12 Settembre 2025

Quali prospettive per il paziente cardiometabolico: Cosa ci dicono le linee guida… …e cosa non ci dicono ancora?

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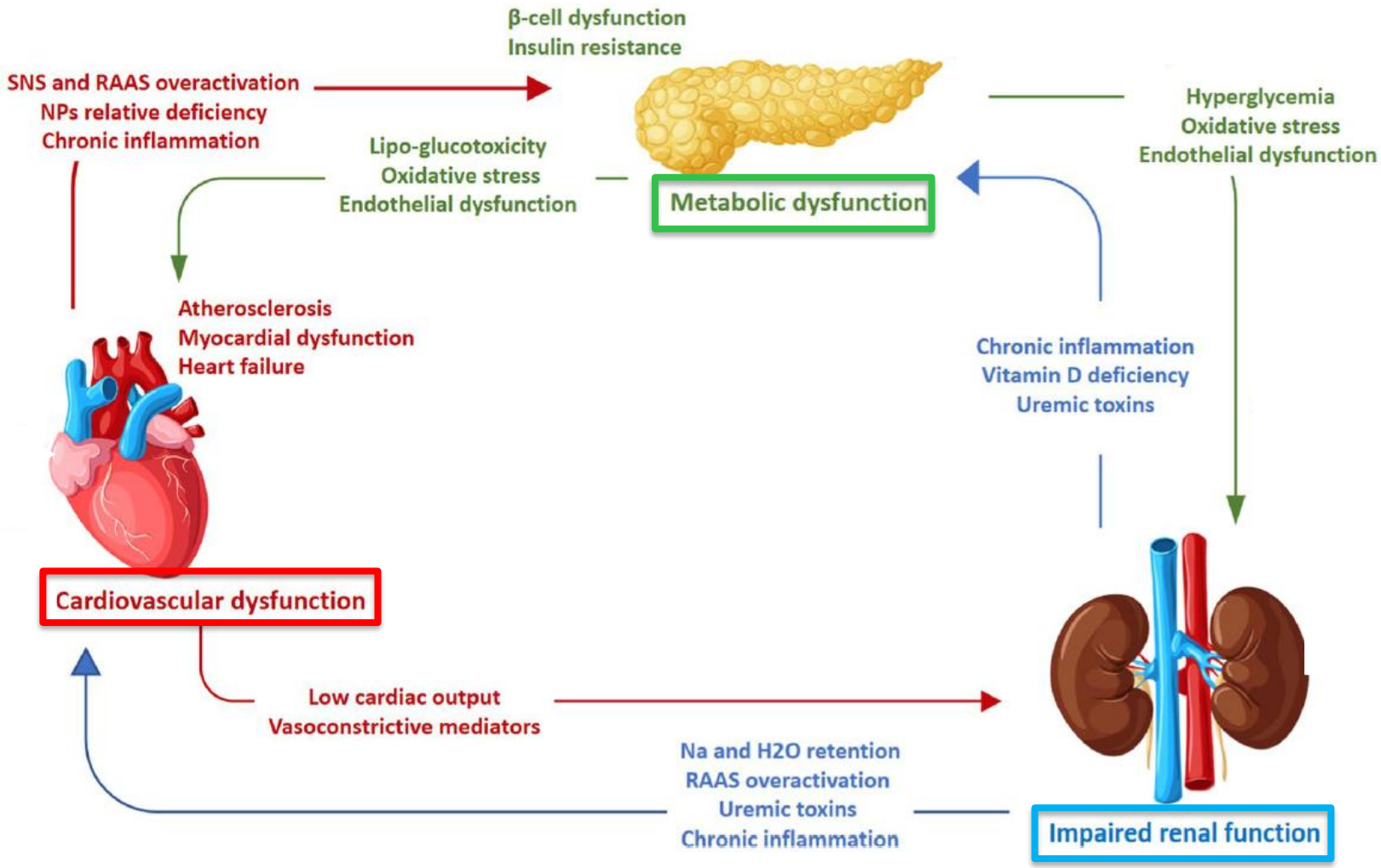
Divisione Cardiovascolare
Unità di Terapia Intensiva Cardiologica
Ospedale Cardinal Massaia – Asti

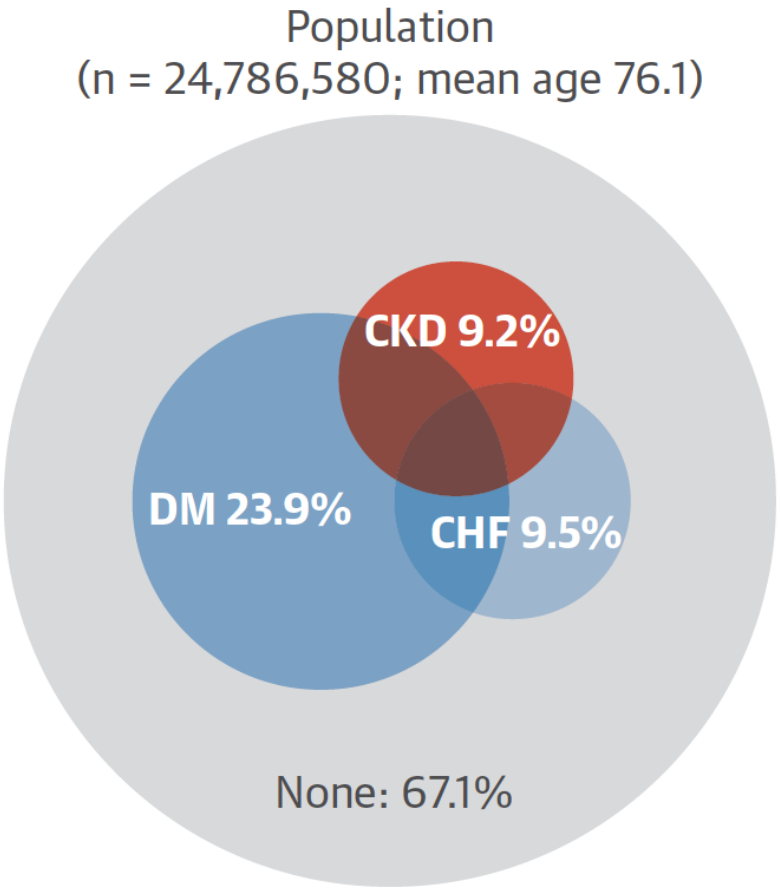
A.S.L. AT
REGIONE PIEMONTE

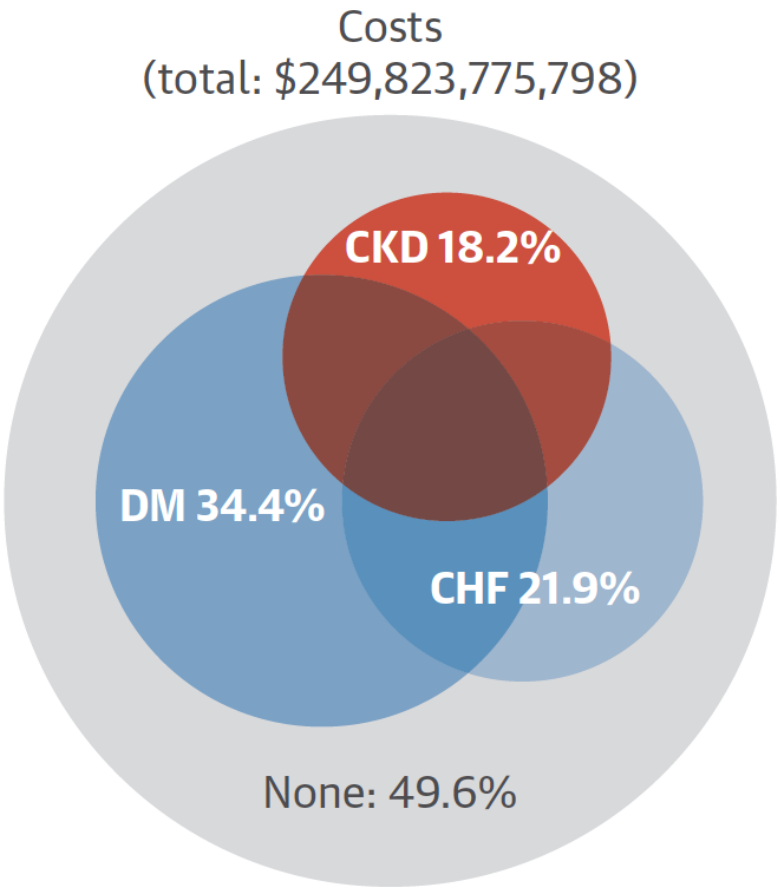
MALATTIA CARDIO-METABOLICO-RENALE (CMR)



Marassi and Fadini *Cardiovascular Diabetology* (2023) 22:195

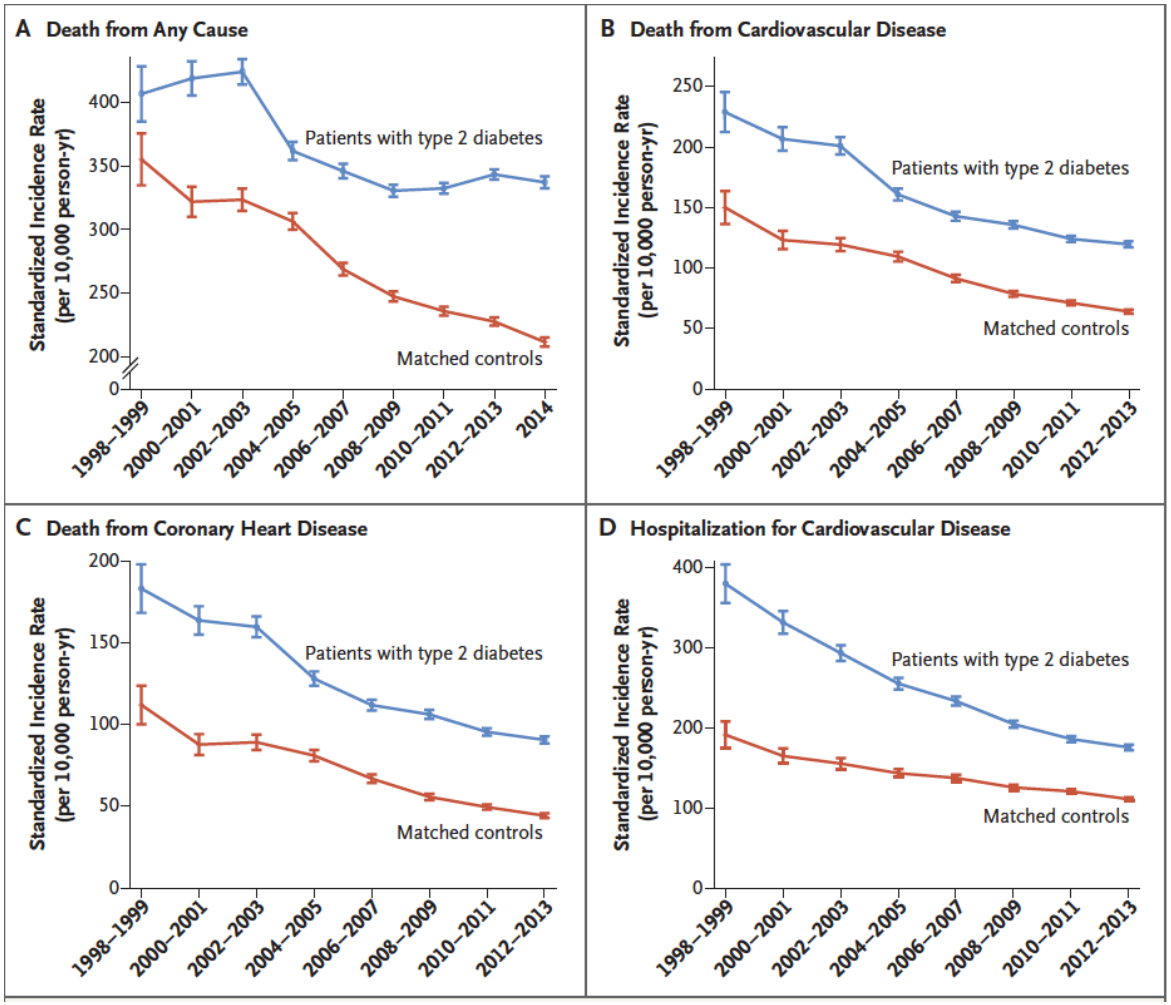
PREVALENZA DELLA SINDROME CMR E SUOI COSTI NEGLI USA (Medicaire)





JACC VOL. 73, NO. 21, 2019

DMT2 E MALATTIE CARDIOVASCOLARI



1/3 dei pz con **DMT2** (32.2%) ha una **malattia cardiovascolare**

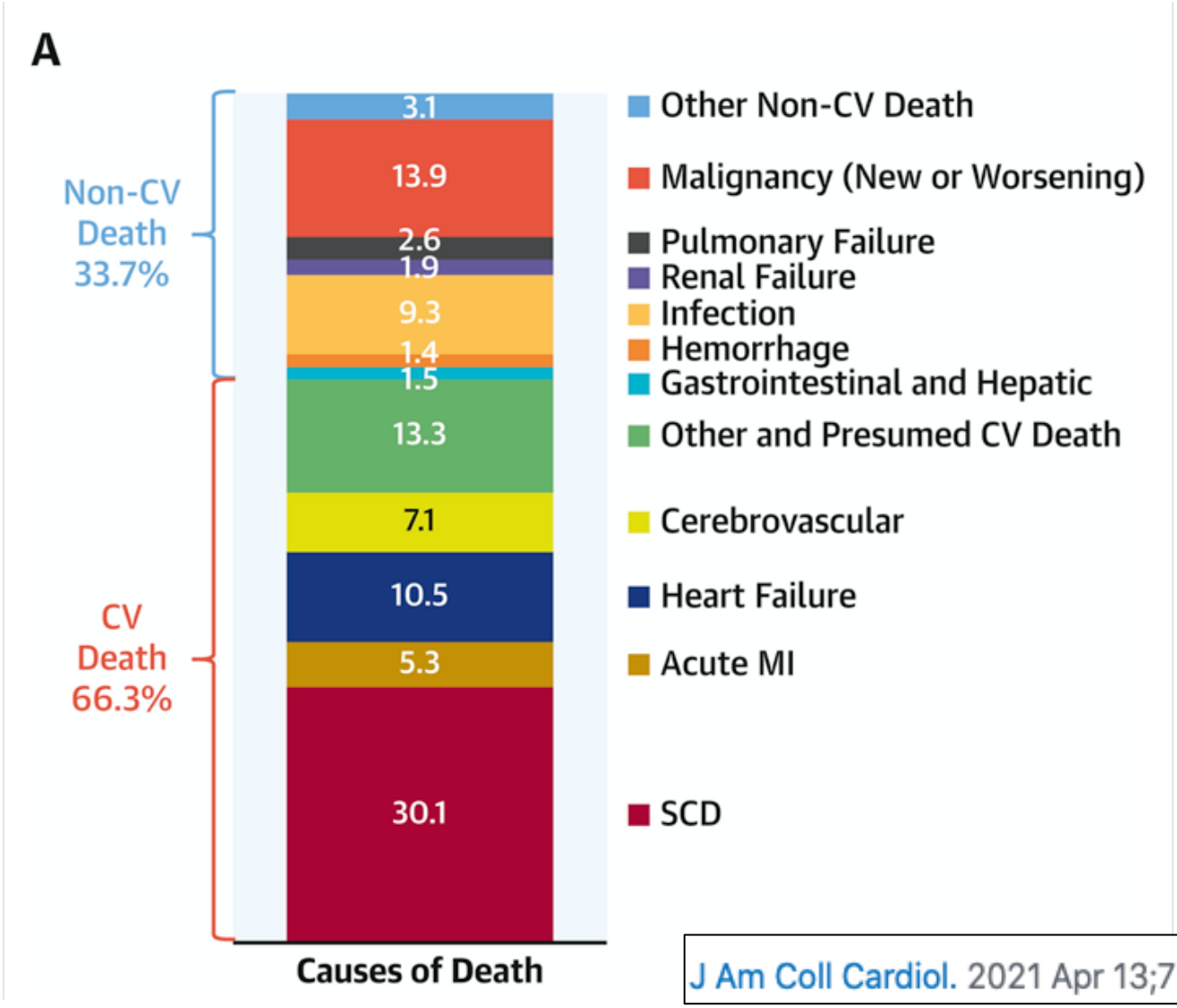
I pz con **DMT2 e malattia cardiovascolare** hanno un **maggio rischio di IMA, stroke, scompenso cardiaco o insufficienza renale** rispetto ai pz con DMT2 e senza malattia cardiovascolare

La **malattia cardiovascolare** si manifesta **più precocemente** ed è la **principale causa di mortalità** nei pz con DMT2

N Engl J Med 2017;376:1407-18.

Einarson *et al. Cardiovasc Diabetol (2018) 17:83*

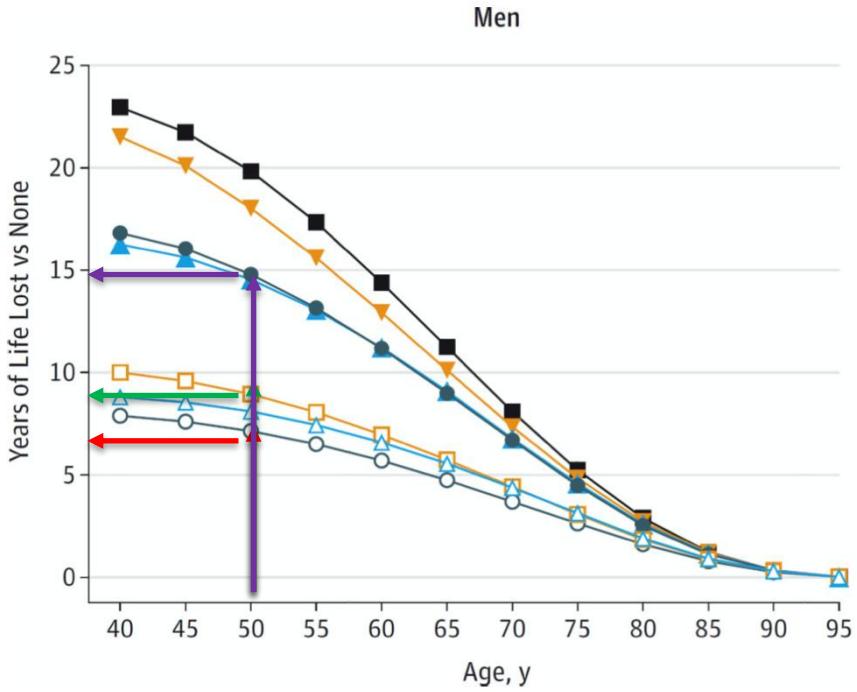
CAUSE DI MORTE NEI PZ CON DMT2

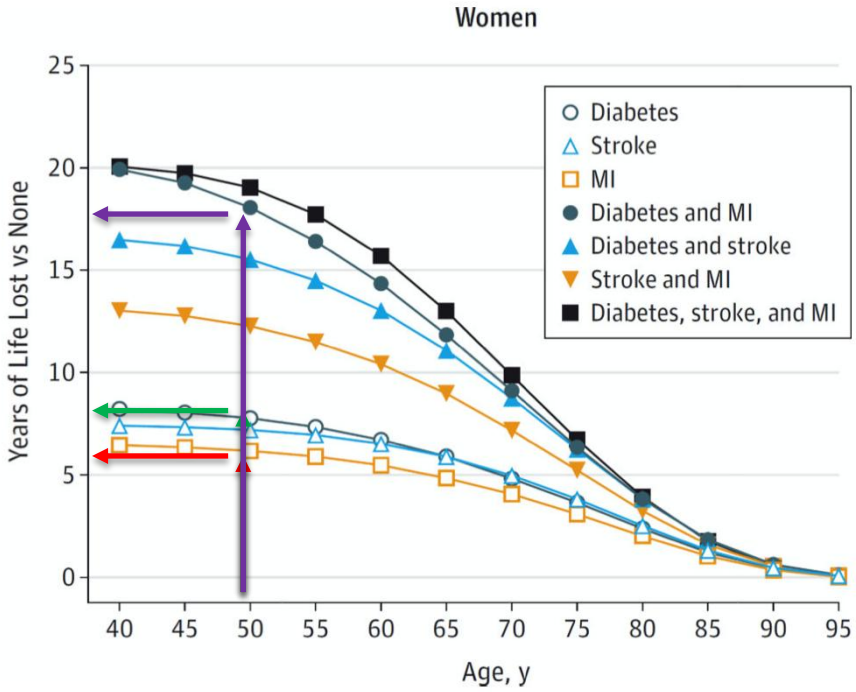


J Am Coll Cardiol. 2021 Apr 13;77(14):1837-1840.

DMT2 Vs IMA

Modeling of Years of Life Lost by Disease Status of Participants at Baseline Compared With Those Free of Diabetes, Stroke, and Myocardial Infarction (MI)





JAMA. 2015 July 7; 314(1): 52–60.

DMT2 E HF

Prevalenza di HF in pz con DMT2: 10-23%

Prevalenza di DMT2 in pz con HF: 40-45%

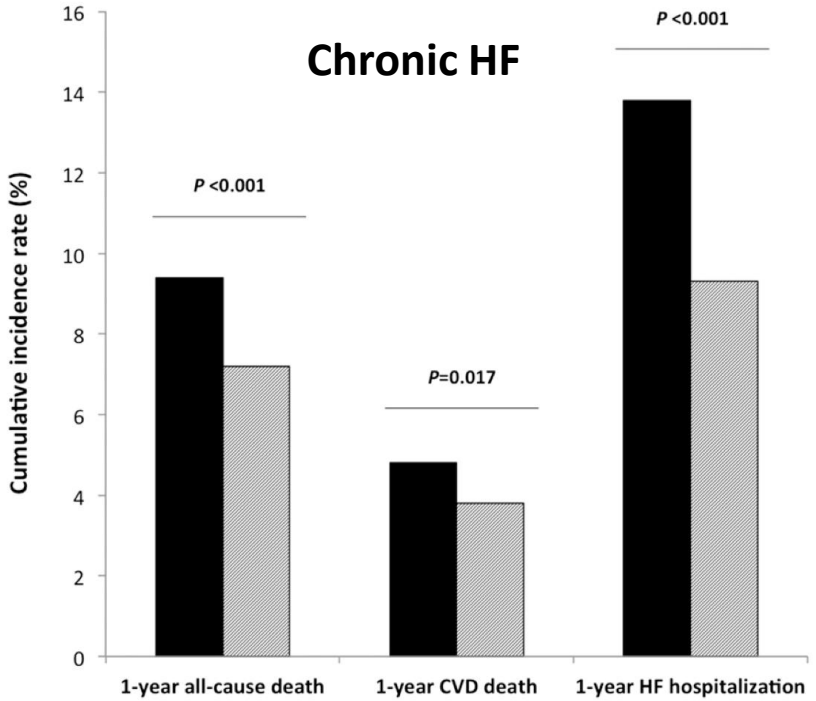


Figure 1—One-year cumulative incidence rates of adverse clinical outcomes in 9,428 outpatients with CHF stratified by diabetes status at baseline. The figure shows the 1-year rates of all-cause death, CVD death, and first hospitalization for worsening HF in 3,440 CHF outpatients with diabetes (black bars) and 5,988 CHF outpatients without diabetes (dashed bars) who were enrolled in the ESC-HFA Heart Failure Long-Term Registry.

Diabetes Care 2017;40:671-678

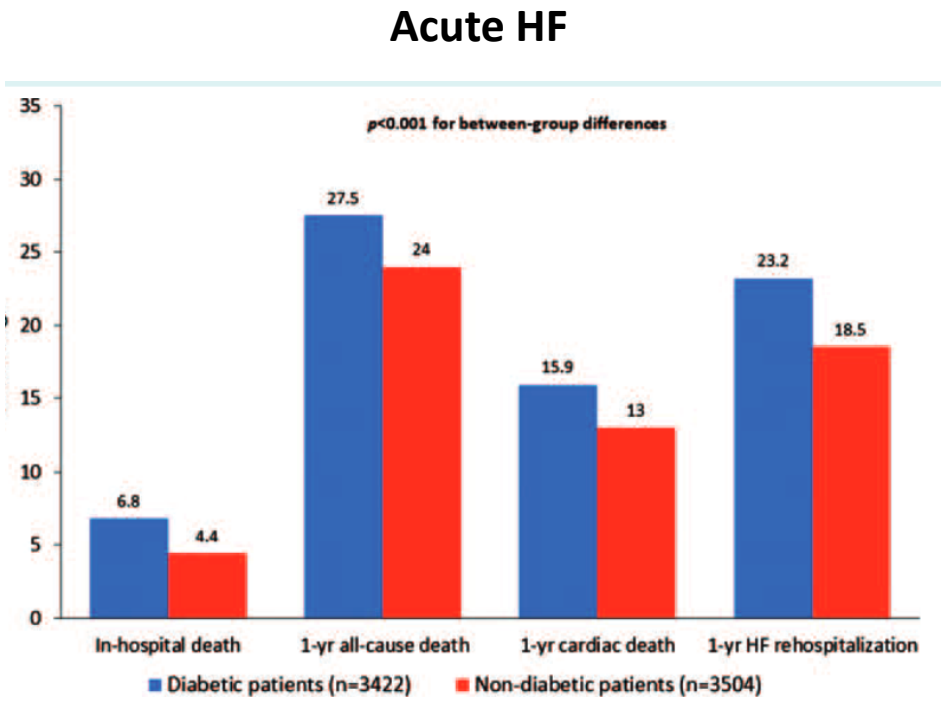
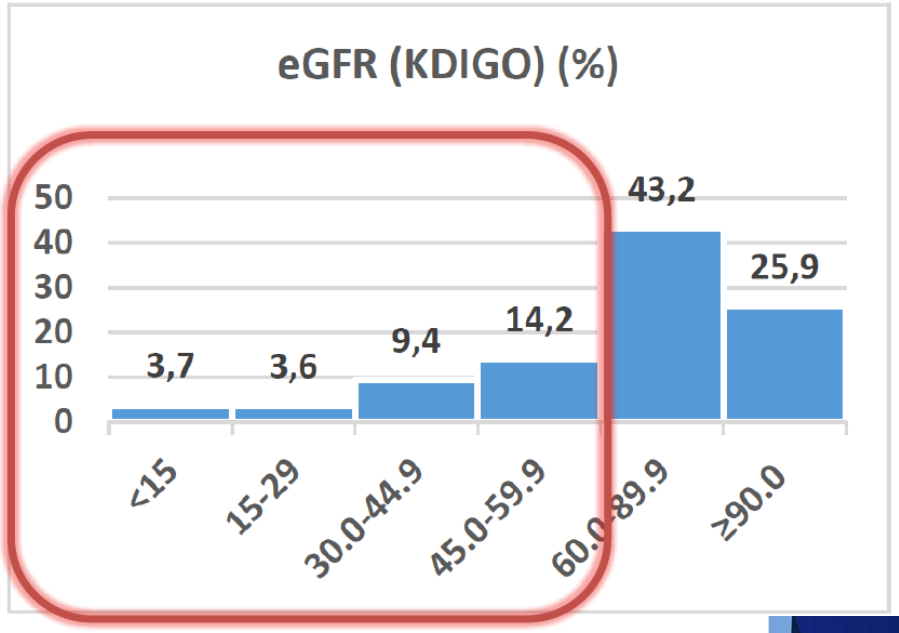


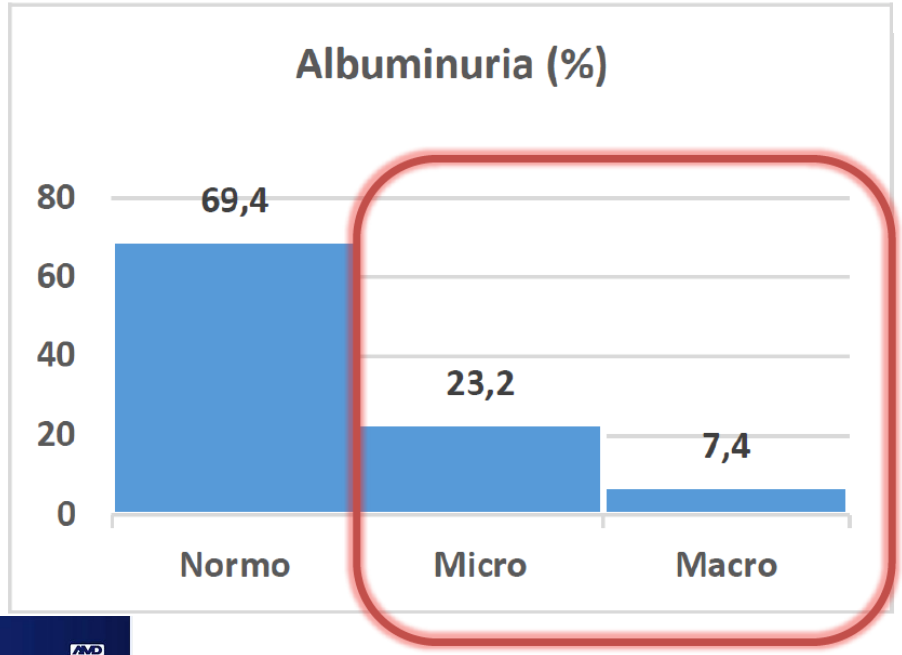
Figure 1 Cumulative incidence rates of in-hospital mortality, 1-year all-cause mortality, 1-year cardiac mortality and 1-year heart failure (HF) re-hospitalization among patients admitted to the hospital for acute HF stratified by diabetes status.

European Journal of Heart Failure (2017) **19**, 54–65

DMT2 E IRC



Il 30% dei soggetti
ha eGFR <60

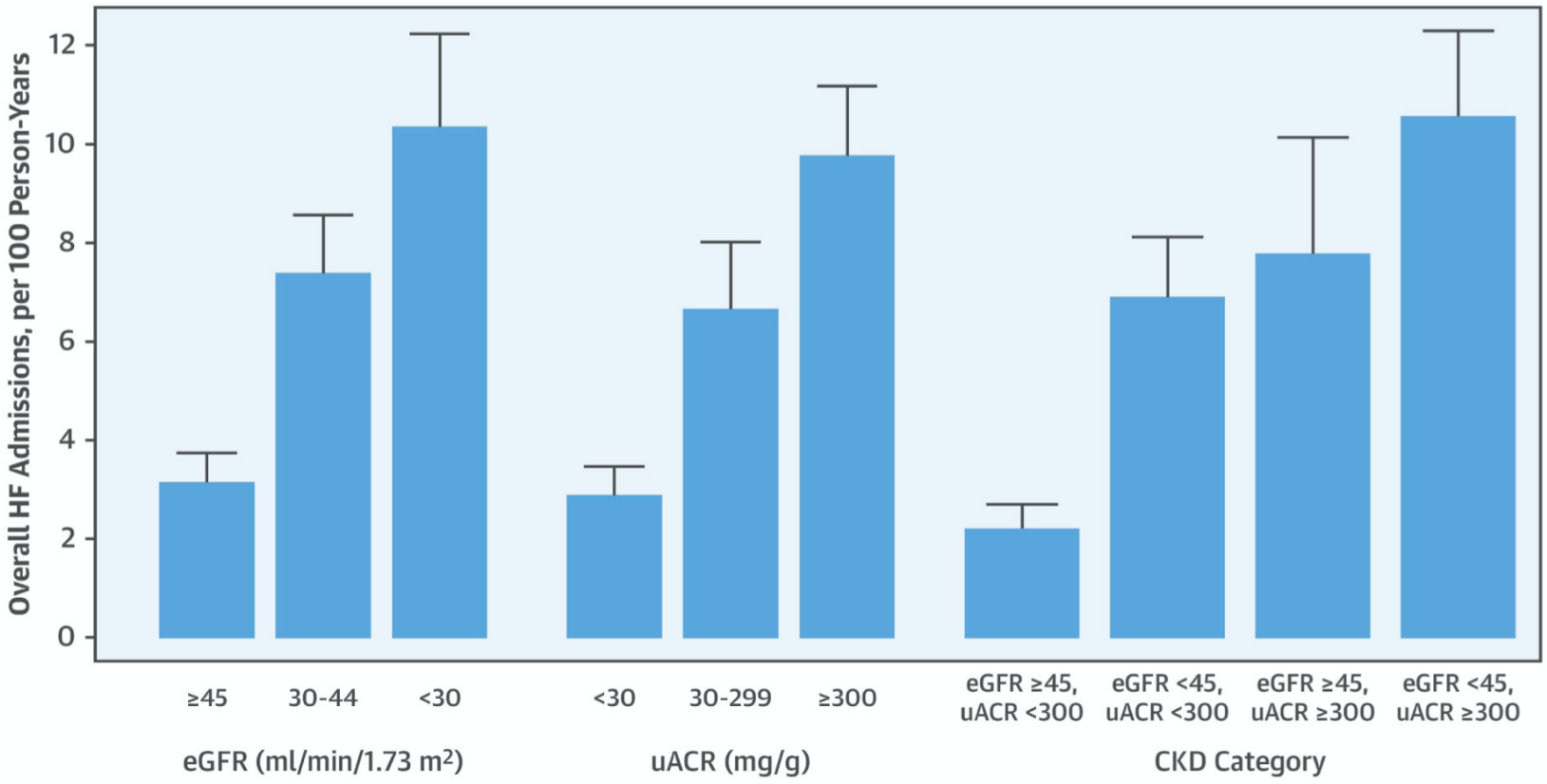


Il 30% dei soggetti
ha albuminuria

Annali AMD, 2023

IRC e HF

CENTRAL ILLUSTRATION: Heart Failure in Chronic Kidney Disease



Bansal, N. et al. J Am Coll Cardiol. 2019;73(21):2691-700.

GFR Vs FE

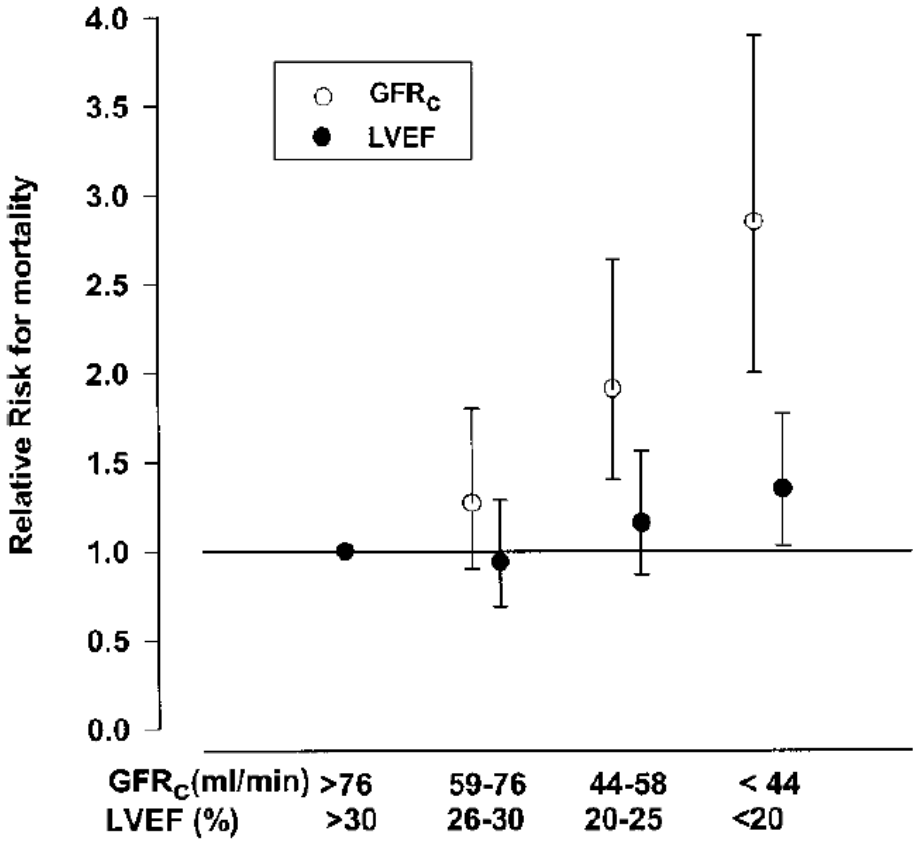


Figure 2. Relation, in quartiles, of LVEF and GFR_c to the risk of mortality using the multivariate proportional hazards regression model.

Hillege HL et al Circulation 2020

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)

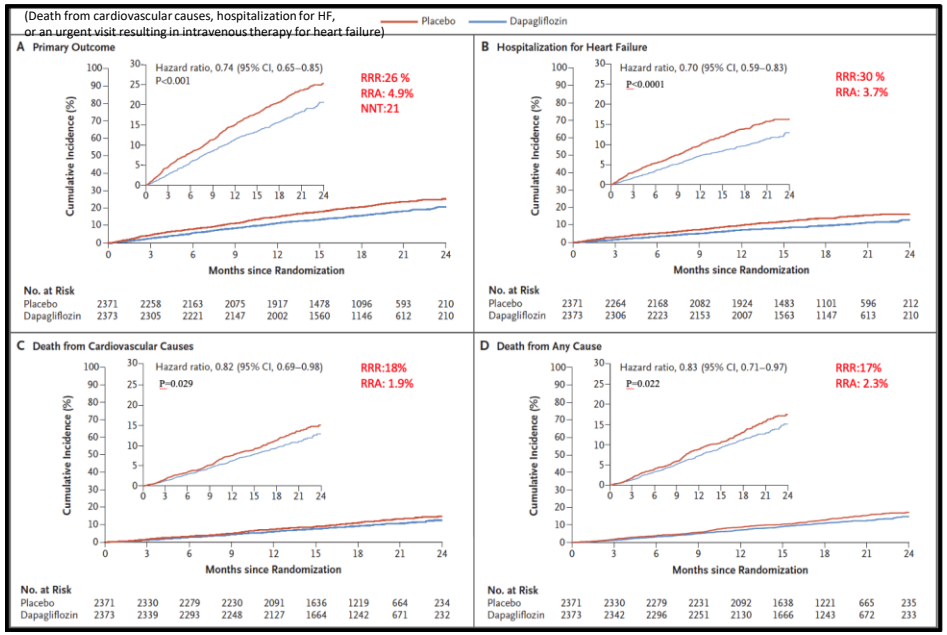
With the special contribution of the Heart Failure Association (HFA) of the ESC

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

DAPA-HF

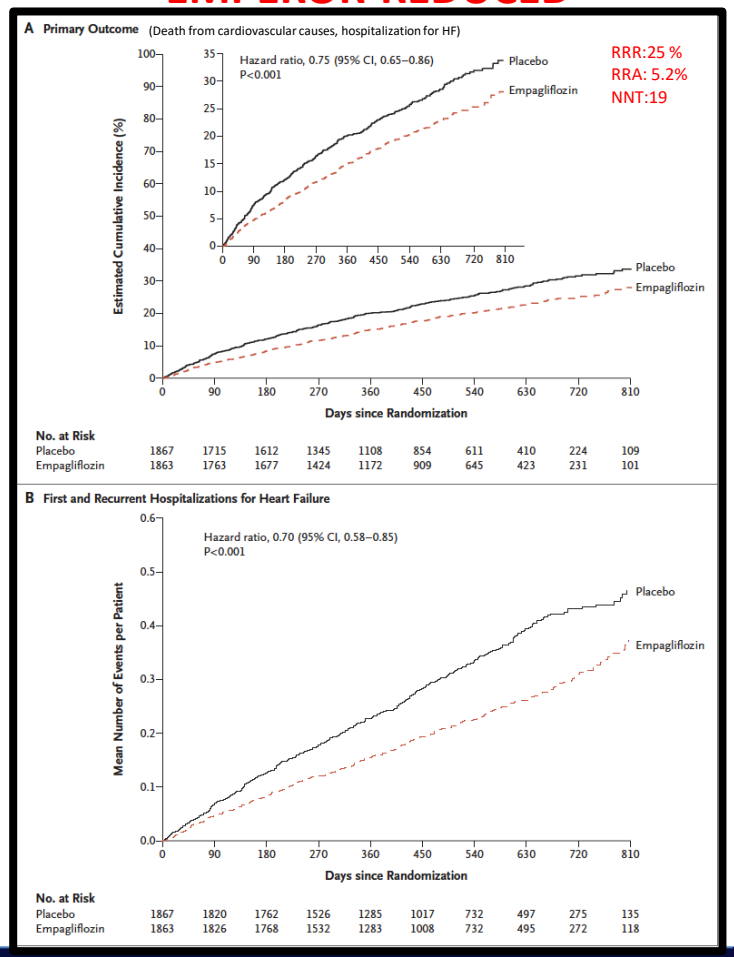


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

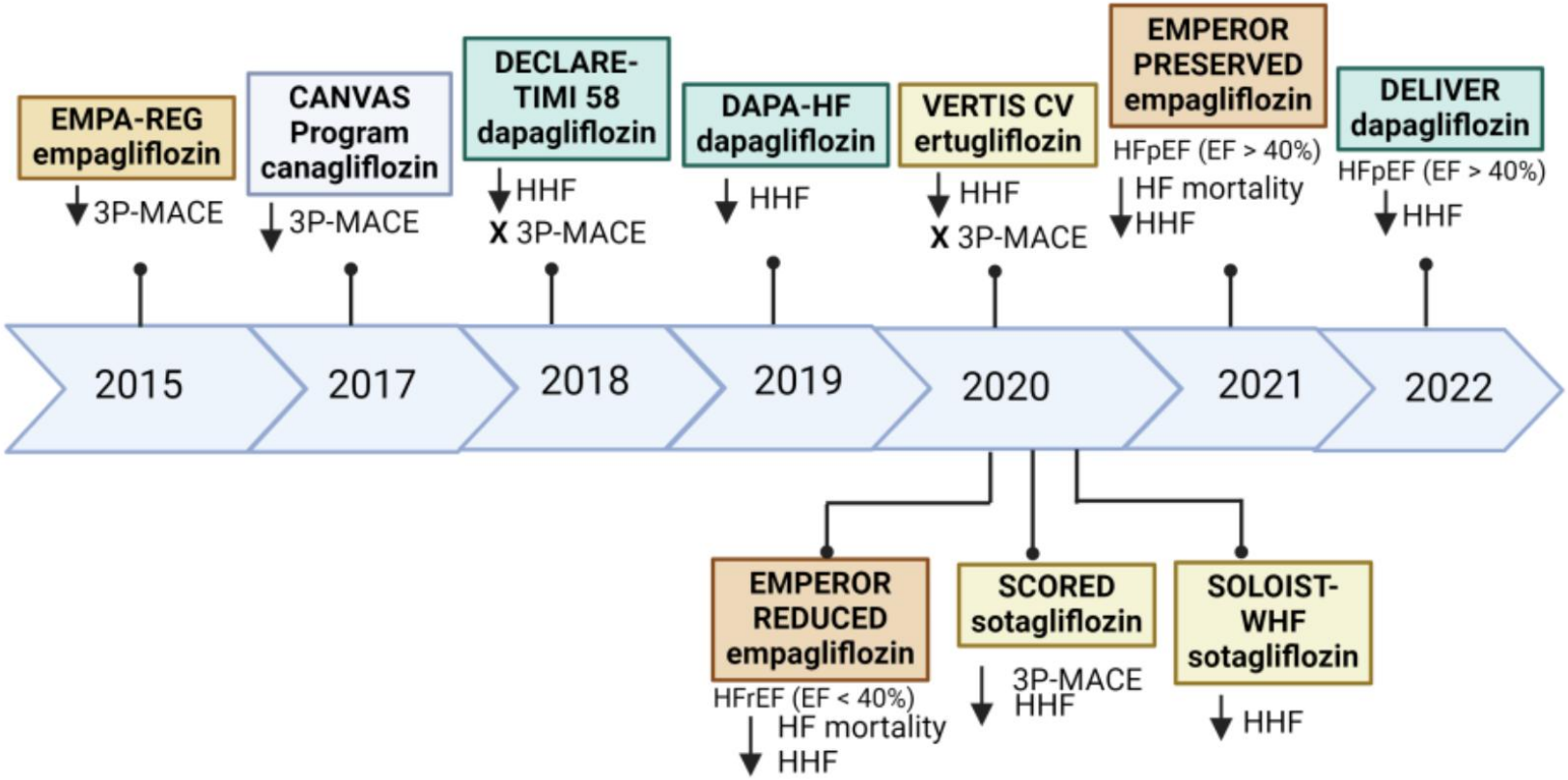
EMPEROR-REDUCED



Management of 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


EMPA-REG empagliflozin
3P-MACE
CANVAS Program canagliflozin
3P-MACE
DECLARE-TIMI 58 dapagliflozin
HHF
X 3P-MACE
DAPA-HF dapagliflozin
HHF
VERTIS CV ertugliflozin
HHF
X 3P-MACE
EMPEROR PRESERVED empagliflozin
HFpEF (EF > 40%)
HF mortality
HHF
DELIVER dapagliflozin
HFpEF (EF > 40%)
HHF
2015
2017
2018
2019
2020
2021
2022
EMPEROR REDUCED empagliflozin
HFrEF (EF < 40%)
HF mortality
HHF
SCORED sotagliflozin
3P-MACE
HHF
SOLOIST-WHF sotagliflozin
HHF

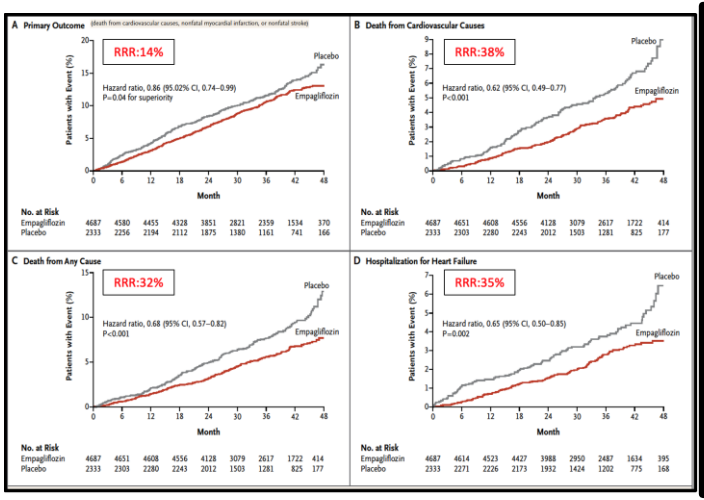
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

EMPA-REG OUTCOME

35% of patients with CV disease did not have a prior atherothrombotic event



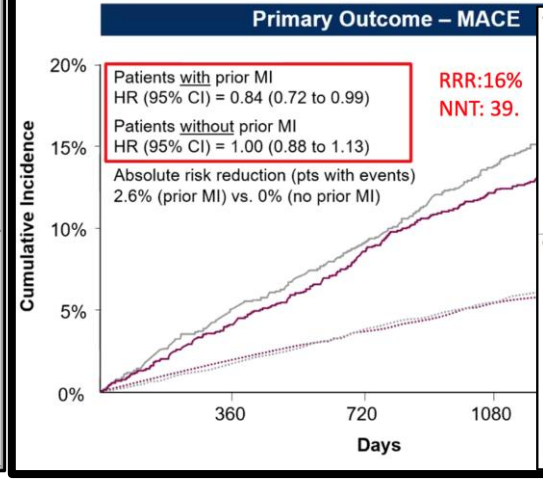
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

DECLARE-TIMI 58

60%: 2 o più fattori di rischio
40%: CAD, PAD, HF, ictus



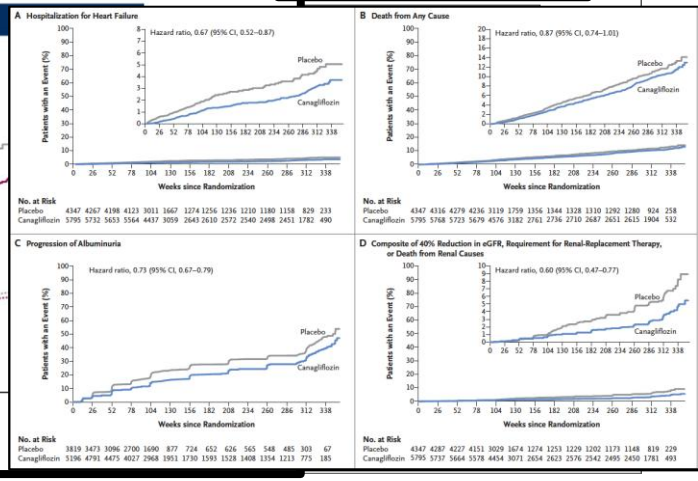
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

CANVAS Program

35%: 2 o più fattori di rischio
65%: CAD, PAD, HF, ictus



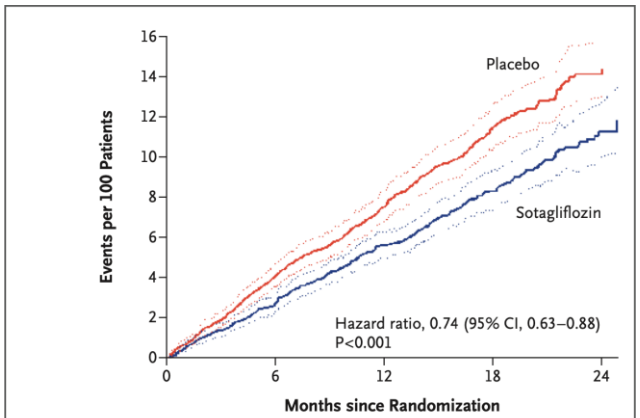


Figure 1. Total Number of Deaths from Cardiovascular Causes, Hospitalizations for Heart Failure, and Urgent Visits for Heart Failure.

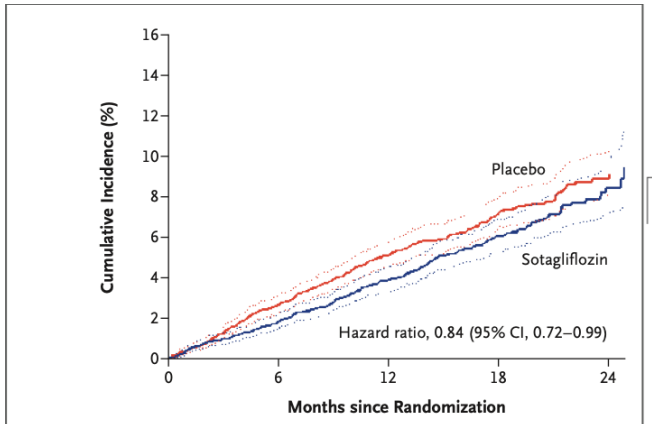


Figure 2. First Occurrence of Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

SCORED

Recommendations for the primary prevention of heart failure in patients with risk factors for its development

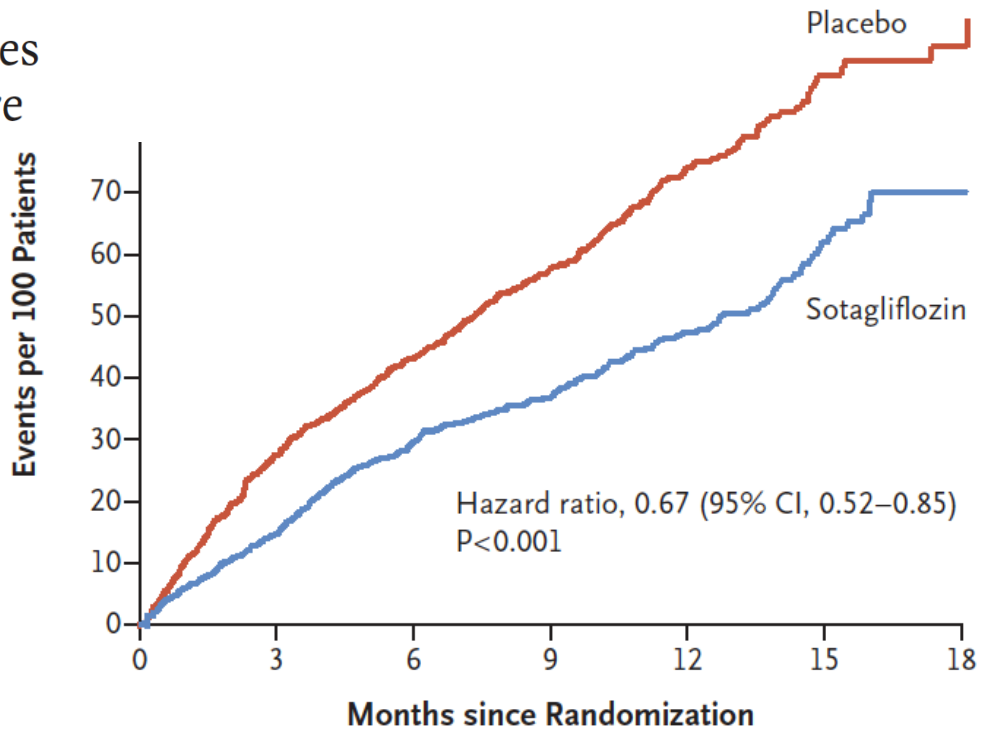
Recommendations	Class[a]	Level[b]
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.[287–290]	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.[291,292]	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.[293–297]	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.[298–302]	I	C

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

SOLOIST-WHF



No. at Risk							
Placebo	614	524	416	305	195	100	25
Sotagliflozin	608	540	430	310	209	97	29

Figure 1. Primary Efficacy End-Point Events.

Shown are the rates of primary efficacy end-point events (deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure) in the sotagliflozin group and the placebo group. Total events after

Recommendations for the treatment of diabetes in heart failure

Recommendation	Class[a]	Level[b]
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.[293–297]	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.[108,109,136]	I	A

ESC European Society of Cardiology

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

ESC GUIDELINES

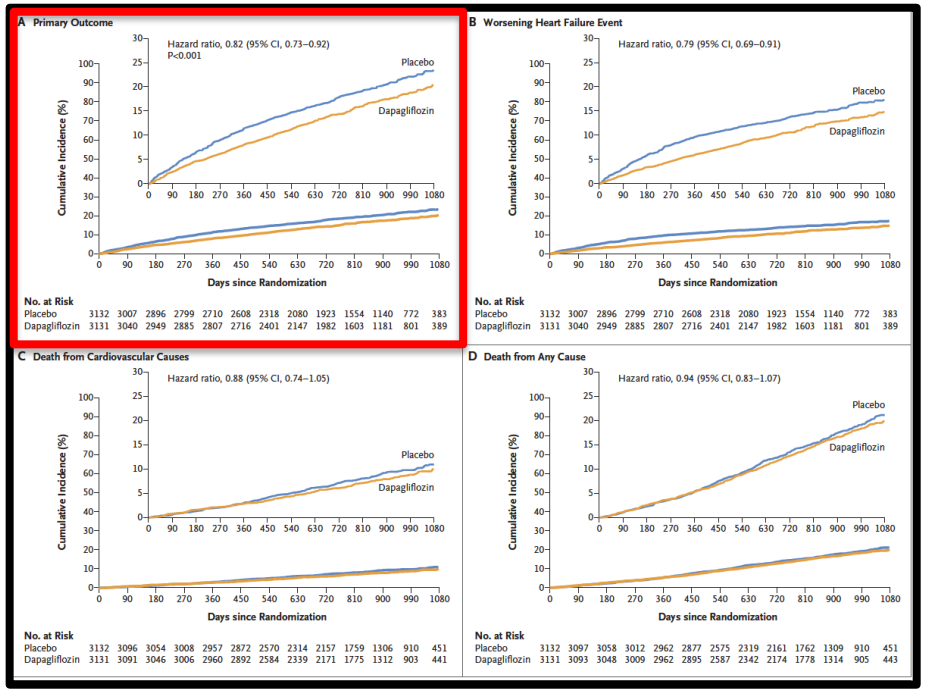
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

DELIVER



18 % RRR

3.1% ARR

p=0.0008[2]

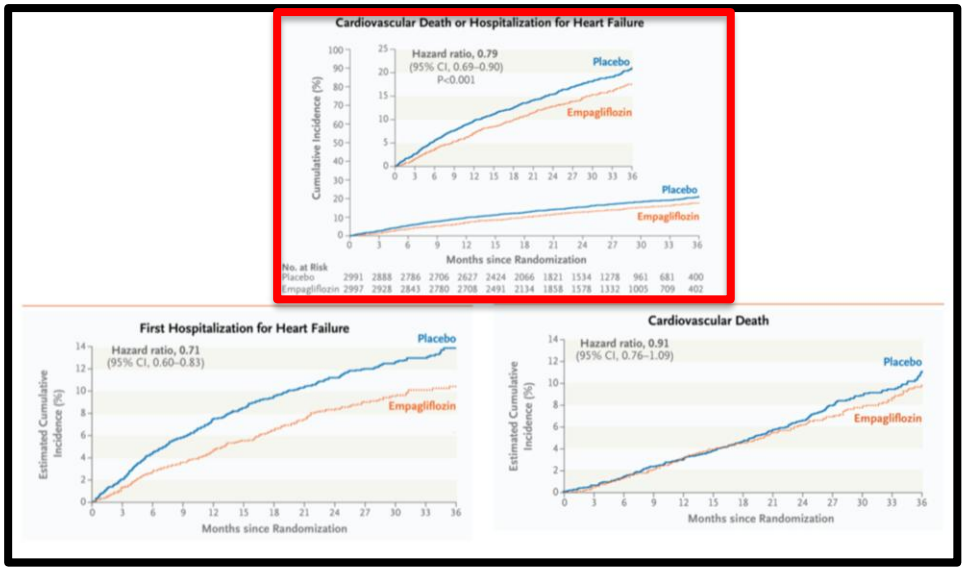
NNT=32

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

EMPEROR Preserved



RRR 21%

ARR 3.3%

NNT*=31

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

Cardiovascular death or heart failure hospitalisation

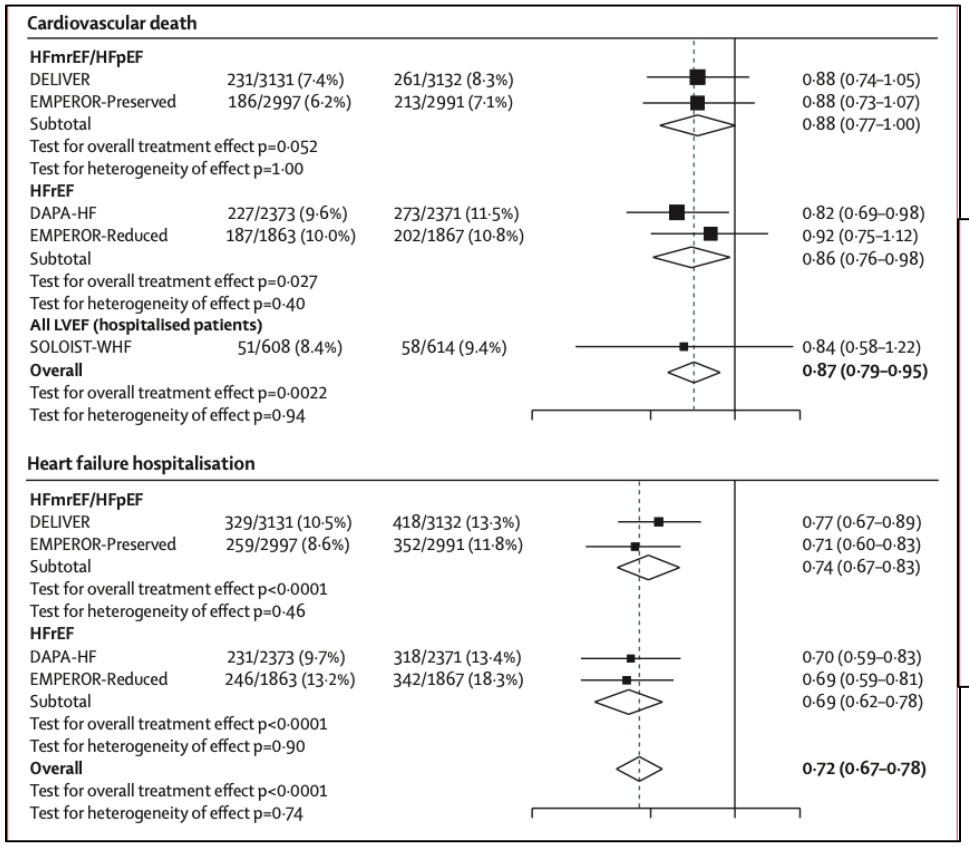
	Number with event/ number of patients (%)		Hazard ratio (95% CI)
	SGLT2 inhibitors	Placebo	
HFmrEF/HFpEF			
DELIVER	475/3131 (15·2%)	577/3132 (18·4%)	0·80 (0·71–0·91)
EMPEROR-Preserved	415/2997 (13·8%)	511/2991 (17·1%)	0·79 (0·69–0·90)
Subtotal			0·80 (0·73–0·87)
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·89			

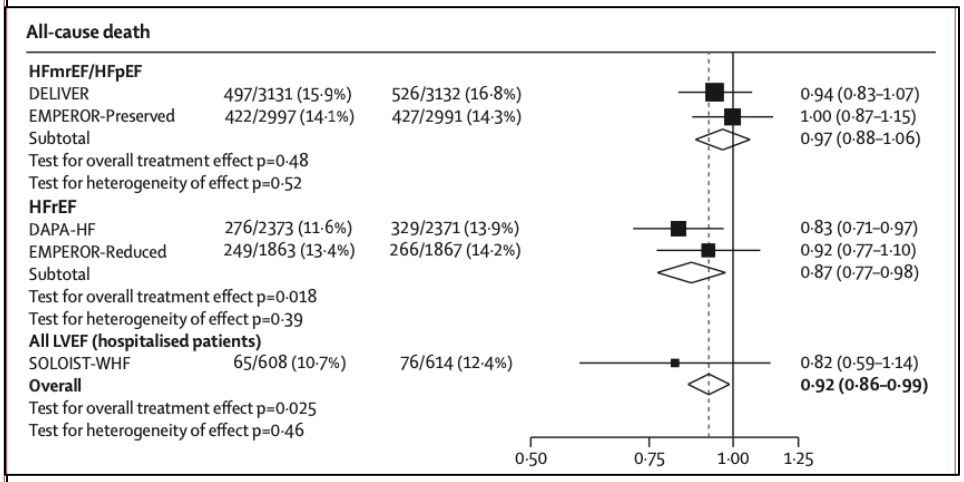
NNT = 25

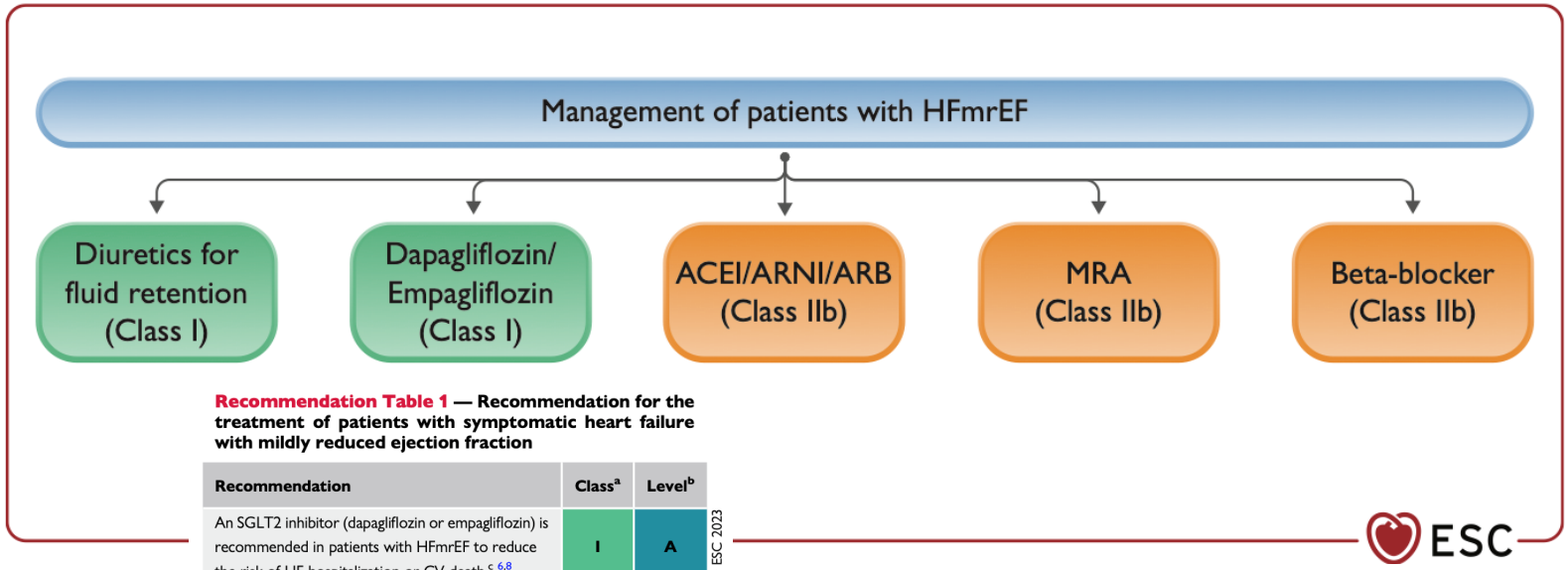
23% DI RIDUZIONE DEL RISCHIO RELATIVO INDIPENDENTEMENTE DAL VALORE DI FE

Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=1·00			
All LVEF (hospitalised patients)			
SOLOIST-WHF			0·71 (0·56–0·89)
Overall			**0·77 (0·72-0·82)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·87			

Lancet 2022; 400: 757–67


Cardiovascular death
HFmrEF/HFpEF
DELIVER 231/3131 (7·4%) 261/3132 (8·3%) 0·88 (0·74–1·05)
EMPEROR-Preserved 186/2997 (6·2%) 213/2991 (7·1%) 0·88 (0·73–1·07)
Subtotal 0·88 (0·77–1·00)
Test for overall treatment effect p=0·052
Test for heterogeneity of effect p=1·00
HFrEF
DAPA-HF 227/2373 (9·6%) 273/2371 (11·5%) 0·82 (0·69–0·98)
EMPEROR-Reduced 187/1863 (10·0%) 202/1867 (10·8%) 0·92 (0·75–1·12)
Subtotal 0·86 (0·76–0·98)
Test for overall treatment effect p=0·027
Test for heterogeneity of effect p=0·40
All LVEF (hospitalised patients)
SOLOIST-WHF 51/608 (8.4%) 58/614 (9.4%) 0·84 (0·58–1·22)
Overall 0·87 (0·79–0·95)
Test for overall treatment effect p=0·0022
Test for heterogeneity of effect p=0·94
Heart failure hospitalisation
HFmrEF/HFpEF
DELIVER 329/3131 (10·5%) 418/3132 (13·3%) 0·77 (0·67–0·89)
EMPEROR-Preserved 259/2997 (8·6%) 352/2991 (11·8%) 0·71 (0·60–0·83)
Subtotal 0·74 (0·67–0·83)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·46
HFrEF
DAPA-HF 231/2373 (9·7%) 318/2371 (13·4%) 0·70 (0·59–0·83)
EMPEROR-Reduced 246/1863 (13·2%) 342/1867 (18·3%) 0·69 (0·59–0·81)
Subtotal 0·69 (0·62–0·78)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·90
Overall 0·72 (0·67–0·78)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·74

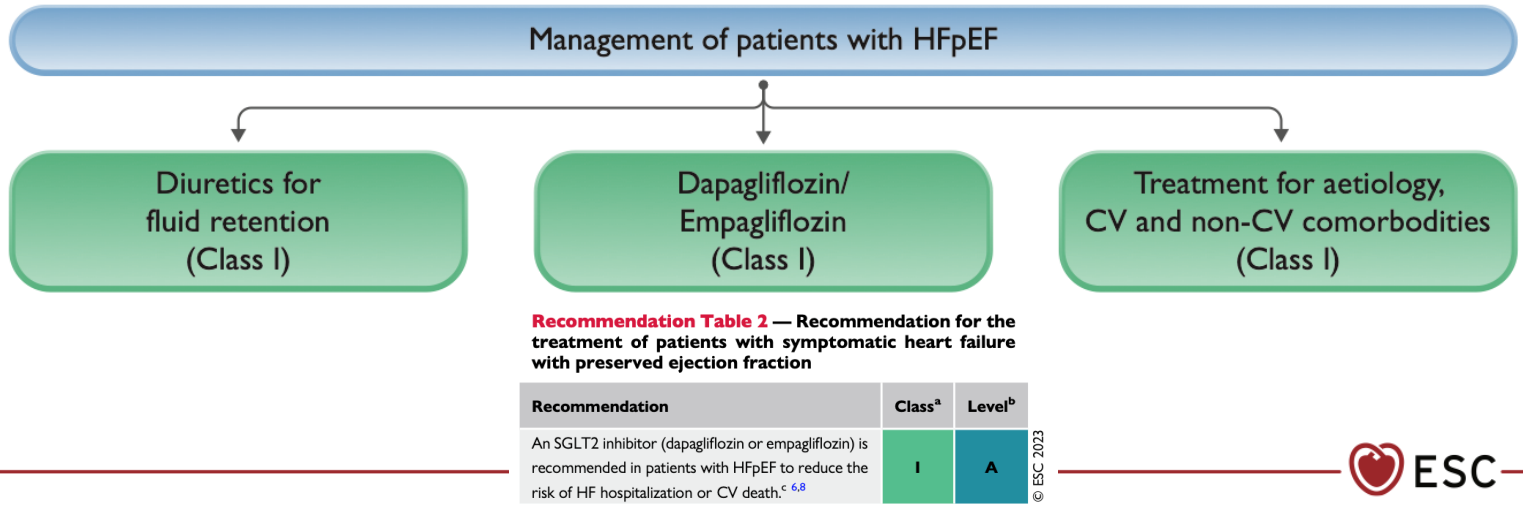

All-cause death
HFmrEF/HFpEF
DELIVER 497/3131 (15·9%) 526/3132 (16·8%) 0·94 (0·83–1·07)
EMPEROR-Preserved 422/2997 (14·1%) 427/2991 (14·3%) 1·00 (0·87–1·15)
Subtotal 0·97 (0·88–1·06)
Test for overall treatment effect p=0·48
Test for heterogeneity of effect p=0·52
HFrEF
DAPA-HF 276/2373 (11·6%) 329/2371 (13·9%) 0·83 (0·71–0·97)
EMPEROR-Reduced 249/1863 (13·4%) 266/1867 (14·2%) 0·92 (0·77–1·10)
Subtotal 0·87 (0·77–0·98)
Test for overall treatment effect p=0·018
Test for heterogeneity of effect p=0·39
All LVEF (hospitalised patients)
SOLOIST-WHF 65/608 (10·7%) 76/614 (12·4%) 0·82 (0·59–1·14)
Overall 0·92 (0·86–0·99)
Test for overall treatment effect p=0·025
Test for heterogeneity of effect p=0·46
0·50
0·75
1·00
1·25



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

ESC



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

ESC

Recommendation Table 4 — Recommendations for the prevention of heart failure in patients with type 2 diabetes mellitus and chronic kidney disease

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death.[35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

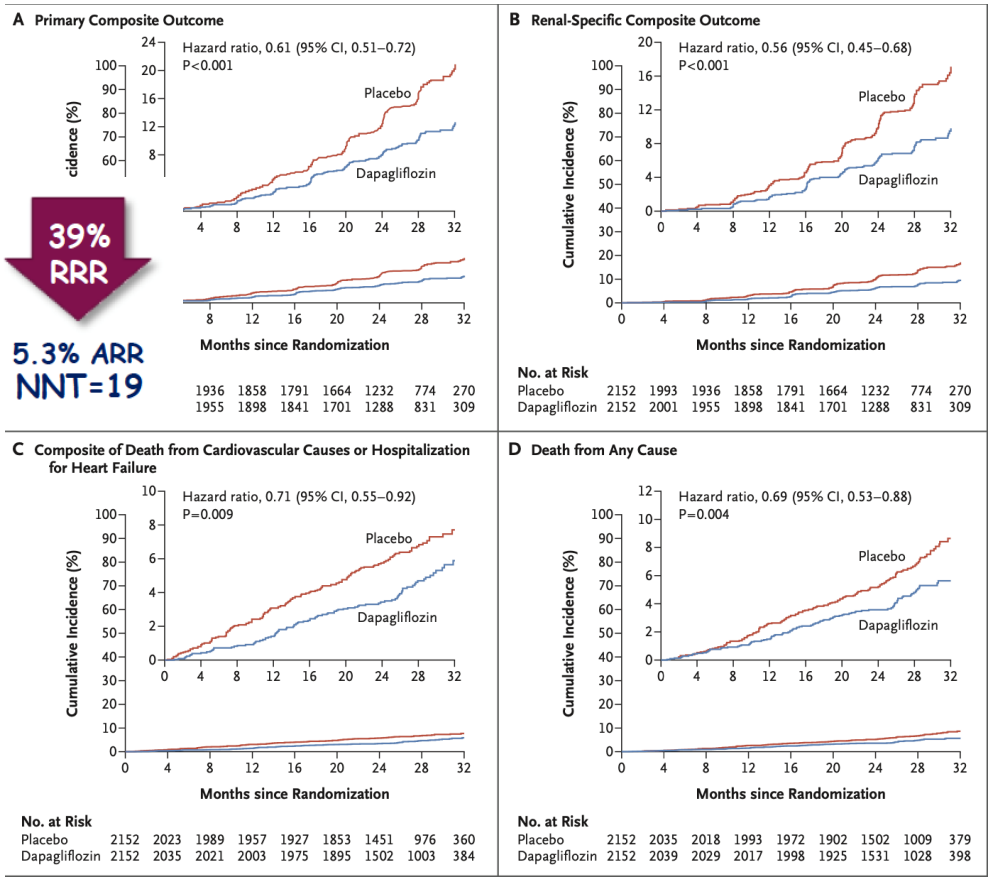
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2020;383:1436-46.

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

67% DMT2

DAPA - CKD



The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2023;388:117-27.

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

96% DMT2
2% DMT1

EMPA - KIDNEY

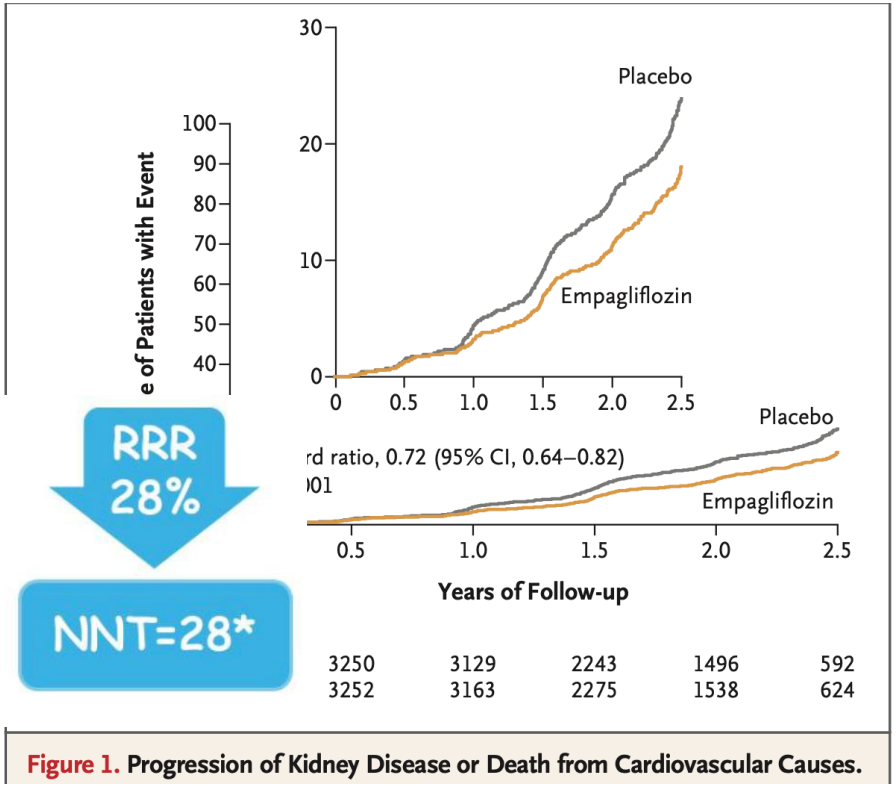


Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2020;383:1436-46.

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

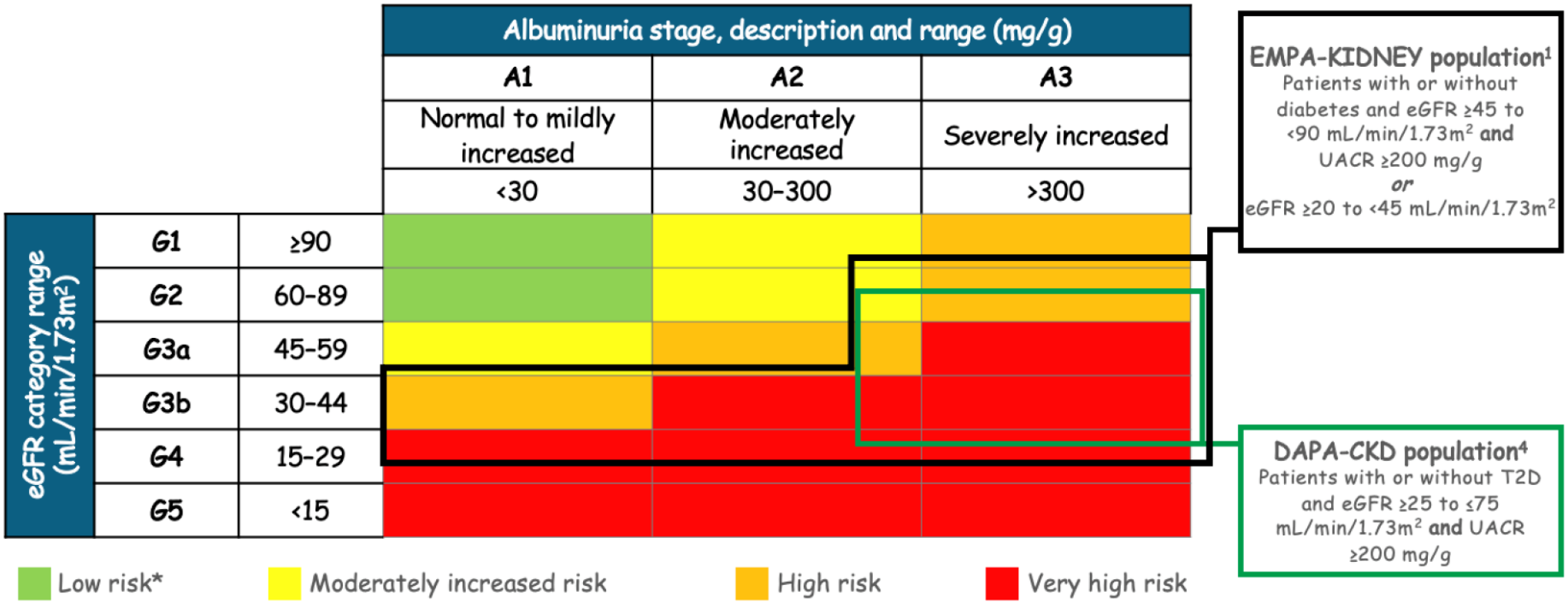
DAPA - CKD

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2023;388:117-27.

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

EMPA - KIDNEY



OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

SUPPLEMENT TO

kidney INTERNATIONAL

KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES

KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

VOLUME 105 | ISSUE 4S | APRIL 2024

www.kidney-international.org

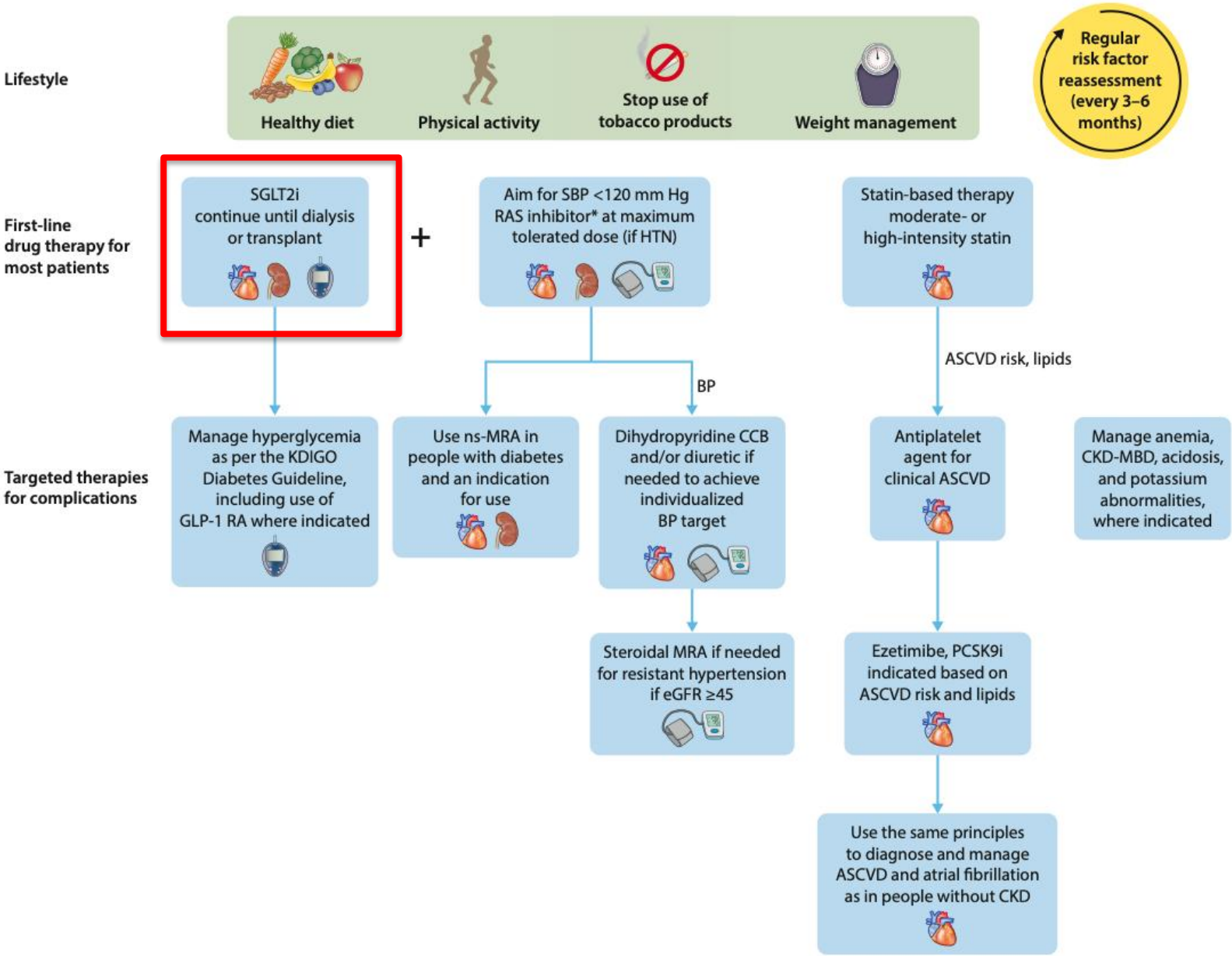
Recommendation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

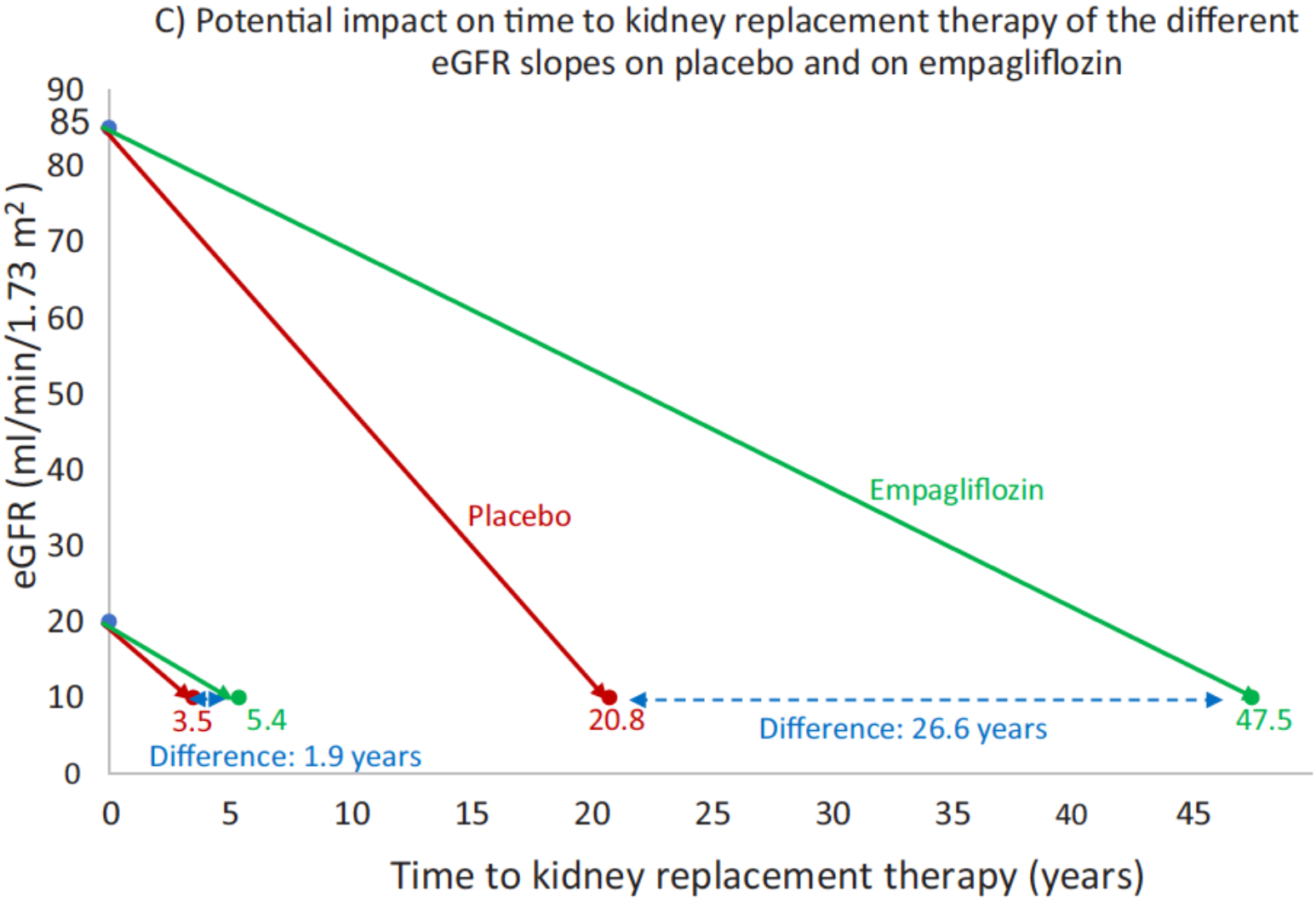
Practice Point 3.7.1: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or KRT is initiated.

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.**

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)*.

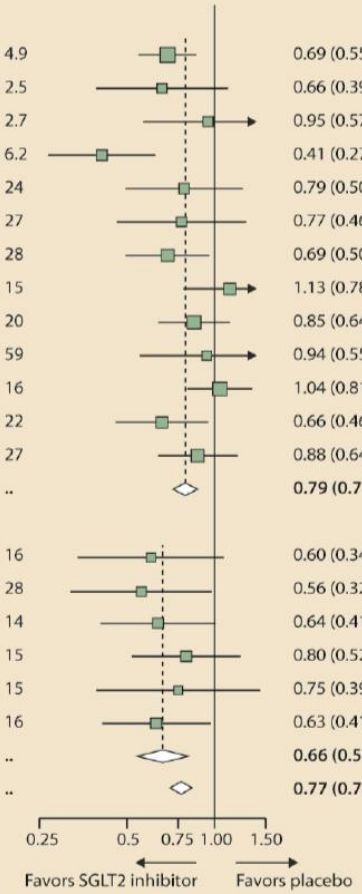

Lifestyle
Healthy diet
Physical activity
Stop use of tobacco products
Weight management
Regular risk factor reassessment (every 3–6 months)
First-line drug therapy for most patients
SGLT2i continue until dialysis or transplant
+
Aim for SBP <120 mm Hg RAS inhibitor* at maximum tolerated dose (if HTN)
Statin-based therapy moderate- or high-intensity statin
ASCVD risk, lipids
BP
Targeted therapies for complications
Manage hyperglycemia as per the KDIGO Diabetes Guideline, including use of GLP-1 RA where indicated
Use ns-MRA in people with diabetes and an indication for use
Dihydropyridine CCB and/or diuretic if needed to achieve individualized BP target
Antiplatelet agent for clinical ASCVD
Manage anemia, CKD-MBD, acidosis, and potassium abnormalities, where indicated
Steroidal MRA if needed for resistant hypertension if eGFR ≥45
Ezetimibe, PCSK9i indicated based on ASCVD risk and lipids
Use the same principles to diagnose and manage ASCVD and atrial fibrillation as in people without CKD



Clinical Kidney Journal, 2023, vol. 16, no. 8, 1187–1198

GLIFOZINE E IRA

	Kidney	Acute kidney injury				
	Mean baseline eGFR, ml/min per 1.73 m²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	
Diabetes						
DECLARE–TIMI 58	85	125/8574	175/8569	3.5	4.9	0.69 (0.55–0.87)
CANVAS Program	77	30/5790	28/4344	1.6	2.5	0.66 (0.39–1.11)
VERTIS CV	76	42/5493	22/2745	2.5	2.7	0.95 (0.57–1.59)
EMPA–REG OUTCOME	74	45/4687	37/2333	2.5	6.2	0.41 (0.27–0.63)
DAPA–HF	63	31/1073	39/1063	19	24	0.79 (0.50–1.25)
EMPEROR–REDUCED	61	26/927	33/929	21	27	0.77 (0.46–1.28)
EMPEROR–PRESERVED	60	60/1466	84/1472	20	28	0.69 (0.50–0.97)
DELIVER	60	59/1578	52/1572	17	15	1.13 (0.78–1.63)
CREDENCE	56	86/2200	98/2197	17	20	0.85 (0.64–1.13)
SOLOIST–WHF	51	25/605	27/611	55	59	0.94 (0.55–1.59)
SCORED	44	116/5291	111/5286	16	16	1.04 (0.81–1.35)
DAPA–CKD	44	48/1455	69/1451	15	22	0.66 (0.46–0.96)
EMPA–KIDNEY	36	73/1525	81/1515	24	27	0.88 (0.64–1.20)
Subtotal: diabetes	**67**	**766/40,664**	**856/34,087**	..	..	**0.79 (0.72–0.88)**
No diabetes						
DAPA–HF	68	18/1295	30/1305	9.9	16	0.60 (0.34–1.08)
EMPEROR–REDUCED	63	20/936	34/938	16	28	0.56 (0.32–0.98)
DELIVER*	63	30/1551	47/1558	8.8	14	0.64 (0.41–1.02)
EMPEROR–PRESERVED	62	37/1531	47/1519	12	15	0.80 (0.52–1.23)
DAPA–CKD	42	16/697	21/701	11	15	0.75 (0.39–1.43)
EMPA–KIDNEY	39	34/1779	54/1790	10	16	0.63 (0.41–0.97)
Subtotal: no diabetes	**56**	**155/7789**	**233/7811**	..	..	**0.66 (0.54–0.81)**
Total: overall	**65**	**921/48,453**	**1089/41,898**	..	..	**0.77 (0.70–0.84)**



Trend across trials sorted by eGFR
Diabetes *P*=0.87;
No diabetes *P*=0.86;
Heterogeneity by diabetes status

Trend across trials sorted by eGFR:
Diabetes *P*=0.02;
No diabetes *P*=0.66;
Heterogeneity by diabetes status: *P*=0.12

Lancet. 2022 Nov 19;400(10365):1788–1801.

Recommendation Table 4 — Recommendations for the prevention of heart failure in patients with type 2 diabetes mellitus and chronic kidney disease

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death.[35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

ORIGINAL ARTICLE

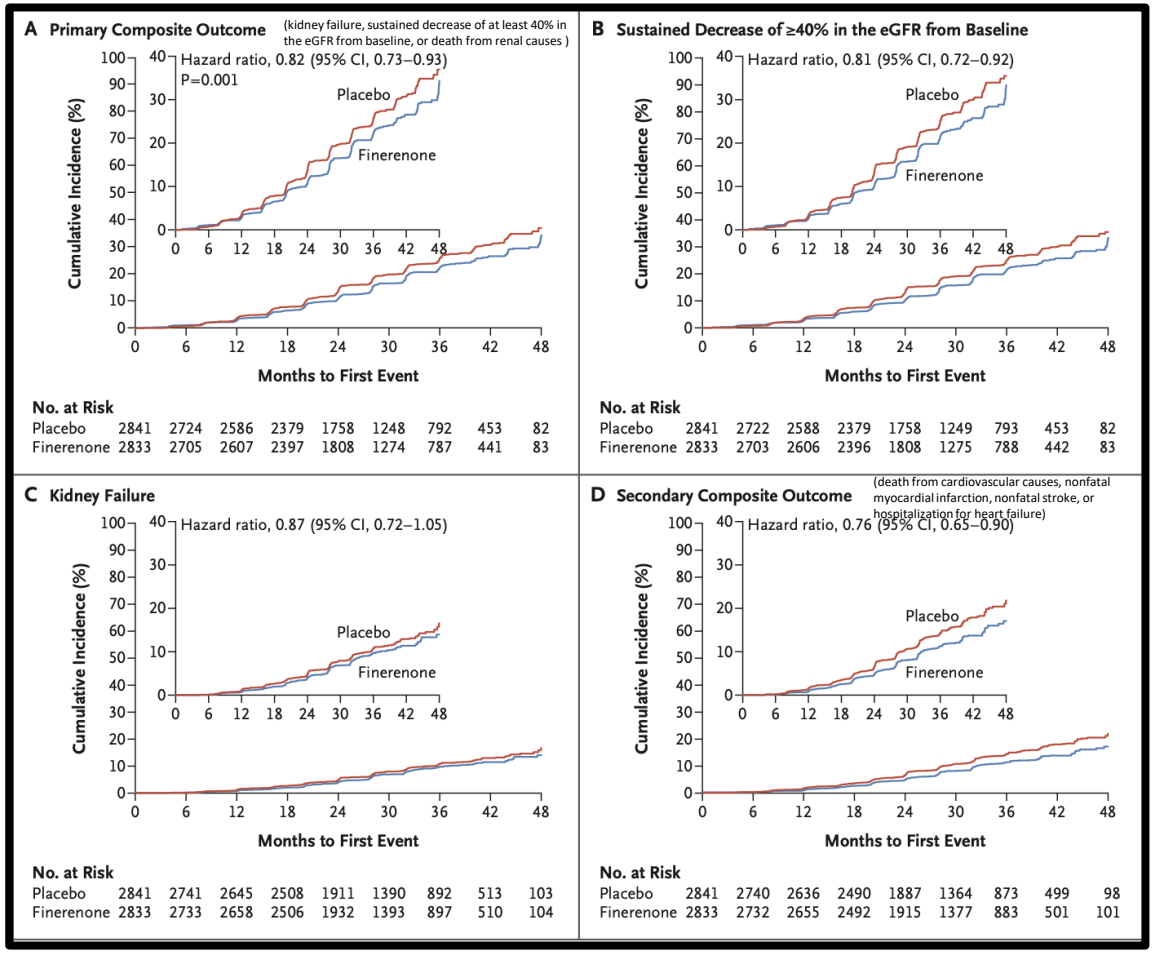
N Engl J Med 2020;383:2219-29.

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

GFR: 25-60, ACR: 30-300 e retinopatia diabetica

GFR: 25-75 e ACR: 300-5000

FIDELIO-DKD



FINEARTS-HF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, M. Vaduganathan, B. Claggett, P.S. Jhund, A.S. Desai, A.D. Henderson, C.S.P. Lam, B. Pitt, M. Senni, S.J. Shah, A.A. Voors, F. Zannad, I.Z. Abidin, M.A. Alcocer-Gamba, J.J. Atherton, J. Bauersachs, M. Chang-Sheng, C.-E. Chiang, O. Chioncel, V. Chopra, J. Comin-Colet, G. Filippatos, C. Fonseca, G. Gajos, S. Goland, E. Goncalvesova, S. Kang, T. Katova, M.N. Kosiborod, G. Latkovskis, A.P.-W. Lee, G.C.M. Linssen, G. Llamas-Esperón, V. Mareev, F.A. Martinez, V. Melenovský, B. Merkely, S. Nodari, M.C. Petrie, C.I. Saldarriaga, J.F.K. Saraiva, N. Sato, M. Schou, K. Sharma, R. Troughton, J.A. Udell, H. Ukkonen, O. Vardeny, S. Verma, D. von Lewinski, L. Voronkov, M.B. Yilmaz, S. Zieroth, J. Lay-Flurrie, I. van Gameren, F. Amarante, P. Kolkhof, and P. Viswanathan, for the FINEARTS-HF Committees and Investigators*

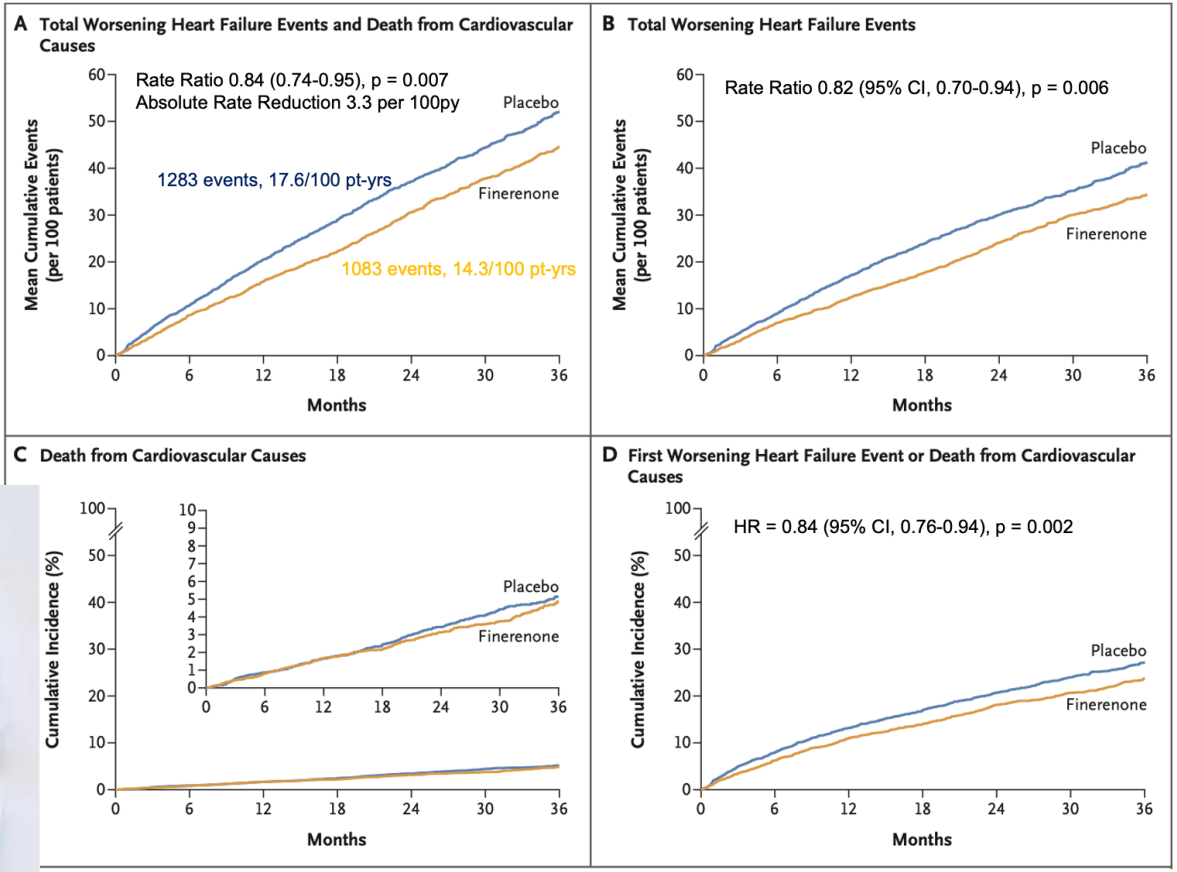
DMT2: 40%

ABSTRACT

BACKGROUND

Steroidal mineralocorticoid receptor antagonists reduce morbidity and mortality among patients with heart failure and reduced ejection fraction, but their efficacy in those with heart failure and mildly reduced or preserved ejection fraction has not been established. Data regarding the efficacy and safety of the nonsteroidal mineralocorticoid receptor antagonist finerenone in patients with heart failure and mildly reduced or preserved ejection fraction are needed.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Solomon can be contacted at ssolomon@bwh.harvard.edu or at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. Dr. McMurray can be contacted at john.mcmurray@glasgow.ac.uk or



ESC
European Society of Cardiology
European Heart Journal (2023) **44**, 4043–4140
https://doi.org/10.1093/eurheartj/ehad192

ESC GUIDELINES

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)

JAMA Cardiology | Original Investigation

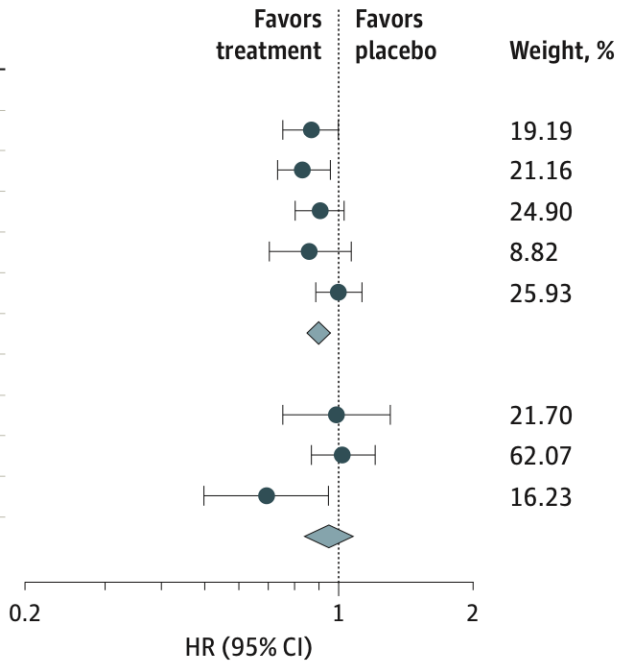
Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes

A Meta-analysis

B MACEs by ASCVD status

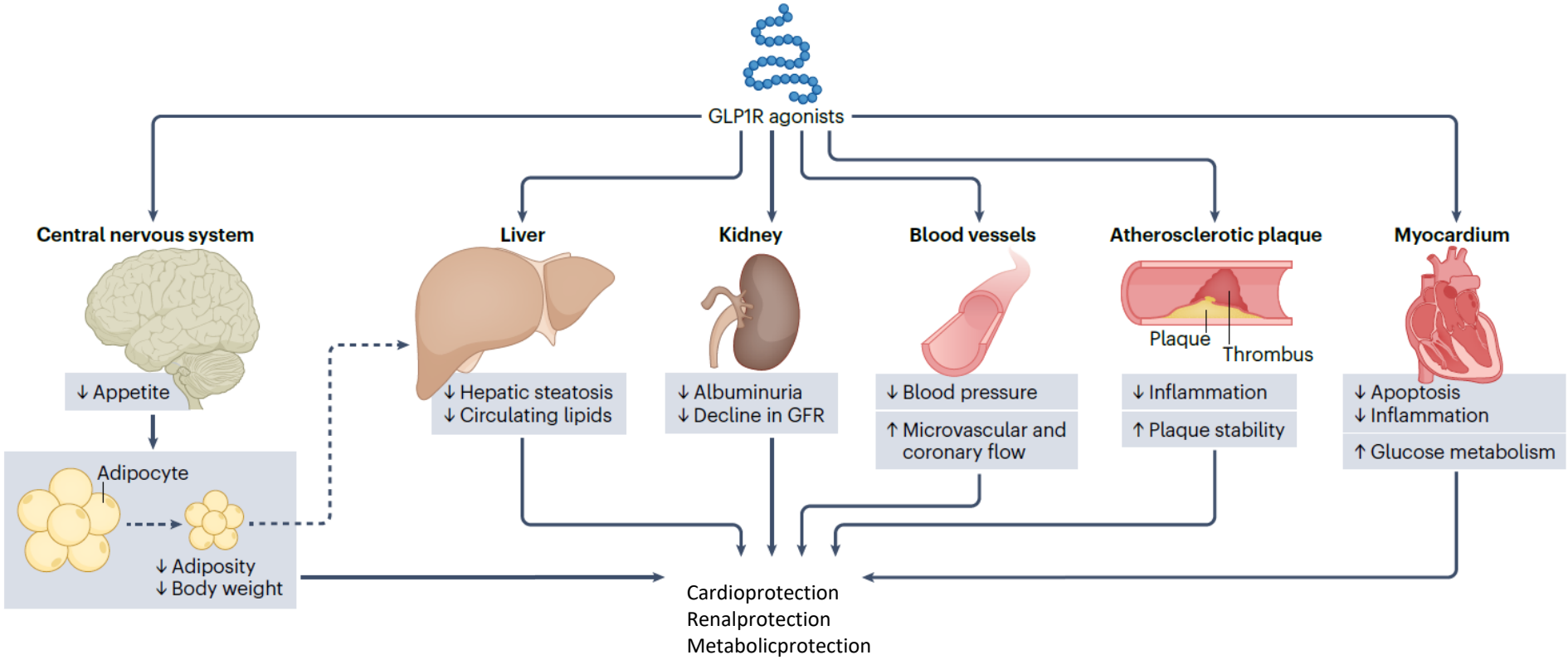
Composite of IMA, Stroke or Cardiovascular Death

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model ($Q = 4.53$; $df = 4$; $P = .34$; $I^2 = 11.8\%$)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model ($Q = 4.59$; $df = 2$; $P = .10$; $I^2 = 56.5\%$)					0.94 (0.83-1.07)



LE GLIFOZINE RIDUCONO I MACE NEI PZ DIABETICI SIA CON CHE SENZA ASCVD

GLP1R agonisti, un'azione su più target con un fine comune: protezione cardio-nefro-metabolica.



Modified from Nature reviews cardiology 2023. https://doi.org/10.1038/s41569-023-00849-3

Table 1 GLP-1 receptor agonists: cardiovascular indications and CVOTs results

GLP-1 receptor agonists	Semaglutide		Lixisenatide	Exenatide	Liraglutide	Dulaglutide	Albiglutide[a]
Administration route	**Oral**	**Subcutaneous**	**Subcutaneous**	**Subcutaneous**	**Subcutaneous**	**Subcutaneous**	**Subcutaneous**
Cardiovascular indication	No	Yes Reduction of MACEs in adults with T2DM and established CVD	No	No	Yes Reduction of MACEs in adults with T2DM and established CVD	Yes Reduction of MACEs in adults with T2DM and established CVD or multiple CV risk factors	No
CVOT [reference]	PIONEER 6 [40]	SUSTAIN 6 [57]	ELIXIA [106]	EXSCEL [107]	LEADER [22]	REWIND [108]	HARMONY [54]
Study population	3183 T2DM patients with established CVD	3297 T2DM patients with established CVD	6068 T2DM patients with acute coronary event in the last 180 days	14,752 T2DM patients with and without established CVD	9340 T2DM patients with established CVD	3183 T2DM patients with established CVD	9463 T2DM patients with established CVD
Intervention	Oral semaglutide 14 mg once a day vs. placebo	Semaglutide 0.5–1.0 mg sc once a week vs. placebo	Lixisenatide 20 µg sc once a day vs. placebo	Exenatide 2.0 mg sc once a week vs. placebo	Liraglutide 1.8 mg sc once a day vs. placebo	Dulaglutide 1.5 mg sc once a week vs. placebo	Albiglutide 30–50 mg sc once a week vs. placebo
Median follow-up	15.9 months	2.1 years	25 months	3.2 years	3.8 years	5.4 years	1.6 years
Primary endpoint: HR; 95%CI; superiority p-value	0.79; 0.57–1.11; p = 0.17	0.74; 0.58–0.95; p = 0.02	1.02; 0.89–1.17; p = 0.81	0.91; 0.83–1.00; p = 0.06	0.87; 0.78–0.97; p = 0.01	0.88; 0.79–0.99; p = 0.026	0.78; 0.68–0.90; p = 0.0006

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2016;375:1834-44.

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

SUSTAIN-6

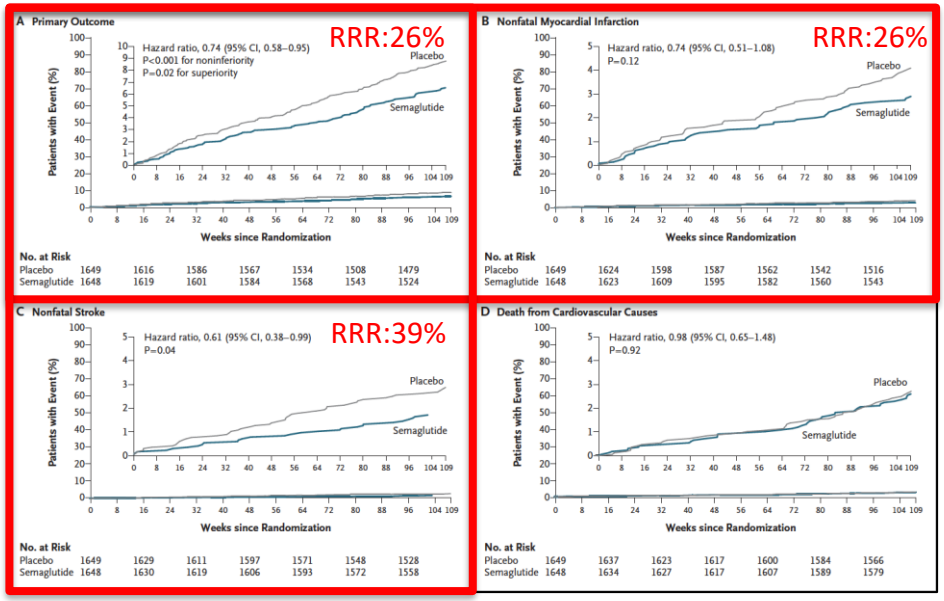


Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

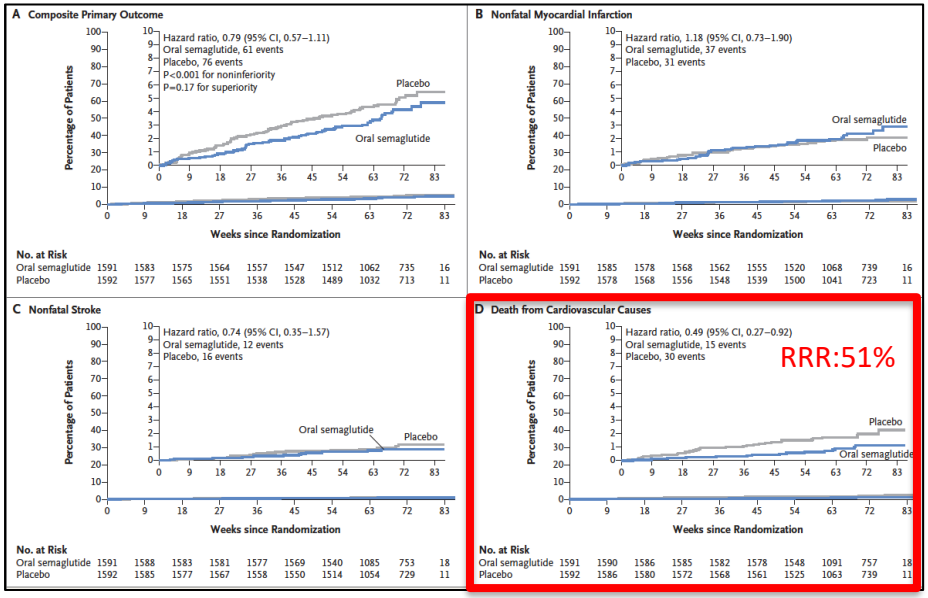
Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	no./100 person-yr	no. (%)	no./100 person-yr		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

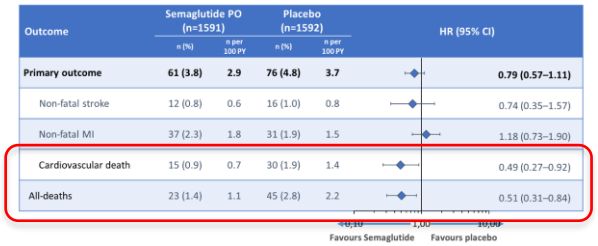
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2019;381:841-51.

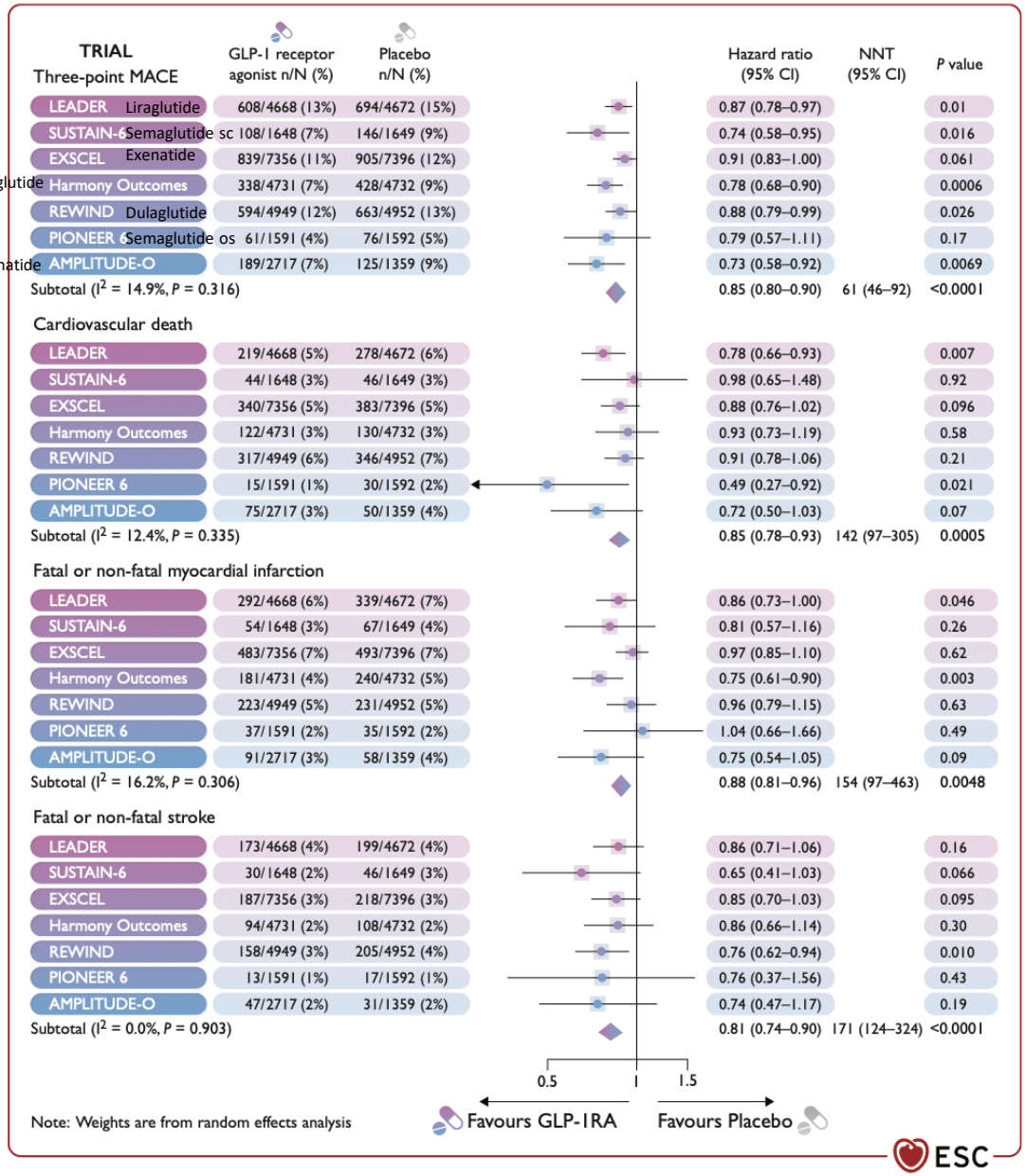
ORIGINAL ARTICLE

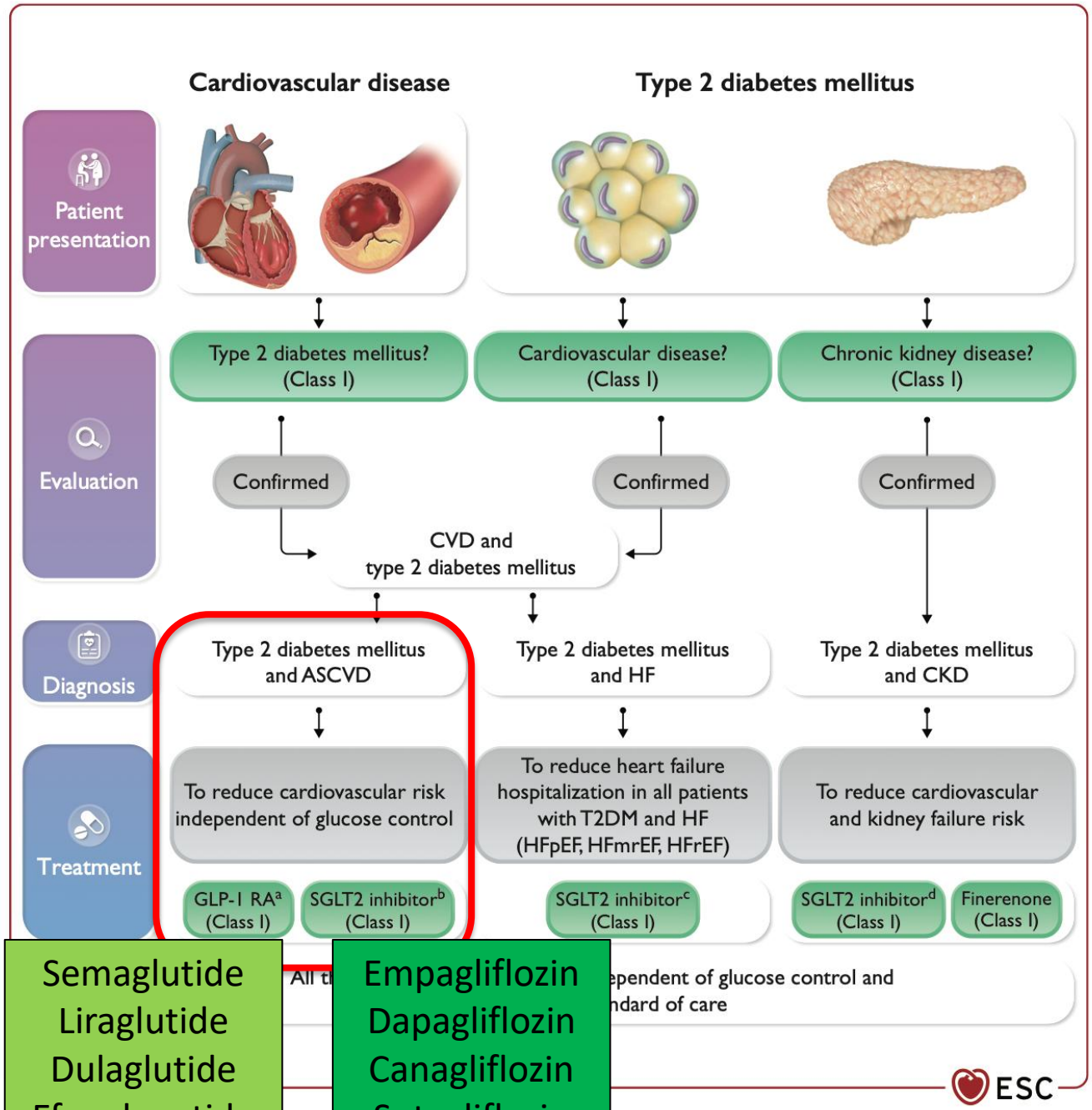
Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

PIONEER 6





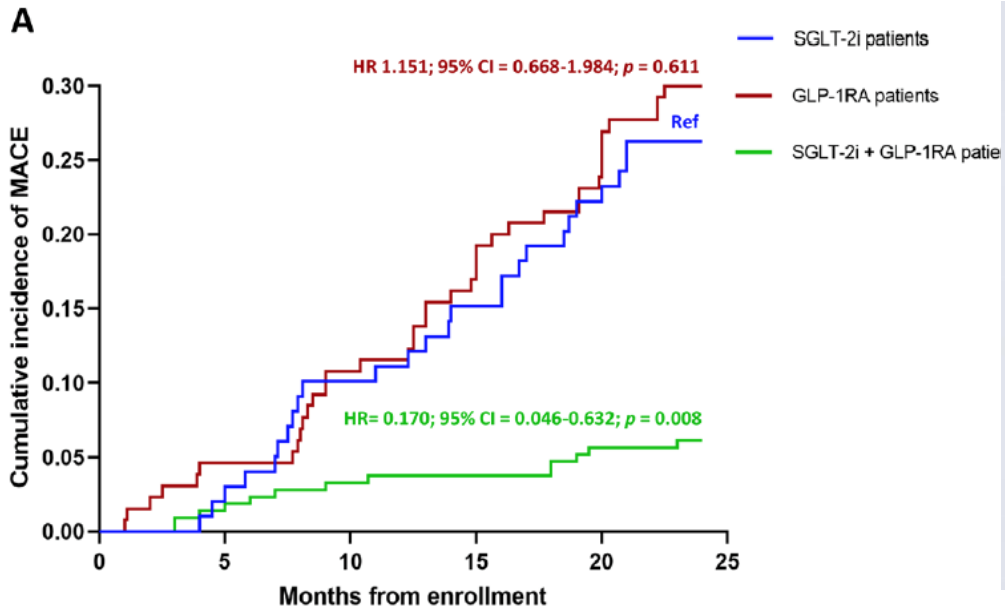

TRIAL
Three-point MACE
GLP-1 receptor agonist n/N (%)
Placebo n/N (%)
Hazard ratio (95% CI)
NNT (95% CI)
P value
LEADER Liraglutide 608/4668 (13%) 694/4672 (15%) 0.87 (0.78–0.97) 0.01
SUSTAIN-6 Semaglutide sc 108/1648 (7%) 146/1649 (9%) 0.74 (0.58–0.95) 0.016
EXSCEL Exenatide 839/7356 (11%) 905/7396 (12%) 0.91 (0.83–1.00) 0.061
Albiglutide Harmony Outcomes 338/4731 (7%) 428/4732 (9%) 0.78 (0.68–0.90) 0.0006
REWIND Dulaglutide 594/4949 (12%) 663/4952 (13%) 0.88 (0.79–0.99) 0.026
PIONEER 6 Semaglutide os 61/1591 (4%) 76/1592 (5%) 0.79 (0.57–1.11) 0.17
Efpeglenatide AMPLITUDE-O 189/2717 (7%) 125/1359 (9%) 0.73 (0.58–0.92) 0.0069
Subtotal (I^2 = 14.9%, P = 0.316) 0.85 (0.80–0.90) 61 (46–92) <0.0001
-15%
Cardiovascular death
LEADER 219/4668 (5%) 278/4672 (6%) 0.78 (0.66–0.93) 0.007
SUSTAIN-6 44/1648 (3%) 46/1649 (3%) 0.98 (0.65–1.48) 0.92
EXSCEL 340/7356 (5%) 383/7396 (5%) 0.88 (0.76–1.02) 0.096
Harmony Outcomes 122/4731 (3%) 130/4732 (3%) 0.93 (0.73–1.19) 0.58
REWIND 317/4949 (6%) 346/4952 (7%) 0.91 (0.78–1.06) 0.21
PIONEER 6 15/1591 (1%) 30/1592 (2%) 0.49 (0.27–0.92) 0.021
AMPLITUDE-O 75/2717 (3%) 50/1359 (4%) 0.72 (0.50–1.03) 0.07
Subtotal (I^2 = 12.4%, P = 0.335) 0.85 (0.78–0.93) 142 (97–305) 0.0005
-15%
Fatal or non-fatal myocardial infarction
LEADER 292/4668 (6%) 339/4672 (7%) 0.86 (0.73–1.00) 0.046
SUSTAIN-6 54/1648 (3%) 67/1649 (4%) 0.81 (0.57–1.16) 0.26
EXSCEL 483/7356 (7%) 493/7396 (7%) 0.97 (0.85–1.10) 0.62
Harmony Outcomes 181/4731 (4%) 240/4732 (5%) 0.75 (0.61–0.90) 0.003
REWIND 223/4949 (5%) 231/4952 (5%) 0.96 (0.79–1.15) 0.63
PIONEER 6 37/1591 (2%) 35/1592 (2%) 1.04 (0.66–1.66) 0.49
AMPLITUDE-O 91/2717 (3%) 58/1359 (4%) 0.75 (0.54–1.05) 0.09
Subtotal (I^2 = 16.2%, P = 0.306) 0.88 (0.81–0.96) 154 (97–463) 0.0048
-12%
Fatal or non-fatal stroke
LEADER 173/4668 (4%) 199/4672 (4%) 0.86 (0.71–1.06) 0.16
SUSTAIN-6 30/1648 (2%) 46/1649 (3%) 0.65 (0.41–1.03) 0.066
EXSCEL 187/7356 (3%) 218/7396 (3%) 0.85 (0.70–1.03) 0.095
Harmony Outcomes 94/4731 (2%) 108/4732 (2%) 0.86 (0.66–1.14) 0.30
REWIND 158/4949 (3%) 205/4952 (4%) 0.76 (0.62–0.94) 0.010
PIONEER 6 13/1591 (1%) 17/1592 (1%) 0.76 (0.37–1.56) 0.43
AMPLITUDE-O 47/2717 (2%) 31/1359 (2%) 0.74 (0.47–1.17) 0.19
Subtotal (I^2 = 0.0%, P = 0.903) 0.81 (0.74–0.90) 171 (124–324) <0.0001
-19%
0.5
1
1.5
Note: Weights are from random effects analysis
Favours GLP-1RA
Favours Placebo
ESC



Semaglutide
Liraglutide
Dulaglutide
Efpeglenatide

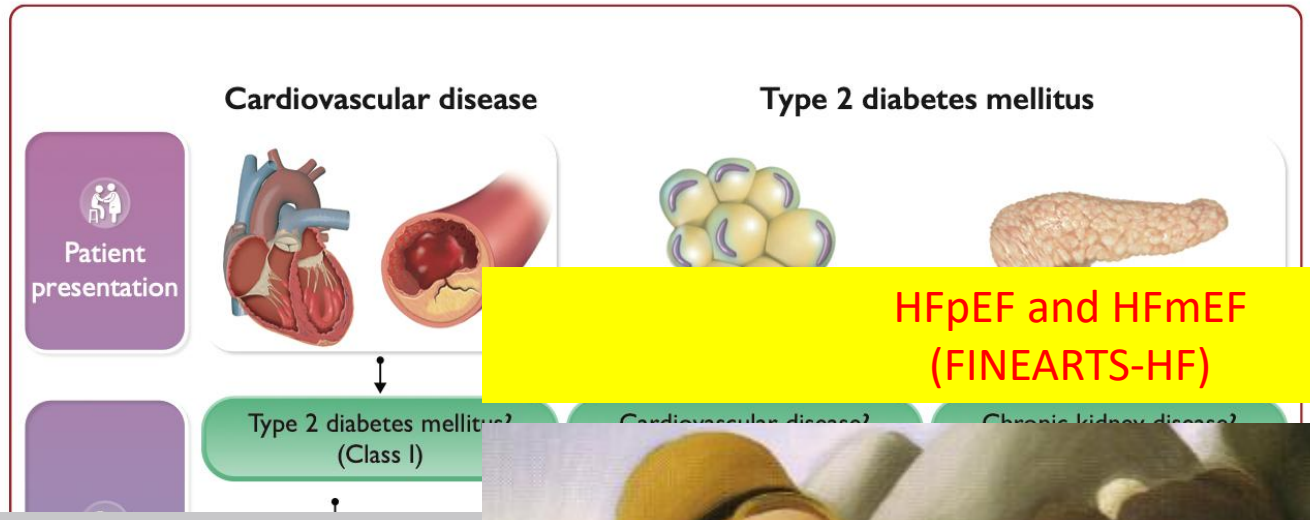
Empagliflozin
Dapagliflozin
Canagliflozin
Sotagliflozin

GLP-1 receptor agonists-SGLT-2 inhibitors combination therapy and cardiovascular events after acute myocardial infarction: an observational study in patients with type 2 diabetes



LP-1RA

Marfella *et al. Cardiovascular Diabetology* (2024) 23:10



HFpEF and HFmEF
(FINEARTS-HF)

Recommendations for additional glucose-lowering ag
type 2 diabetes if additional glucose control is neede

GLP-1 RAs (lixisenatide, liraglutide, semaglutide, exenatide EF
hospitalization, and should be considered for glucose-lowerin

HFpEF
(SELECT, SUMMIT Trial)

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

Recommendatio

A SGLT2 inhibitor
dapagliflozin)[d] is re
T2DM and CKD wi
to reduce the risk
failure.[150,153,542,543,

Finerenone is recon
or ARB in patients
min/1.73 m^2 with a
g), or eGFR 25–60
≥3 mg/mmol (≥30
kidney failure.[718–72

A GLP-1 RA is reco
1.73 m^2 to achieve
to low risk of hypog
weight, CV risk, anc

All-cause mortality, hospital admission for heart failure, and kidney outcomes

Trial	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0.94 (0.78, 1.13)		0.50
LEADER	381/4668 (8%)	447/4672 (10%)	0.85 (0.74, 0.97)		0.02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1.05 (0.74, 1.50)		0.79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0.86 (0.77, 0.97)		0.016*
Harmony Outcomes	196/4731 (4%)	205/4732 (4%)	0.95 (0.79, 1.16)		0.64
REWIND	536/4949 (11%)	592/4952 (12%)	0.90 (0.80, 1.01)		0.067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0.51 (0.31, 0.84)		0.008
AMPLITUDE-O	111/2717 (4%)	69/1359 (5%)	0.78 (0.58, 1.06)		0.11
Subtotal (I-squared = 10.1%, p = 0.351)			0.88 (0.82, 0.94)	114 (76 to 228)	<0.001
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0.96 (0.75, 1.23)		0.75
LEADER	218/4668 (5%)	248/4672 (5%)	0.87 (0.73, 1.05)		0.14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1.11 (0.77, 1.61)		0.57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0.94 (0.78, 1.13)		0.485
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0.71 (0.53, 0.94)		0.019
REWIND	213/4949 (4%)	226/4952 (5%)	0.93 (0.77, 1.12)		0.46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0.86 (0.48, 1.55)		0.59
AMPLITUDE-O	40/2717 (1%)	31/1359 (2%)	0.61 (0.38, 0.98)		0.04
Subtotal (I-squared = 3.0%, p = 0.407)			0.89 (0.82, 0.98)	258 (158 to 1422)	0.013
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0.84 (0.68, 1.02)		0.083
LEADER	268/4668 (6%)	337/4672 (7%)	0.78 (0.67, 0.92)		0.003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0.64 (0.46, 0.88)		0.005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0.88 (0.76, 1.01)		0.065
REWIND	848/4949 (17%)	970/4952 (20%)	0.85 (0.77, 0.93)		0.0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0.68 (0.57, 0.79)		<0.0001
Subtotal (I-squared = 47.5%, p = 0.090)			0.79 (0.73, 0.87)	47 (37 to 77)	<0.001
[illegible]					
ELIXA	41/3031 (1%)	35/3032 (1%)	1.16 (0.74, 1.83)		0.513
LEADER	87/4668 (2%)	97/4672 (2%)	0.89 (0.67, 1.19)		0.43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1.28 (0.64, 2.58)		0.48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0.88 (0.74, 1.05)		0.164
REWIND	169/4949 (3%)	237/4952 (5%)	0.70 (0.57, 0.85)		0.0004
AMPLITUDE-O	7/2717 (0%)	7/1359 (1%)	0.35 (0.10, 1.27)		0.11
Subtotal (I-squared = 43.0%, p = 0.119)			0.86 (0.72, 1.02)	241 (120 to -1694)†	0.089

NOTE: Weights are from random effects analysis

.5 1 1.5

Favours GLP-1RA Favours placebo

Lancet Diabetes and Endocrinology, 9(10), pp. 653-662. (doi: 10.1016/S2213-8587(21)00203-5)

sease?

ellitus

ascular
e risk

herenone
(Class I)

Canagliflozin

sc

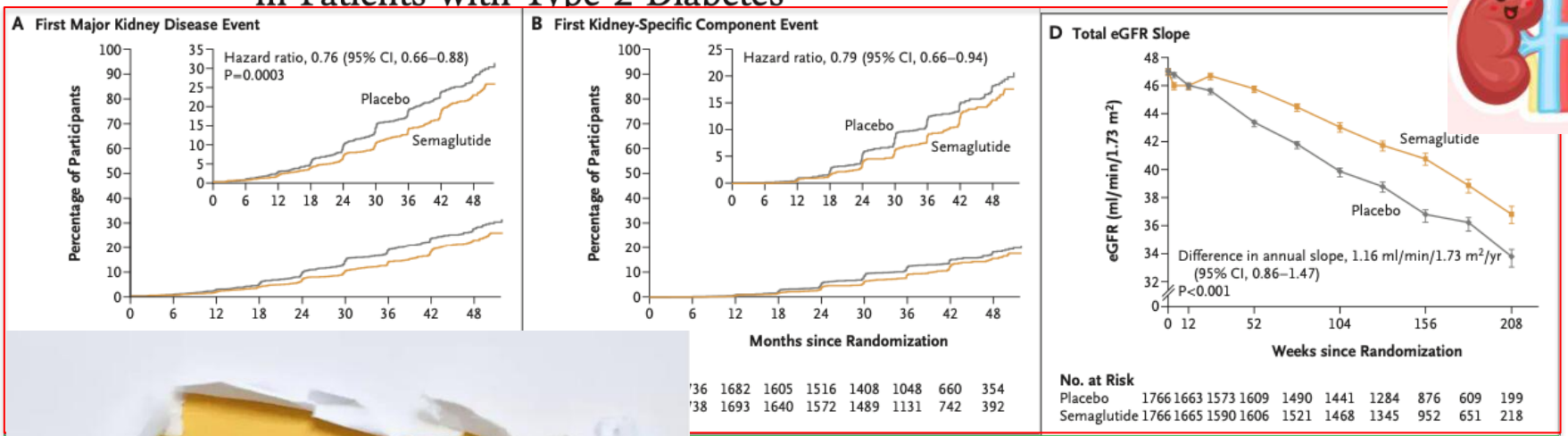
The NEW ENGLAND JOURNAL of MEDICINE

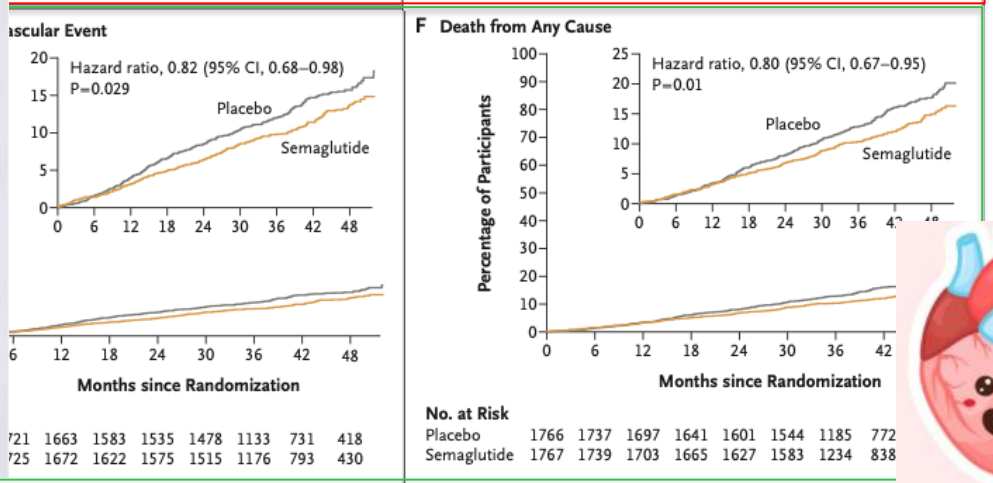
ESTABLISHED IN 1812 JULY 11, 2024 VOL. 391 NO. 2

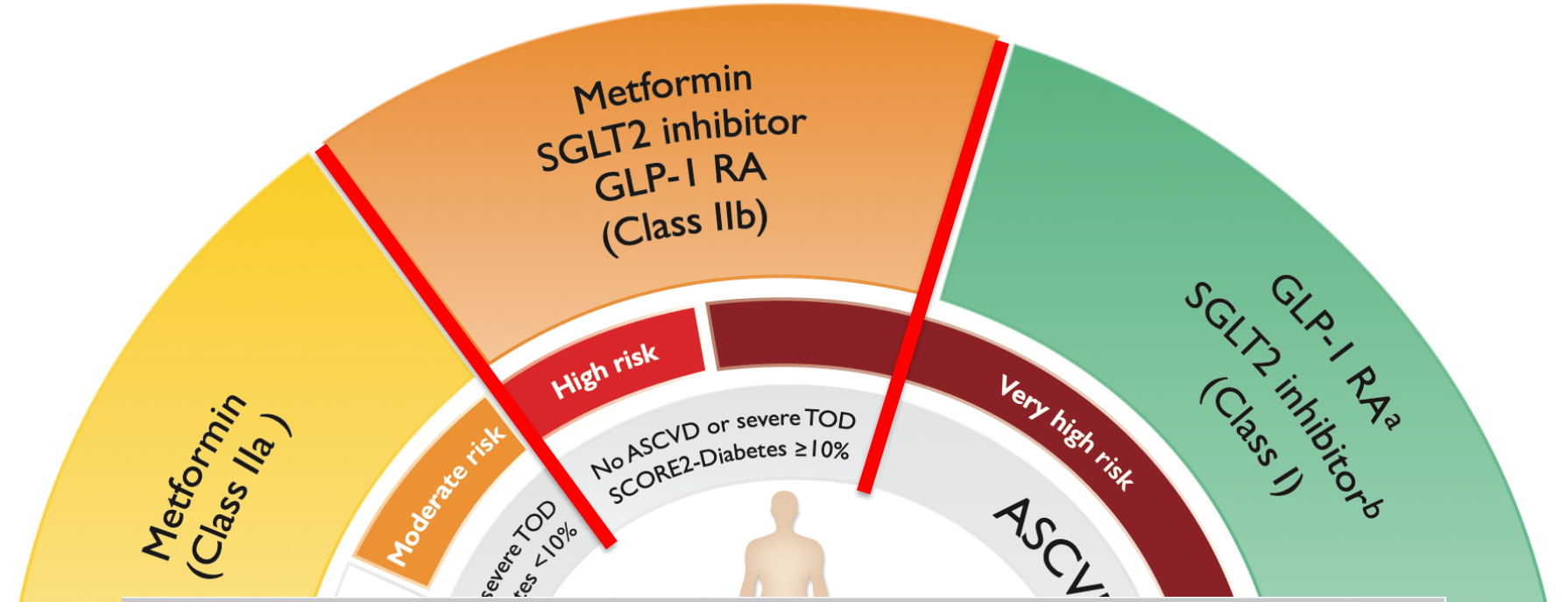
GFR: 25-50, ACR: 100-5000

GFR: 50-75 e ACR: 300-5000

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes







Atherosclerotic cardiovascular disease risk reduction by glucose-lowering medications in diabetes—*Section 5.3*					
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk to reduce CV events.	I	A	SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
			In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk ≥10%, treatment with an SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.	IIb	C
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk to reduce CV events.	I	A	GLP-1 RAs with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
			In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk ≥10%, treatment with an SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.	IIb	C

An Observational Study of Cardiovascular Outcomes of Tirzepatide vs Glucagon-Like Peptide-1 Receptor Agonists

Recommendation Table 3 — Recommendations for reducing weight in patients with type 2 diabetes with

5.1.1. Weight reduction

In patients with obesity and T2DM, reducing weight is one of the cornerstones of treatment.[63] Weight loss of >5% improves glycaemic control, lipid levels, and BP in overweight and obese adults with T2DM.[64,65] These effects can be achieved by improving energy balance and/or introducing obesity medications. Orlistat, naltrexone/bupropion, and phentermine/topiramate are each associated with achieving >5% weight loss at 52 weeks compared with placebo.[66] However, glucose-lowering agents such as GLP-1 RAs, the dual agonist tirzepatide, and SGLT2 inhibitors also significantly reduce body weight.[67,68] Adding exercise to a GLP-1 RA (liraglutide) had a greater effect on weight reduction and maintenance.[69] Comparing the effects on weight reduction between GLP-1 RAs and SGLT2 inhibitors, the former seems to be superior. Given the additional beneficial effects of GLP-1 RAs and SGLT2 inhibitors on CV outcomes in T2DM (*Section 5.3*), these agents should be the preferred glucose-lowering medication in overweight and obese patients with CVD and T2DM, as obesity medications have, to date, not shown to reduce CV events.[70–72]

Associazione Medici Endocrinologi
Per la qualità clinica in Endocrinologia

LINEA GUIDA PER LA TERAPIA DEL SOVRAPPESO E DELL'OBESITÀ RESISTENTI AL TRATTAMENTO COMPORTAMENTALE NELLA POPOLAZIONE ADULTA CON COMORBILITÀ METABOLICHE

ISTITUTO SUPERIORE DI SANITÀ 2023

Associazione Italiana di Dietetica e Nutrizione Clinica (ADI)

Società Italiana dell'Obesità (SIO)

Società Italiana di Chirurgia dell'Obesità e delle malattie metaboliche (SICOB)

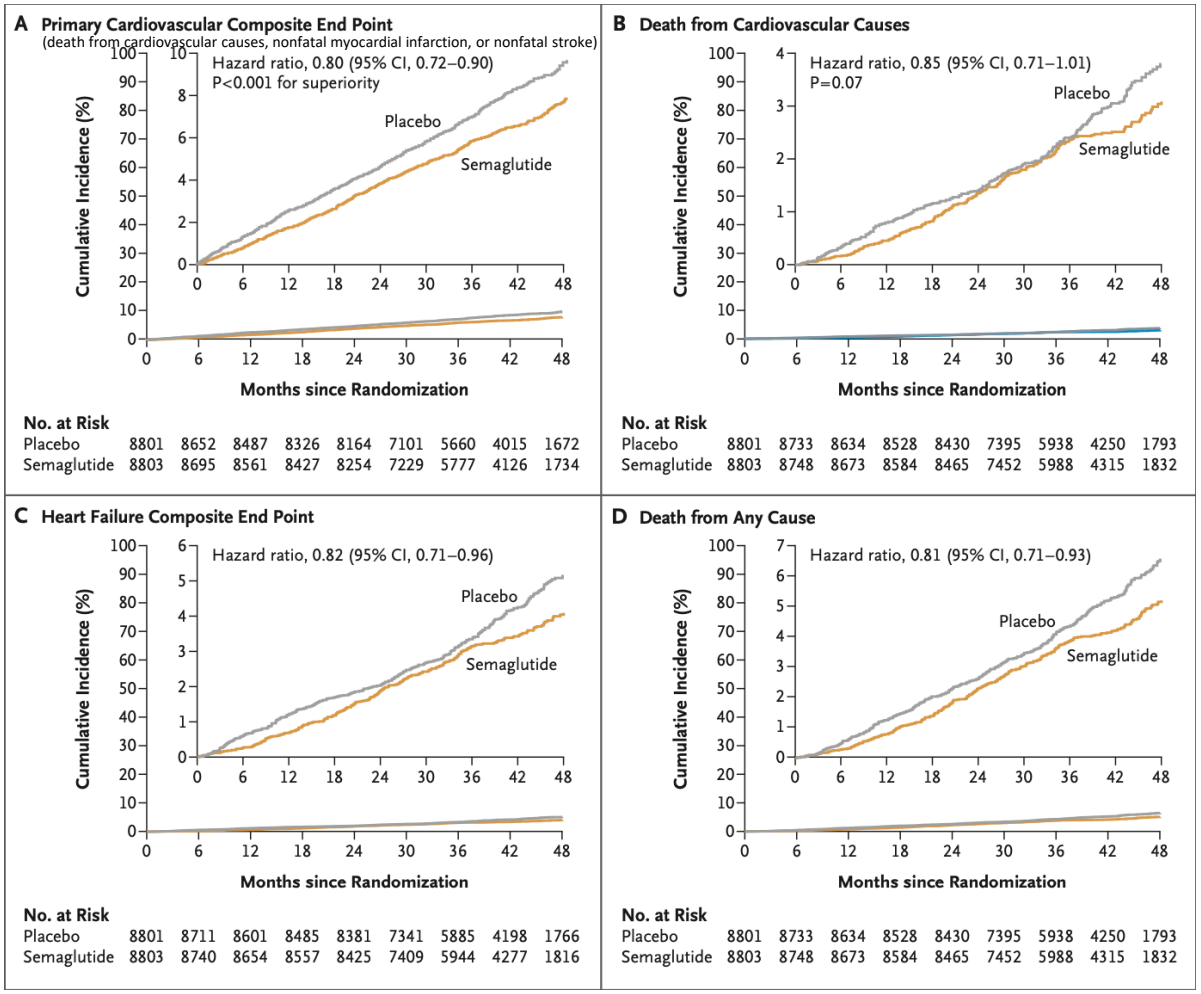
Società Italiana Gastroenterologia ed Endoscopia Digestiva (SIGE)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

SELECT Trial

17.604 pz
BMI ≥ 27
IMA, PAD o stroke pregresso
No DM

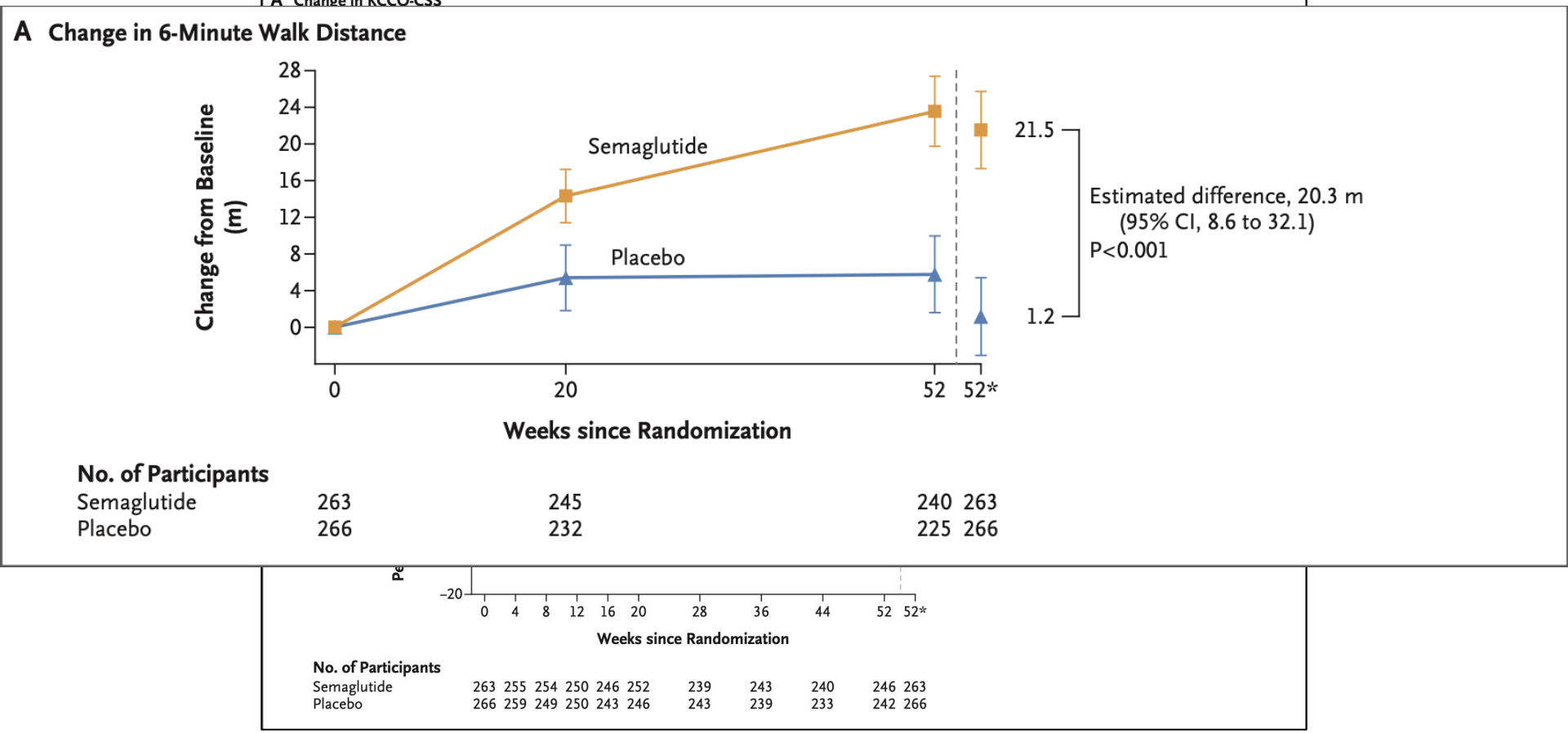


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

529 pz
HFpEF
BMI ≥ 30
No DM



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2025;392:427-437

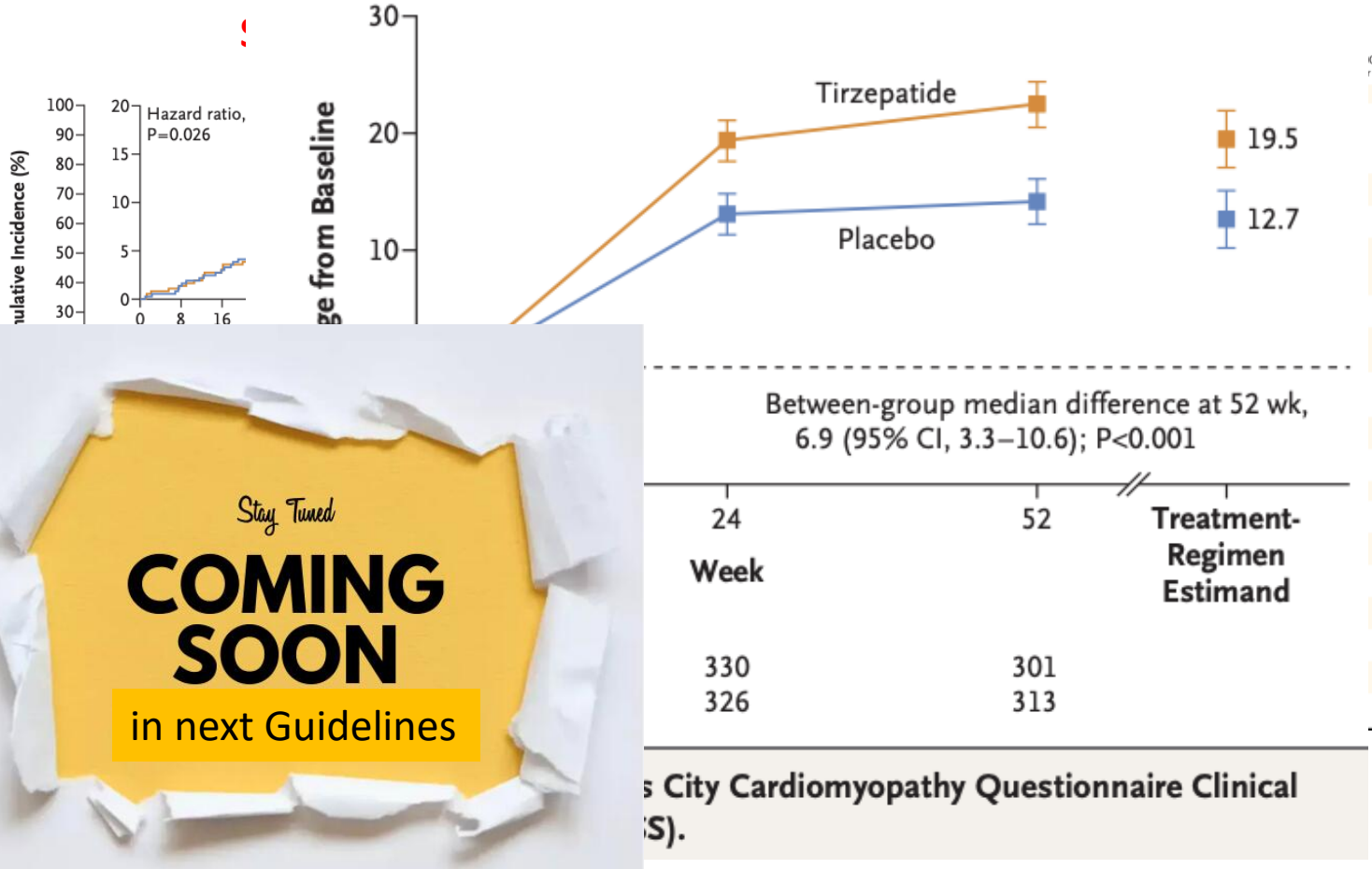
ORIGINAL ARTICLE

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

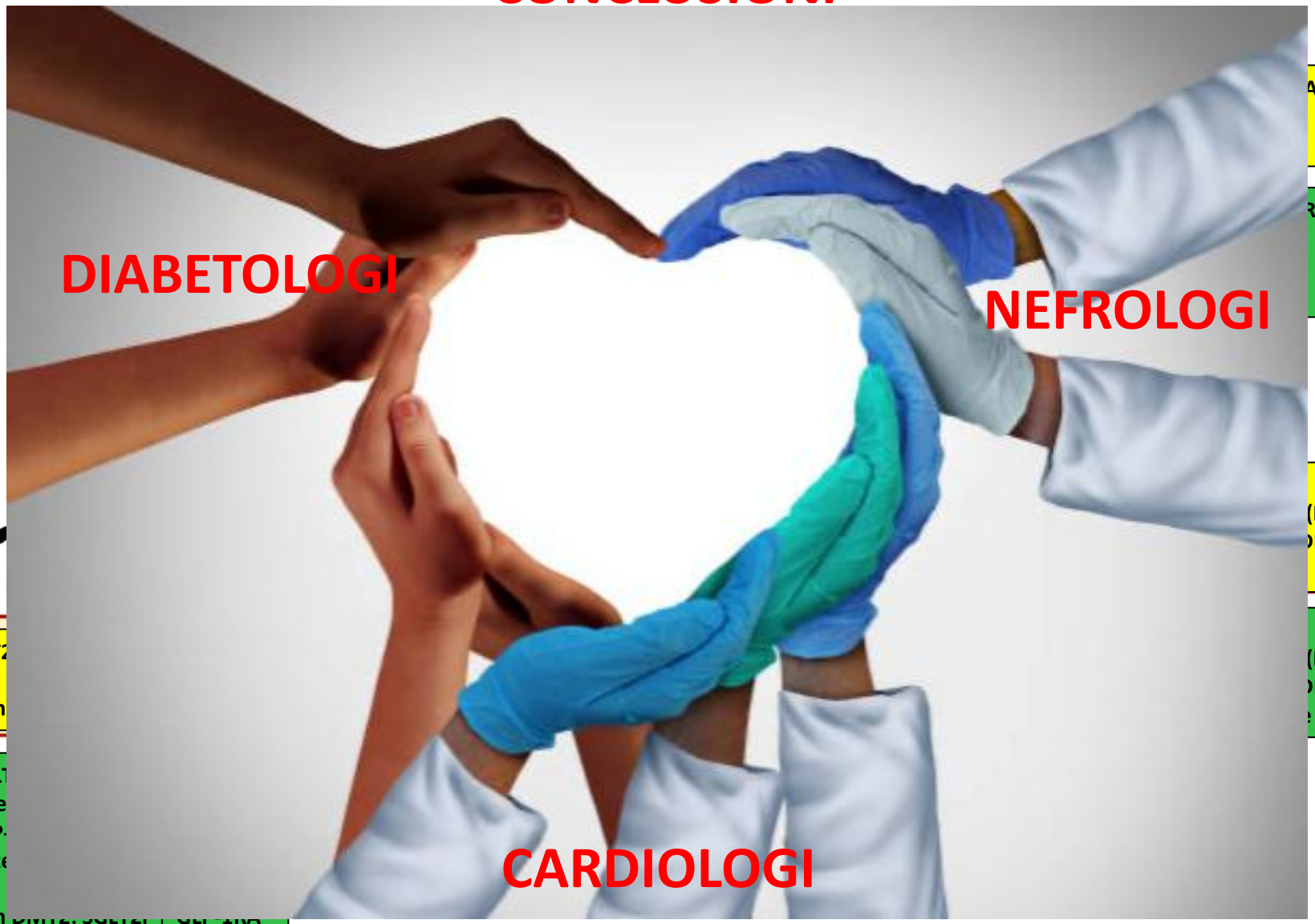
731 pz

BMI ≥ 30

DMT2 48%, CAD 30%



CONCLUSIONI



GRAZIE DELL'ATTENZIONE

jperversi@asl.at.it