LA CURA DELLA PERSONA CON DIABETE NELL' ERA DELL' INTELLIGENZA ARTIFICIALE TRAGUARDI, SFIDE E NUOVI ORIZZONTI

CONGRESSO REGIONALE SID-AMD MARCHE 2025

CONTROLLO METABOLICO E CARDIONEFROPROTEZIONE IN DIABETOLOGIA TRA NOTA 100 E LINEE GUIDA : L' EFFICACIA DEGLI SGLT2i

Dr. Alessandro Micillo
Endocrinologia e Diabetologia - PESARO

Dichiarazione dei conflitti d'interesse

IL SOTTOSCRITTO DICHIARA

DI NON AVERE CONFLITTI DI INTERESSE

Retrospective analysis of data from >1.1 million patients with T2D

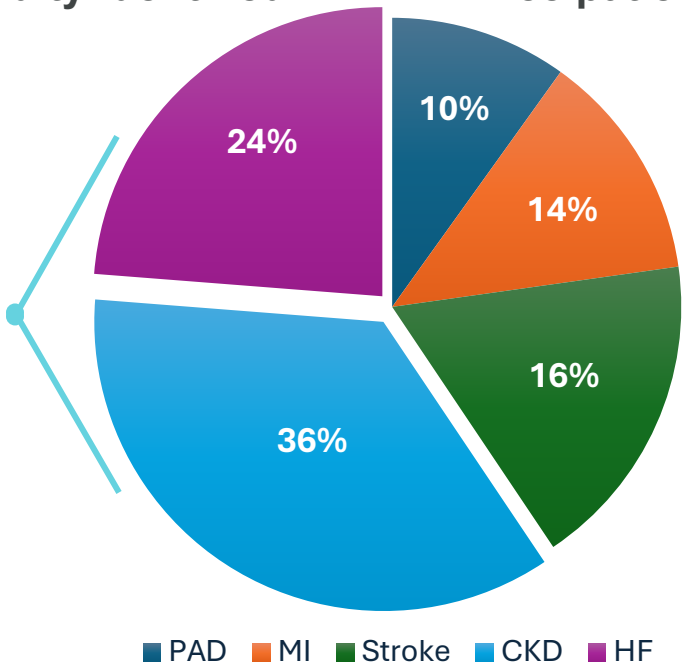
Initially, the majority (66%) of patients were CVRD-free

Mean follow-up: 4.5 years

137,081 patients (18% of total CVRD-free patient population) developed a CVRD manifestation

First comorbidity identified in CVRD-free patients with T2D

Cardiorenal diseases (HF or CKD) **60%**



Compared with comorbidity-free patients with T2D, **cardiorenal disease was associated with a greater risk of mortality** than stroke, PAD and MI

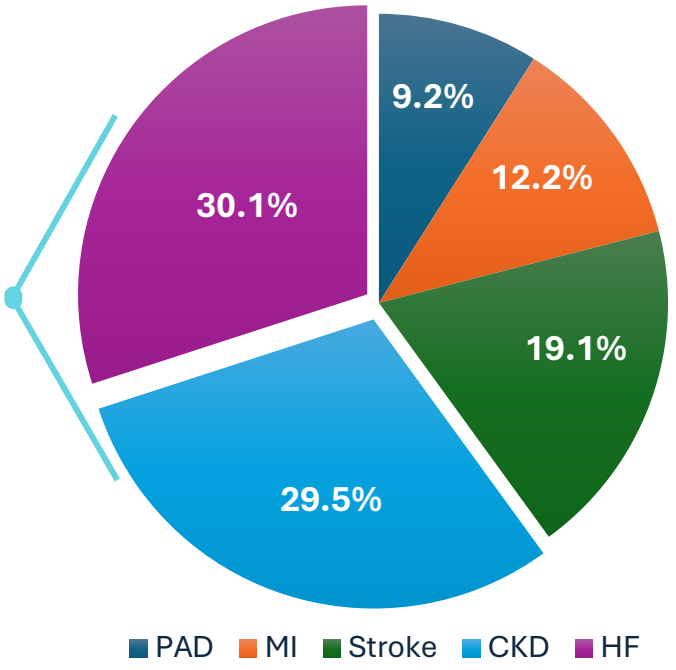
T2D and cardiorenal disease are interlinked

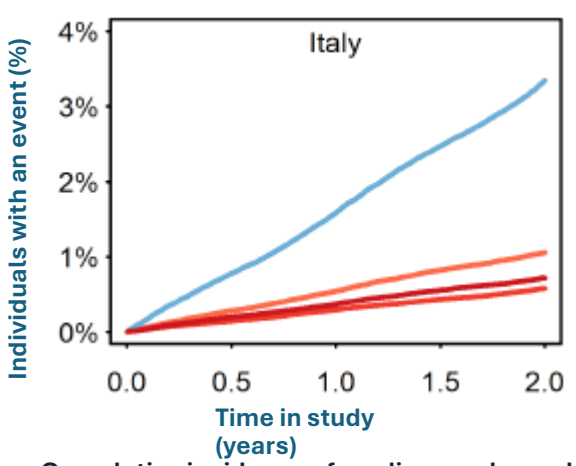
Birkeland KI et al. *Diabetes Obes Metab*. 2020;22:1607-1618.

Italy is no exception, and the costs reflect the onset of comorbidities

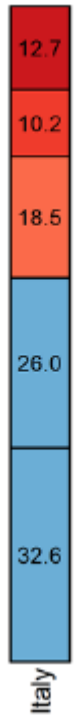
Distribution of 1.1 billion USD CVRD health care cost

Cardiorenal disease (HF or CKD) **60%**





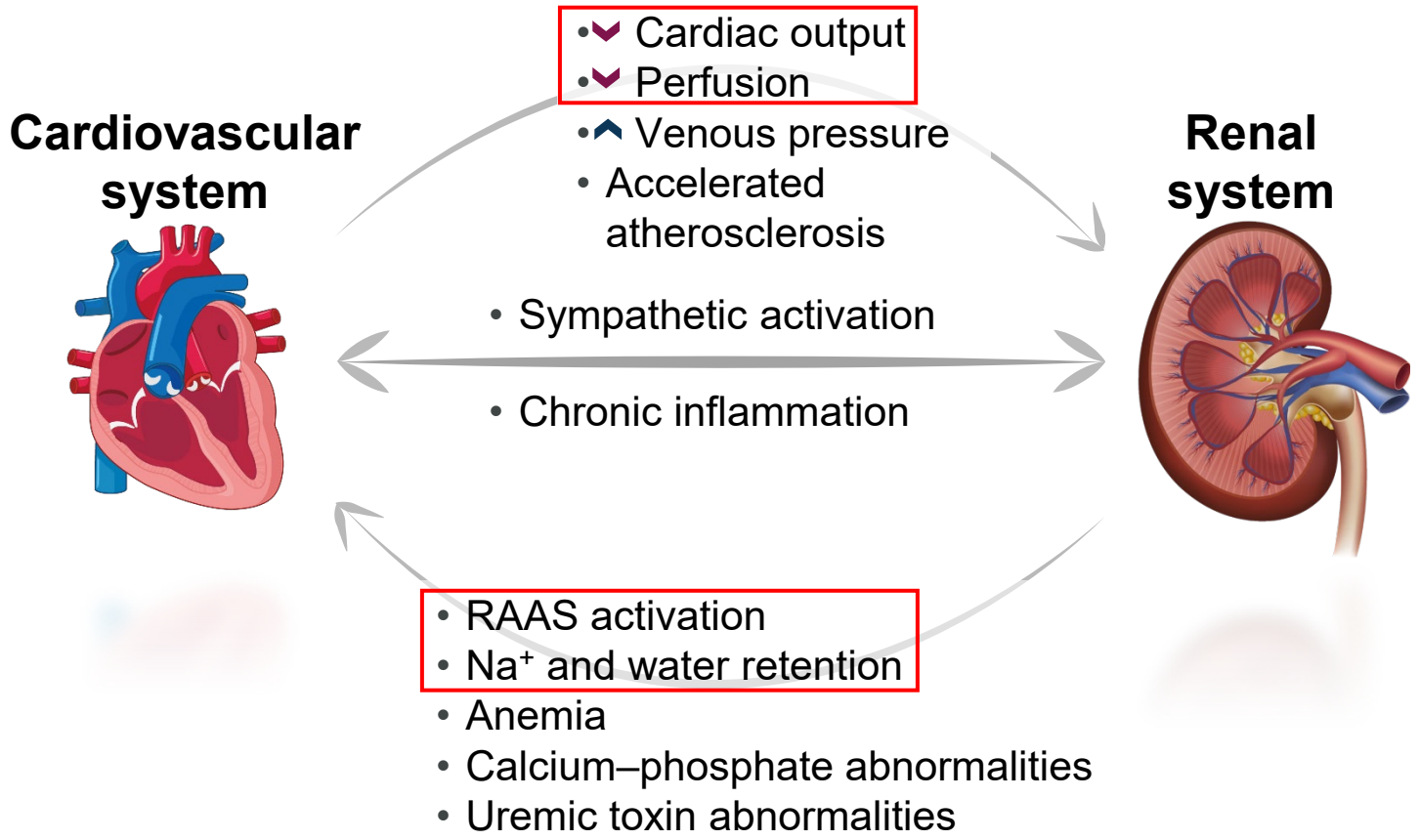
Cumulative incidence of cardiovascular and renal disease in 295,940 individuals with type 2 diabetes, initially free from any prior cardiovascular and renal disease.



Peripheral artery disease (PAD)
Myocardial infarction (MI)
Stroke
Cardiorenal disease (HF or CKD)

Diabetes Obes Metab. 2022 Mar 23.

HF and CKD are notable drivers of disease progression in one another



CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; RAAS, renin–angiotensin–aldosterone system

Ronco C, et al. *J Am Coll Cardiol* 2008;52:1527–1539

Multinational observational cohort study in 772,336 complication-free T2D patients (mean follow-up of 4.5 years)

HF
- ↑ CV death risk (HR 2.76)
- ↑ All-cause death risk (HR 2.30)

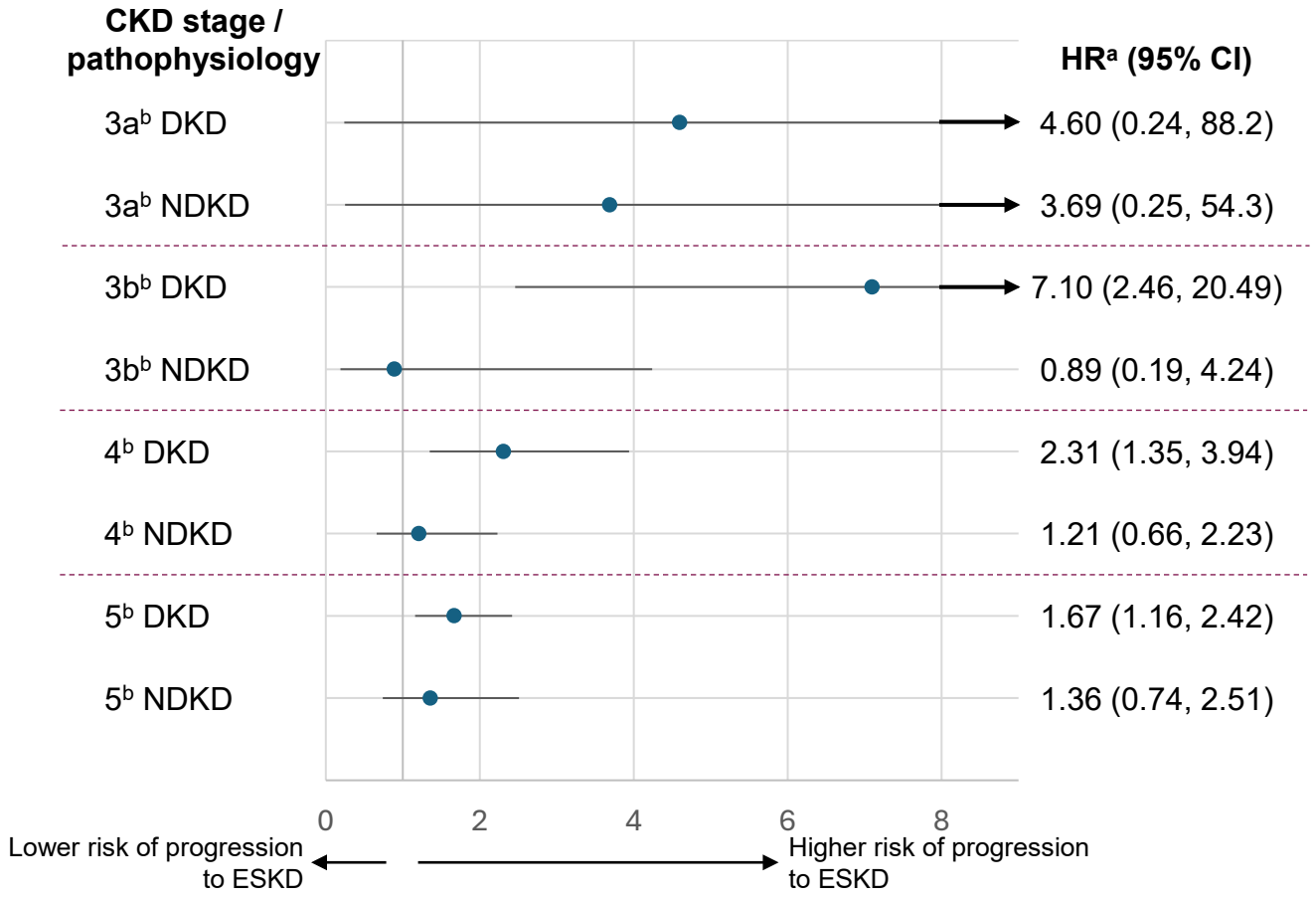
CKD
- ↑ CV death risk (HR 1.79)
- ↑ All-cause death risk (HR 1.88)

HF or CKD
- ↑ CV death risk (HR 2.05)
- ↑ All-cause death risk (HR 2.02)

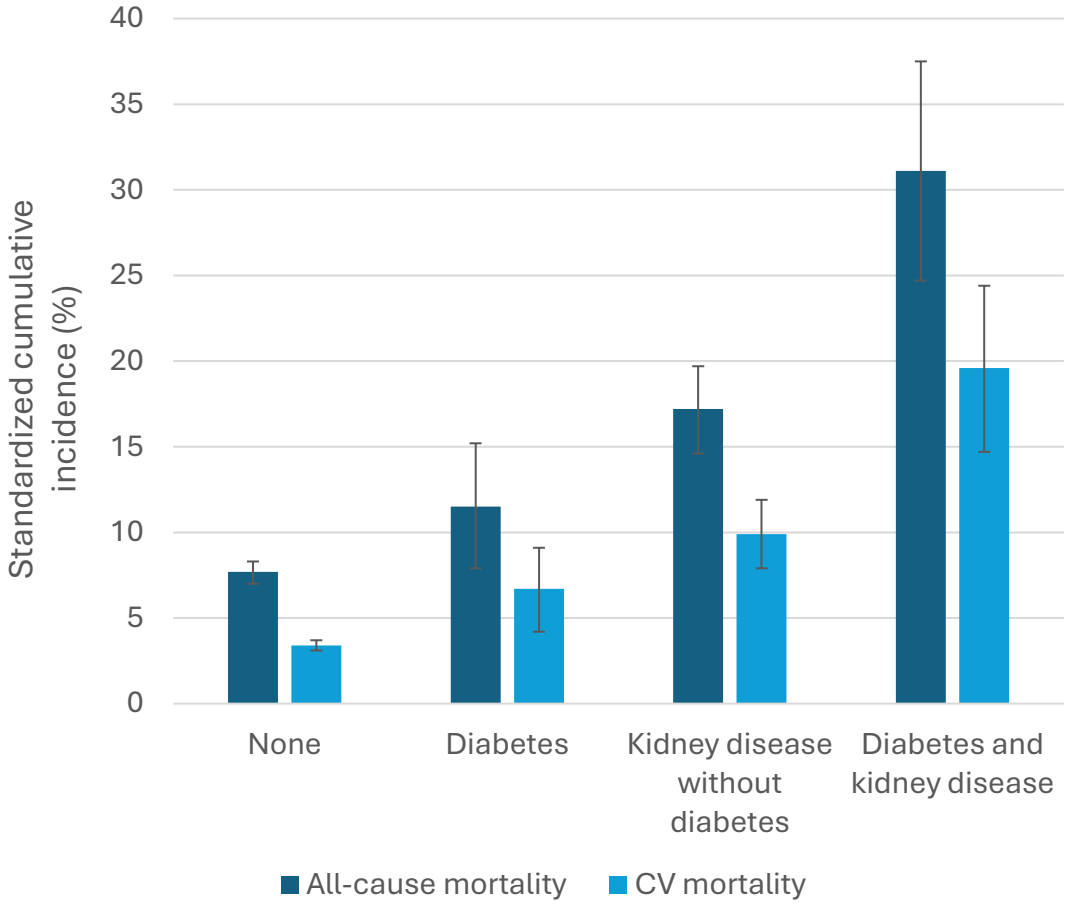
HF and CKD
- ↑ CV death risk (HR 3.91)
- ↑ All-cause death risk (HR 3.14)

Birkeland KI et al. *Diabetes Obes Metab*. 2020;22:1607-1618.

Risk for progression to ESKD in patients with diabetes and DKD versus NDKD

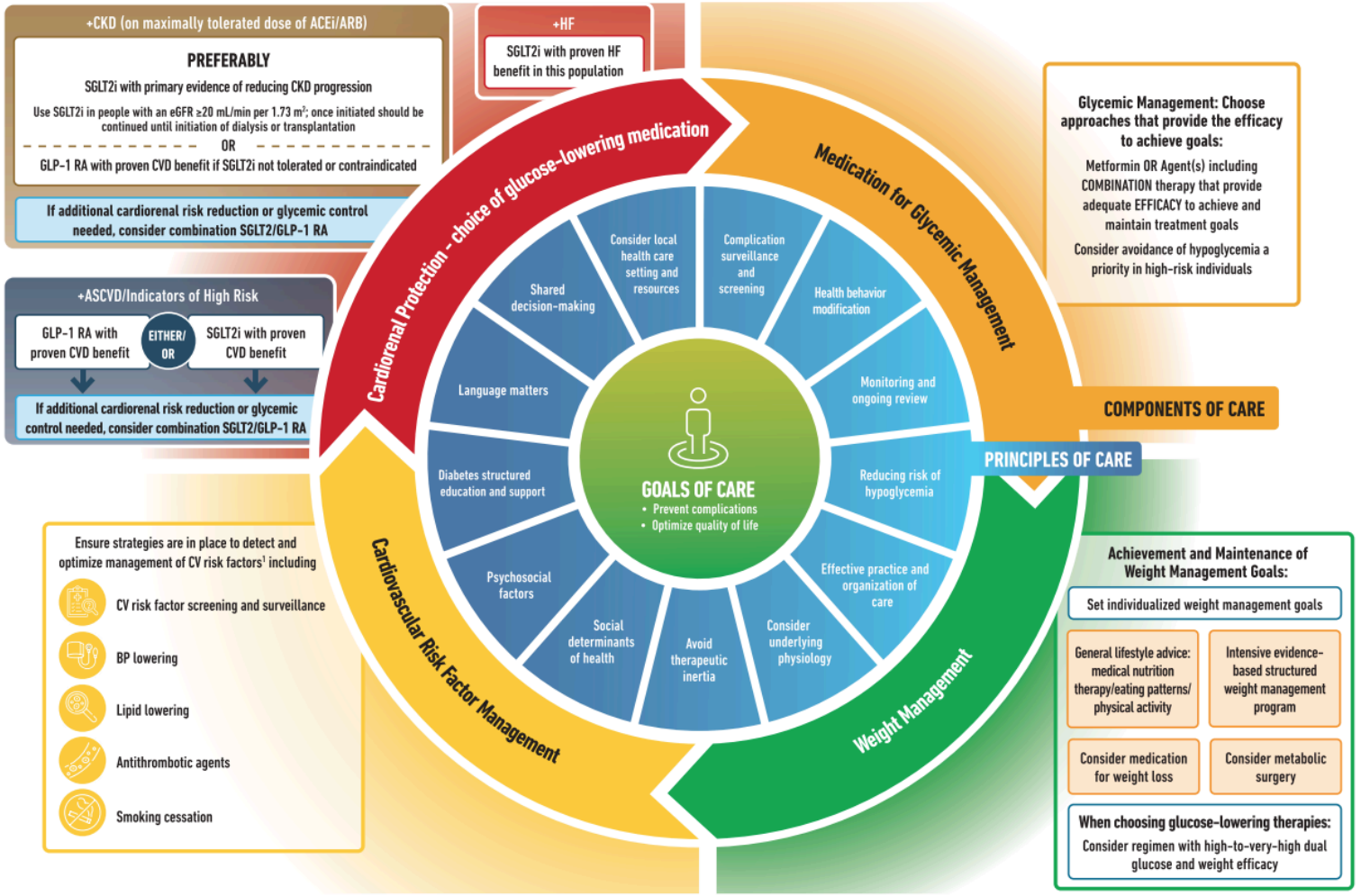


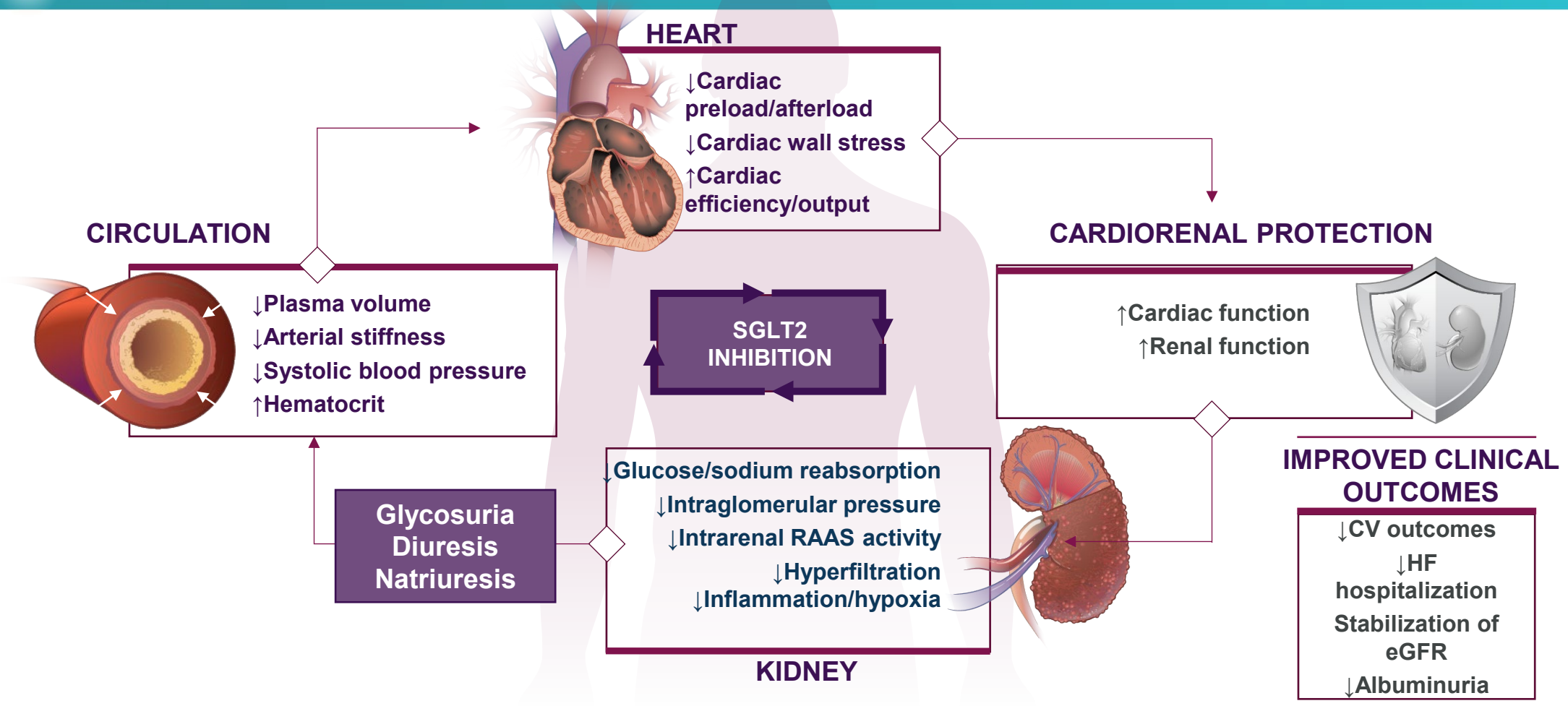
10-year standardized all-cause and CV mortality, by diabetes and kidney disease status



1. Iwai T, et al. *Clin Exp Nephrol* 2018;22:328–336; 2. Afkarian M, et al. *J Am Soc Nephrol* 2013;24:302–308

HOLISTIC PERSON-CENTERED APPROACH TO T2DM MANAGEMENT





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

The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes

Antonio Ceriello,[a,*] Giuseppe Lucisano,[b] Francesco Prattichizzo,[a,**] Rosalba La Grotta,[a] Chiara Frigé,[a] Salvatore De Cosmo,[c] Paolo Di Bartolo,[d] Graziano Di Cianni,[e] Paola Fioretto,[f] Carlo Bruno Giorda,[g] Roberto Pontremoli,[h] Giuseppina Russo,[i] Francesca Viazzi,[h] and Antonio Nicolucci,[b] AMD Annals study group,[i]

A delay in reaching the target HbA1c in patients with newly diagnosed type 2 diabetes (T2D) is associated with an increased long-term risk of developing cardiovascular disease (CVD), a phenomenon referred to as a **LEGACY EFFECT.**

UKPDS demonstrated that intensive blood glucose treatment in the early stages of type 2 diabetes significantly reduces the risk of microvascular and cardiovascular complications, highlighting the importance of legacy effect in early blood glucose control.

More recent clinical studies have shown that SGLT-2i not only lower blood glucose, but significantly reduce cardiovascular mortality, the risk of heart failure and the progression of diabetic nephropathy

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1577-89. doi: 10.1056/NEJMoa0806470. Epub 2008 Sep 10. PMID: 18784090.

Ceriello A, Lucisano G, Prattichizzo F, La Grotta R, Frigé C, De Cosmo S, Di Bartolo P, Di Cianni G, Fioretto P, Giorda CB, Pontremoli R, Russo G, Viazzi F, Nicolucci A; AMD Annals study group. The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes. Lancet Reg Health Eur. 2023 Jun 12;31:100666. doi: 10.1016/j.lanepe.2023.100666. PMID: 37547276; PMCID: PMC10398589.

The study used the Italian clinical database **Annali AMD**, which collects detailed information on patients with type 2 diabetes treated **in 230 Italian diabetes clinics from 2004 to 2021**

251,339 newly-diagnosed T2D patients without baseline CVD

Inclusion criteria
- Newly diagnosed T2D,
- No baseline CVD
- Follow-up data availability.

Exclusion criteria
- Existing CVD at baseline,
- Missing data for glycemic control measurements.

Study Period:

- Baseline to early exposure periods of **1, 2,or 3 years**.
- Follow-up:Average 4.6± 2.9 years.

The population was then stratified into three categories based on HbA1c level

- **HbA1c≤7%**
- **HbA1c between 7,1-8%**
- **HbA1c >8%**

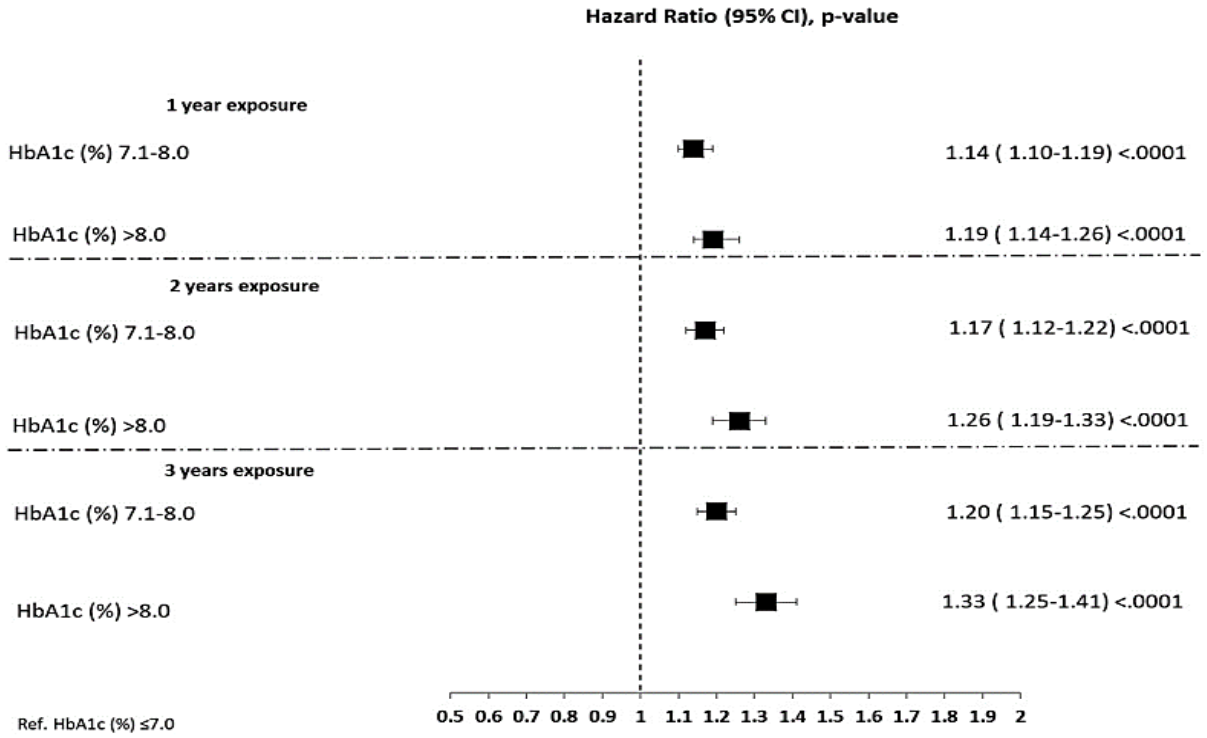
Endpoints

1: Evaluate the development of major cardiovascular events, as assessed through a **composite of myocardial infarction, ischaemic stroke, coronary or peripheral revascularization and coronary or peripheral bypass graft.**

2:To investigate whether early introduction of sodium-glucose co-transporter-2 **(SGLT 2i) inhibitors may mitigate the legacy effect**

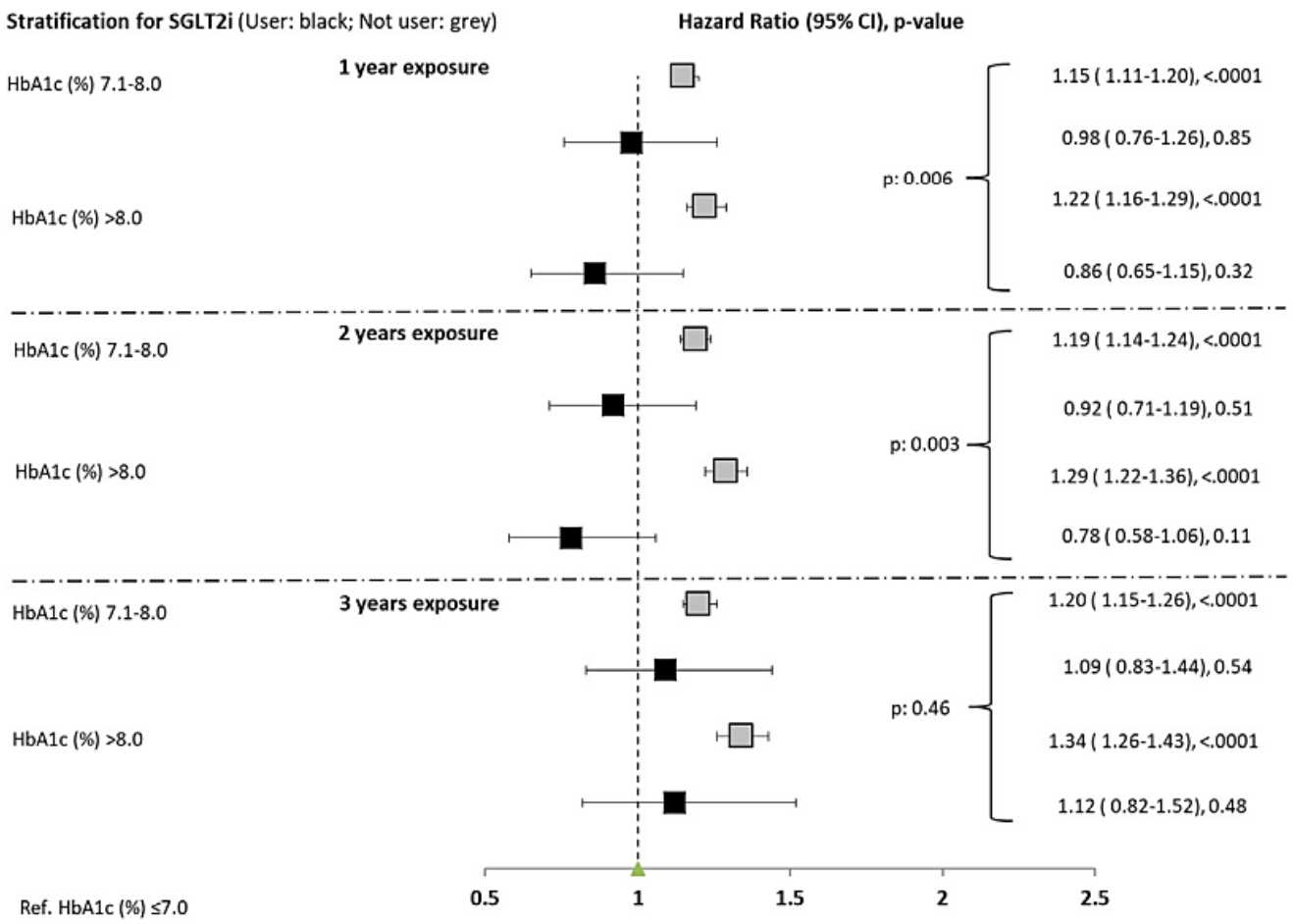
3: Understand if there is an optimal time to start SGLT2i therapy in order to obtain long-term benefit on CVDs

Ceriello A, Lucisano G, Prattichizzo F, La Grotta R, Frigé C, De Cosmo S, Di Bartolo P, Di Cianni G, Fioretto P, Giorda CB, Pontremoli R, Russo G, Viazzi F, Nicolucci A; AMD Annals study group. The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes. Lancet Reg Health Eur. 2023 Jun 12;31:100666. doi: 10.1016/j.lanepe.2023.100666. PMID: 37547276; PMCID: PMC10398589.



Inadequate Glycemic Control: In the early years following T2D diagnosis, **inadequate glycemic control (HbA1c > 7%) is associated with a significant increase in cardiovascular** risk.

Ceriello A, Lucisano G, Prattichizzo F, La Grotta R, Frigé C, De Cosmo S, Di Bartolo P, Di Cianni G, Fioretto P, Giorda CB, Pontremoli R, Russo G, Viazzi F, Nicolucci A; AMD Annals study group. The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes. Lancet Reg Health Eur. 2023 Jun 12;31:100666. doi: 10.1016/j.lanepe.2023.100666. PMID: 37547276; PMCID: PMC10398589.



Without SGLT2-i

SGLT2-i

1. The results of this study confirm the bound effect in type 2 diabetes, showing **that inadequate glycaemic control in the early years after diagnosis is linked to an increased long-term cardiovascular risk**.

2. Early use of **SGLT-2 inhibitors can eliminate the association with increased cardiovascular risk**. This suggests that these drugs may alter the disease's natural progression and prevent the irreversible vascular damage of **the legacy effect**

3. **SGLT-2 inhibitors are most effective against cardiovascular risks if used within two years of a type 2 diabetes diagnosis.**

Reduced risk

	CANVAS Program[2,3] (canagliflozin)	DECLARE-TIMI 58[4] (dapagliflozin)	EMPA-REG OUTCOME[5,6] (empagliflozin)	VERTIS CV[7–9] (ertugliflozin)	CREDENCE*[10] (canagliflozin)
	T2D + ASCVD or ≥2 CV risk factors	T2D + established ASCVD or multiple risk factors	T2D + CVD	T2D + established ASCVD	T2D + albuminuric CKD
3P-MACE†	**14% RRR** **(95% CI 0.75, 0.97; *p*=0.02)**	7% RRR (95% CI 0.84, 1.03; *p*=0.17)	**14% RRR** **(95% CI 0.74, 0.99; *p*=0.04)**	**3% RRR** **(95.6% CI 0.85, 1.11; *p*<0.001 for non-inferiority)**	**20% RRR** **(95% CI 0.67, 0.95; *p*=0.01)**
CV death or HHF‡	**22% RRR§** **(95% CI 0.67, 0.91; *p*=0.002)**	**17% RRR¶** **(95% CI 0.73, 0.95 *p*=0.005)**	**34% RRR§** **(95% CI 0.55, 0.79; *p*<0.001)**	12% RRR (95.8% CI 0.75, 1.03; *p*=0.11)	**31% RRR** **(95% CI 0.57, 0.83; *p*<0.001)**
CV death‡	13% RRR** (95% CI 0.72, 1.06)	2% RRR** (95% CI 0.82, 1.17)	**38% RRR§** **(95% CI 0.49, 0.77; *p*<0.001)**	8% RRR** (95.8% CI 0.77, 1.11)	22% RRR (95% CI 0.61, 1.00; *p*=0.05)
HHF‡	33% **RRR§** (95% CI 0.52, 0.87; p=0.002)	27% RRR** (95% CI 0.61, 0.88)	**35% RRR§** **(95% CI 0.50, 0.85; *p*=0.002)**	30% RRR (95.8% CI 0.54, 0.90)	**39% RRR** **(95% CI 0.47, 0.80; *p*<0.001)**
Composite kidney outcome‡,††	40% RRR‡,** (95% CI 0.47, 0.77)	47% RRR‡,** (95% CI 0.43, 0.66)	**39% RRR‡§** **(95% CI 0.53, 0.70; *p*<0.001)**	**34% RRR‡‡** **(95% CI 0.50, 0.88; *p*<0.01)**	**30% RRR§§** **(95% CI 0.59, 0.82; *p*=0.00001)**

Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

% values represent relative risk reduction; values in parentheses are HR. Values in bold are associated with a p-value <0.05. *CREDENCE was a kidney outcomes trial; †Primary endpoint was 3P-MACE in EMPA-REG OUTCOME and CANVAS Program (co-primary endpoint in DECLARE-TIMI 58), p-values are for superiority, except for 3P-MACE in VERTIS CV, which is for non-inferiority; ‡Secondary or exploratory endpoints as defined in the study protocols; §Nominal p-value <0.05; ¶Co-primary endpoint in DECLARE-TIMI 58; **p-value not reported in publication; ††Composite kidney endpoints were defined differently across trials; ‡‡Prespecified exploratory kidney composite outcome in VERTIS CV[9]; §§Primary endpoint in CREDENCE

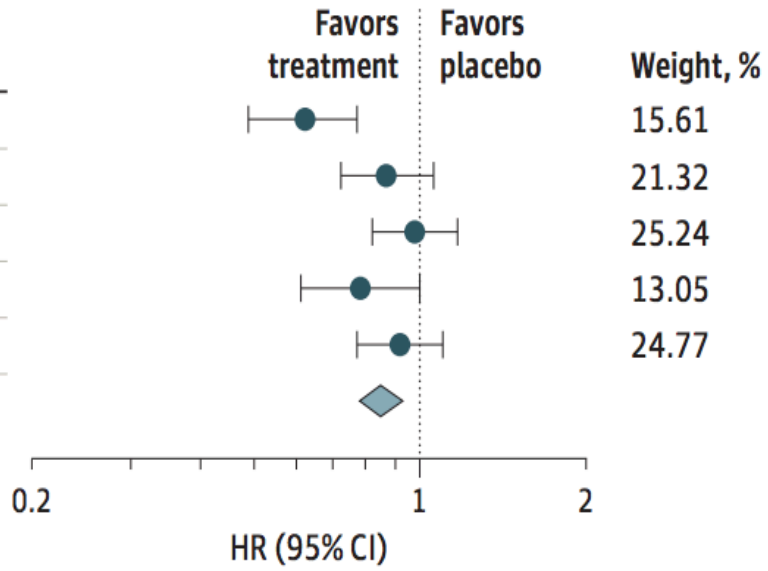
3P-MACE, 3-point major adverse cardiovascular events; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HHF, hospitalisation for heart failure; RRR, relative risk reduction; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

1. McGuire DK et al. JAMA Cardiol 2021;6:148; 2. Neal B et al. N Engl J Med 2017;377:644; 3. Radholm K et al. Circulation 2018;138:458; 4. Wiviott S et al. N Engl J Med 2019;380:347; 5. Zinman B et al. N Engl J Med 2015;373:2117; 6. Wanner C et al. N Engl J Med 2016;375:323; 2.7. Cannon CP et al. N Engl J Med 2020;383:1425; 8. Cosentino F et al. Circulation 2020;142:2205; 9. Cherney DZI et al. Diabetologia 2021;64:1256; 10. Perkovic V et al. N Engl J Med 2019;380:2295

Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular Death

A Overall CV death

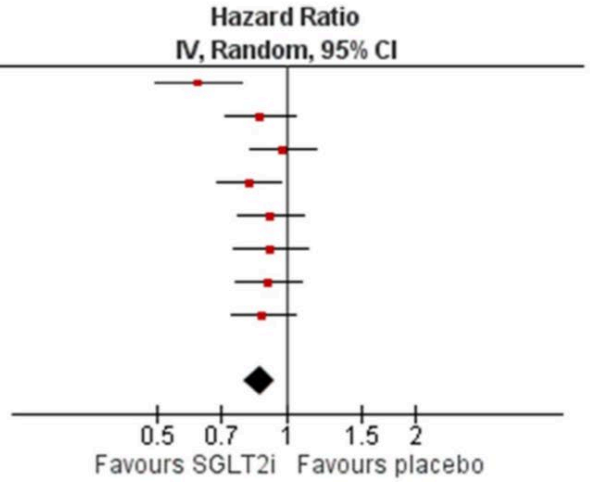
	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)
Fixed-effects model ($Q = 11.22$; $df = 4$; $P = .02$; $I^2 = 64.3\%$)					0.85 (0.78-0.93)



JAMA Cardiol. 2021;6(2):148-158.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
EMPA REG 2015	-0.478	0.1201	9.1%	0.62 [0.49, 0.78]	2015
Canvas 2017	-0.1393	0.0966	12.3%	0.87 [0.72, 1.05]	2017
DECLARE TIMI 58 2018	-0.0202	0.0909	13.3%	0.98 [0.82, 1.17]	2018
DAPA HF 2019	-0.1985	0.0881	13.8%	0.82 [0.69, 0.97]	2019
VERTIS CV 2020	-0.0834	0.0908	13.3%	0.92 [0.77, 1.10]	2020
EMPEROR reduced 2020	-0.0834	0.1042	11.2%	0.92 [0.75, 1.13]	2020
EMPOROR Preserved 2021	-0.0943	0.0919	13.1%	0.91 [0.76, 1.09]	2021
DELIVER 2022	-0.1278	0.0884	13.8%	0.88 [0.74, 1.05]	2022
Total (95% CI)			**100.0%**	**0.87 [0.80, 0.94]**	

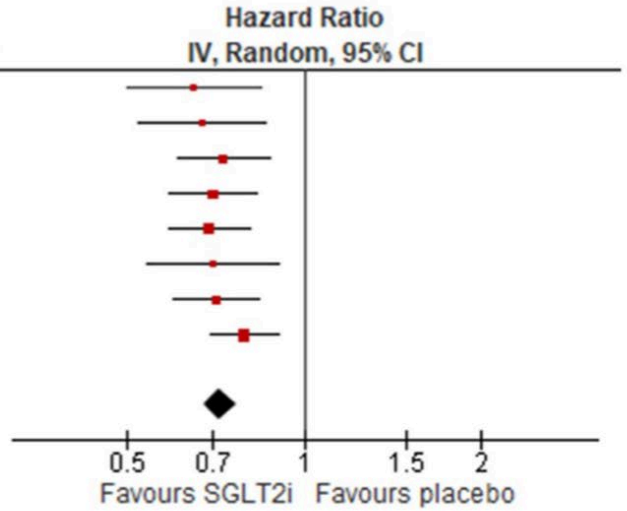
Heterogeneity: Tau² = 0.01; Chi² = 11.04, df = 7 (P = 0.14); I² = 37%
Test for overall effect: Z = 3.34 (P = 0.0008)



Deaths due to Cardiovascular causes.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
EMPA REG 2015	-0.4308	0.1339	6.0%	0.65 [0.50, 0.85]	2015
Canvas 2017	-0.4005	0.1293	6.5%	0.67 [0.52, 0.86]	2017
DECLARE TIMI 58 2018	-0.3147	0.0916	12.9%	0.73 [0.61, 0.87]	2018
DAPA HF 2019	-0.3567	0.0872	14.2%	0.70 [0.59, 0.83]	2019
EMPEROR reduced 2020	-0.3711	0.0799	16.9%	0.69 [0.59, 0.81]	2020
VERTIS CV 2020	-0.3567	0.1324	6.2%	0.70 [0.54, 0.91]	2020
EMPOROR Preserved 2021	-0.3425	0.0859	14.7%	0.71 [0.60, 0.84]	2021
DELIVER 2022	-0.2357	0.0691	22.6%	0.79 [0.69, 0.90]	2022
Total (95% CI)			**100.0%**	**0.72 [0.67, 0.77]**	

Heterogeneity: Tau² = 0.00; Chi² = 3.17, df = 7 (P = 0.87); I² = 0%
Test for overall effect: Z = 10.08 (P < 0.00001)

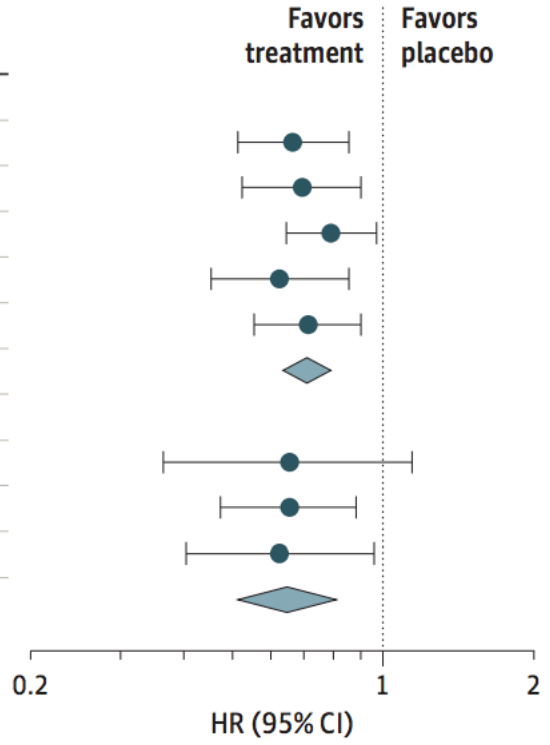


Hospitalisations due to heart failure.

Waseem et al. Annals of Medicine & Surgery (2025)

B HHF by ASCVD status

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
Patients with ASCVD								
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			19.62
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)			17.13
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)			29.66
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)			12.74
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			20.84
Fixed-effects model ($Q = 1.97$; $df = 4$; $P = .74$; $I^2 = 0.0\%$)					0.70 (0.62-0.78)			
Patients without ASCVD								
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)			16.38
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)			55.07
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)			28.56
Fixed-effects model ($Q = 0.03$; $df = 2$; $P = .99$; $I^2 = 0.0\%$)					0.63 (0.50-0.80)			



JAMA Cardiol. 2021;6(2):148-158.

EMPULSE:studied the effect of empagliflozin in patients hospitalized for acute heart failure

Patients hospitalized due to HF must have
HF symptoms at the time of hospital admission

MANDATORY

Persistent dyspnoea at rest or with minimal exertion

+

MANDATORY

Signs of decompensation

At least two of **the** following must apply

- Congestion on chest X-ray
- Rales on chest auscultation
- Clinically relevant oedema (e.g. ≥1+ on a 0–3+ scale), indicating indentation of skin with mild digital pressure that requires 10 or more seconds to resolve in any dependent area
- Elevated jugular venous pressure

	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *p*-value
	Number of patients			
All patients	265	265	1.36 (1.09, 1.68)	
NT-proBNP at baseline, pg/mL				0.7904
<Median	125	130	1.36 (0.99, 1.85)	
≥Median	130	126	1.44 (1.06, 1.96)	
eGFR (CKD-EPI) at baseline, mL/min/1.73 m²				0.7562
<60	161	145	1.38 (1.04, 1.83)	
≥60	88	106	1.48 (1.04, 2.13)	
Atrial fibrillation/flutter at baseline				0.1129
No	123	133	1.68 (1.22, 2.32)	
Yes	142	132	1.18 (0.88, 1.59)	
Baseline LVEF, %				0.9008
≤40	182	172	1.35 (1.04, 1.75)	
>40	76	93	1.39 (0.95, 2.03)	

c) First hospitalisation for heart failure or cardiovascular death

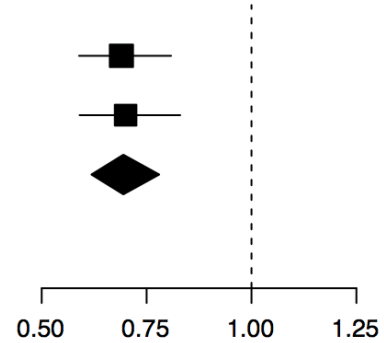
	SGLT2i no. with event/no. of patients (%)	Placebo no. with event/no. of patients (%)	HR (9
EMPEROR–Reduced	361/1863 (19.4)	462/1867 (24.7)	0.75 (0
DAPA–HF	386/2373 (16.3)	502/2371 (21.2)	0.74 (0
Total			0.74 (0

Test for overall treatment effect, p<0.0001
Test for heterogeneity of effect, p=0.89

d) First hospitalisation for heart failure

	SGLT2i no. with event/no. of patients (%)	Placebo no. with event/no. of patients (%)	HR (95% CI)
EMPEROR–Reduced	246/1863 (13.2)	342/1867 (18.3)	0.69 (0.59, 0.81)
DAPA–HF	231/2373 (9.7)	318/2371 (13.4)	0.70 (0.59, 0.83)
Total			0.69 (0.62, 0.78)

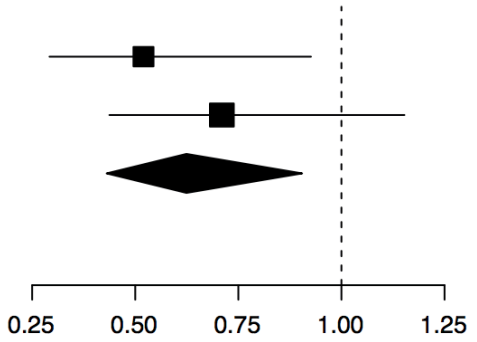
Test for overall treatment effect, p<0.0001
Test for heterogeneity of effect, p=0.90



e) First kidney composite*

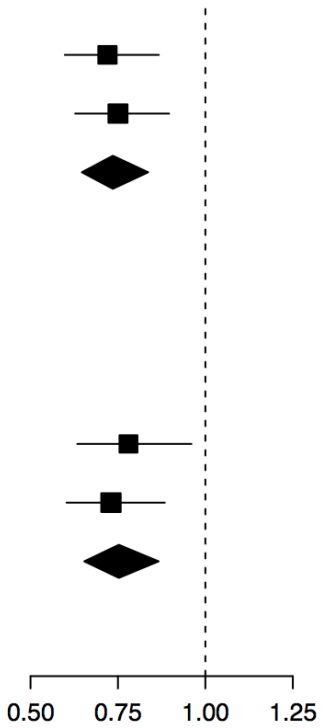
	SGLT2i no. with event/no. of patients (%)	Placebo no. with event/no. of patients (%)	HR (95% CI)
EMPEROR–Reduced	18/1863 (1.0)	33/1867 (1.8)	0.52 (0.29, 0.92)
DAPA–HF	28/2373 (1.2)	39/2371 (1.6)	0.71 (0.44, 1.16)
Total			0.62 (0.43, 0.90)

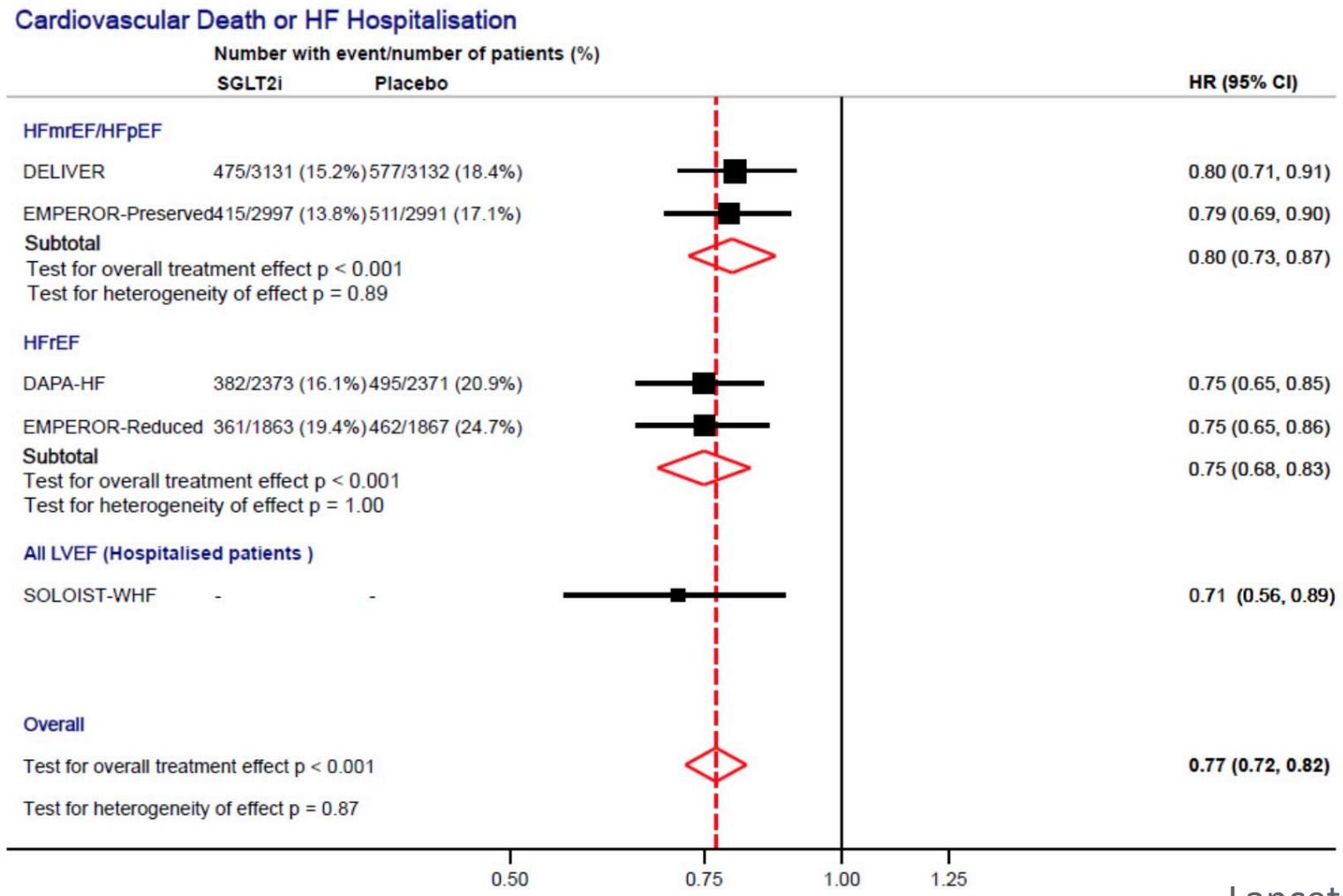
Test for overall treatment effect, p=0.0128
Test for heterogeneity of effect, p=0.42



a) Diabetes status

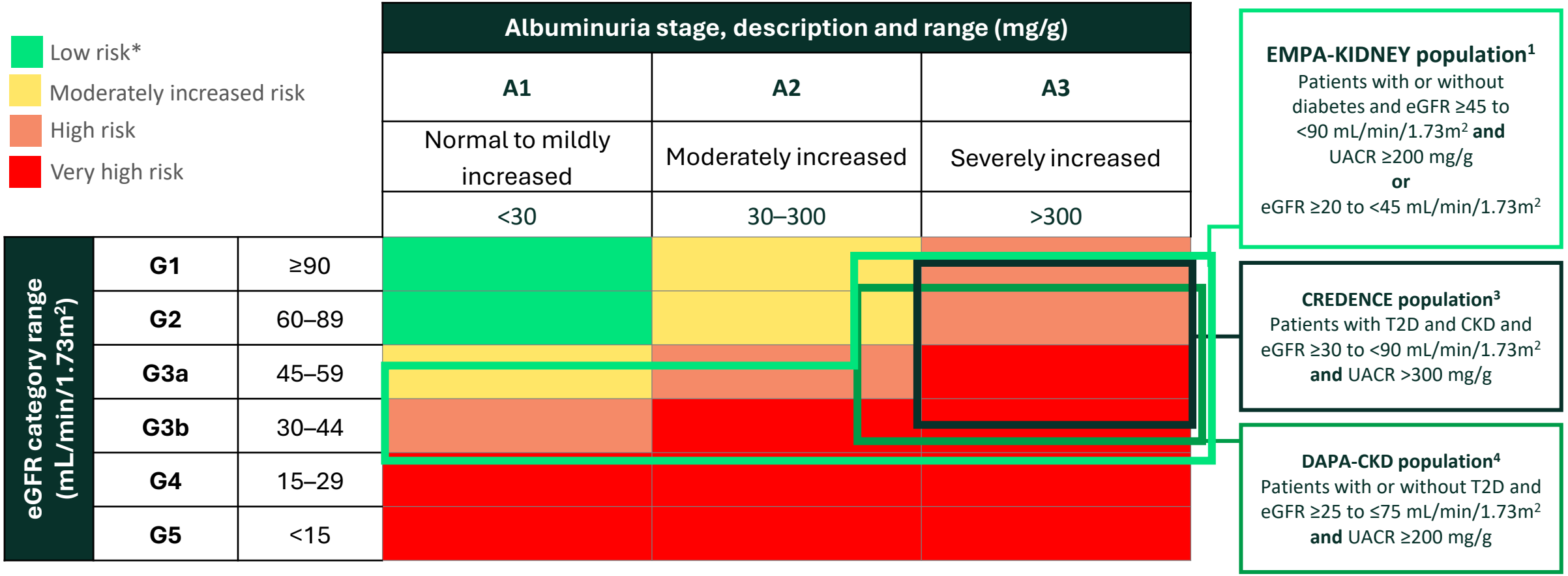
	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
With diabetes			
EMPEROR–Reduced	200/927 (21.6)	265/929 (28.5)	0.72 (0.60, 0.87)
DAPA–HF	215/1075 (20.0)	271/1064 (25.5)	0.75 (0.63, 0.90)
Subtotal			0.74 (0.65, 0.84)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.76			
Without diabetes			
EMPEROR–Reduced	161/936 (17.2)	197/938 (21.0)	0.78 (0.64, 0.97)
DAPA–HF	171/1298 (13.2)	231/1307 (17.7)	0.73 (0.60, 0.88)
Subtotal			0.75 (0.65, 0.87)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.65			
Test for treatment by subgroup interaction, p=0.81			





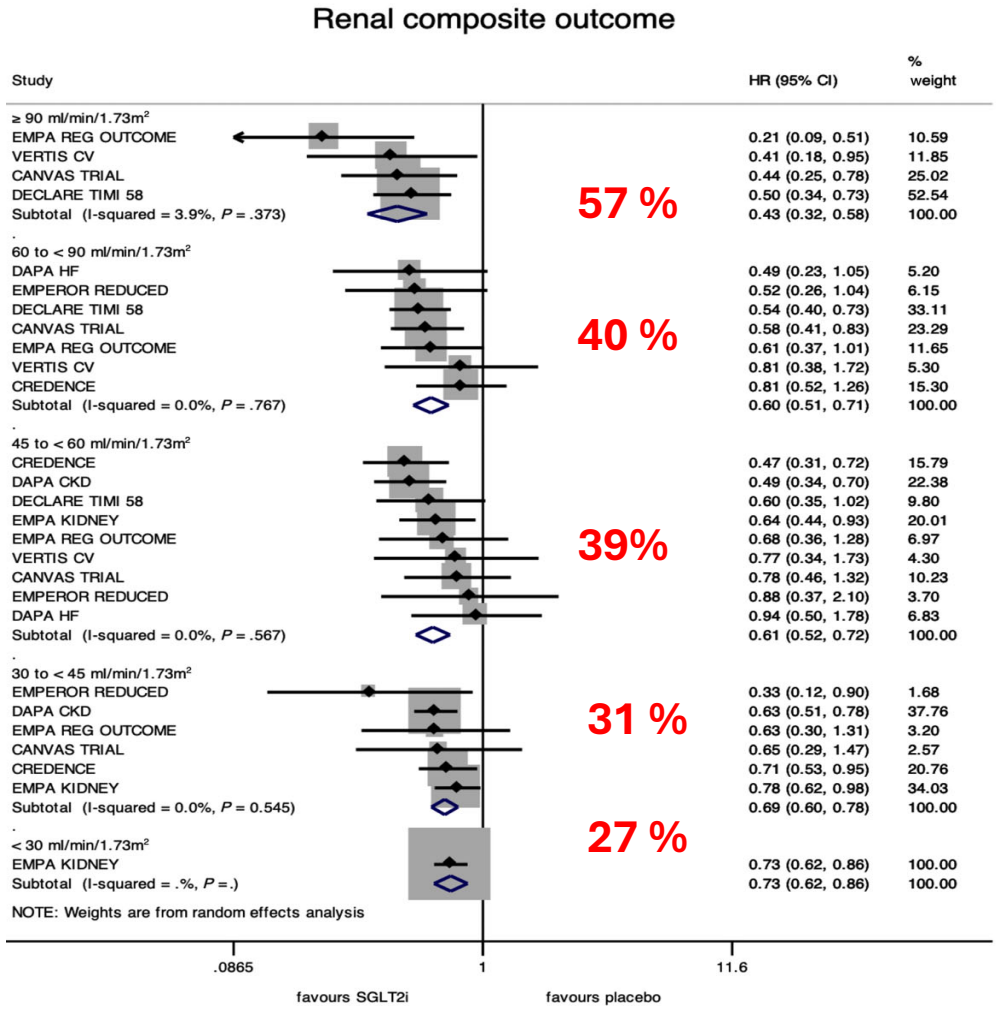
Lancet. 2022 Sep 3;400(10354):757-767.

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.



- 9 RCT, 65.694 partecipanti
- 41,9% eGFR 60-90 ml/min/1,73 m^2
- 21,7% eGFR > 90 ml/min/1,73 m^2
- Ridotto rischio di esiti renali in tutte le categorie di eGFR
- Maggiori benefici se iniziati ad un eGFR più elevato

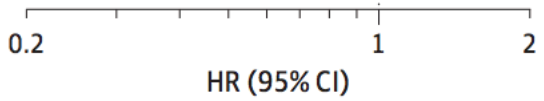
Diabetes Obes Metab. 2023 May;25(5):1341-1350

A Overall kidney outcomes

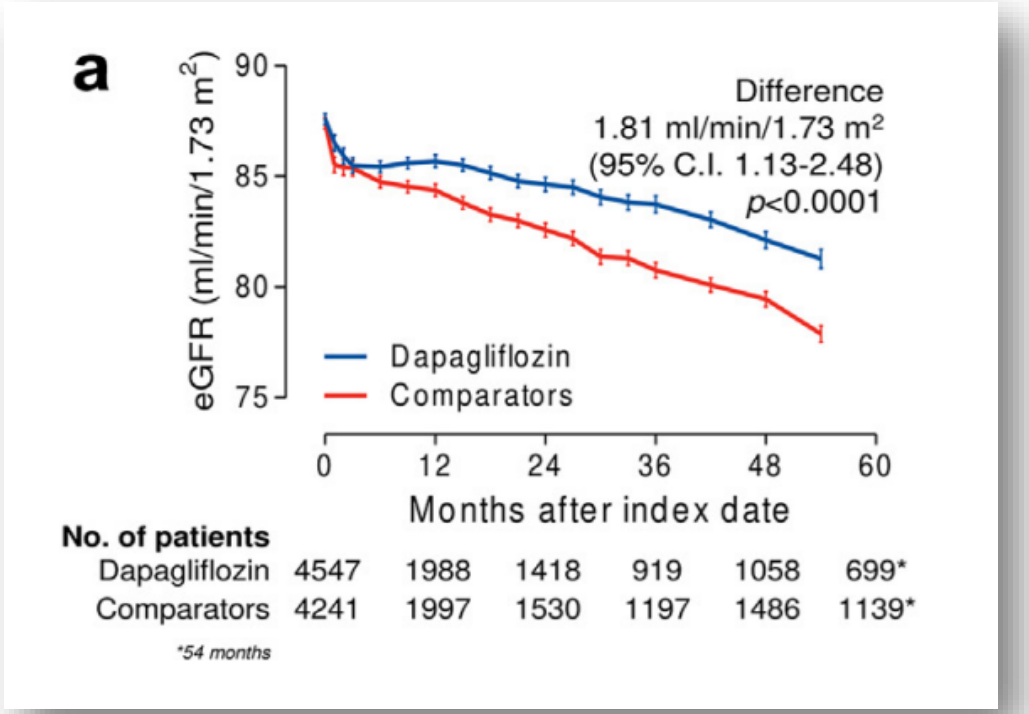
	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)			11.51

B Kidney outcomes by ASCVD status

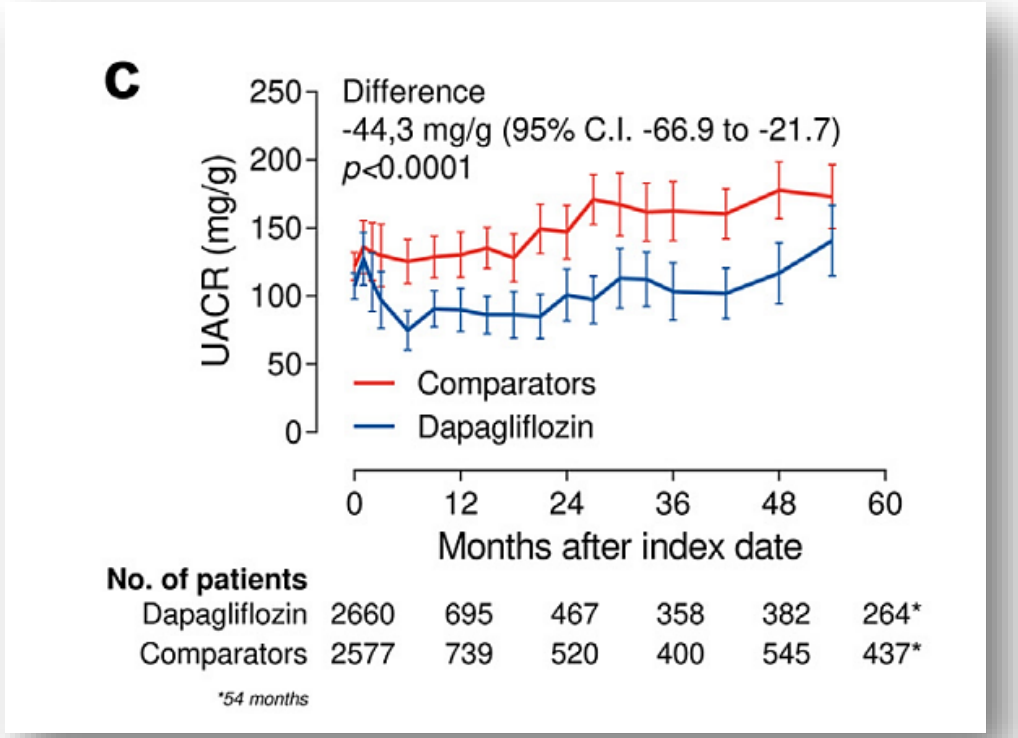
	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
Patients with ASCVD								
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)			16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)			19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)			18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)			17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)			28.66
Fixed-effects model ($Q = 6.09$; $df = 4$; $P = .19$; $I^2 = 34.4\%$)					0.64 (0.56-0.72)			
Patients without ASCVD								
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)			15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)			37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)			46.87
Fixed-effects model ($Q = 1.86$; $df = 2$; $P = .40$; $I^2 = 0.0\%$)					0.60 (0.50-0.73)			



Primary outcome: Change in eGFR over time



Secondary outcome: Change in albuminuria over time



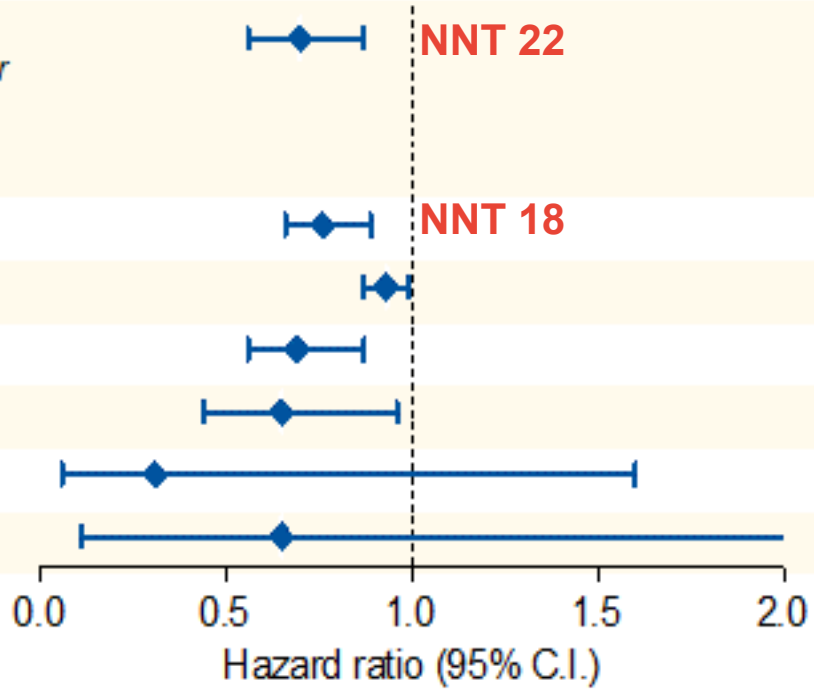
- ✓ **Difference in eGFR = +1.8 in favor of Dapa**(p<0,0001)
- ✓ **Annual slope = -1.2 in Dapa vs -1.8 for the comparators**(p<0,0001)

DARWIN RENAL: A REAL WORLD STUDY

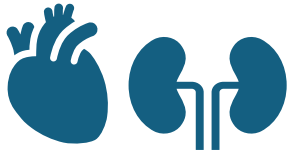
Fadini et al. The Lancet Regional Health –Europe 2024

A) Dapagliflozin

Endpoint	Crude rates / 1000 PYE Dapagl.	Controls	Adjusted hazard ratio (95% C.I.)	p-value
Composite renal *Sustained >40% eGFR reduction or* *End-stage kidney disease or* *Dialysis*	16.3	25.5 RRR 30%	0.70 (0.56 - 0.87)	0.002
New-onset CKD	28.3	39.4 RRR 24%	0.76 (0.66 - 0.89)	<0.001
Worsening CKD class	237.5	250.4	0.93 (0.87 - 0.99)	0.037
Sustained >40% eGFR reduction	16.2	25.5 RRR 31%	0.69 (0.56 - 0.87)	0.002
Sustained >57% eGFR reduction	4.9	8.5	0.65 (0.44 - 0.96)	0.035
End-stage kidney disease	0.2	0.9	0.32 (0.06 - 1.63)	0.169
Dialysis	0.2	0.3	0.65 (0.11 - 3.70)	0.658



Fadini et al, Diabetes Care, 2024

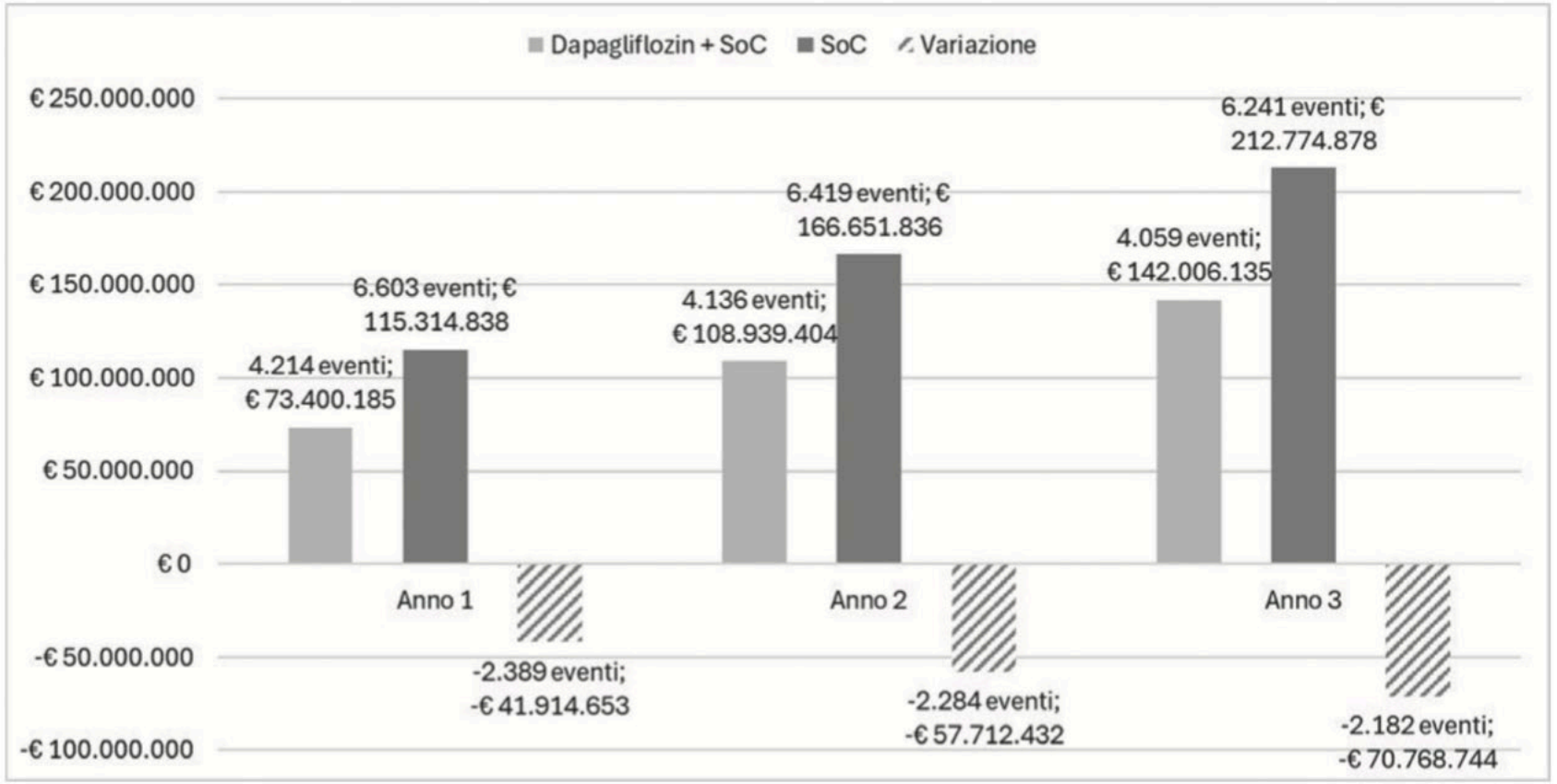


	Primary composite outcome[1,a,b]	All-cause mortality[1,c,d]	Composite of CV death or hHF[1,c,e]
Patients with T2D	36% RRR	26% RRR	30% RRR
Patients without T2D	50% RRR	48% RRR	21% RRR

[a]Sustained ≥50% eGFR decline, ESKD, kidney or CV death; [b]*p* interaction=0.24; [c]Secondary endpoint; [d]*p* interaction=0.25; [e]*p* interaction=0.78.

1. Wheeler DC et al. *Lancet Diabetes Endocrinol*. 2021;9(1):22-31; 2. Garcia Sanchez JJ et al. *Adv Ther*. 2022;39(1):193-220.

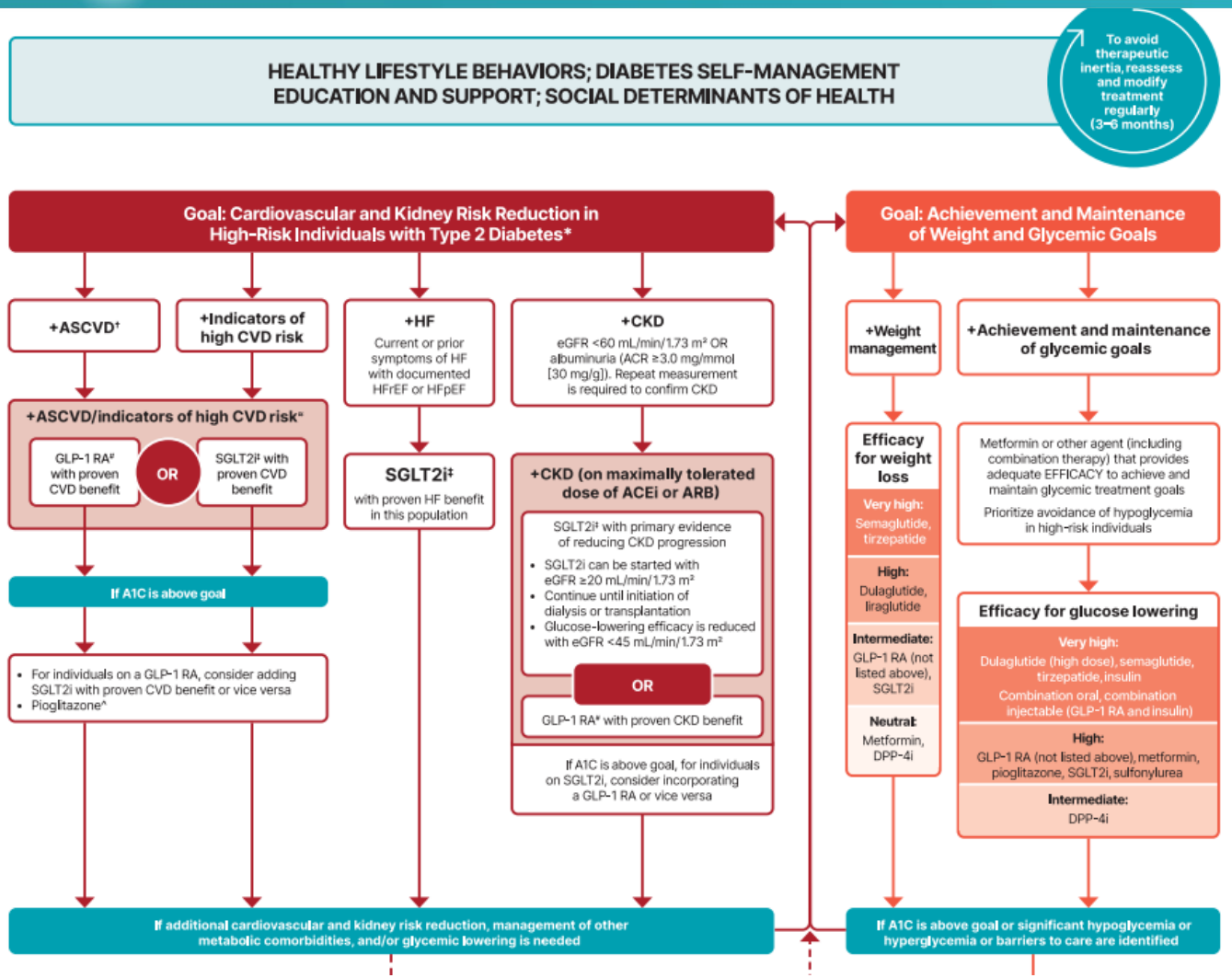
Economic impact of dapagliflozin in the management of chronic kidney disease in Italy: results from a micro- simulation model



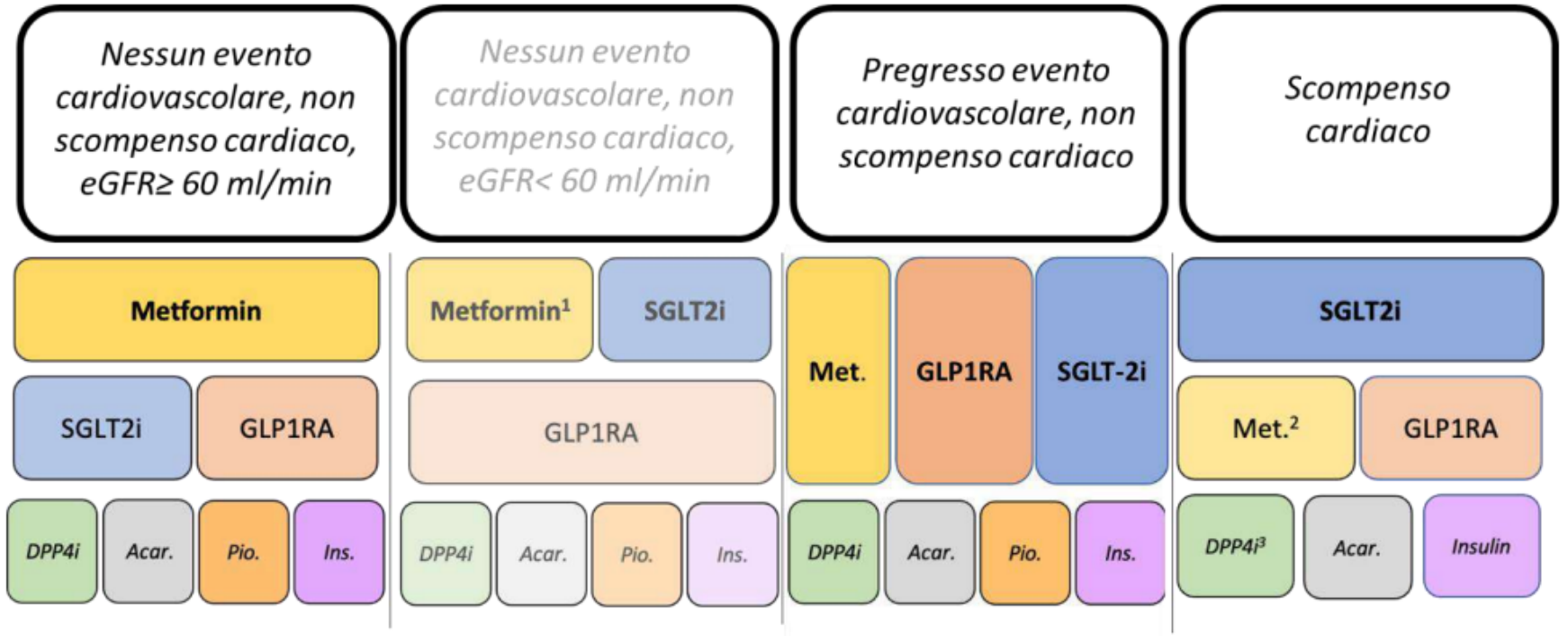
Glob Reg Health Technol Assess 2024; 11: 233

2025 ADA Standards of Care in Diabetes

Use of Glucose-Lowering Medications in the Management of T2D



Diabetes Care Volume 48, Supplement 1, January 2025



[1]Se la metformina non è controindicata per ridotto eGFR.
[2]Se la metformina non è controindicata per ridotta funzione cardiaca.
[3]Eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.
La raccomandazione sui pazienti con eGFR< 60ml/min è debole per carenza di studi clinici effettuati su questa popolazione
Si raccomanda la deprescrizione di sulfanilurre e glinidi

Linee Guida SID AMD 2023

https://www.siditalia.it/clinica/linee-guida-societari/send/80-linee-guida-documenti-societari/5633-aggiornamento-linee-guida-della-societa-italiana-di-diabetologia-sid-e-dell-associazione-dei-medici-diabetologi-amd-la-terapia-del-diabete-mellito-di-tipo-2-versione-aggiornata-a-dicembre-2022

- **SGLT2i** is recommended in patients with T2D, CKD, and an eGFR ≥20 mL/min/1.73 m^2 (1A)

  Practice Point:[b,c]

  - *Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 mL/min/1.73 m^2, unless it is not tolerated or KRT is initiated*
  - *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)*

- **SGLT2i** is recommended in adults with CKD for the following (1A):
  - eGFR ≥20 mL/min/1.73 m^2 with UACR ≥200 mg/g, or
  - Heart failure, irrespective of level of albuminuria

  Practice Point:

  - *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*

- **SGLT2i** is suggested in adults with eGFR ≥20 to 45 mL/min/1.73 m^2 with UACR <200 mg/g (2B)

2024 KDIGO Evaluation and Management of CKD Guideline: Summary of SGLT2 Inhibitor Use

KDIGO CKD Work Group. *Kidney Int.* 2024;105(4S): S117–S314.


GRAZIE
It's dapagliflozin for T2DM with high CVD risk to decrease CVD
In T2DM with high CVD but without CKD, dapagliflozin and empagliflozin may prevent CKD