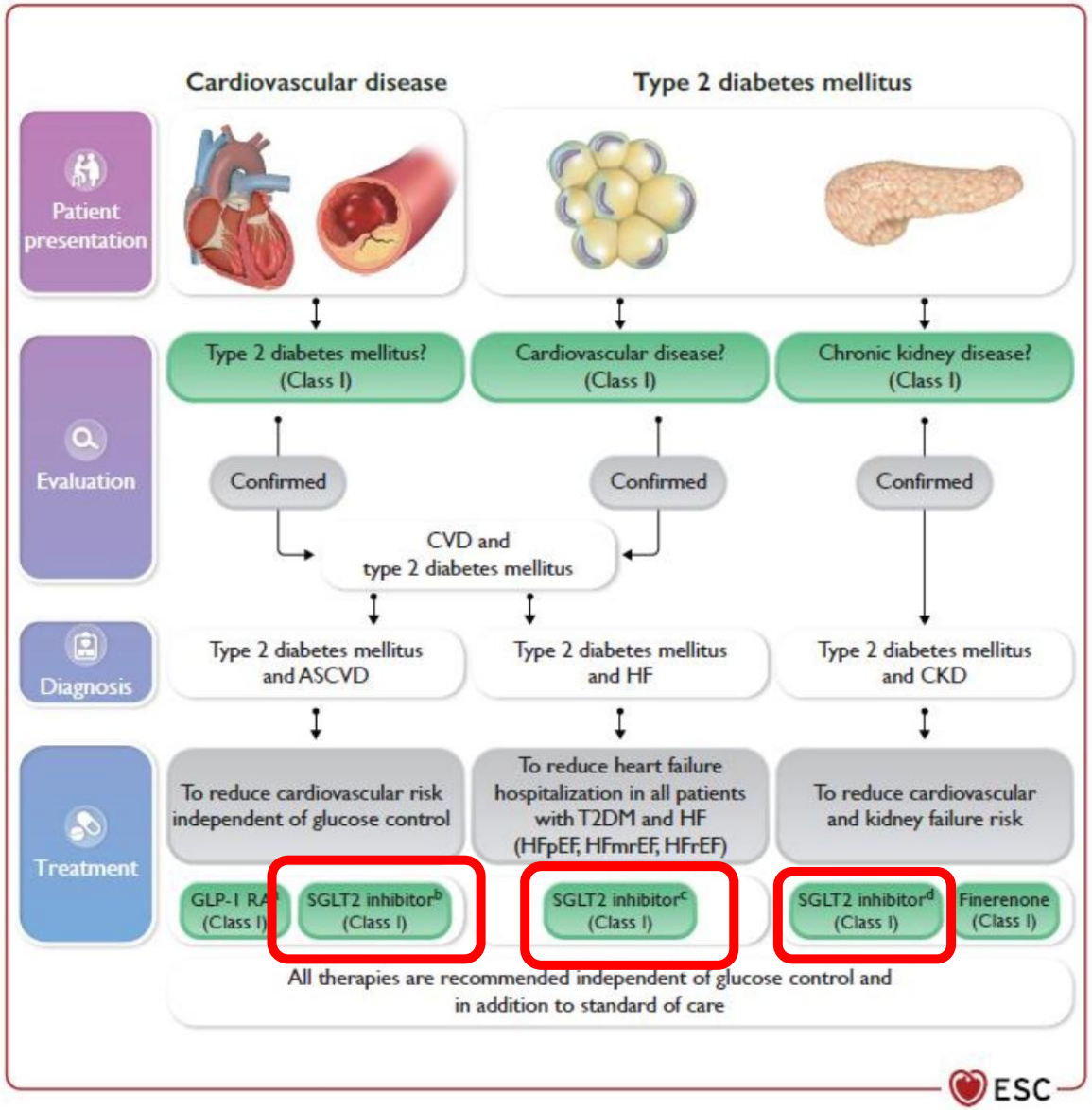
Dapagliflozin in Patients with Chronic Kidney Disease

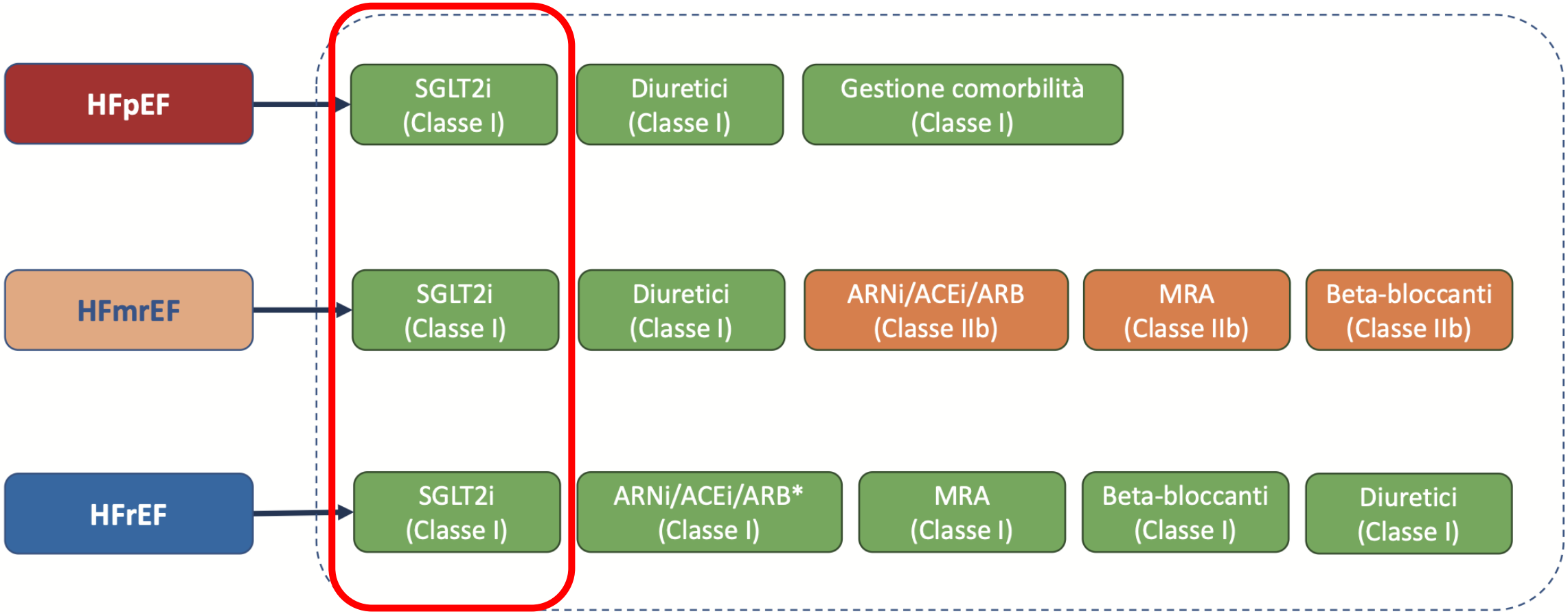


Potential Effects by Which SGLT-2 Inhibition Improves Renal Outcomes

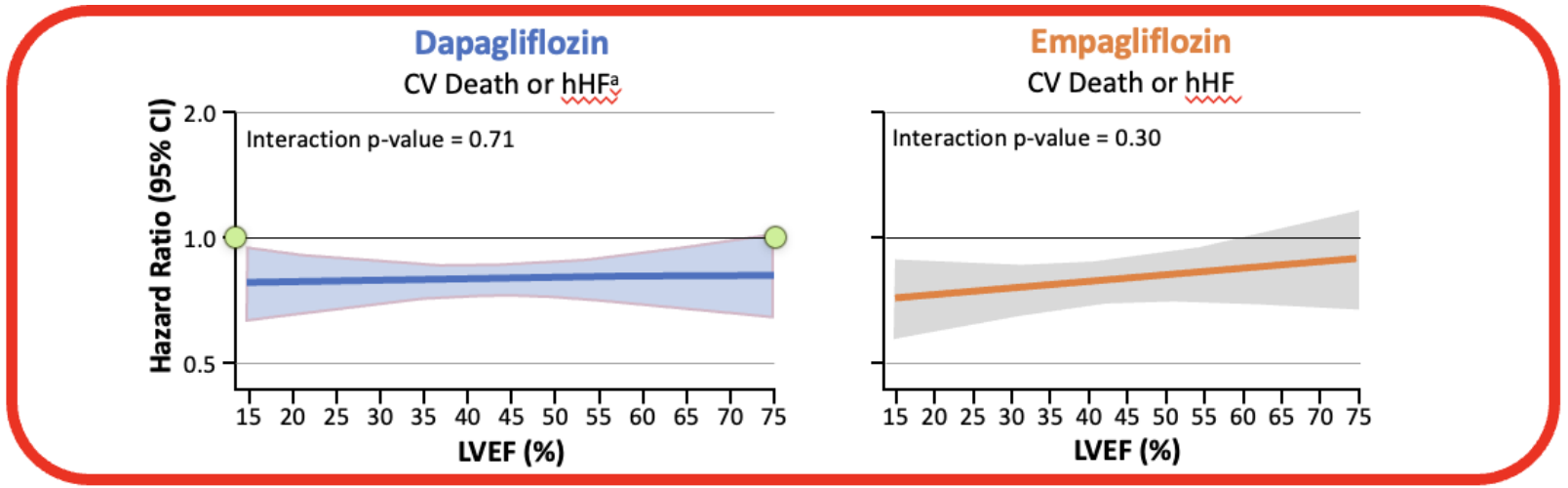


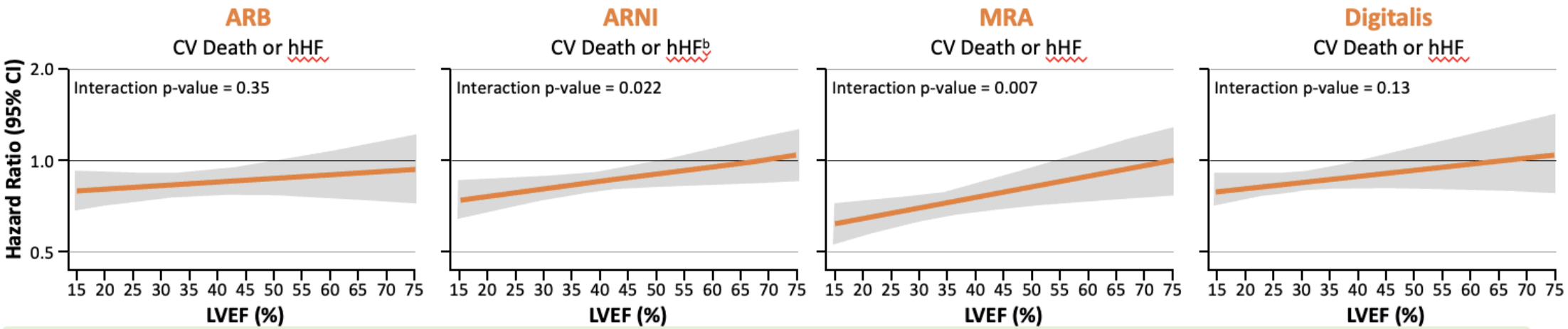
Management of CVD in patients with T2D: clinical approach and recommendations – ESC 2023





Adapted from: McDonagh TA et al. Eur Heart J. 2021; McDonagh TA et al. Online ahead of print. Eur Heart J. 2023.





Differences among trial design, patient population, and treatment groups impact ability to directly compare results across different trials.

Modelli di regressione lineare di morte CV e ospedalizzazioni per HF; cfr con placebo tranne ARNI cfr con ACEi/ARB

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

Recommendation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

Practice Point 3.7.1: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or KRT is initiated.

Practice Point 3.7.2: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when people may be at greater risk for ketosis).

Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following *(1A)*:
- **eGFR ≥20 ml/min per 1.73 m^2 with urine ACR ≥200 mg/g (≥20 mg/mmol), or**
- **heart failure, irrespective of level of albuminuria.**

Practice Point 3.7.3: SGLT2i initiation or use does not necessitate alteration of frequency of CKD monitoring and the reversible decrease in eGFR on initiation is generally not an indication to discontinue therapy.

Recommendation 3.7.3: We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i *(2B)*.

Oliva et al Journal of Cardiac Failure 2025

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–2
doi:10.1093/eurheartj/ehab765

CARDIOPULSE

Braunwald's Corner

SGLT2 inhibitors: the statins of the 21st century

Eugene Braunwald [1,2*]

Braunwald European Heart Journal 2021

ESC European Society of Cardiology
European Heart Journal (2025) **46**, 682–684
https://doi.org/10.1093/eurheartj/ehae775
https://doi.org/10.1093/eurheartj/ehae775
CardioPulse

Braunwald's Corner

From cardiorenal to cardiovascular–kidney–metabolic syndromes

Eugene Braunwald [1,2,*]

During the last decade, three new drug classes that improve clinical outcomes in both CRS and CKM have become available. Sodium–glucose cotransporter 2 inhibitors (SGLT2i),[17] introduced as glucosuric agents for the treatment of T2D, were found, unexpectedly, to be both effective in the management of HF across ejection fraction classes and CKD.[18] These agents are currently administered to patients with one, two, or all three components of CKM.

Braunwald et al. European Heart Journal 2025

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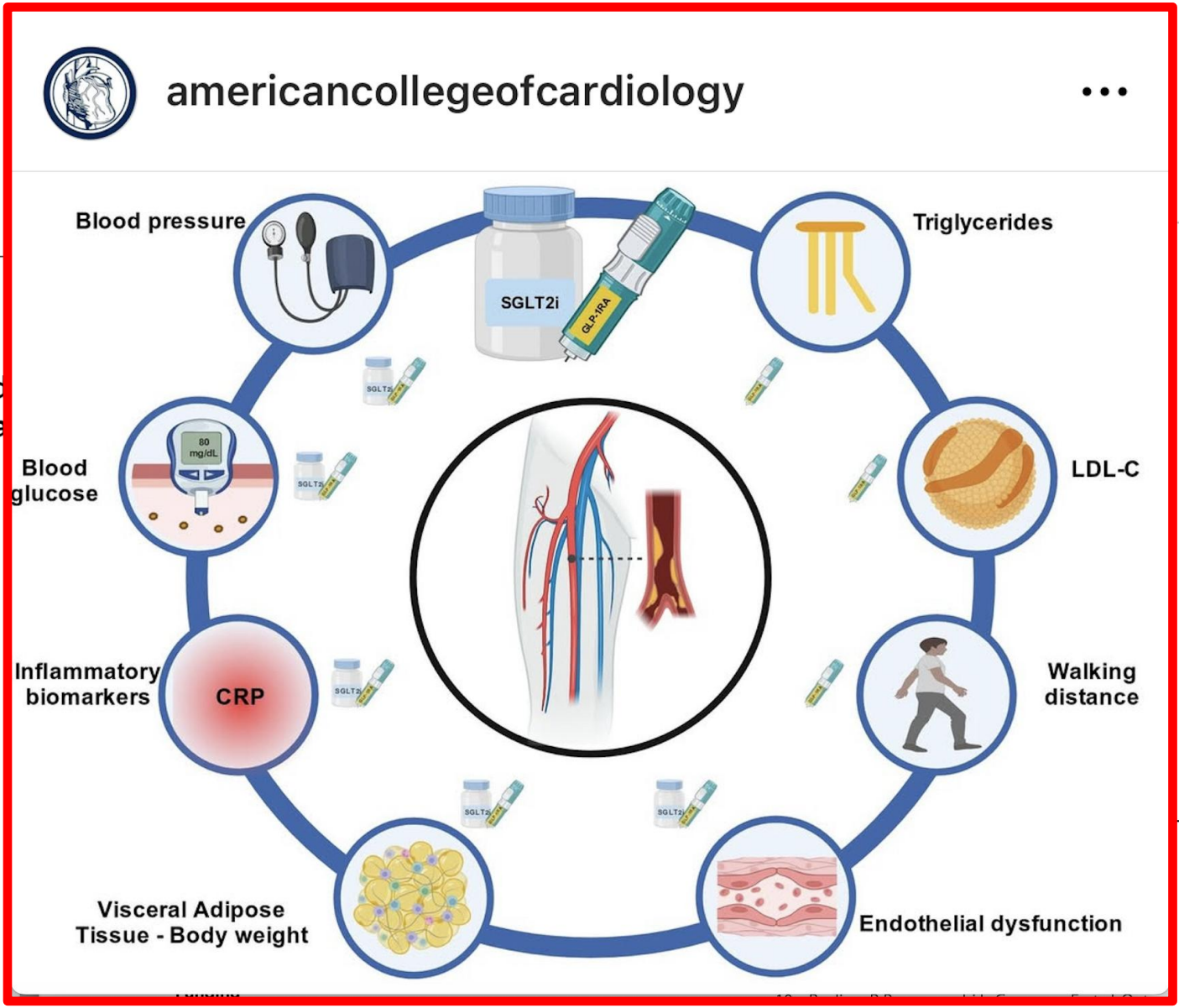
DOI: 10.1111/dom.16078

ORIGINAL ARTICLE

**One or two? Comparison of the card
combination therapy and monothera
or GLP1RA**

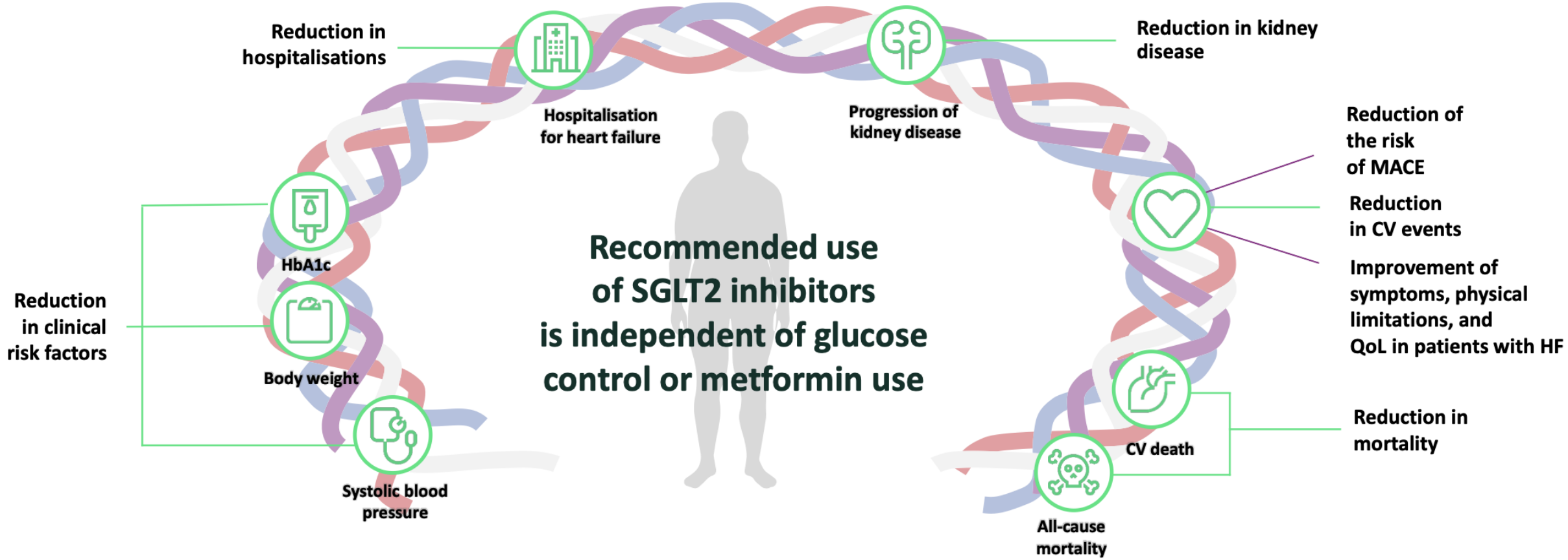


	RR (95% CI)	% Weight
	0.41 (0.17, 0.97)	11.45
	0.68 (0.40, 1.15)	19.19
	0.71 (0.49, 1.02)	24.10
	0.66 (0.50, 0.88)	54.75
	0.28 (0.17, 0.46)	20.07
	0.73 (0.52, 1.01)	25.18
	0.46 (0.18, 1.18)	45.25
	0.55 (0.38, 0.80)	100.00

5.88

Zhang et al. Diabetes Obes

Why wait to confront the risk?



GRAZIE PER L'ATTENZIONE