Gli SGLT2 inibitori: effetto metabolico o cardio-nefrovascolare?

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** Chair of the AMD Annals Study Group*

con il patrocinio di:

Palermo, 15/16 novembre 2024

Hotel La Torre

Dichiarazione sul Conflitto di Interessi

La sottoscritta___**Giuseppina Russo**_____ in qualità di:

□ moderatore □ docente □**x** relatore □ tutor

dell'evento

ai sensi dell'Accordo Stato-Regione in materia di formazione continua nel settore "Salute" (Formazione ECM) vigente,

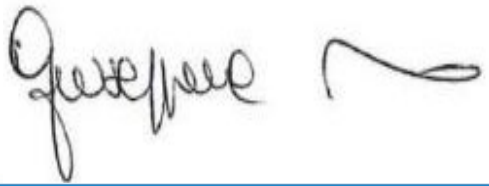
Dichiara

□ che negli ultimi due anni NON ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

X□ che negli ultimi due anni ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario (indicare quali):

Lecturer, Scientific consultant for:

Boehringer Ingelheim, Eli-Lilly, Novo-Nordisk, Astra Zeneca, Sanofi



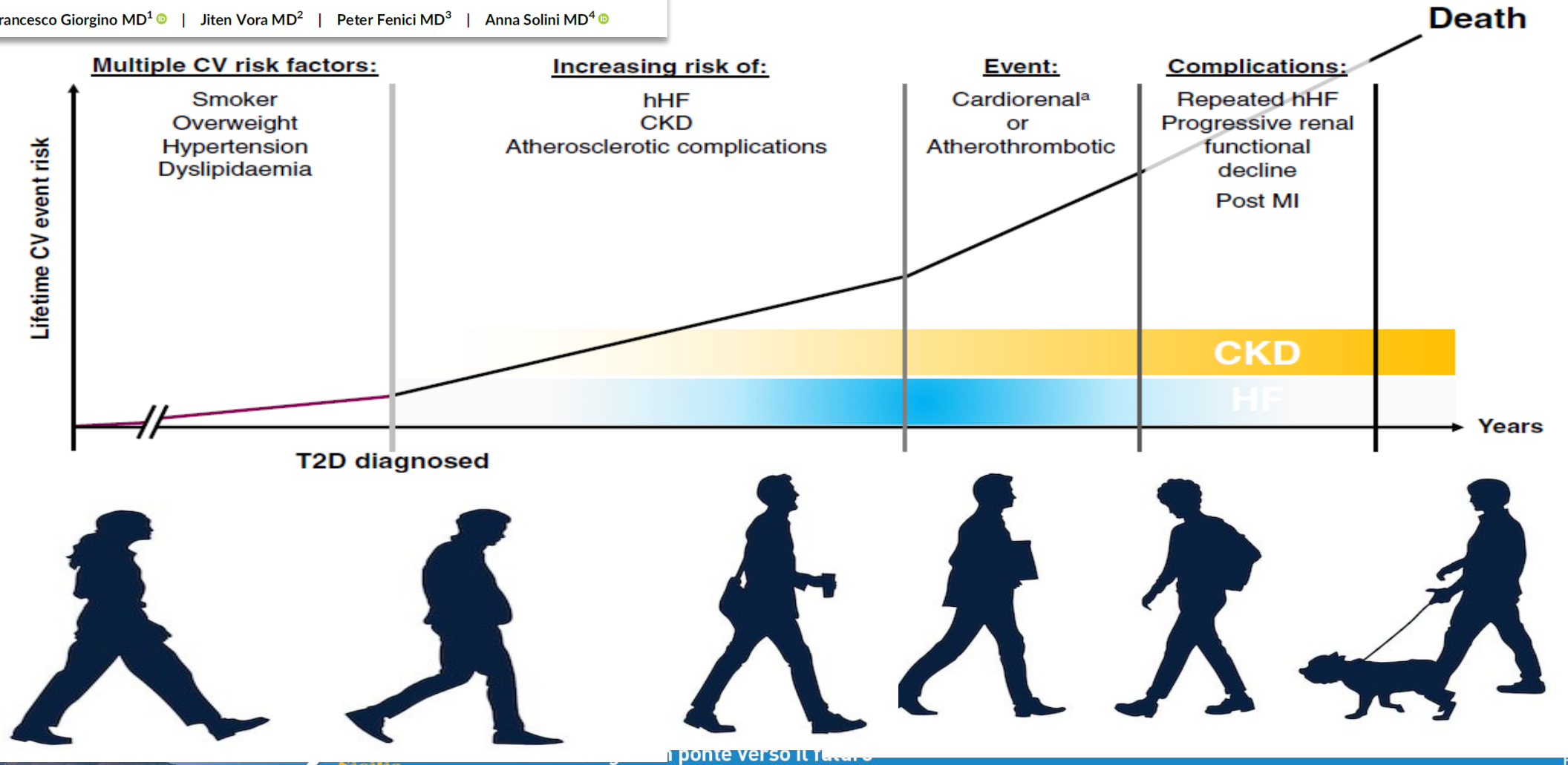
Received: 2 December 2019 | Revised: 4 April 2020 | Accepted: 5 April 2020
DOI: 10.1111/dom.14055

REVIEW ARTICLE

WILEY

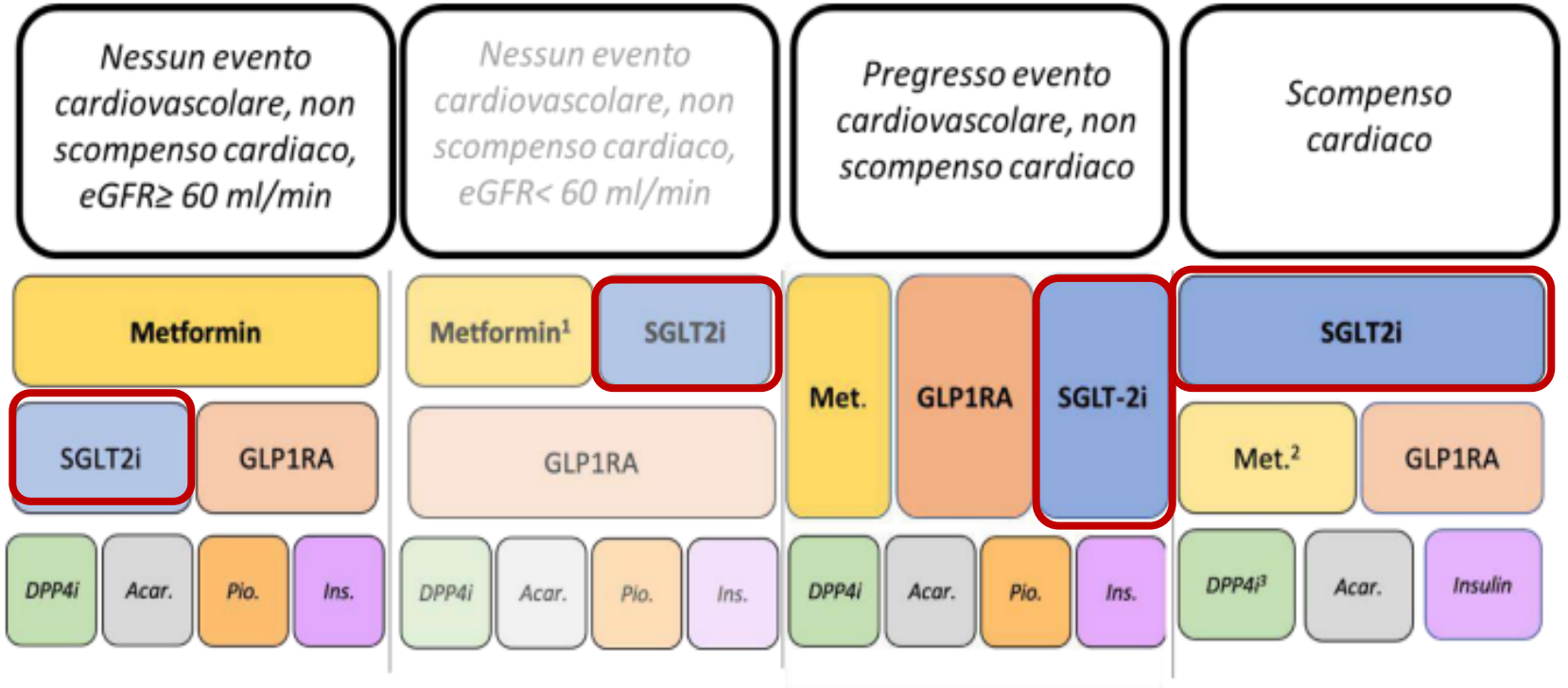
Cardiovascular protection with sodium-glucose co-transporter-2 inhibitors in type 2 diabetes: Does it apply to all patients?

Francesco Giorgino MD[1] | Jiten Vora MD[2] | Peter Fenici MD[3] | Anna Solini MD[4]

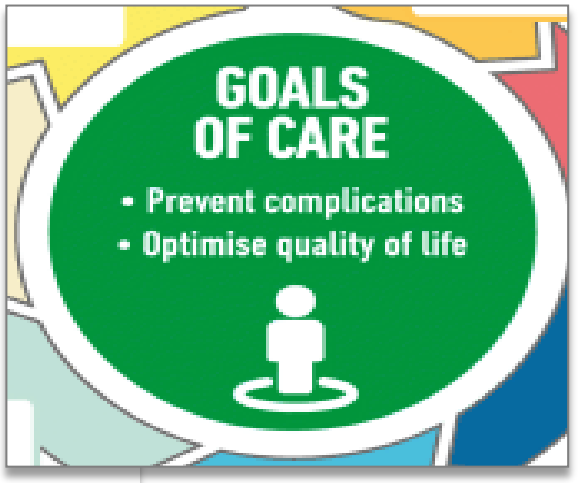


Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)
Obiettivi terapeutici

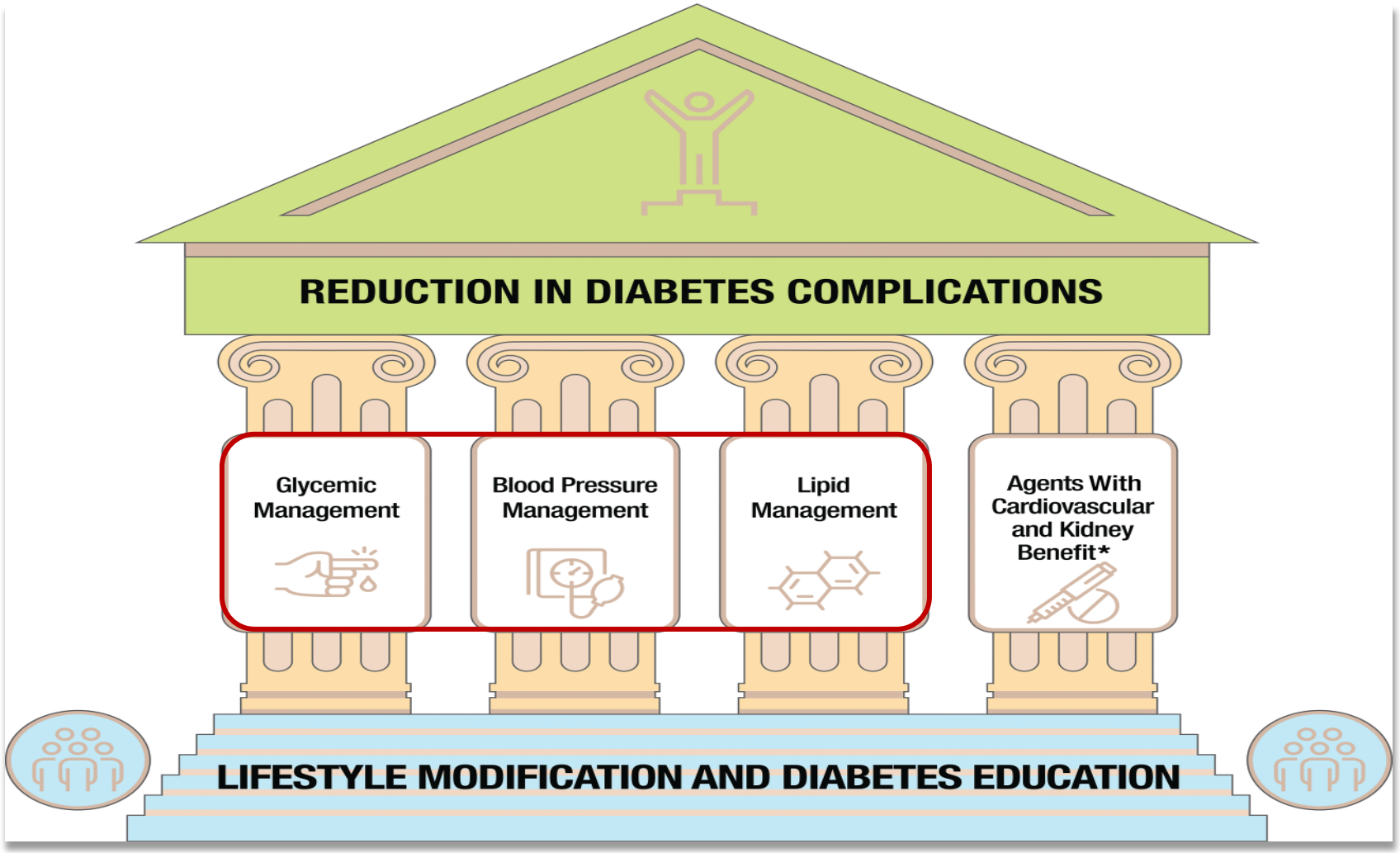
5. Terapia farmacologica



[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



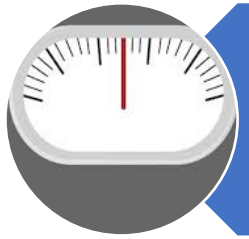
Le associazioni tra più farmaci devono essere prescritte secondo le indicazioni delle rispettive schede tecniche.



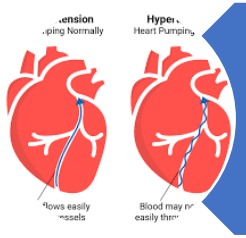
Glycemic goals and hypoglycemia: ADA standards of medical care in diabetes 2024 – Diabetes Care 2024

Hence what do we need in "*early*" T2D Management?

Glycemic Control



Weight & CVD RFs Management

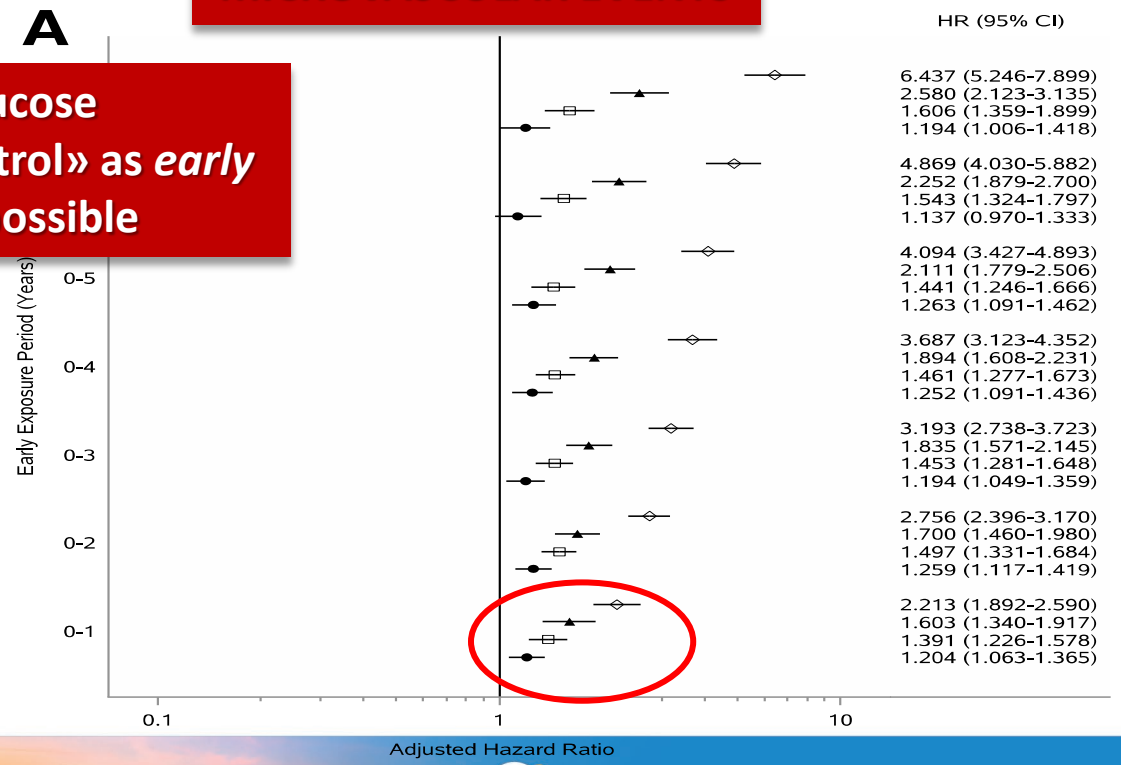


Managing Comorbidities

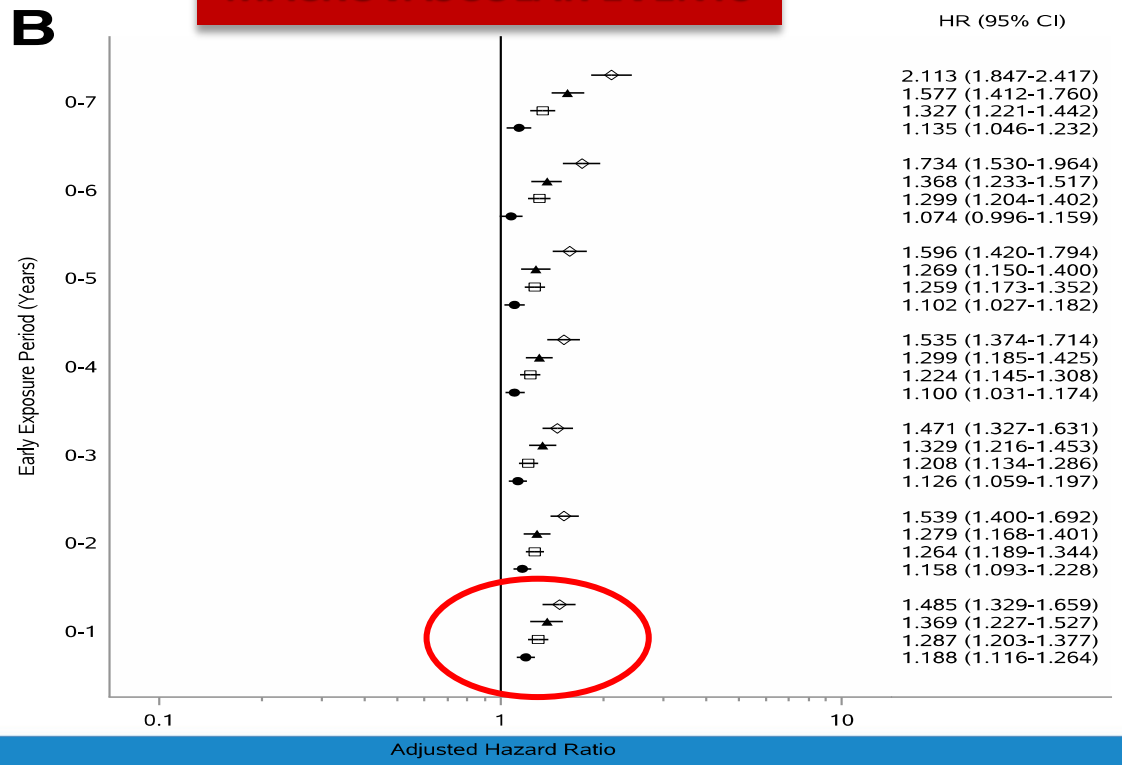
Safety including low hypoglycemic risk

MICROVASCULAR EVENTS

«glucose control» as *early* as possible



MACROVASCULAR EVENTS

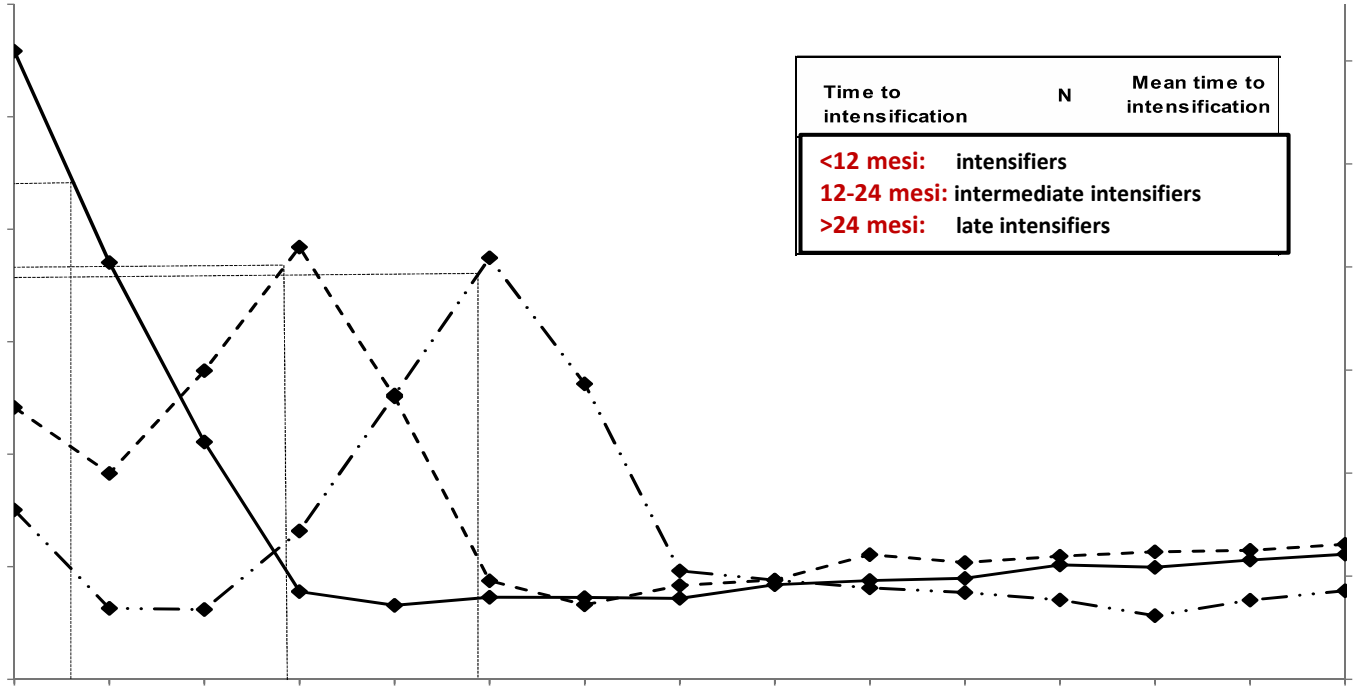


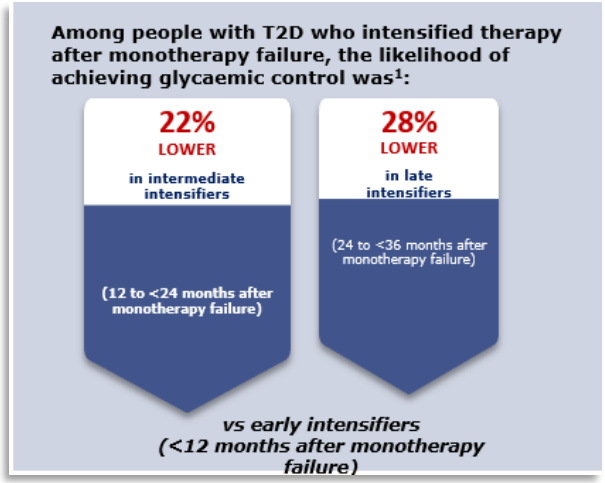
Time to Treatment Intensification After Monotherapy Failure and Its Association With Subsequent Glycemic Control Among 93,515 Patients With Type 2 Diabetes

Diabetes Care 2018;41:2096–2104 | https://doi.org/10.2337/dc17-0662

Delayed glucose control is associated with failure to achieve it subsequently

«glucose control» as *early* as possible

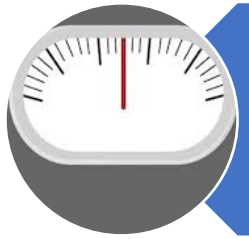




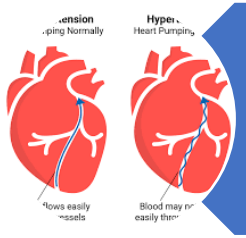
Hence what do we need in "*early*" T2D Management?

Effects of SGLT2-i on

Glycemic Control



Weight Management



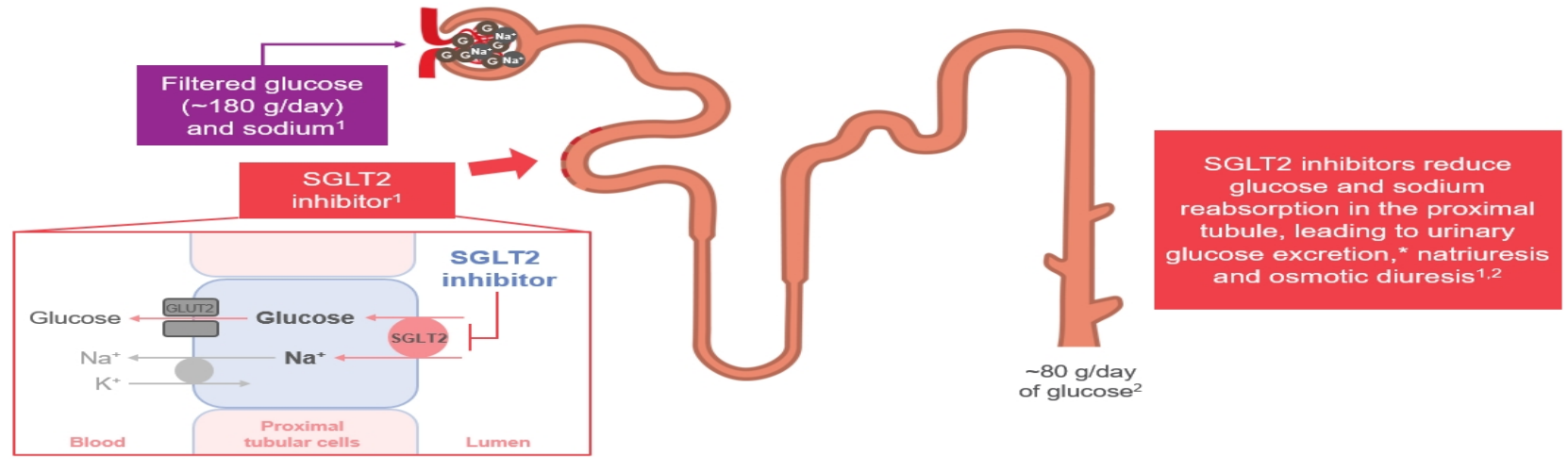
Managing Comorbidities

Safety including low hypoglycemic risk

Effects of SGLT2 inhibitors on major cardiorenal risk factors

SGLT2 inhibitor with background metformin	Empagliflozin 10 mg[1]	Canagliflozin 100 mg[2]	Dapagliflozin 10 mg[3]
HbA1c, %	-0.70*	-0.73†	-0.84‡

SGLT2 inhibitors enhance the excretion of glucose, sodium and water into the urine



*Loss of ~80 g/day of glucose = 240 cal/day
GLUT2; glucose transporter 2; SGLT2, sodium-glucose co-transporter-2
1. Bakris GL *et al. Kidney Int* 2009;75:1272; 2. Boehringer Ingelheim Pharmaceuticals, Inc. Jardiance® (empagliflozin) summary of product characteristics. May 2020

5

Pay attenion to:

Glucose-lowering effects

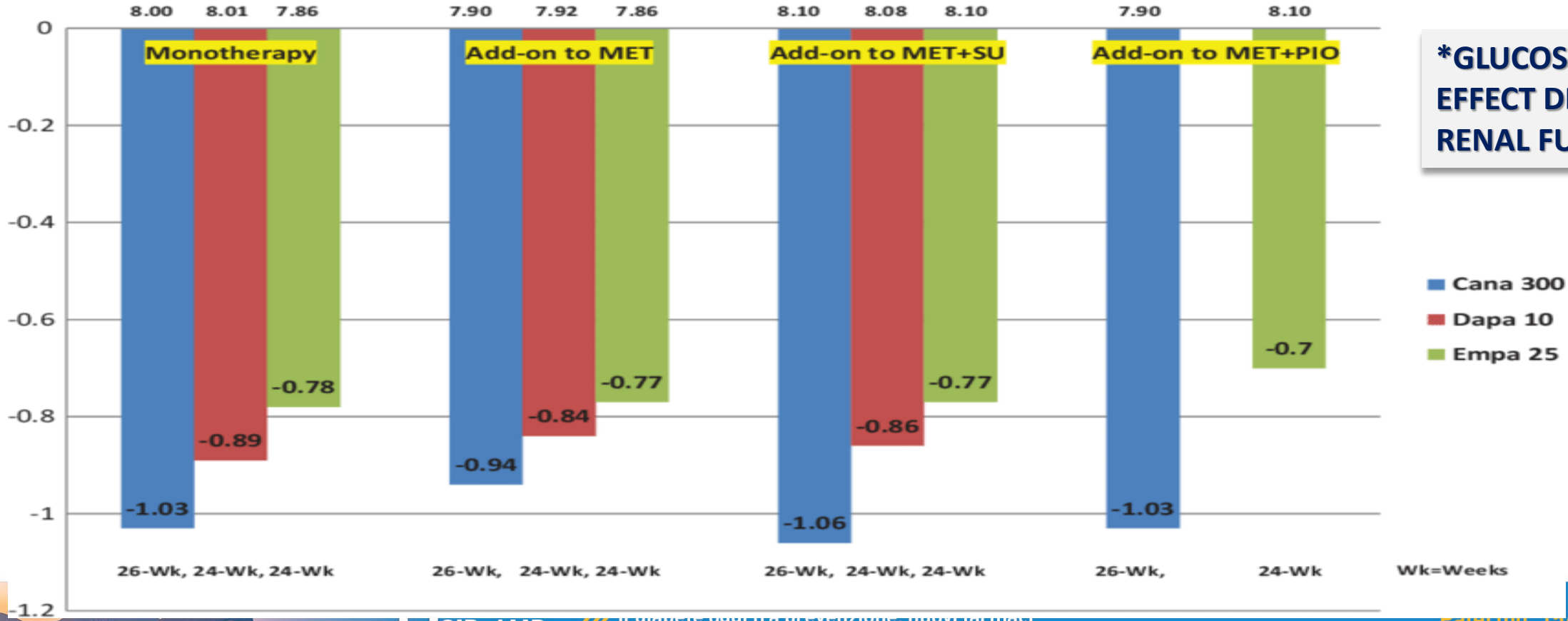
depends on renal function,

dose and selectivity;

SGLT2i HbA1c lowering effect

Molecola	Formulazione	Indicazioni		
		DM2	SC	MRC
Dapagliflozin	cp 5-10 mg	*	*	*
Canagliflozin	cp 100-300 mg	*		
Empagliflozin	cp 10-25 mg	*	*	*
Ertugliflozin	cp 5-15 mg	*		

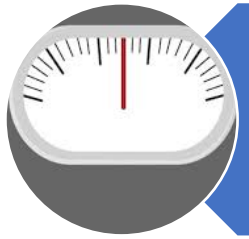
HbA1c



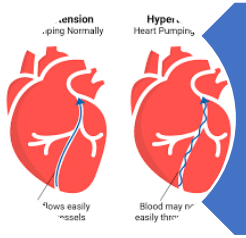
***GLUCOSE LOWERING EFFECT DEPENDS ON RENAL FUNCTION**

Hence what do we need in "*early*" T2D Management?

Glycemic Control



Weight & CVD RFs Management



Managing Comorbidities

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HbA1c, %	-0.70*	-0.73†	-0.84‡
Weight, kg	-2.08*	-3.3†	-2.9‡
Systolic blood pressure, mmHg	-4.5*	-3.5†	-5.1§
Diastolic blood pressure, mmHg	-2.0*	-1.8†	-1.8§

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

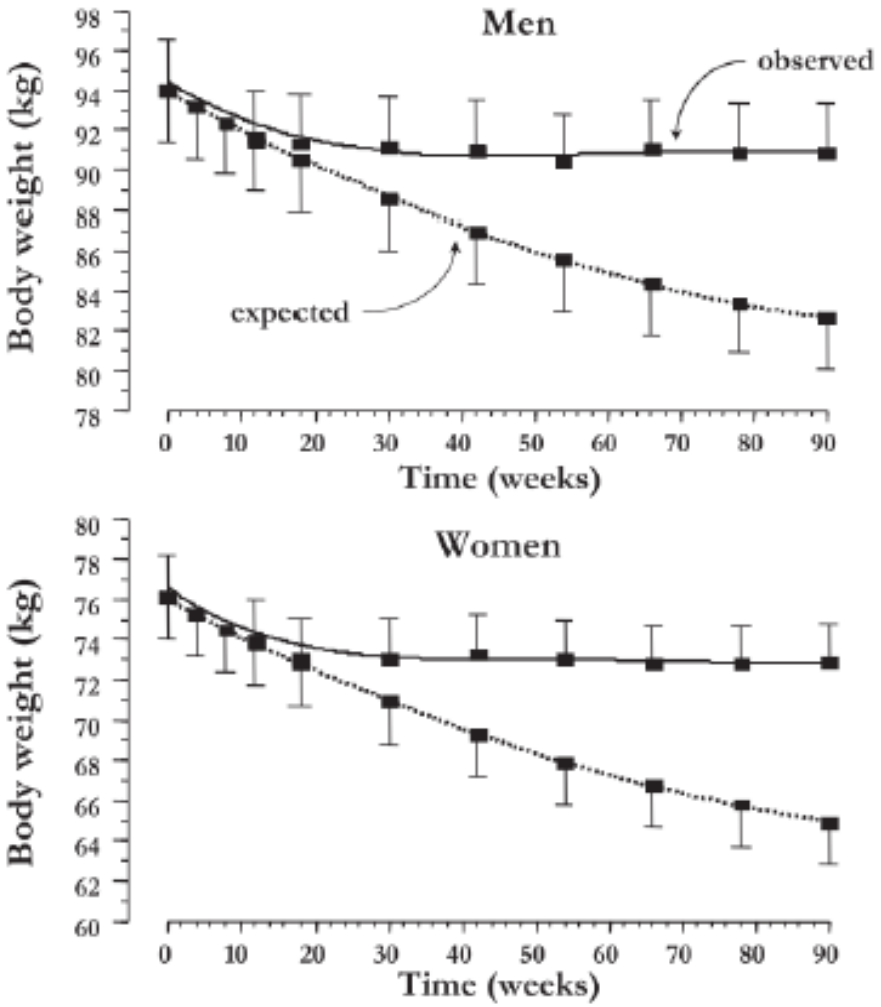
*Adjusted mean change from baseline at Week 24; †Least squares mean change from baseline at Week 52; ‡Adjusted mean change from baseline at Week 24; §Mean change from baseline at Week 24

1. Häring H-U *et al. Diabetes Care* 2014;37:1650; 2. Lavelle-Gonzalez FJ *et al. Diabetologia* 2013;56:2582; 3. Bailey CJ *et al. Lancet* 2010;375:2223

Pay attenion to:

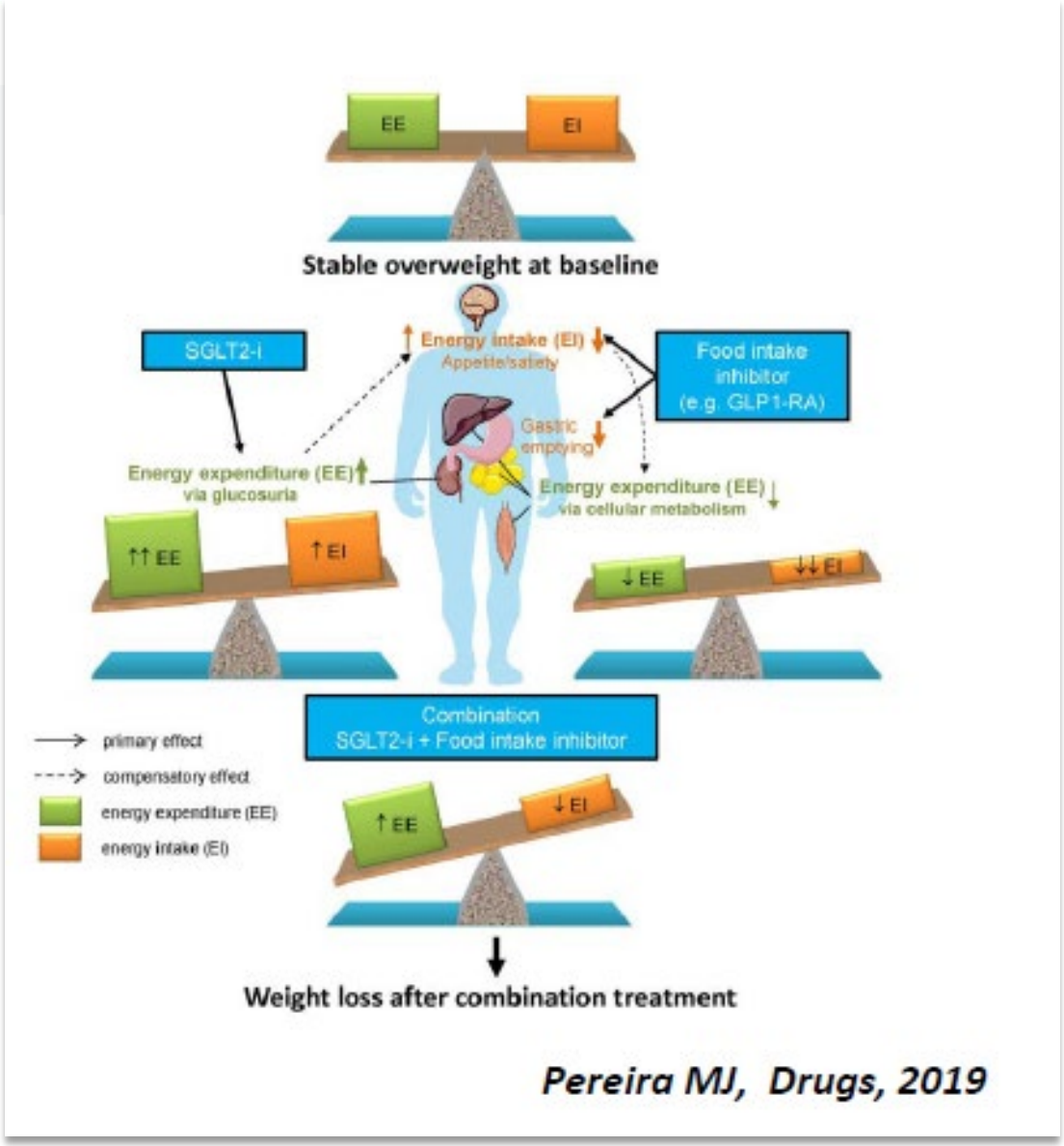
- Glucose-lowering effects depends on renal function, dose and selectivity;
- **Effects on body weight are self-limiting, dose dipendent and irrespective of co-morbidities;**
- **Potent effects on BP and uric acid lowering**

Time course of observed and predicted (by glycosuria) weight loss in men and women with T2DM treated with empagliflozin (25 mg/day) for 90 weeks



Ferrannini G et al, Diabetes Care, 2015

Chronic glycosuria elicits an adaptive increase in energy intake



Pereira MJ, Drugs, 2019

Bhandari M *et al*. SGLT-2 inhibitors across the HF spectrum

Effects of SGLT2-i on major cardiorenal risk factors

Diuresis

There is osmotic diuresis and natriuresis due to glycosuria.
Preferential reduction of interstitial fluid rather than plasma volume.

Cardiac metabolism

There is a shift to more efficient substrate for O_2 production like ketone bodies.
Reduced metabolic stress by autophagy.

Weight loss

There is increase in Glucagon/insulin ratio.
Reduces serum leptin and increases adiponectin.

Blood pressure reduction

There is improvement in endothelial function.
Decrease in arterial stiffness and sympathetic system activation.

Hematological

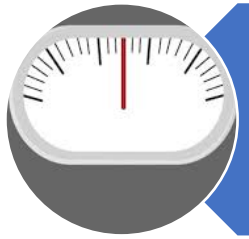
There is an increase in RBC and hematocrit via EPO production.

Figure 1 Mechanism of action of sodium glucose cotransporter-2 inhibitors in heart failure. EPO: Erythropoietin; O_2: Oxygen; RBC: Red blood cell.

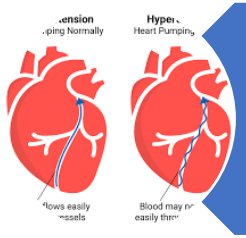
↓ Hyper-glycaemia	↓ Visceral adiposity	↓ Serum uric acid	↓ Oxidative stress	↓ Inflam-mation	↑ Adipo-nectin

Hence what do we need in "*early* " T2D Management?

Glycemic Control



Weight & CVD RFs Management



Managing Comorbidities

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Received: 2 December 2019 | Revised: 4 April 2020 | Accepted: 5 April 2020
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REVIEW ARTICLE

WILEY

Cardiovascular protection with sodium-glucose co-transporter-2 inhibitors in type 2 diabetes: Does it apply to all patients?

Beneficio cardio-renale

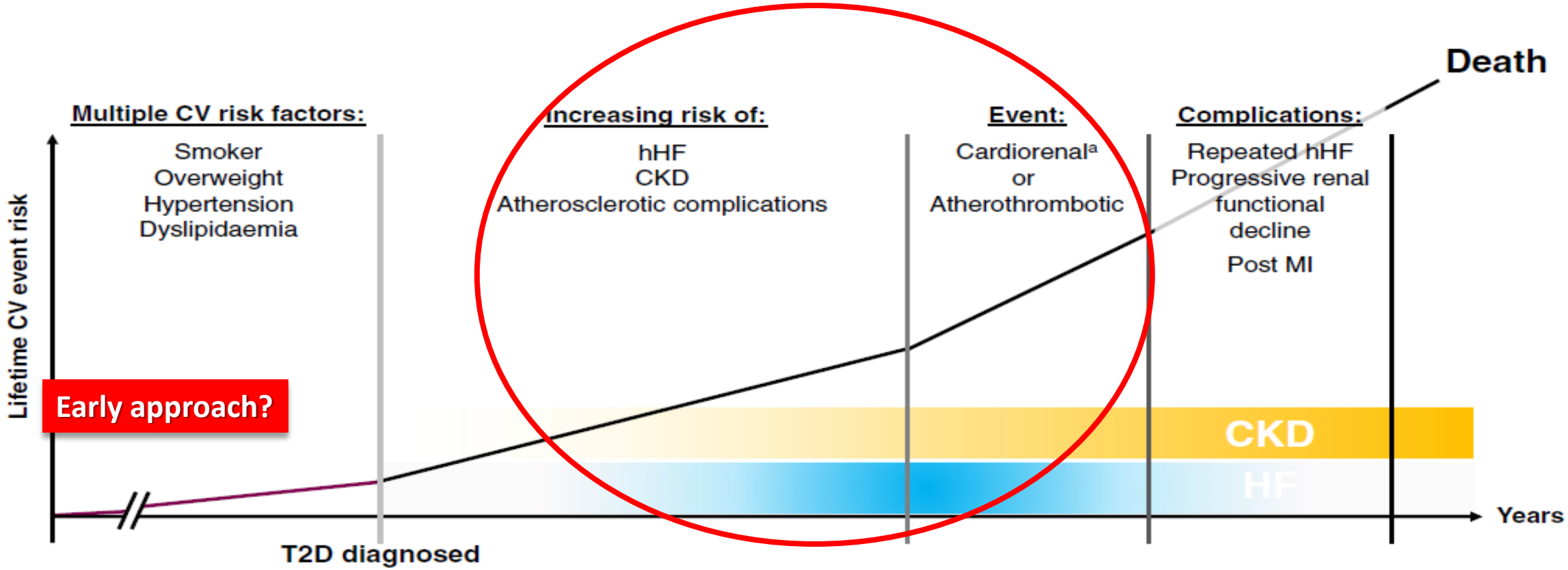


FIGURE 1 The cardiovascular (CV) risk continuum in patients with type 2 diabetes (T2D).[5] The slope of the CV risk is illustrative. CKD, chronic kidney disease; hHF, hospitalization for heart failure; MI, myocardial infarction. [a]hHF and/or CKD progression

Cardiorenal Disease is the Most Frequent *First* Comorbidity in T2D

Retrospective analysis of data from >1.1 million patients with T2D

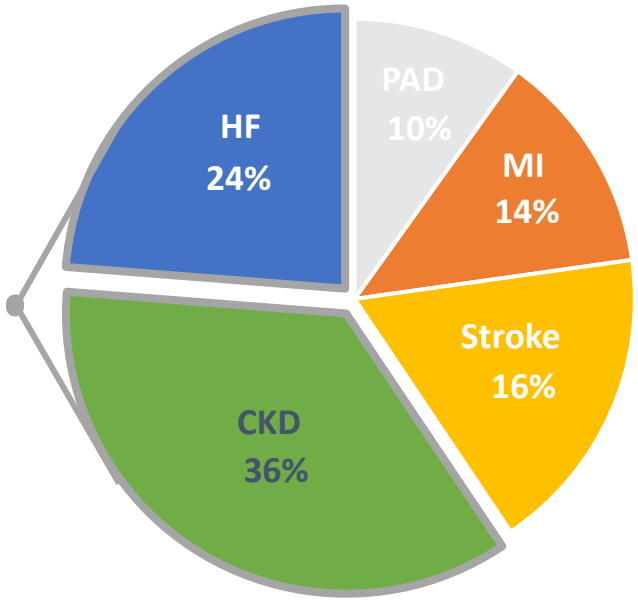
Initially, the majority (66%) of patients were CVRD-free

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

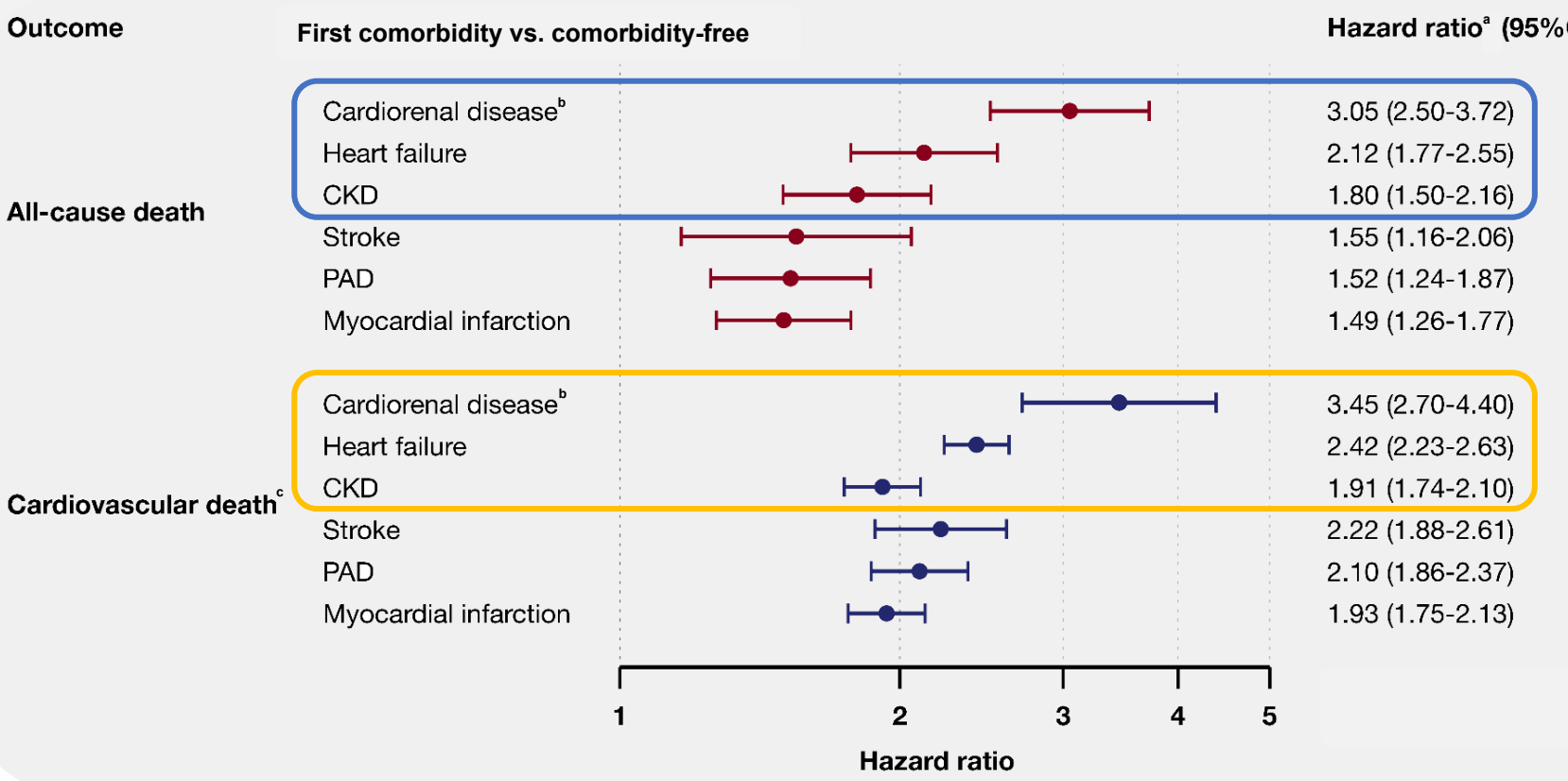
T2D and cardiorenal disease are interlinked

CKD = chronic kidney disease; CV = cardiovascular; CVRD = cardiovascular or renal disease; HF = heart failure; MI = myocardial infarction; PAD = peripheral artery disease; T2D = type 2 diabetes.

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

Cardiorenal disease (HF and/or CKD) was associated with highest mortality risks in T2D

Multinational observational cohort study including 645,180 comorbidity-free T2D patients
(mean follow-up of 4.3 years)



Bidirectional Risk Associations[d]

Compared with comorbidity-free T2D patients,

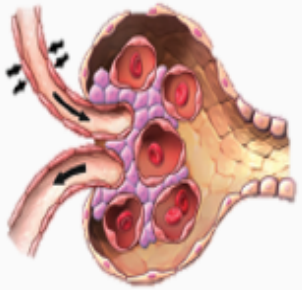
- **HF was associated with >2-fold increased risk of CKD;**
- **CKD was associated with >2-fold increased risk of HF.**

[a]Adjusted for age and sex; [b]Defined as presence of HF and/or CKD; [c]Data on [illegible] Norway and Sweden.
CKD = chronic kidney disease; HF = heart failure; PAD = peripheral artery disease; T2D = type 2 diabetes; [d]Detailed data not shown.
Birkeland KI et al. Poster presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA. Poster 206-LB.

Effects of SGLT2-i inhibitors on cardiorenal risk

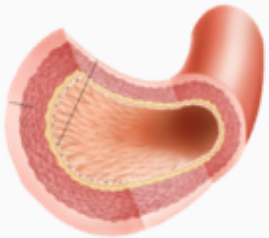
SGLT2i

KIDNEY



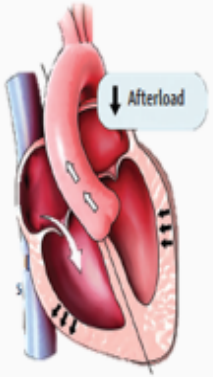
SGLT2i causes afferent arteriolar constriction, decreasing intraglomerular pressure

CIRCULATION



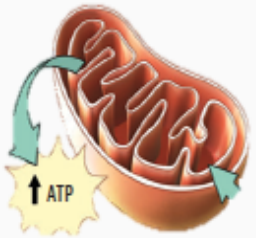
↓ Intravascular/ECF volume leads to ↑ haematocrit and ↓ systolic blood pressure

HEART



Reduction in preload, afterload and LV wall stress improve filling conditions

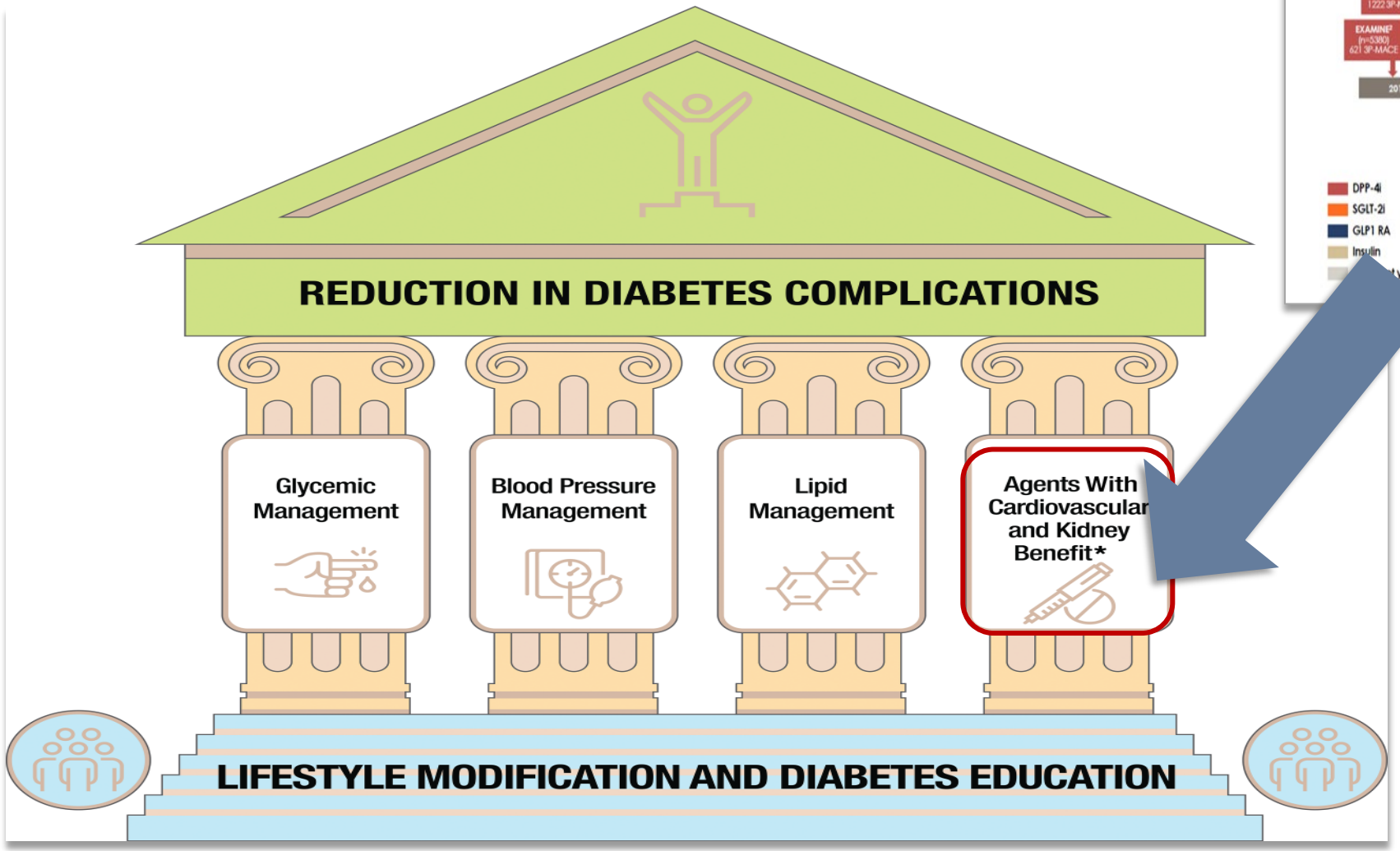
Improvements in myocardial contractility and efficiency

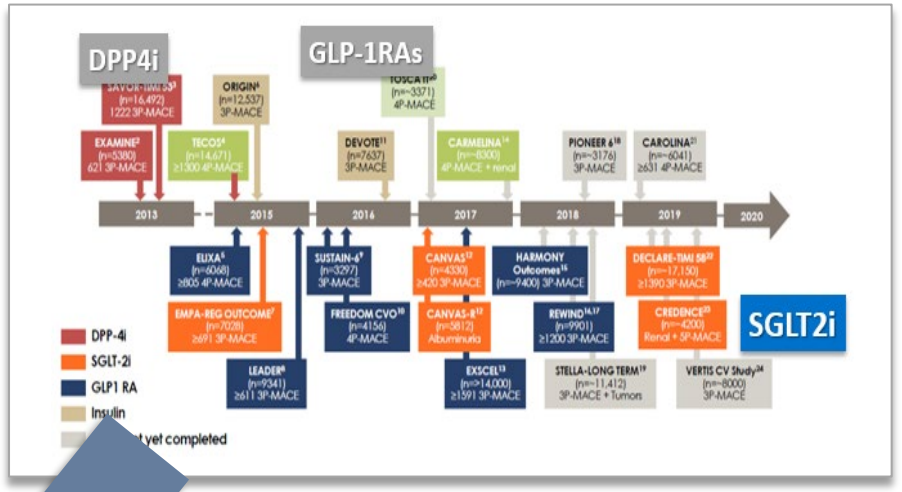


Improvement of myocardial energetics

Shifting fuel utilisation toward **ketone bodies**

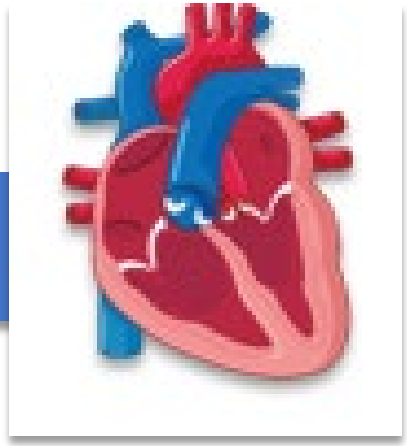
Improved renal function





Glycemic goals and hypoglycemia: ADA standards of medical care in diabetes 2024 - Diabetes Care 2024

SGLT2i-benefici CVD



CVOTs in the continuum of CVD risk in T2DM

add VERTIS
DAPA_CKD
EMPA_KIDNEY

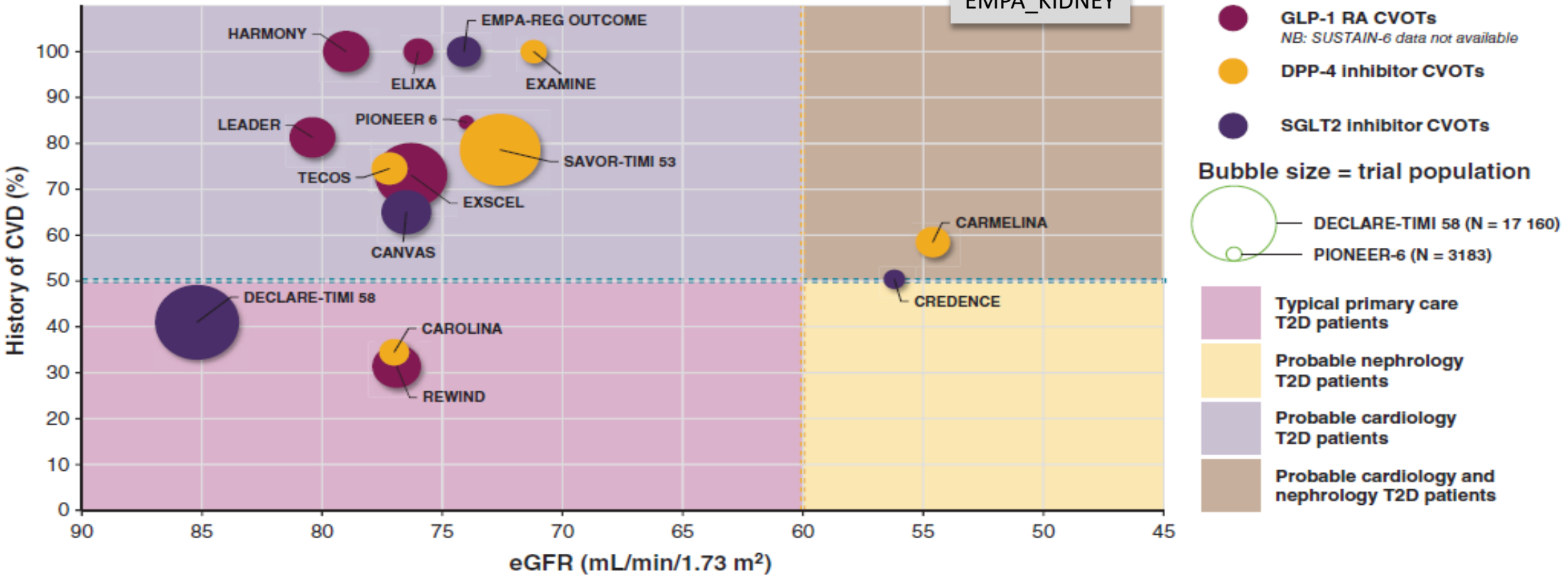
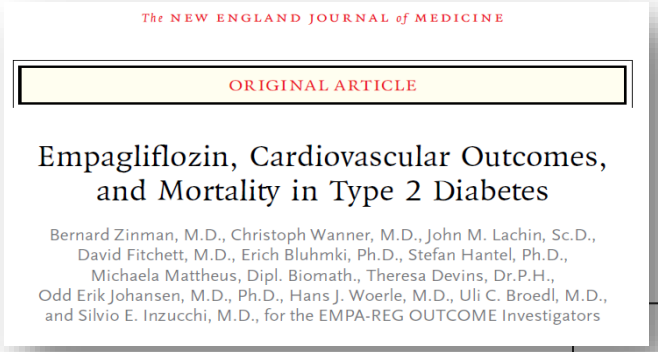
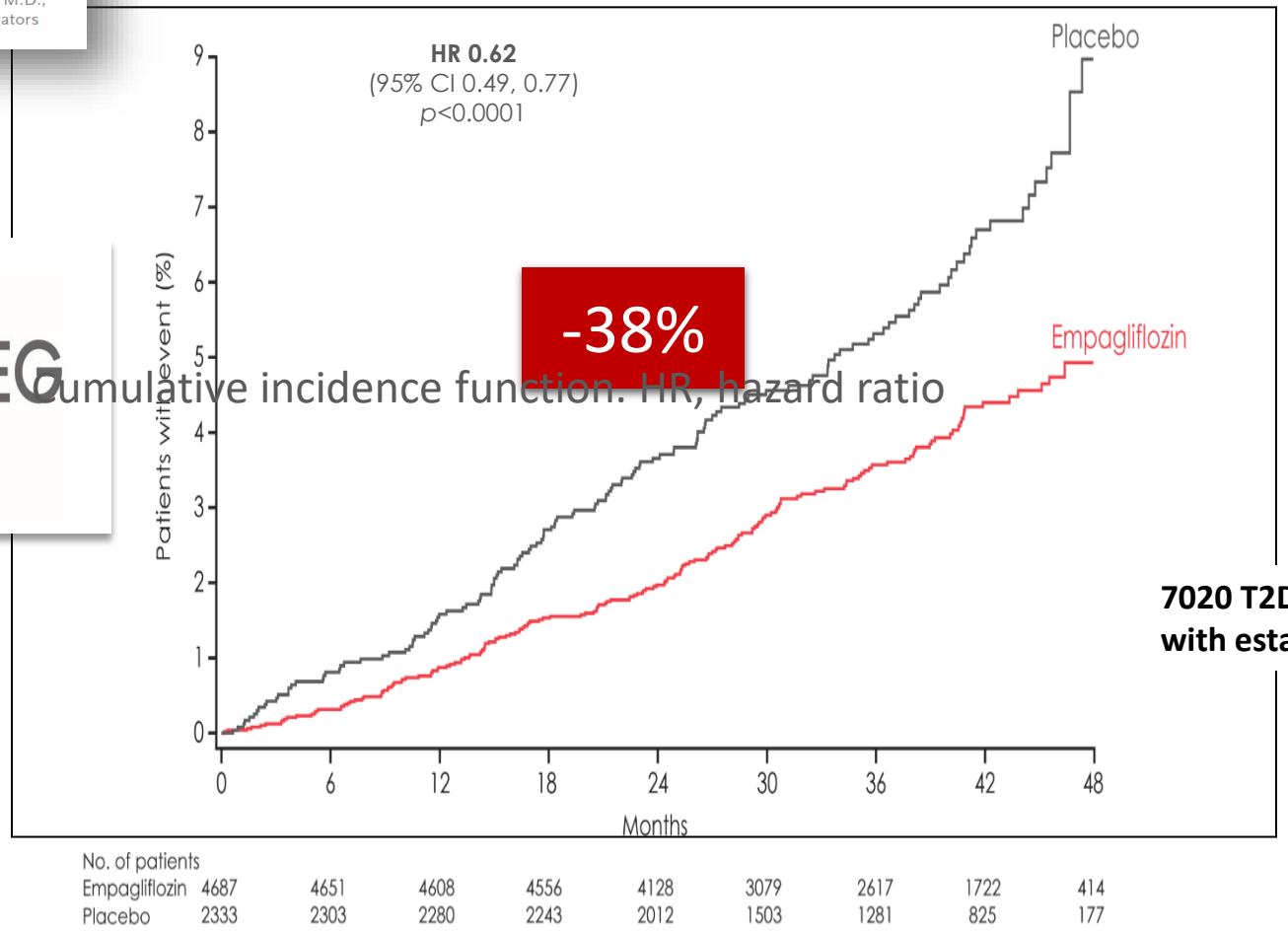


FIGURE 2 Patient populations in major cardiovascular outcomes trials (CVOTs) with sodium-glucose co-transporter-2 (SGLT2) inhibitors,[11,32,33,36] glucagon-like peptide-1 receptor agonists (GLP-1 RAs)[38,96–100] and dipeptidyl peptidase-4 (DPP-4)[39,40,101–103] inhibitors according to levels of cardiovascular disease (CVD) and renal risk as measured by estimated glomerular filtration rate (eGFR). Bubble size is proportional to number of patients. T2D, type 2 diabetes



Mortalità CVD

EMPA-REG OUTCOME®



Cumulative incidence function. HR, hazard ratio

7020 T2D subjects with established CVD

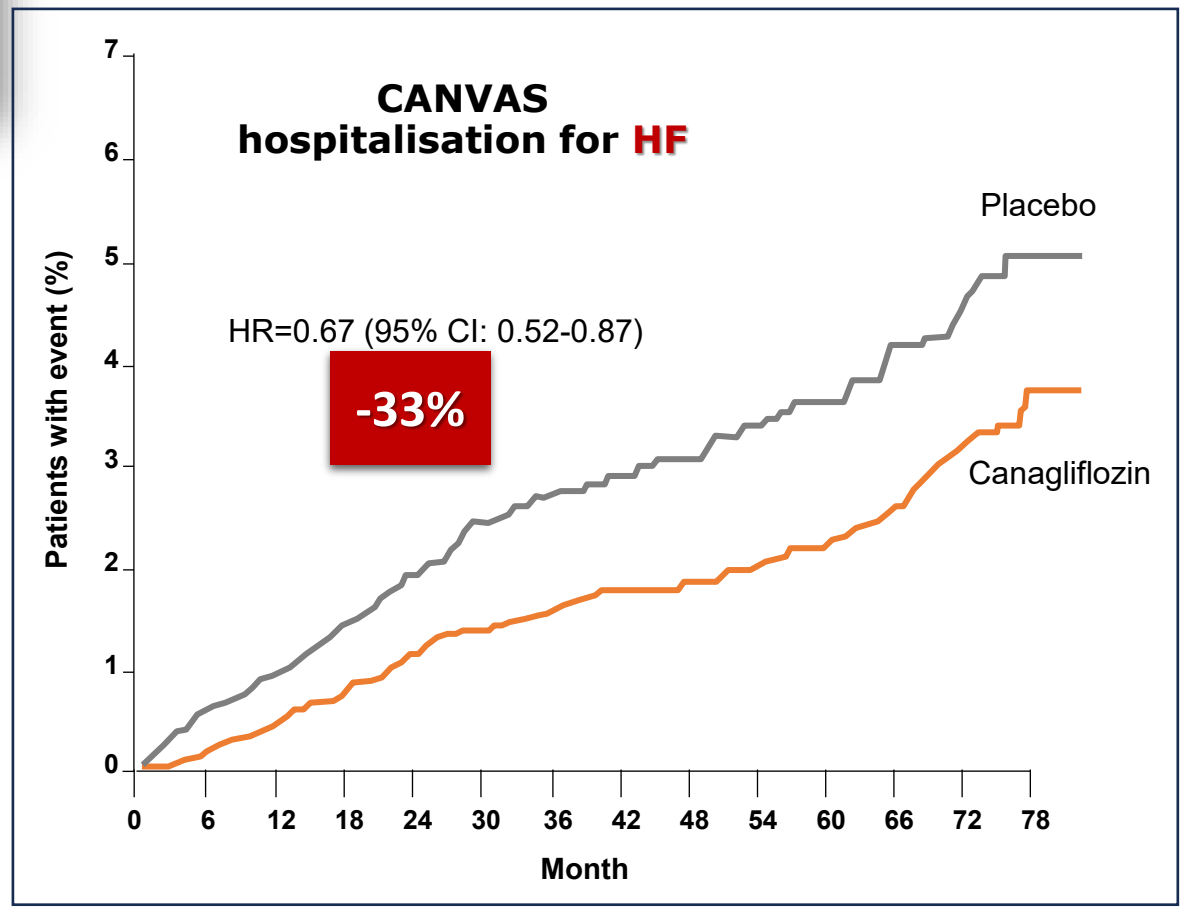
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

6656 T2D subjects with established atherosclerotic disease (66%)
3486 at high risk for CVD events (34 %)



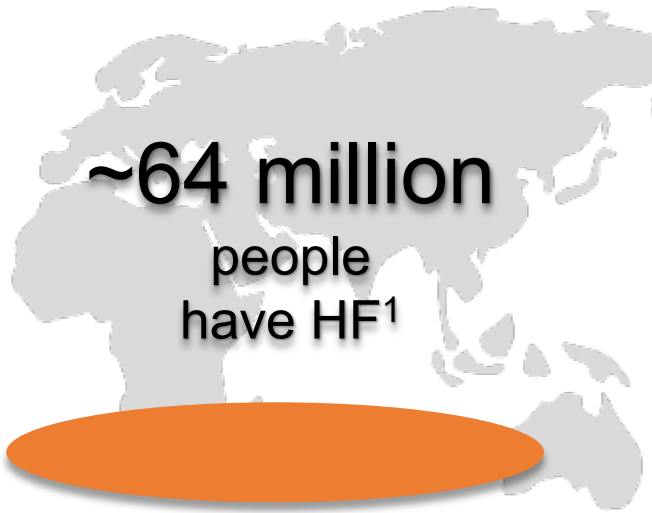
N Engl J Med, June 2017

Heart Failure is a Major Public Health Problem Worldwide

Hospitalization

Quality of life

No recover



Epidemiology
Projected **~24% rise in cases** between 2012 and 2030[2]

Mortality
5-year **mortality rate ~50%**[3]

HF **mortality risk is similar** to some of the **common cancers** in both men and women[4]

Costs
Economic burden ~350 billion US dollars[2]

Complexity
Over 50% of patients with HF have **HFpEF**[5]

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; US = United States.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2018;392:1789-1858; 2. Lippi G et al. *AME Med J.* 2020;5:15; 3. Jones NR et al. *Eur J Heart Fail*. 2019;21:1306-1325; 4. Mamas AM et al. *Eur J Heart Fail*. 2017;19:1095-1104; 5. Omote K et al. Online ahead of print. *Annu Rev Med.* 2021.

DAPAHF

EW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

DAPA-HF: The first and only SGLT2 inhibitor to significantly reduce CV mortality in HFrEF patients, with and without T2D[1,2]

DAPAHF[1]

N=4744

- LVEF ≤40%
- Elevated NT-proBNP
- eGFR ≥30 mL/min/1.73 m²

1:1 randomization

DAPA 10 mg | Placebo

Median follow-up: 18.2 months

Primary endpoint[1]

Composite of CV death or worsening HF (hHF or an urgent HF visit)

Secondary endpoints[1]

- CV death or hHF
- Total number of hHF (first and recurrent) and CV death
- Change in KCCQ-TSS from baseline to 8 months
- ≥50% sustained decline in eGFR, ESKD or renal death
- All-cause mortality

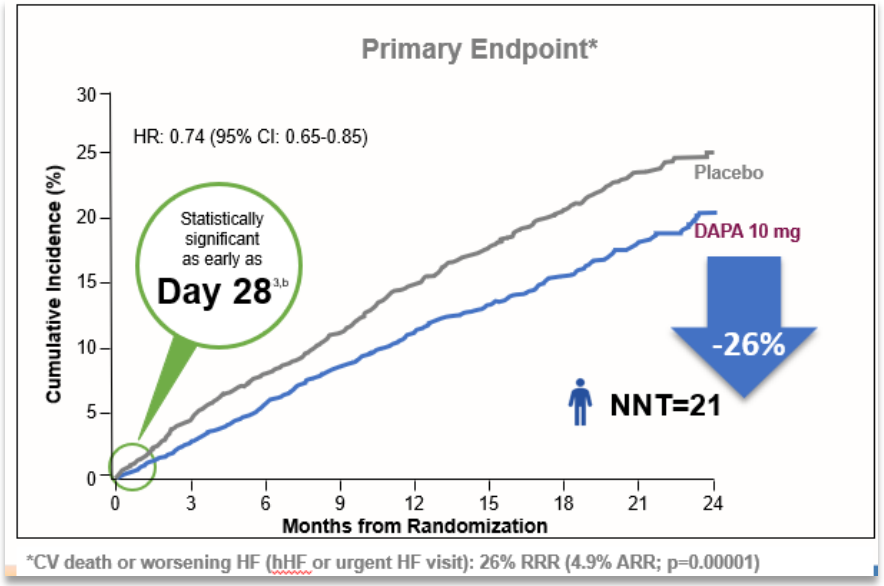
Baseline characteristics[3]

1437 pg/mL Median NT-proBNP

31% Average LVEF

55% Without T2D

41% With an eGFR <60 mL/min/1.73 m²



Secondary Endpoint

CV death	Worsening HF[a]	All-cause mortality
18% RRR	30% RRR	17% RRR
1.9% ARR	3.7% ARR	2.3% ARR
p=0.029	p=0.00003	p=0.022[c]

- 1. McMurray JJV et al. *N Engl J Med.* 2019;381(21):1995-2008; 2. Packer M et al. *N Engl J Med.* 2020;383(15):1413-1423; 3. McMurray JJV et al. *Eur J Heart Fail*. 2019;21:140

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

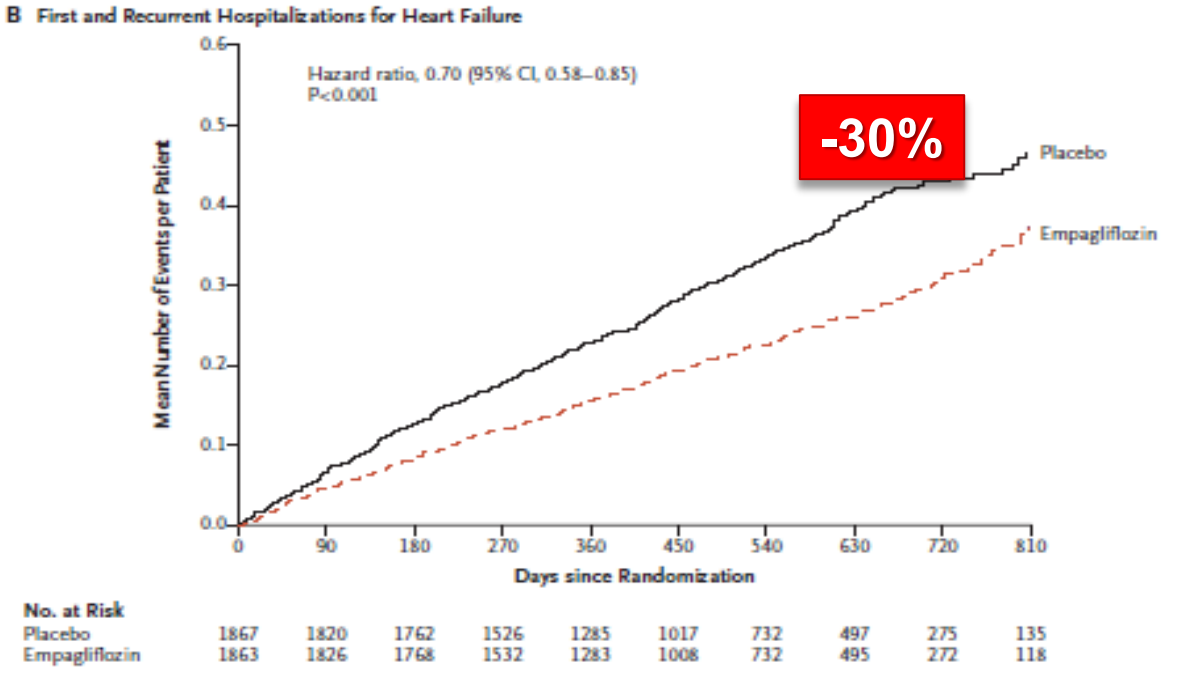
Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

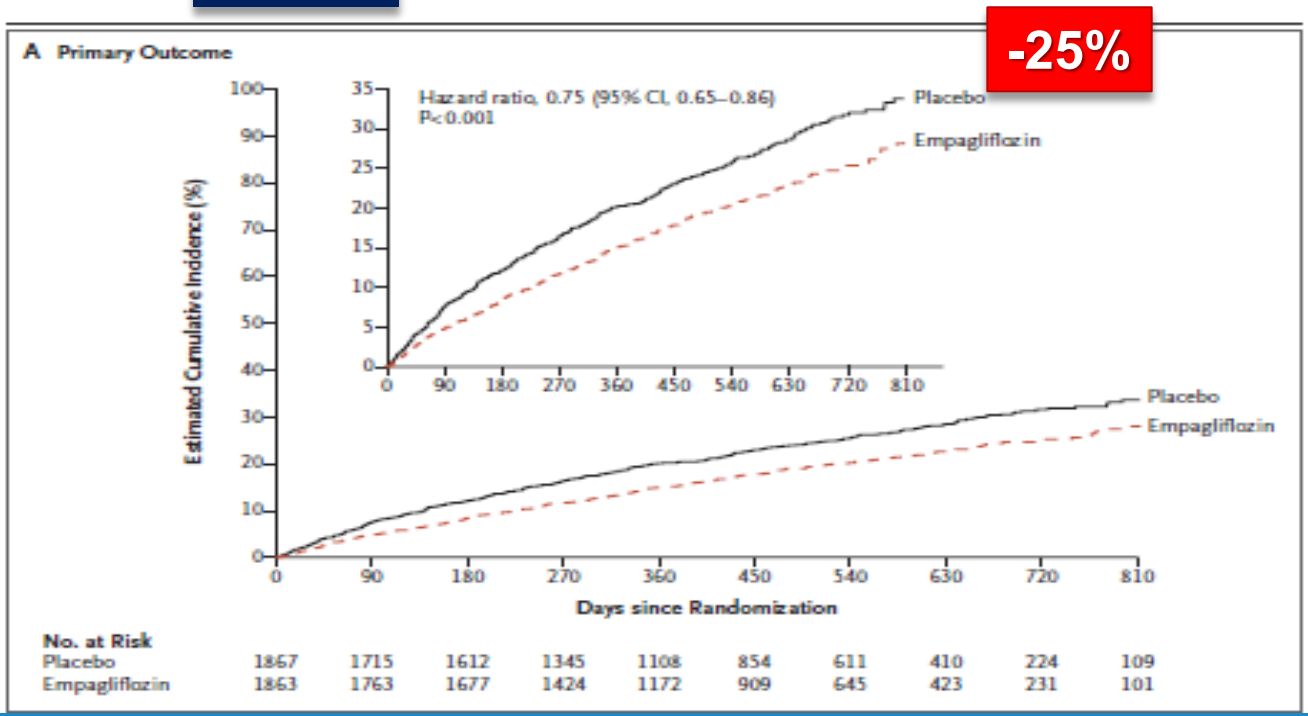
M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, 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*

EMPEROR Reduced Trial

3730 patients with HF
(class II - IV)
and EF ≤ 40%
T2DM : 49.8%
More than 70% with EF ≤ 30%

NNT 19





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 authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Anker at the Department of Cardiology and BCRT (Campus CVK), Charité Universitätsmedizin Berlin, 13353 Berlin, Germany, or at s.anker@cachexia.de, or to Dr. Butler at the Department of Medicine, University of Mississippi Medical Center, 2500 North State St., Jackson, MS 39216, or at jbutler4@umc.edu.

*The EMPEROR-Preserved Trial Investigators are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Anker and Butler contributed equally to this article.

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DOI: 10.1056/NEJMoa2107038

CME at NEJM.org

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

METHODS

In this double-blind trial, we randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS

Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

CONCLUSIONS

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).

EMPEROR PRESERVED

NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)

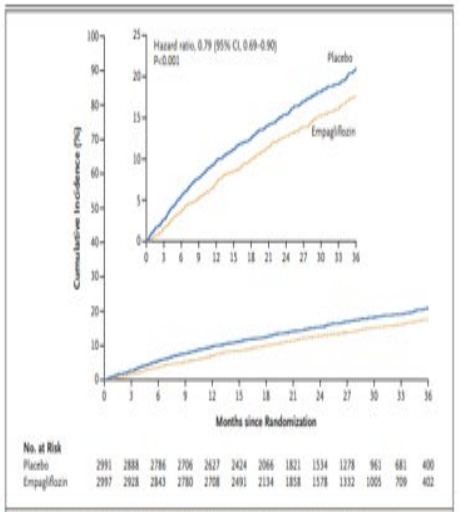


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

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*

ABSTRACT

BACKGROUND

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with heart failure and a left ventricular ejection fraction of 40% or less. Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

METHODS

We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis.

RESULTS

Over a median of 2.3 years, the primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 273 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Functional capacity and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with and without diabetes. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

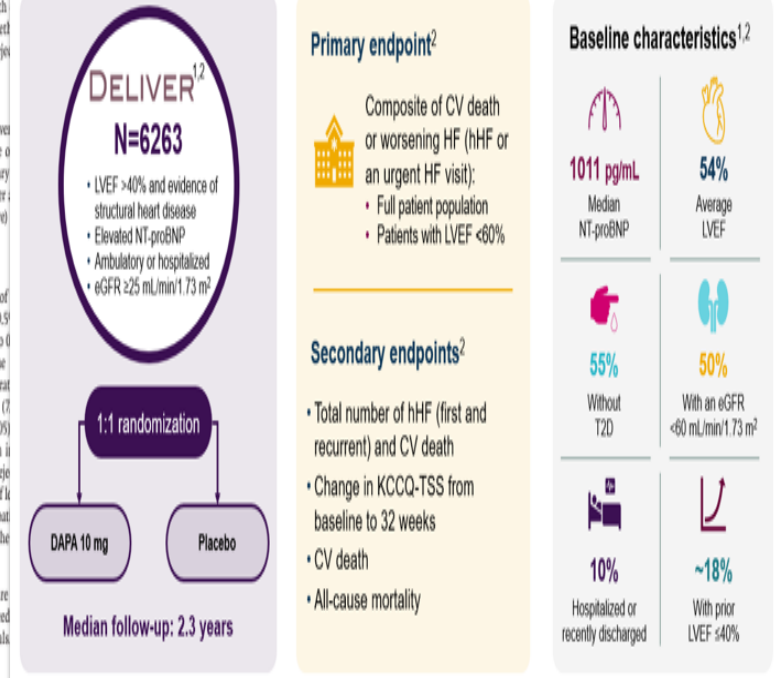
Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER, ClinicalTrials.gov number, NCT03619213.)

N ENGL J MED 387;12 NEJM.ORG SEPTEMBER 22, 2022

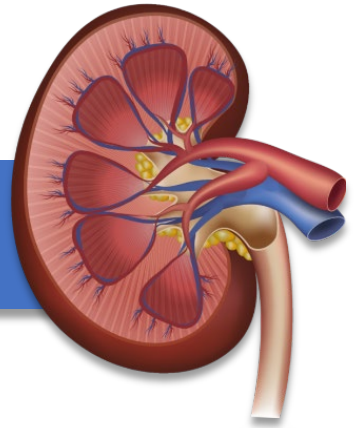
DELIVER: The largest and broadest trial to date in patients with **LVEF >40%**[1]

6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy.

The primary outcome was a composite of **worsening heart failure** (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) **or cardiovascular death**, as assessed in a time-to-event analysis.



SGLT2i-benefici renali



La malattia renale nel diabete tipo 2: Diagnosi, *staging* fenotipizzazione

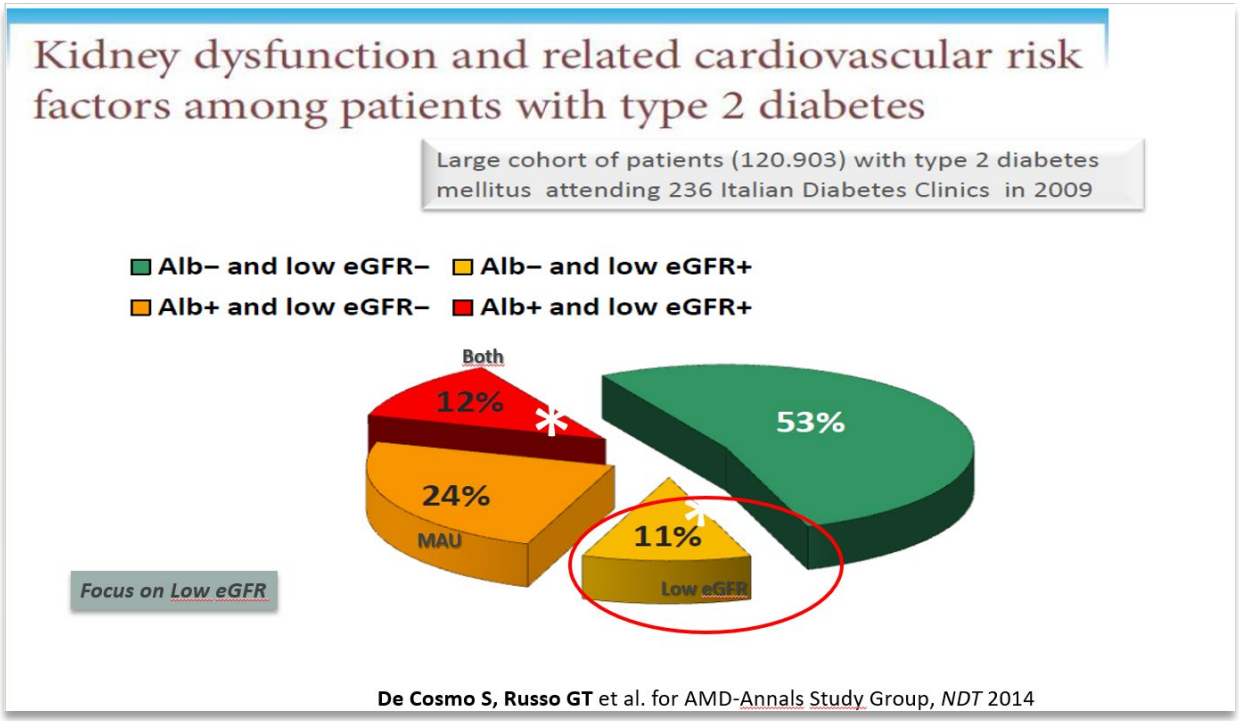
Staging KDIGO della CKD

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

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

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Figure 1 | Staging of CKD.[15] Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk. Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1–150. Copyright © 2013 KDIGO. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.



KDIGO distribution of DKD in T1D and T2D AMD Annals participants 2023

MICRO/MACROALBUMINURIA (%)	30.6
eGFR <60 ml/min (%)	30.8

1 /10 at very high risk

T1D subjects

Andamento per classi di malattia renale (Classi KDIGO) (%)

			Categorie di albuminuria persistente		
			A1	A2	A3
			Normale o lievemente aumentato	Moderatamente aumentato	Severamente aumentato
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
Categorie di eGFR (ml/min*1,73 m²)	Normale o elevato	≥90	51,9	8,0	1,3
	Lievemente diminuito	60-89	23,1	4,4	1,1
	Da lievemente a moderatamente diminuito	45-59	2,5	1,0	0,5
	Da moderatamente a severamente diminuito	30-44	0,8	0,5	0,4
	Severamente diminuito	15-29	0,2	0,2	0,3
	Insufficienza renale	<15	3,0	0,5	0,4

¼ at high-very high risk.

T2D subjects

Andamento per classi di malattia renale (Classi KDIGO) (%)

			Categorie di albuminuria persistente		
			A1	A2	A3
			Normale o lievemente aumentato	Moderatamente aumentato	Severamente aumentato
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
Categorie di eGFR (ml/min*1,73 m²)	Normale o elevato	≥90	19,6	5,1	1,0
	Lievemente diminuito	60-89	31,8	9,2	2,1
	Da lievemente a moderatamente diminuito	45-59	9,0	3,8	1,3
	Da moderatamente a severamente diminuito	30-44	5,0	2,9	1,4
	Severamente diminuito	15-29	1,3	1,1	1,0
	Insufficienza renale	<15	2,6	1,1	0,7

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Original Article

Prevalence and clinical determinants of rapid eGFR decline among patients with newly diagnosed type 2 diabetes

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ARTICLE INFO

Keywords:
Diabetic nephropathy
Albuminuria
Glomerular filtration rate
Diabetic kidney disease
Chronic kidney disease

ABSTRACT

Background: Diabetic kidney disease is the most common cause of end-stage kidney disease (ESKD) in the western world. Rapid estimated glomerular filtration rate (eGFR) decline is an independent predictor of ESKD and death in the general population and in subjects with type 2 diabetes mellitus (T2D).

Aim: We investigated in a large sample of subjects with newly diagnosed T2D the prevalence and clinical determinants of fast eGFR decline, taking advantage from the dataset of the Associazione Medici Diabetologi (AMD) Annals initiative.

Methods: The eGFR trajectories were evaluated by applying a linear mixed model for repeated measures (LMMRM) and rapid eGFR decline defined as an eGFR decline greater than 5 mL/min/1.73 m2 per year at 3 years.

Results: Among 105,163 (57.7% M) subjects with newly diagnosed T2D, 13,587 (12.9 %) subjects showed a rapid eGFR loss. The independent significant predictors were age, female gender, HbA1c, smoking, high baseline eGFR, albuminuria and retinopathy.

Conclusion: Our study demonstrates that a significant percentage of newly diagnosed T2D subjects have a rapid eGFR decline. Given the association between dynamic changes in eGFR and the risk of ESKD or death, we suggest to include this variable in the definition of CKD.

1. Introduction

Diabetic kidney disease (DKD) is the most common cause of end-stage kidney disease (ESKD) in the western world, accounting for more than 40 % of patients that require kidney replacement therapy [1]. It is also associated with higher cardiovascular and all-cause mortality [2].

In patients with diabetes, variations in estimated glomerular filtration rate (eGFR) and in urinary albumin excretion should be monitored over time as they provide useful information on the trajectory of DKD progression [2]. Because of age-related structural changes, starting from the age of 40 years, the annual rate of eGFR decline in healthy persons is

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Eur J Int Med, 2024

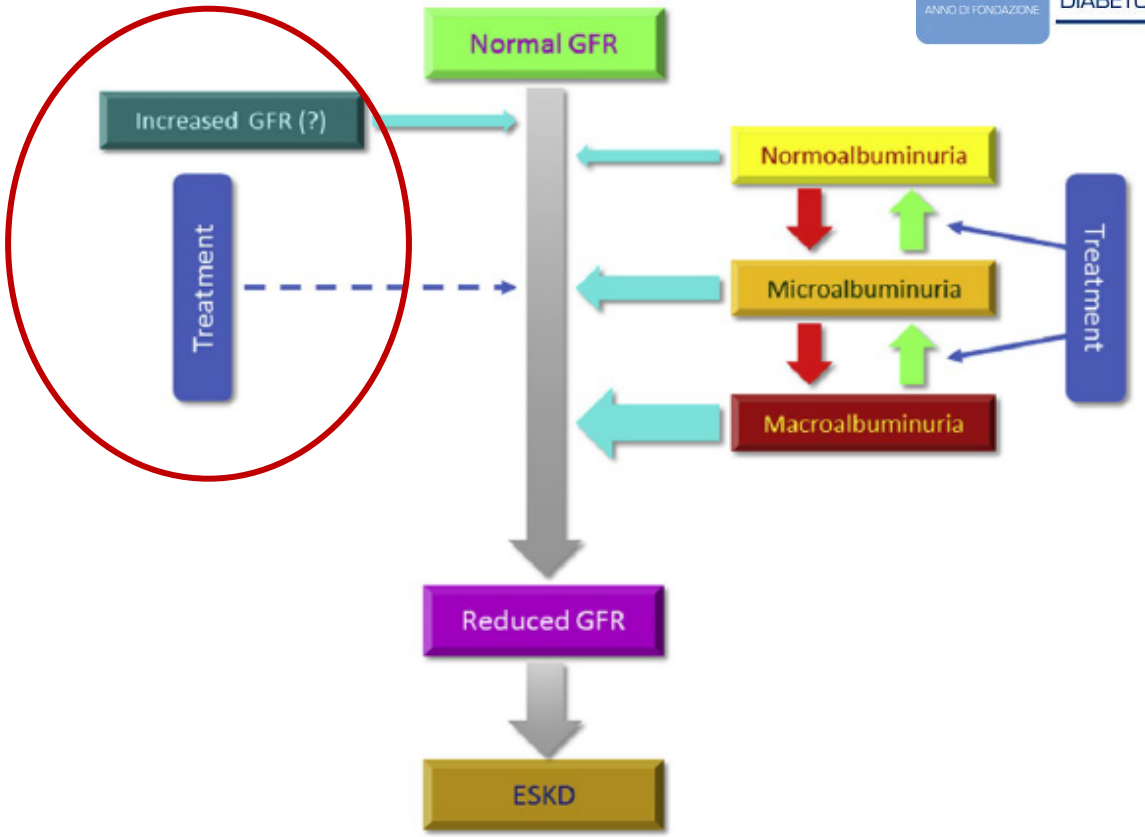


Fig. 1 Albuminuric and nonalbuminuric pathways of DKD progression. *DKD* diabetic kidney disease, *GFR* glomerular filtration rate, *ESKD* end-stage kidney disease

Journal of Nephrology (2020) 33:9–35

Table 1. Clinical and/or biochemical features according to the outcome.

FAST DECLINERS

	Whole population n= 105,163	Fast decline: No n= 91,576	Fast decline: Yes n= 13,587	p-value
Time on study (years)	2.8±0.4	2.8±0.4	2.8±0.4	<0.0001
Age (years)	64.7±12.1	64.5±12.1	65.7±12.3	<0.0001
Male n (%)	6,0725 (57.7)	53,239(58.1)	7,486 (55.1)	<0.0001
EGFR T0 (ml/min/1.73 m²)	82.2±19.9	81.7±20.1	86.1±18.5	<0.0001
EGFR FU (ml/min/1.73 m²)	79.7±21.4	82.7±19.5	59.4±22.3	<0.0001
HbA1c (%)	7.3±1.7	7.3±1.7	7.4±1.8	<0.0001
Total Cholesterol (mg/dl)	190.4±43.7	190.8±43.5	188.2±44.9	<0.0001
LDL-c (mg/dl)	112.3±36.9	112.7±36.8	109.6±37.3	<0.0001
HDL-c (mg/dl)	48.1±12.9	48.3±12.9	47.3±13.0	<0.0001
Triglycerides (mg/dl)	155.1±102.3	153.9±100.7	163.1±112.8	<0.0001
SBP (mmHg)	134.5±18.2	134.3±18.1	135.4±19.1	<0.0001
DBP (mmHg)	79.1±10.1	79.1±10.0	78.9±10.5	0.09
BMI (Kg/m²)	30.1±5.7	30.1±5.6	30.3±6.0	0.01
Smokers (%)	11285 (19.4)	9,831 (19.3)	1454 (19.8)	0.32
GLP1-RA (%)	2,741 (3.3)	2,317 (3.2)	424 (3.9)	0.0002
Insulin (%)	18,763 (17.8)	15,548 (17.0)	3,215 (23.7)	<0.0001
Lipid-lowering agents (%)	34,131 (32.5)	29,697 (32.4)	4,434 (32.6)	0.63
Antihypertensive treatment (%)	47,258 (44.9)	40,739 (44.5)	6,519 (48.0)	<0.0001
Previous CVE n (%)	2,133 (2.0)	1,783 (1.9)	350 (2.6)	<0.0001
Retinopathy (%)	5,419 (15.6)	4,373 (14.5)	1,046 (22.5)	<0.0001
RAAS inhibitors Yes vs No	38,414 (36,5)	33,157 (36,2)	5,257 (38,7)	<0.0001

Mean ± SD, n (%): absolute frequency (percentage) and ^median (range).
CVE, cardiovascular events; *BMI*, body mass index; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *HDL-c*, high-density lipoprotein cholesterol; *LDL-c*, low-density lipoprotein cholesterol; *HbA1c*, Glycated hemoglobin; *eGFR*, estimated glomerular filtration rate; *FU*, follow up; *DPPIVi*, Dipeptidyl Peptidase IV Inhibitors; *SGLT2i*, Sodium-glucose co-transporter 2 inhibitors; *GLP1-RA*, glucagon-like peptide 1 receptor agonist; *RAAS inhibitors*, Renin-angiotensin-aldosterone system inhibitors.

In conclusion, our study identified 12.9% of subjects with rapid eGFR decline in a large sample of subjects with newly diagnosed T2D. We also described the independent clinical and biochemical determinants of rapid eGFR decline such as such as age, female gender, HbA1c, smoking, high baseline eGFR, albuminuria and retinopathy

Table 2. List of variables related to fast eGFR decline.

Effect	OR	95% CI
eGFR 60-89 vs. 30-59 mL/min/1.73 m²	**0.41**	**0.39-0.44**
eGFR 90-119 vs. 30-59 mL/min/1.73 m²	**1.37**	**1.31-1.43**
eGFR ≥120 vs. 30-59 mL/min/1.73 m²	**3.26**	**2.86-3.71**
Male vs. Female	**0.89**	**0.86-0.93**
Age 55-64 vs. <55 years	**1.30**	**1.23-1.38**
Age 65-74 vs. <55 years	**1.59**	**1.50-1.69**
Age ≥75 vs. <55 years	**2.34**	**2.19-2.51**
BMI 27-29 vs. <27	0.99	0.93-1.05
BMI 30-34 vs. <27	**1.07**	**1.01-1.13**
BMI ≥35 vs. <27	**1.18**	**1.11-1.26**
HbA1c 7.0-8.0 vs. <7.0 %	1.04	0.99-1.09
HbA1c 8.1-9.0 vs. <7.0 %	**1.09**	**1.02-1.17**
HbA1c >9.0 vs. <7.0 %	**1.12**	**1.05-1.19**
Smoking status Yes vs. No	1.05	0.98-1.12
Micro/macroalbuminuria Yes vs. No	**1.40**	**1.33-1.48**
Retinopathy Yes vs. No	**1.53**	**1.42-1.66**
Previous CVE Yes vs. No	**1.32**	**1.17-1.49**
Glucose-lowering drugs/statins Yes vs. No	0.98	0.94-1.02
Antihypertensive medication Yes vs. No	**1.22**	**1.17-1.28**
Insulin Yes vs. No	**1.50**	**1.43-1.57**
Metformin Yes vs. No	1.02	0.97-1.07
Sulphonylureas Yes vs. No	**1.18**	**1.11-1.26**
DPP4i Yes vs. No	**1.29**	**1.20-1.39**
Glinides Yes vs. No	**1.24**	**1.10-1.40**
Glitazones Yes vs. No	0.95	0.81-1.10
GLP1-RAs Yes vs. No	**1.18**	**1.06-1.32**
SGLT-2i Yes vs. No	1.04	0.95-1.14
Acarbose Yes vs. No	**1.25**	**1.05-1.47**
RAAS inhibitors Yes vs. No	0.97	0.91-1.04

OR, odds ratio; *95% CI*, 95% confidence intervals; *eGFR*, estimated glomerular filtration rate; *BMI*, body mass index; *HbA1c*, Glycated hemoglobin; *CVE*, cardiovascular events; *DPPIVi*, Dipeptidyl Peptidase IV Inhibitors; *SGLT2i*, Sodium-glucose co-transporter 2 inhibitors; *GLP1-RA*, glucagon-like peptide 1 receptor agonist; *RAAS inhibitors*, Renin-angiotensin-aldosterone system inhibitors.

Eur J Int Med, 2024

I risultati dei CVOTs con SGLT2i

	EMPA-REG OUTCOME[1,2] (empagliflozin)	CANVAS Program[3] (canagliflozin)	DECLARE-TIMI 58[4] (dapagliflozin)	VERTIS-CV[5,6] (ertugliflozin)	CREDENCE[7] (canagliflozin)
3P-MACE	▼ 14%*	▼ 14%*	NS	▼ 3%†	▼ 20%‡
CV death	▼ 38%‡	NS	NS	NS	▼ 22%‡
HHF	▼ 35%‡	▼ 33%‡	▼ 27%‡	▼ 30%‡	▼ 39%‡
Kidney outcomes¶	▼ 39%‡	▼ 40%‡	▼ 24%‡	NS	▼ 34%‡

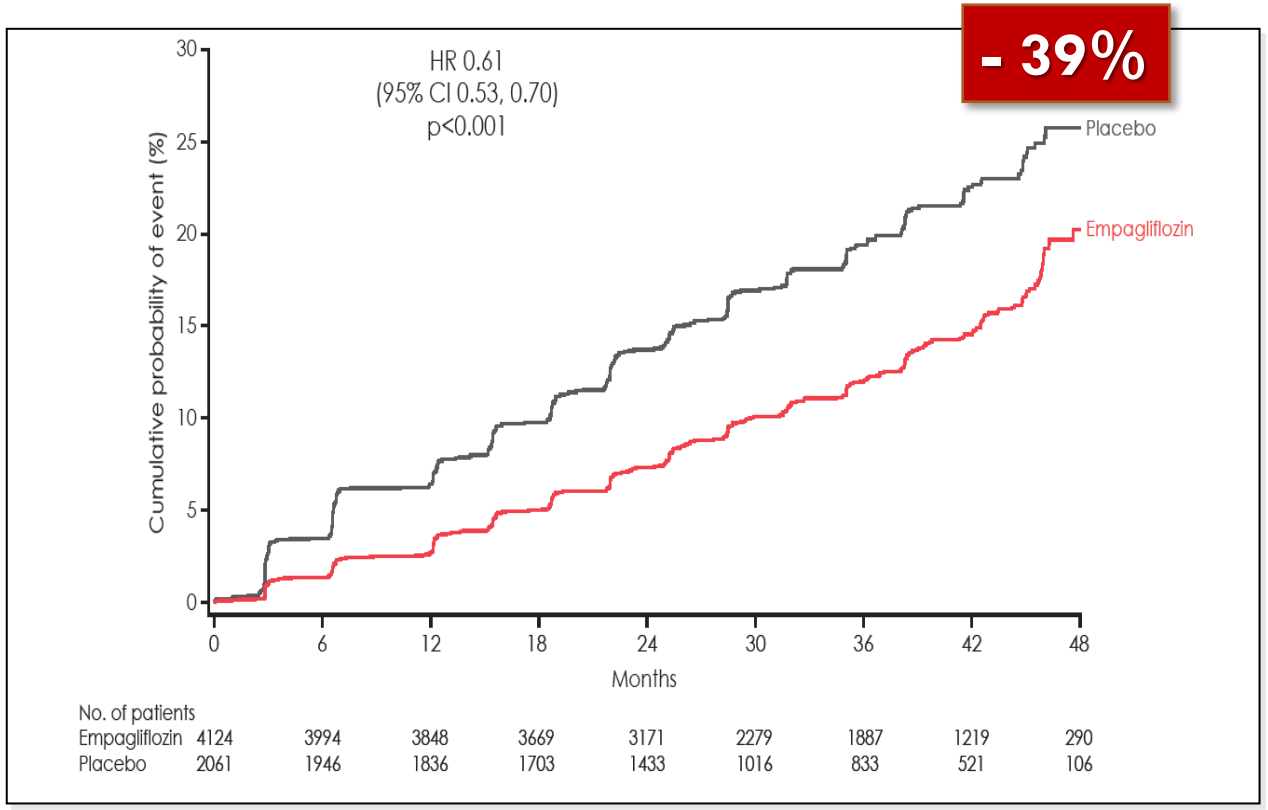
Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

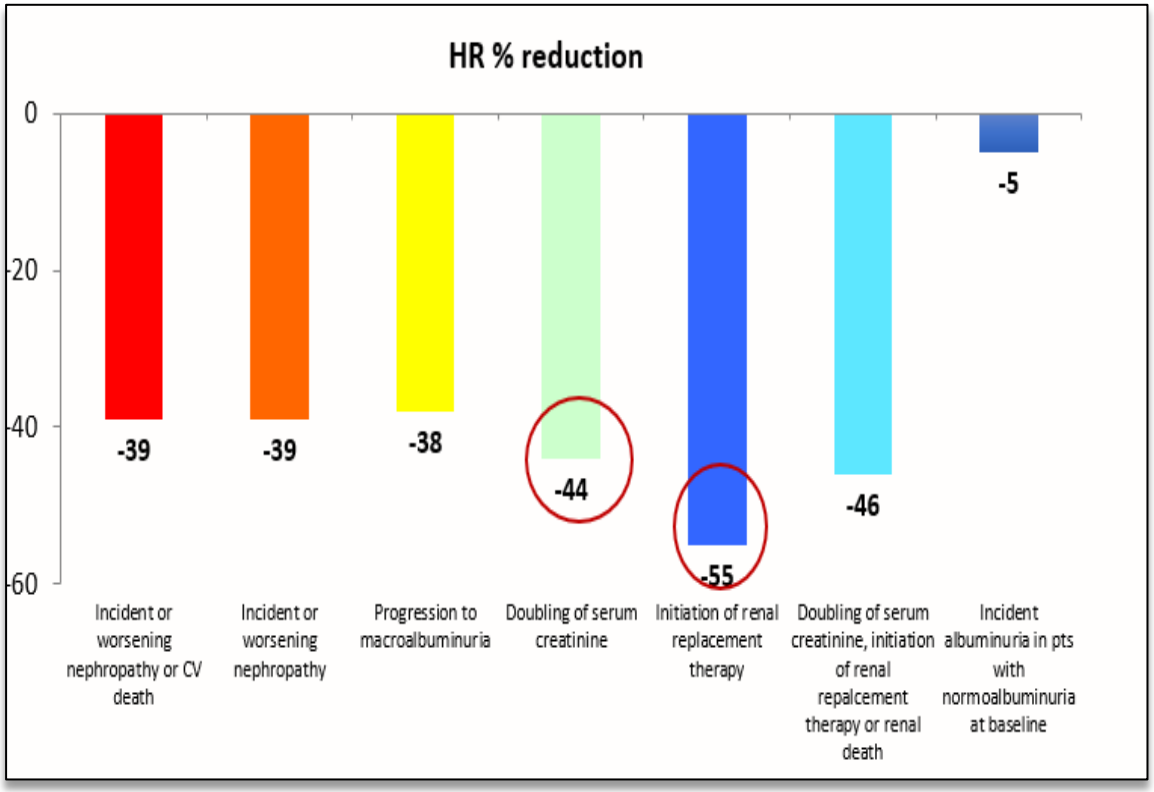
*Testing for superiority for 3P-MACE was the primary endpoint (co-primary for dapagliflozin); †Testing for non-superiority for 3P-MACE was the primary endpoint; ‡Secondary endpoints as defined in the study protocols; ¶EMPA-REG OUTCOME: progression to macroalbuminuria (UACR >300 mg/g), doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73 m^2), initiation of KRT or death from kidney disease; CANVAS Program: 40% reduction in eGFR, KRT or renal death; DECLARE-TIMI 58: 40% decrease in eGFR to <60 ml/min/1.73 m^2, ESKD, or death from renal or CV cause; VERTIS-CV: renal death, dialysis/transplant, doubling of serum creatinine; CREDENCE: ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml/min/1.73 m^2), doubling of serum creatinine or death from kidney causes

See slide notes for abbreviations and references

Renal protection in T2D patients with high CVD risk with no CKD

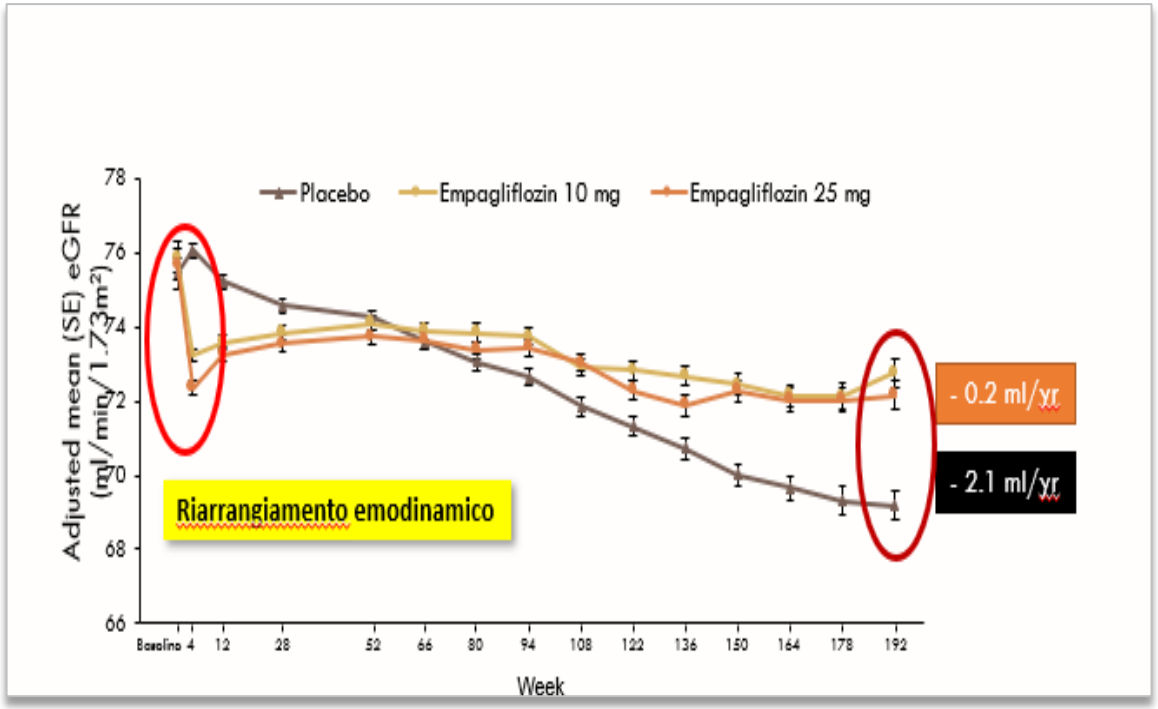
EMPA-REG: Incident or worsening nephropathy



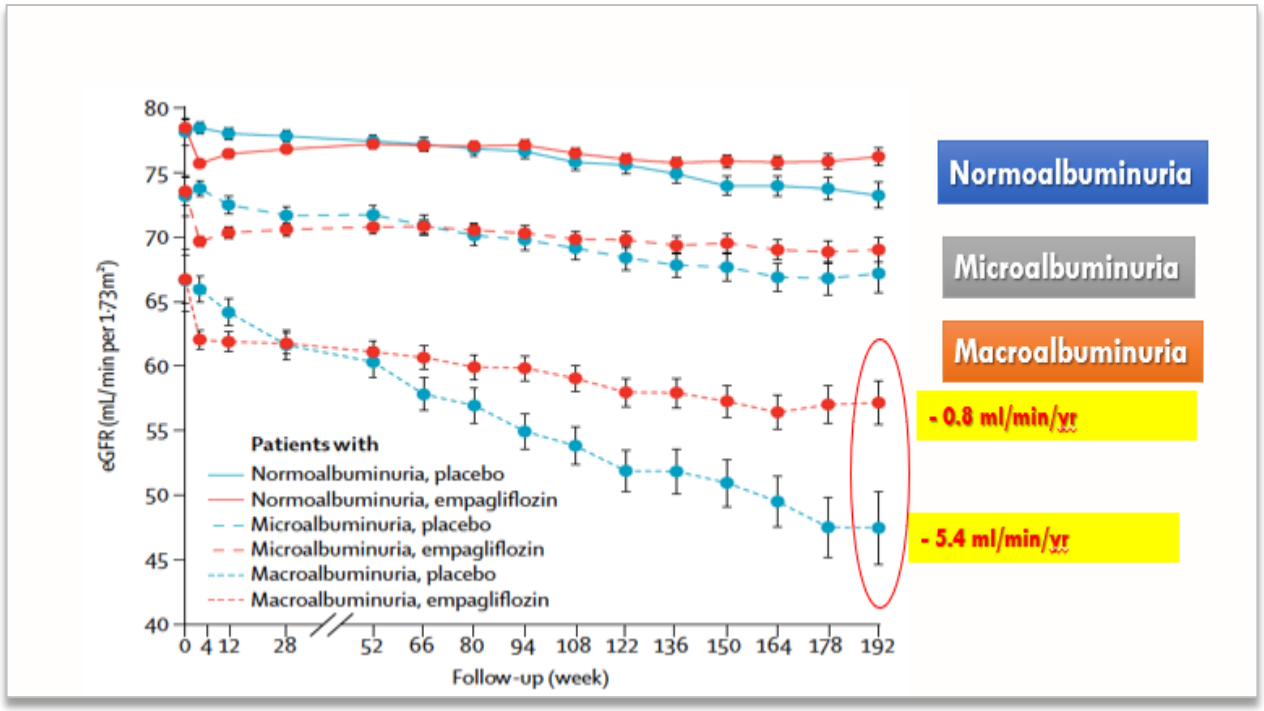


N Engl J Med 2015;373:2117-28

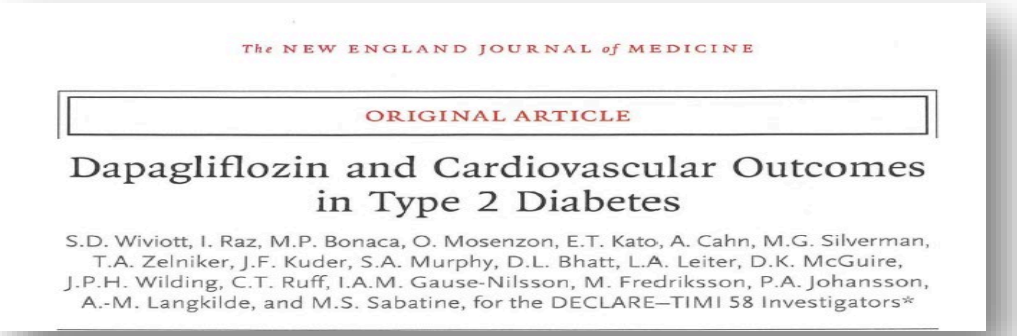
EMPAREG-OUTCOME Study: eGFR decline during the study



Wanner et al. NEJM 2016



Lancet Diabetes Endocrinol 2017; 5: 610–21



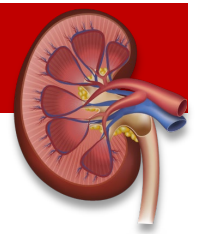
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

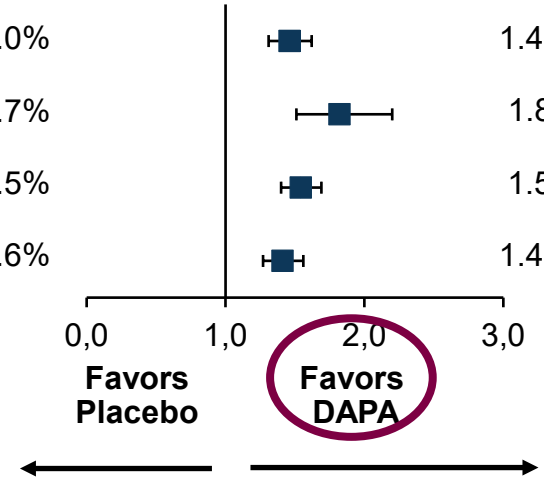
S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI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

DECLARE-TIMI 58



Improvement of Albuminuria Category from Baseline

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate	Hazard Ratio (95% CI)	Cox p-value
Endpoints						
Improvement from baseline						
Micro to Normo	774/2017 (38.4)	38.90%	576/2013 (28.6)	29.0%	1.46 (1.31, 1.62)	<0.0001
Macro to Normo/Micro	282/594 (47.5)	48.10%	175/575 (30.4)	31.7%	1.82 (1.51, 2.2)	<0.0001
Macro to Normo/Micro or Micro to Normo	1056/2611 (40.4)	41.00%	751/2588 (29.0)	29.5%	1.54 (1.4, 1.69)	<0.0001
Micro/Macro to Normo	809/2611 (31.0)	31.50%	604/2588 (23.3)	23.6%	1.41 (1.27, 1.56)	<0.0001

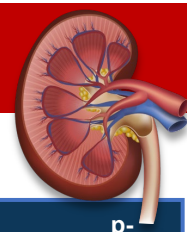


DAPA = dapagliflozin; KM = Kaplan-Meier; macro = macroalbuminuria; micro = microalbuminuria; normo = normoalbuminuria; UACR = urine albumin-to-creatinine ratio.

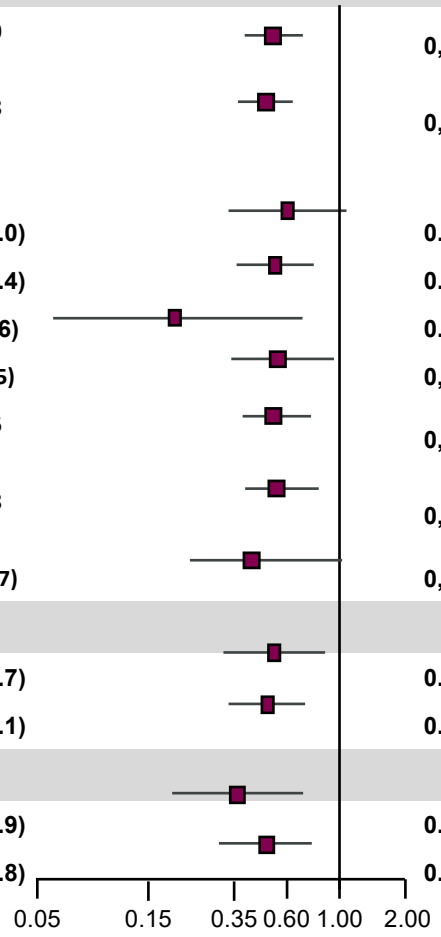
Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA 244-OR.

Reductions in the Renal-Specific Composite[a] Were Consistent Across Key Subgroups

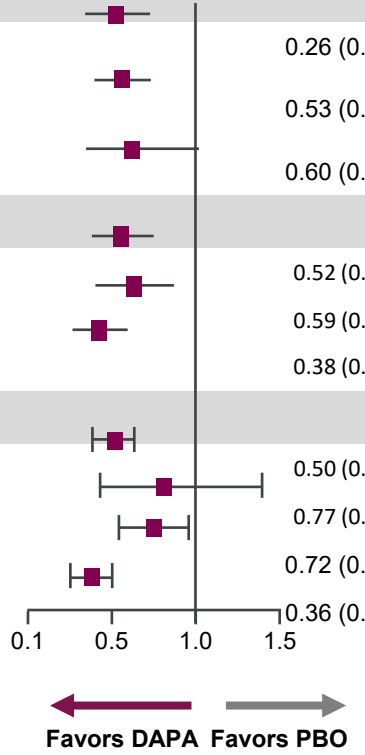
DECLARE-TIMI 58



Subgroup	DAPA n/N (%)	PBO n/N (%)	Hazard Ratio (95% CI)	p-value
Baseline CV disease or risk factor				
Established ASCVD	65/3474 (1.9)	118/3500 (3.4)	0,55 (0,41-0,75)	0,72
Multiple risk factors	62/5108 (1.2)	120/5078 (2.4)	0,51 (0,37-0,69)	
Number of additional risk factors				
One	17/1440 (1.2)	28/1422 (2.0)	0.60 (0.33-1.09)	0.282
Two	42/3257 (1.3)	78/3263 (2.4)	0.53 (0.37-0.78)	
Three	3/406 (0.7)	14/386 (3.6)	0.20 (0.06-0.69)	
History of HF	27/852 (3.2)	48/872 (5.5)	0,58 (0,36-0,92)	0,78
No History of HF	100/7730 (1.3)	190/7706 (2.5)	0,52 (0,41-0,66)	
History of HPT	122/7769 (1.6)	222/7658 (2.9)	0,54 (0,43-0,67)	0,41
No History of HPT	5/813 (0.6)	16/920 (1.7)	0,36 (0,13-0,98)	
Diabetes duration				
≤10 years	23/2552 (0.9)	43/2569 (1.7)	0.53 (0.32-0.89)	0.794
>10 years	39/2556 (1.5)	77/2509 (3.1)	0.49 (0.33-0.72)	
HbA1c				
<8.0%	21/2465 (0.9)	46/2436 (1.9)	0.44 (0.26-0.74)	0.515
≥8.0%	41/2641 (1.6)	74/2638 (2.8)	0.55 (0.38-0.80)	



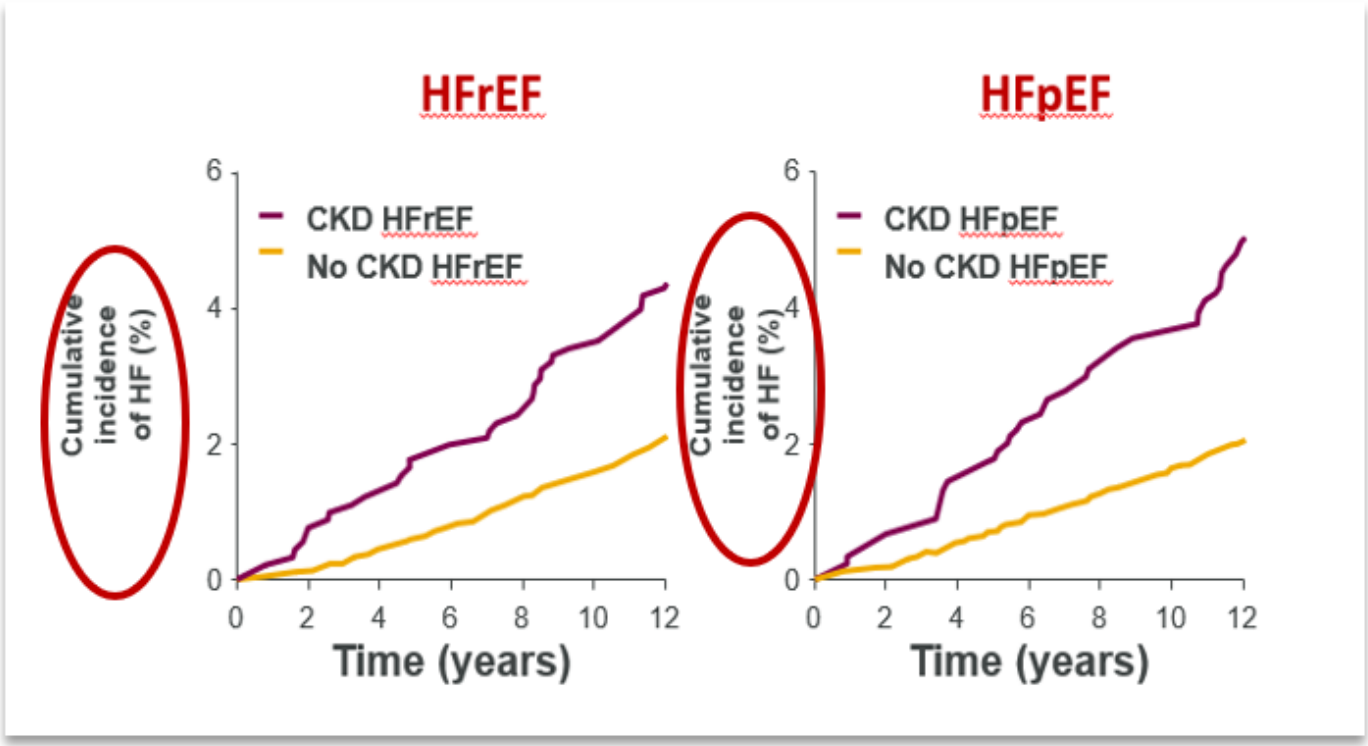
Subgroup	DAPA n/N (%)	PBO n/N (%)	Hazard Ratio (95% CI)	p-value
Baseline renal function: eGFR†				
<60 mL/min/1.73 m²	6/325 (1.8)	20/297 (6.7)	0.26 (0.11-0.66)	0.269
60 to <90 mL/min/1.73 m²	33/2281 (1.4)	62/2313 (2.7)	0.53 (0.35-0.81)	
≥90 mL/min/1.73 m²	23/2501 (0.9)	38/2468 (1.5)	0.60 (0.36-1.00)	
Baseline UACR				
UACR <30 mg/g	50/5819 (0.9)	95/5825 (1.6)	0.52 (0.37-0.74)	0.30
UACR 30-300 mg/g	39/2017 (1.9)	66/2013 (3.3)	0.59 (0.39-0.87)	
UACR >300 mg/g	31/594 (5.2)	75/575 (13.0)	0.38 (0.25-0.58)	
Baseline medication use				
ACEi/ARB use	106/6977 (1.5)	211/6973 (3.0)	0.50 (0.39-0.63)	0.16
no ACEi/ARB use	21/1605 (1.3)	27/1605 (1.7)	0.77 (0.44-1.37)	
Diuretic use	81/3488 (2.3)	111/3479 (3.2)	0.72 (0.54-0.95)	0.0021
No Diuretic use	46/5094 (0.9)	127/5099 (2.5)	0.36 (0.26-0.50)	



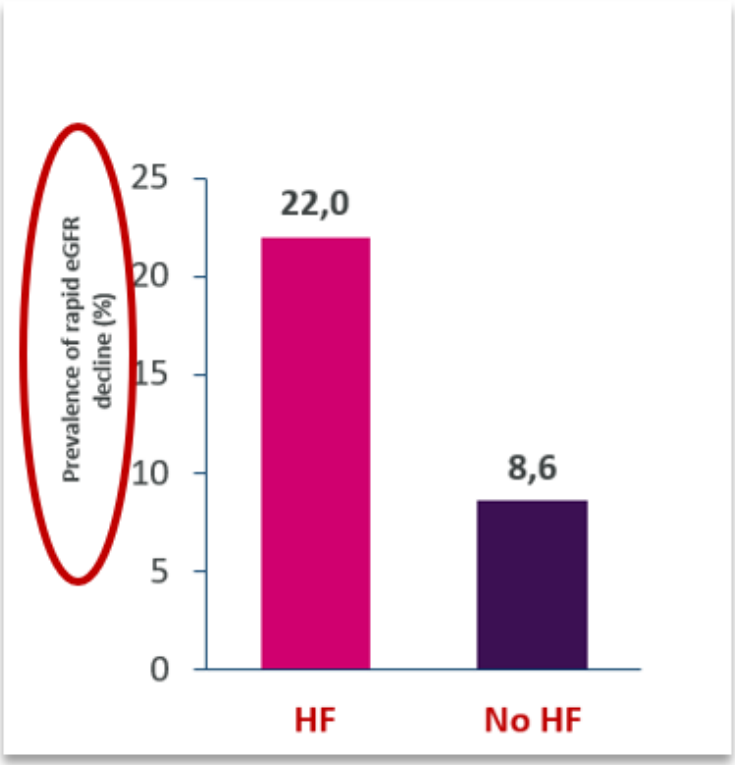
Favors DAPA Favors PBO

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; UACR = urine albumin to creatinine ratio; HF = hearth failure; HPT = hypertension; ACEi = angiotensin converting enzyme inhibitor; ACR = albumin:creatinine ratio; ARB = angiotensin receptor blocker; ESRD = end-stage renal disease; PBO = placebo;

Mosenzon O et al. *Lancet Diabetes Endocrinol.* 2019;7:606-617.; Cahn A et al. Poster presented at: Virtual EASD Annual Meeting; September 21-25, 2020.



CKD aumenta rischio di HF



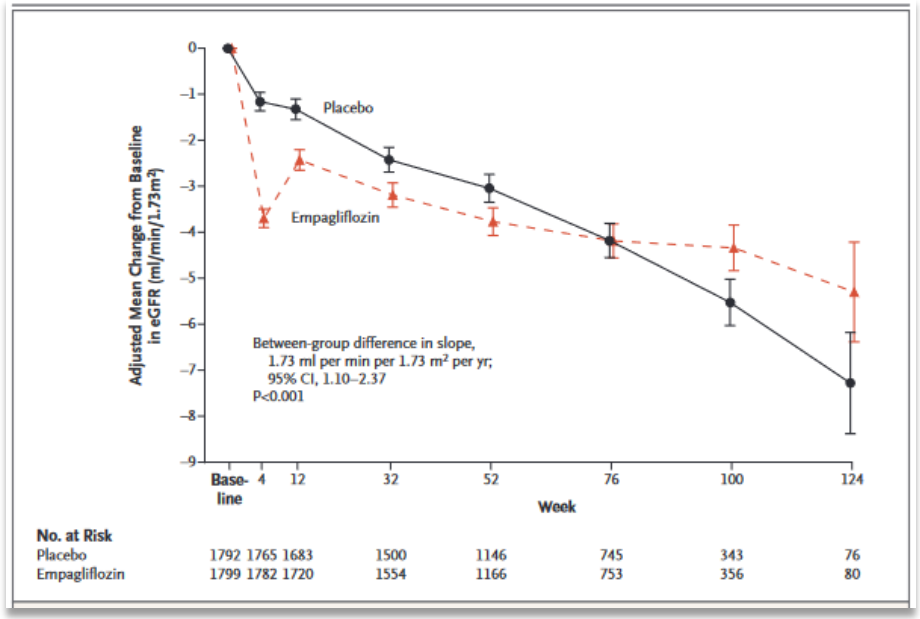
HF aumenta rischio di CKD

[a]Rapid rate of eGFR decline was defined as slopes steeper than −5 mL/min/1.73 m²/year.
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.
1. Nayor M et al. *Eur J Heart Fail*. 2017;19:615–623; 2. George LK et al. *Circ Heart Fail*. 2017;10:e003825.

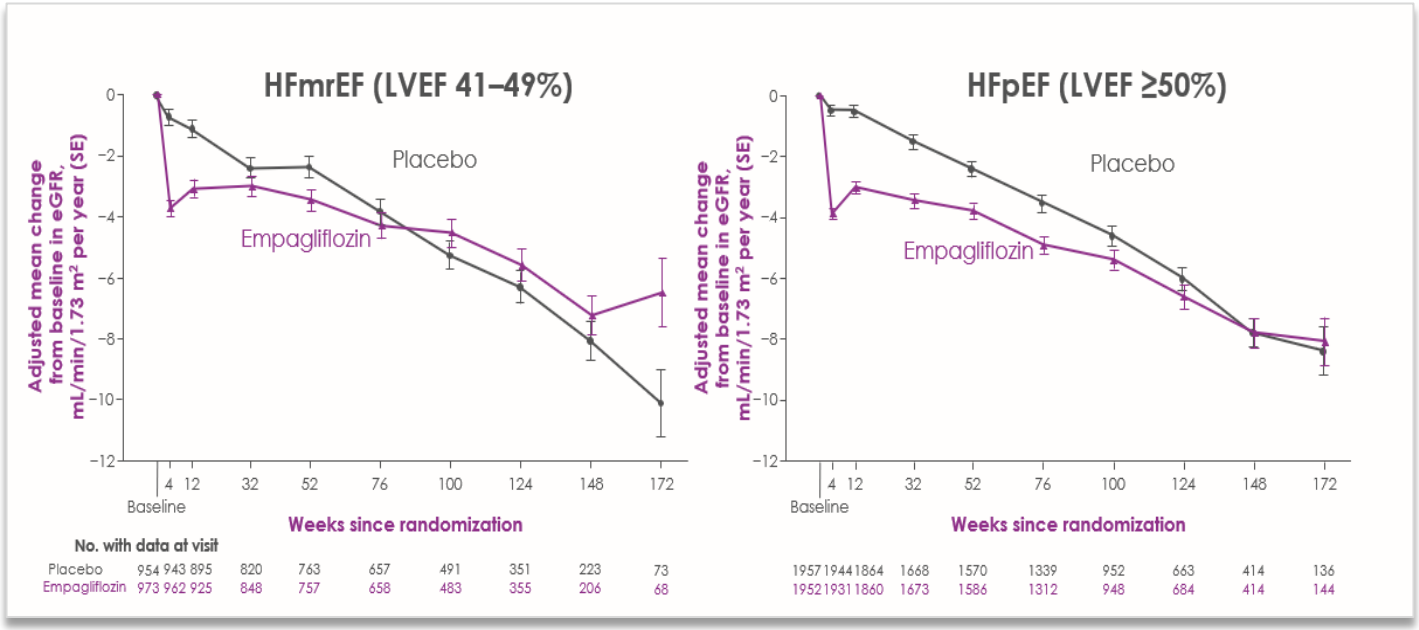
Renal protection in patients with HF

Effect of empagliflozin on the mean change in eGFR in patients with HF

EMPEROR-Reduced



EMPEROR-Preserved



Data are presented as adjusted mean and standard error. Change in eGFR was analysed using a mixed model for repeated measures.
eGFR, estimated glomerular filtration rate
N Engl J Med 2020;383:1413-24. DOI: 10.1056/NEJMoa2022190.

Data are presented as adjusted mean and standard error. Change in eGFR was analysed using a mixed model for repeated measures.
eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; SE, standard error.
Anker SD *et al. Nat Med.* 2022; doi:10.1038/s41591-022-02041-5.

Renal protection in patients CKD

Renal protection in T2D patients with CKD

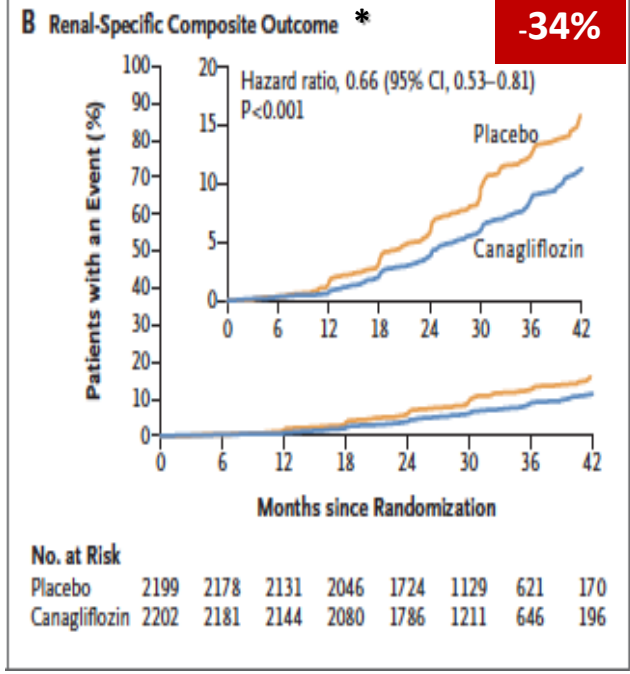
CREDENCE

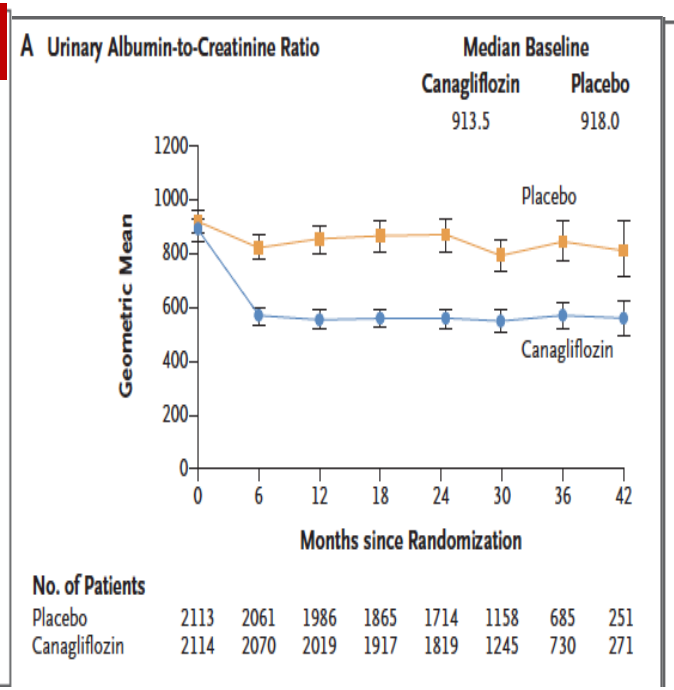
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

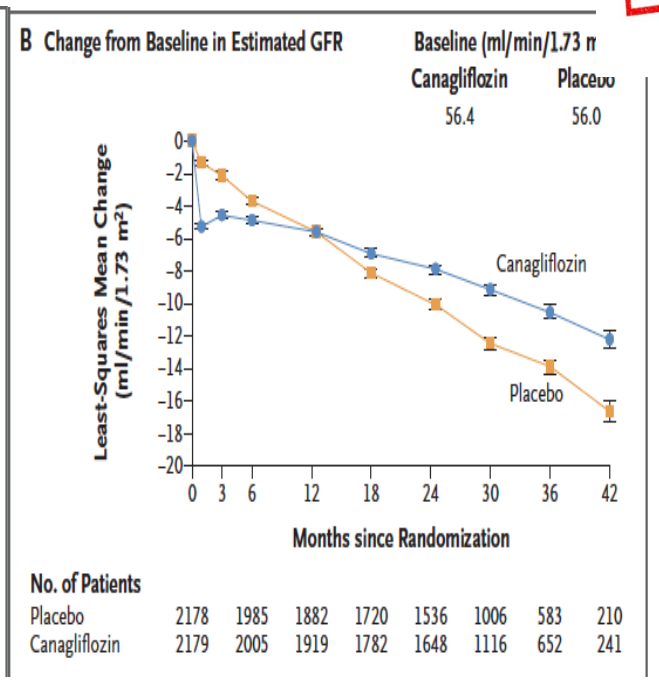
* **Renal specific Outcome** was a composite of end-stage kidney disease, doubling of the serum creatinine level, or renal death

PRESS RELEASE

-34%







Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	-40%
End-stage kidney disease **	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	-32%
Renal death	2/2202	5/2199	0.3	0.9	NA	

** **Endstage kidney disease** :dialysis, kidney transplantation, or an eGFR of <15 ml per minute per 1.73 m2

V Perkovic; NEJM; Online April 14, 2019

DAPACKD

ND JOURNAL of MEDICINE

INAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

Primary end-point: composite of sustained decline in eGFR at least of 50%, ESRD, or death from renal or CVD causes

Secondary outcomes (also assessed in time-to-event analyses) were, in hierarchical order, the **composite kidney outcome** of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes; **a composite cardiovascular outcome,** defined as hospitalization for heart failure or death from cardiovascular causes; and **death from any cause.**

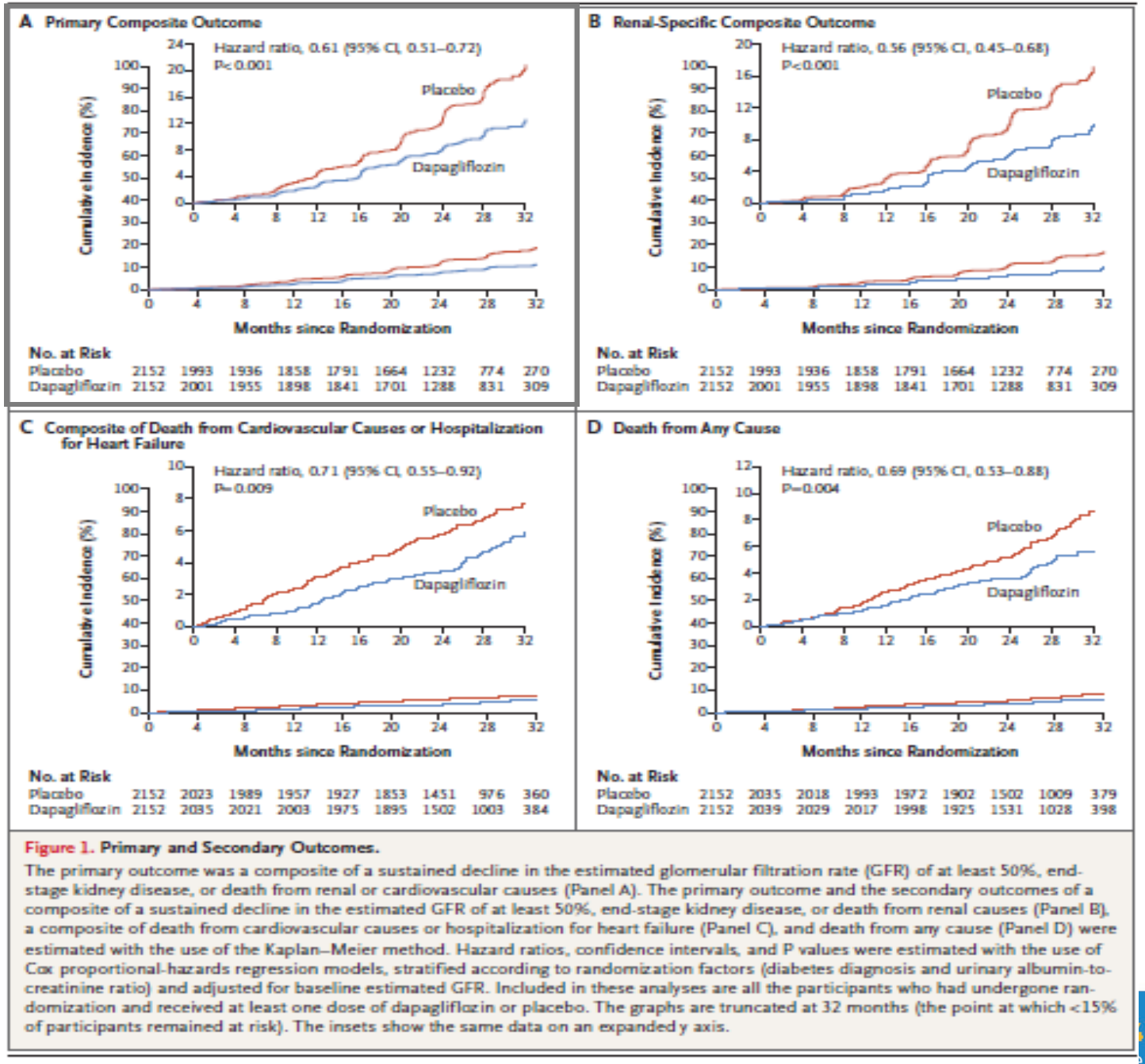


Figure 1. Primary and Secondary Outcomes.

The primary outcome was a composite of a sustained decline in the estimated glomerular filtration rate (GFR) of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes (Panel A). The primary outcome and the secondary outcomes of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes (Panel B), a composite of death from cardiovascular causes or hospitalization for heart failure (Panel C), and death from any cause (Panel D) were estimated with the use of the Kaplan–Meier method. Hazard ratios, confidence intervals, and P values were estimated with the use of Cox proportional-hazards regression models, stratified according to randomization factors (diabetes diagnosis and urinary albumin-to-creatinine ratio) and adjusted for baseline estimated GFR. Included in these analyses are all the participants who had undergone randomization and received at least one dose of dapagliflozin or placebo. The graphs are truncated at 32 months (the point at which <15% of participants remained at risk). The insets show the same data on an expanded y axis.

N Engl J Med 2020;383:1436-46.

Cardiorenal and mortality benefits in DAPA-CKD were consistent *regardless of T2D status*

DAPACKD

	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

DAPACKD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

EMPAKIDNEY

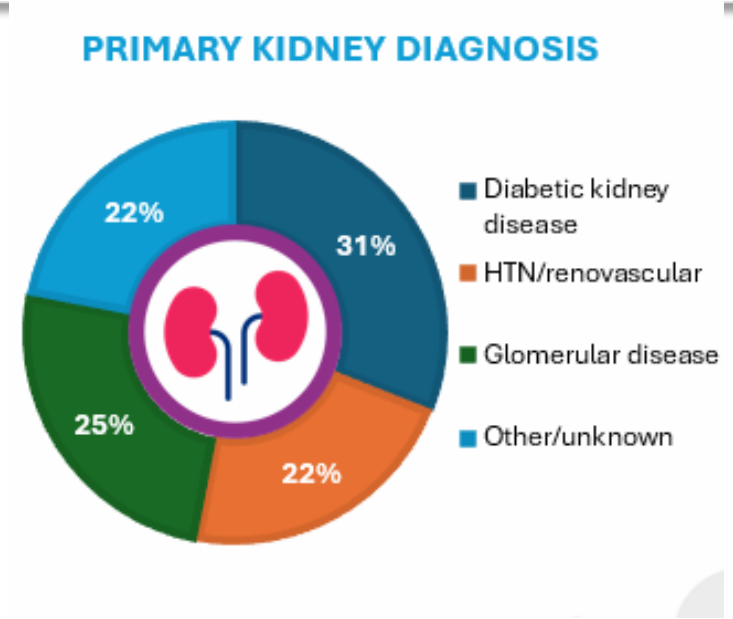


Table 1. (Continued.)

Characteristic	Empagliflozin (N=3304)	Placebo (N=3305)
Cause of kidney disease — no. (%)		
Diabetic kidney disease	1032 (31.2)	1025 (31.0)
Hypertensive or renovascular disease	706 (21.4)	739 (22.4)
Glomerular disease	853 (25.8)	816 (24.7)
Other	387 (11.7)	421 (12.7)
Unknown	326 (9.9)	304 (9.2)

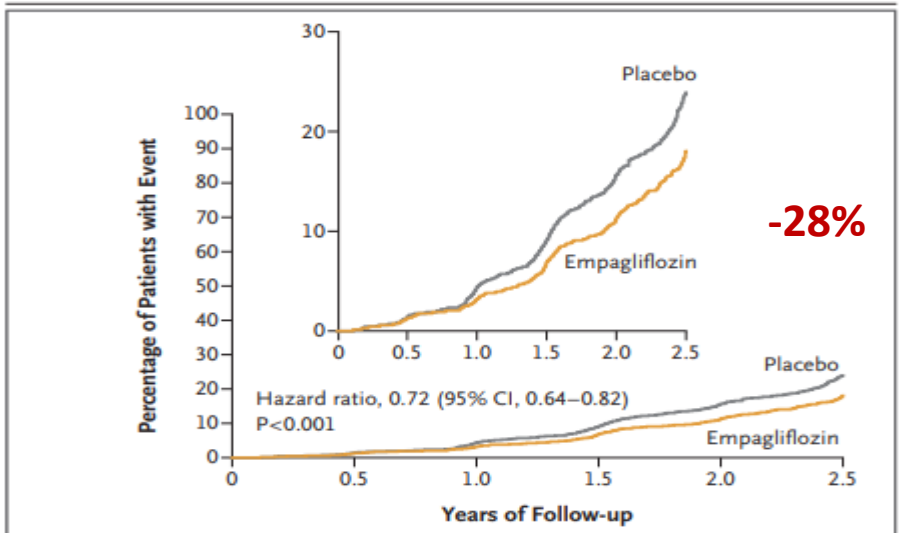
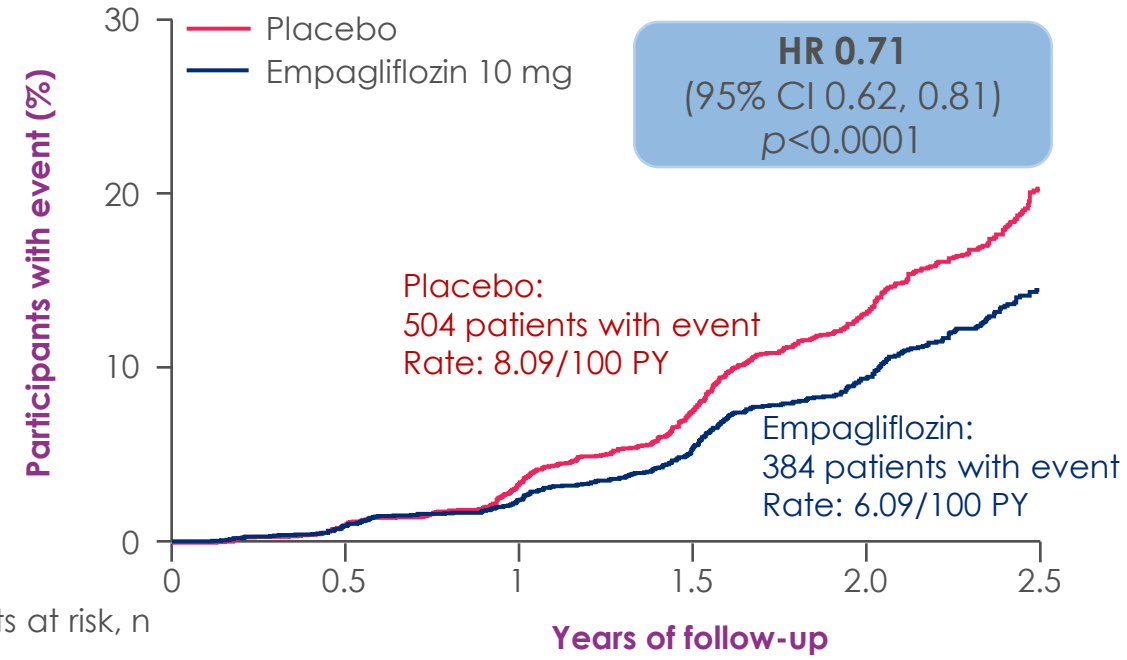


Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.
Shown are the results of the primary composite outcome of progression of kidney disease or death from cardiovascular causes. Over a median of 2 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 patients (13.1%) in the empagliflozin group and in 558 patients (16.9%) in the placebo group, representing 42 fewer primary-outcome events per 1000 patients in the empagliflozin group than in the placebo group over 2 years. The inset shows the same data on an enlarged y axis.

NOVEMBRE 2022

EmpaKidney Components of the primary outcome[1]

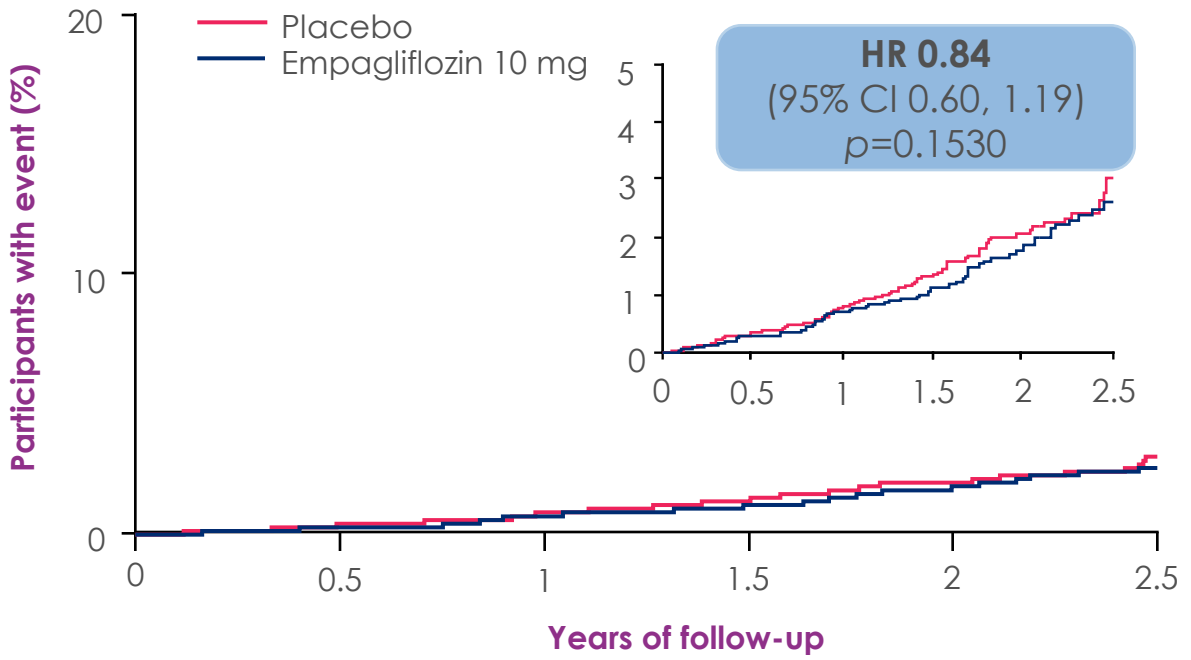
Kidney disease progression



Patients at risk, n

Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

CV death

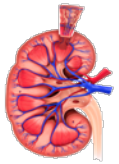


	3305	3282	3235	2387	1646	679
	3304	3283	3239	2371	1649	689

Kidney disease progression defined as end-stage kidney disease, a sustained decline in eGFR to <10 ml/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization
CV, cardiovascular; eGFR, estimated glomerular filtration rate; PY, patient-years; UACR, urine albumin-to-creatinine ratio

1. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117.

EMPA-KIDNEY enrolled a CKD population with a broad range of eGFR, with and without albuminuria[1]



EMPA-KIDNEY

Primary composite renal outcome:
ESKD, >40% sustained eGFR decline, or renal/CV death

2023

Secondary pre-specified exploratory endpoint: incident or worsening nephropathy,. Defined as progression to macroalbuminuria, doubling of serum creatinine initiation of renal replacement therapy or death from kidney disease.

Prognosis of CKD by eGFR and albuminuria categories[2]

eGFR category range (mL/min/1.73m²)			Albuminuria stage, description and range (mg/g)		
			A1	**A2**	**A3**
			Normal to mildly increased	Moderately increased	Severely increased
			<30	30–300	>300
	G1	≥90			
	G2	60–89			
	G3a	45–59			
	G3b	30–44			
	G4	15–29			
	G5	<15			

Low risk* | Moderately increased risk | High risk | Very high risk

EMPA-KIDNEY population[1]
Patients with or without diabetes and eGFR ≥45 to <90 mL/min/1.73m² **and** UACR ≥200 mg/g
or
eGFR ≥20 to <45 mL/min/1.73m²

CREDENCE population[3]
Patients with T2D and CKD and eGFR ≥30 to <90 mL/min/1.73m² **and** UACR >300 mg/g

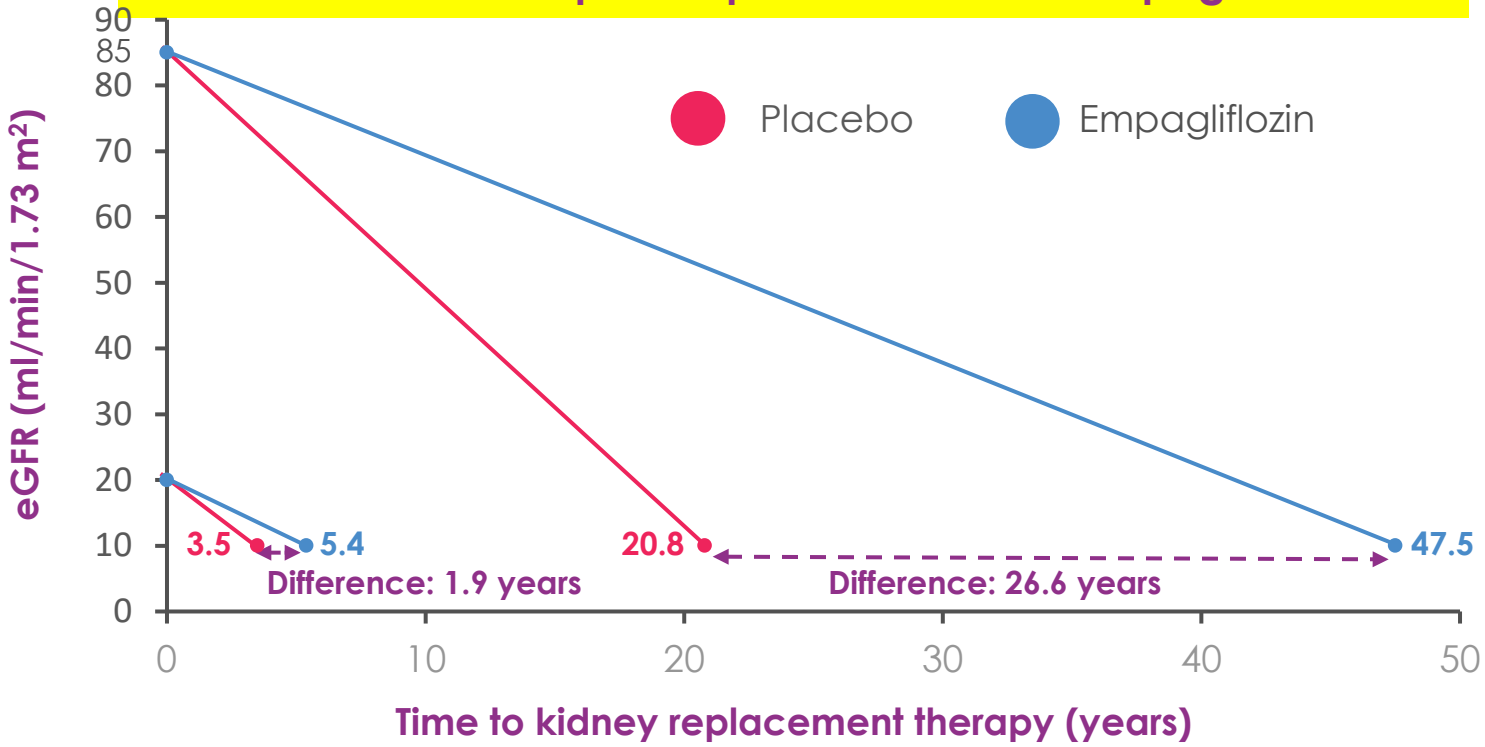
DAPA-CKD population[4]
Patients with or without T2D and eGFR ≥25 to ≤75 mL/min/1.73m² **and** UACR ≥200 mg/g

*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.

EMPA-KIDNEY: time to kidney replacement therapy

Hypothetical transformation of chronic eGFR slopes into time to kidney replacement therapy
Fernández-Fernandez B *et al*. Editorial comment

Potential impact on time to kidney replacement therapy of the different eGFR slopes on placebo and on empagliflozin*



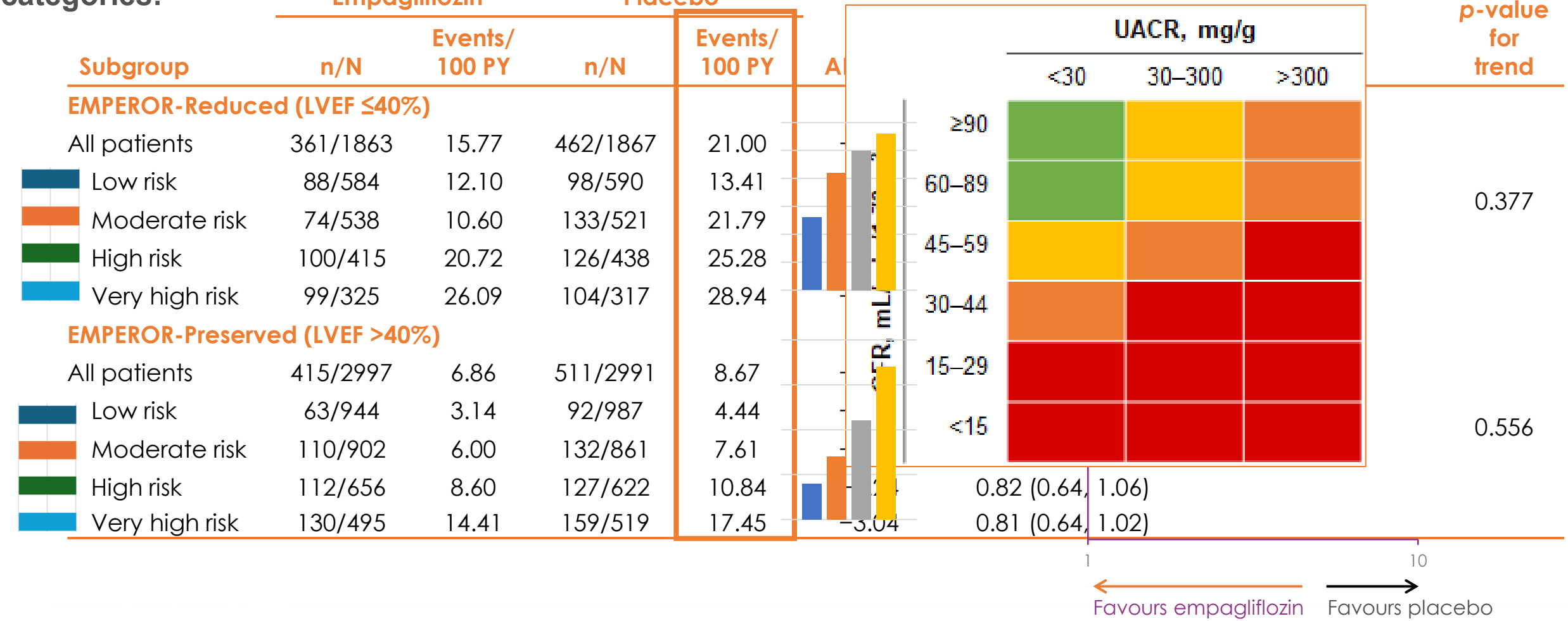
- Graphical presentation of representative chronic eGFR slopes from baseline to kidney failure
- Hypothetical lines have been traced starting from extremes of the baseline eGFR inclusion criteria values (20 and 85 ml/min/1.73 m^2) to eGFR 10 ml/min/1.73 m^2, corresponding to chronic eGFR slopes of participants on placebo and on empagliflozin within each baseline eGFR subgroup

*The difference in the time to kidney failure corresponds to the values in the figure on the previous slide for baseline eGFR 20 and 85 ml/min/1.73m^2.
eGFR, estimated glomerular filtration rate
Fernández-Fernandez B *et al. Clin Kidney J* 2023;0:1

Renal protection in all KDIGO categories patients with HF

KDIGO risk categories:

Subgroup	Empagliflozin n/N	Empagliflozin Events/ 100 PY	Placebo n/N	Placebo Events/ 100 PY	p-value for trend
EMPEROR-Reduced (LVEF ≤40%)					
All patients	361/1863	15.77	462/1867	21.00	
Low risk	88/584	12.10	98/590	13.41	0.377
Moderate risk	74/538	10.60	133/521	21.79	
High risk	100/415	20.72	126/438	25.28	
Very high risk	99/325	26.09	104/317	28.94	
EMPEROR-Preserved (LVEF >40%)					
All patients	415/2997	6.86	511/2991	8.67	
Low risk	63/944	3.14	92/987	4.44	0.556
Moderate risk	110/902	6.00	132/861	7.61	
High risk	112/656	8.60	127/622	10.84	
Very high risk	130/495	14.41	159/519	17.45	



ARR is expressed as events prevented per 100 PY of follow-up. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; LVEF, left ventricular ejection fraction; PY, patient-years.

Butler J *et al. J Am Coll Cardiol.* 2023;81:1902.

Hence what do we need in T2D Management?

- Glycemic Control
- Weight Management
- Managing Comorbidities
- Safety including low hypoglycemic risk

SGLT2i !!

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)
Obiettivi terapeutici

5. Terapia farmacologica

Nessun evento cardiovascolare, non scompenso cardiaco, eGFR≥ 60 ml/min	*Nessun evento cardiovascolare, non scompenso cardiaco, eGFR< 60 ml/min*	*Pregresso evento cardiovascolare, non scompenso cardiaco*	*Scompenso cardiaco*
Metformin	**Metformin[1]** + **SGLT2i**	**Met.** + **GLP1RA** + **SGLT-2i**	**SGLT2i**
SGLT2i + **GLP1RA**	**GLP1RA**		**Met.[2]** + **GLP1RA**
DPP4i / *Acar.* / *Pio.* / *Ins.*	*DPP4i* / *Acar.* / *Pio.* / *Ins.*	*DPP4i* / *Acar.* / *Pio.* / *Ins.*	*DPP4i[3]* / *Acar.* / *Insulin*

Hence what do we need in T2D Management?

- Glycemic Control
- Weight Management
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Metformin	**Metformin[1]**	**Met.**	**SGLT2i**
SGLT2i	**SGLT2i**	**GLP1RA**	**Met.[2]**
GLP1RA	**GLP1RA**	**SGLT-2i**	**GLP1RA**
DPP4i	*DPP4i*	*DPP4i*	*DPP4i[3]*
Acar.	*Acar.*	*Acar.*	*Acar.*
Pio.	*Pio.*	*Pio.*	*Insulin*
Ins.	*Ins.*	*Ins.*	

How should we treat early T2D patients with SGLT2-i?

Diabetes Ther (2021) 12:1445–1461
https://doi.org/10.1007/s13300-021-01045-7

ORIGINAL RESEARCH

The "Early Treatment" Approach Reducing Cardiovascular Risk in Patients with Type 2 Diabetes: A Consensus From an Expert Panel Using the Delphi Technique

Giuseppina Russo · Matteo Monami · Gianluca Perseghin · Angelo Avogaro · Pasquale Perrone Filardi · Michele Senni · Claudio Borghi · Aldo P. Maggioni

Received: December 30, 2020 / Accepted: March 2, 2021 / Published online: March 25, 2021

CONCLUSIONS

The results of the Delphi survey suggest that Italian diabetologists recognized the pivotal importance of adopting a tailored approach for patients with T2DM and CV risk factors; moreover, they emphasized the strategic role of the early treatment with GLP-1RAs and SGLT2 inhibitors in the treat-to-benefit approach.

A paradigm shift to enhance treatment adherence should therefore be implemented by focusing the attention not only on metabolic control but also on the long-term benefits of glucose-lowering agents with proven CV efficacy.

There are still some aspects where consensus was not achieved, reflecting open issues yet to be addressed.

Key Summary Points

Why carry out this study

Current guidelines and consensus recommend the use of hypoglycemic drugs with proven CV benefit for patients with type 2 diabetes (T2DM) and established CVD, heart failure, and/or chronic kidney disease.

Clear recommendations for the treatment of patients with newly diagnosed T2DM to prevent cardiovascular disease are not yet available.

The study aims to provide expert opinion on the hypoglycemic treatment and CV risk management in patients with newly diagnosed T2DM.

What was learned from the study?

Italian diabetologists consider the importance of adopting a personalized approach for patients with T2DM and CV risk factors

GLP-1RAs and SGLT2 inhibitors were recognized as key strategies in the treat-to-benefit approach.

A paradigm shift should be implemented to focus clinicians' attention not only on metabolic control but also on the long-term CV benefits, even at early stages.

The NEW ENGLAND JOURNAL of MEDICINE

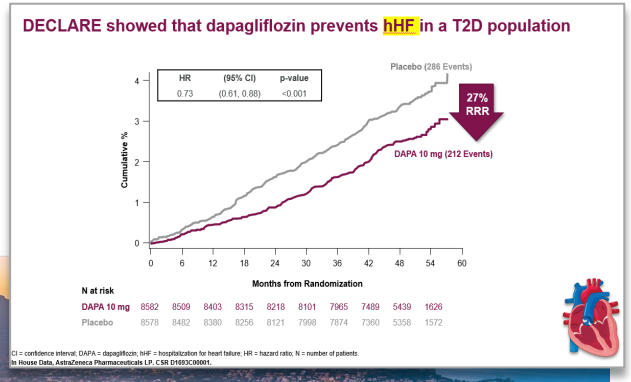
ORIGINAL ARTICLE

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*

DECLARE

In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of the 95% confidence interval [CI], but it did result in a lower rate of cardiovascular death or hospitalization for heart failure and of renal composite events.



The NEW ENGLAND JOURNAL of MEDICINE

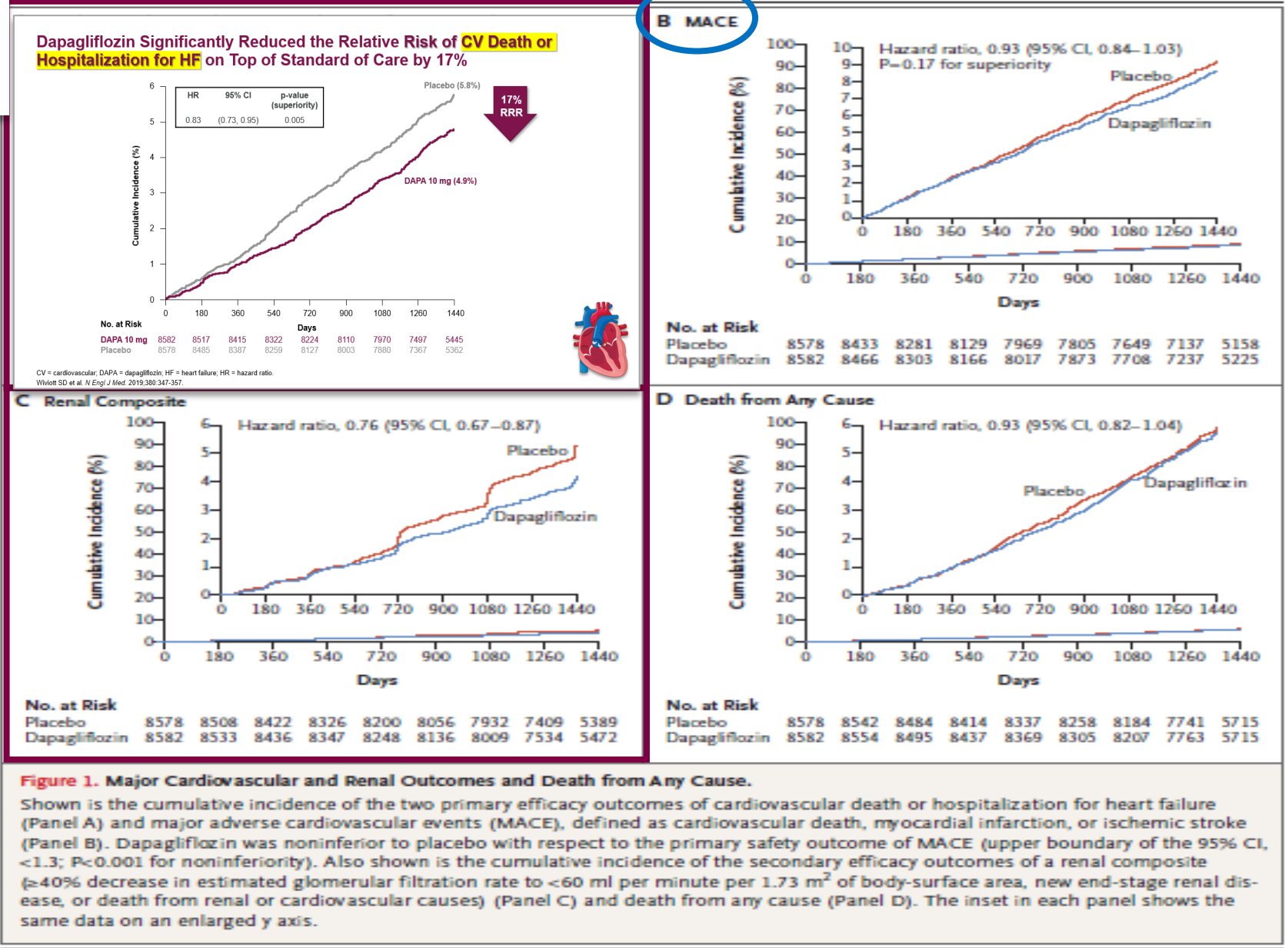


Figure 1. Major Cardiovascular and Renal Outcomes and Death from Any Cause.

Shown is the cumulative incidence of the two primary efficacy outcomes of cardiovascular death or hospitalization for heart failure (Panel A) and major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke (Panel B). Dapagliflozin was noninferior to placebo with respect to the primary safety outcome of MACE (upper boundary of the 95% CI, <1.3; P<0.001 for noninferiority). Also shown is the cumulative incidence of the secondary efficacy outcomes of a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) (Panel C) and death from any cause (Panel D). The inset in each panel shows the same data on an enlarged y axis.

Rappresentatività CVOts nella popolazione Annali AMD

Adv Ther
https://doi.org/10.1007/s12325-019-01043-z

ORIGINAL RESEARCH

Generalizability of Cardiovascular Safety Trials on SGLT2 Inhibitors to the Real World: Implications for Clinical Practice

Antonio Nicolucci · Riccardo Candido · Domenico Cucinotta · Giusi Graziano · Alberto Rocca · Maria C. Rossi · Franco Tuccinardi · Valeria Manicardi

Received: June 18, 2019

ABSTRACT

estimated the proportions of this patient pop-

Adv Ther

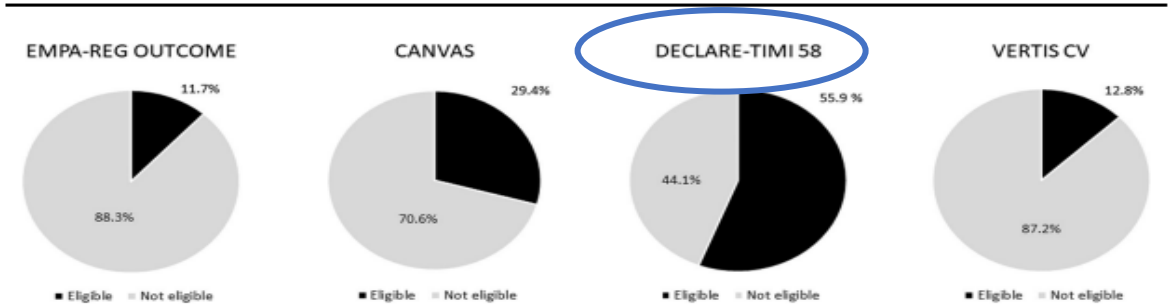


Fig. 1 Percentages of adults with type 2 diabetes in the AMD Annals database who would have met inclusion criteria for cardiovascular outcomes trials with empagliflozin, canagliflozin, dapagliflozin, or ertugliflozin

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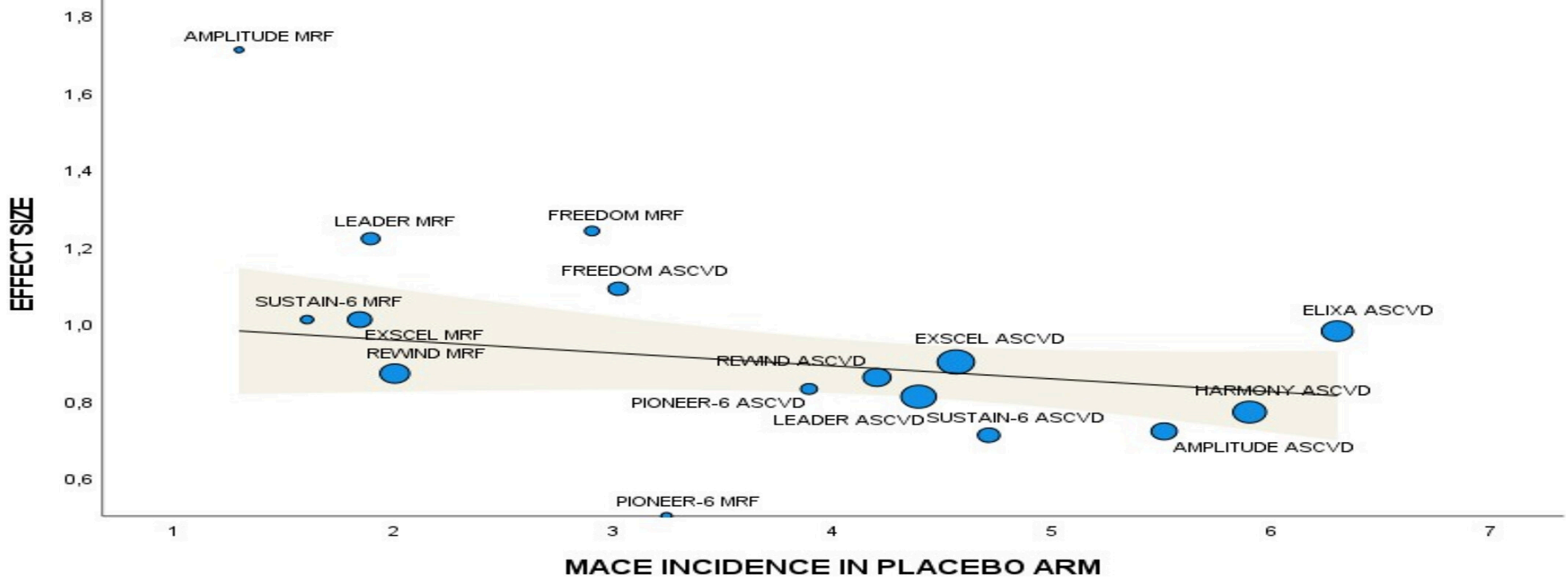
Received: 21 May 2023 | Revised: 11 July 2023 | Accepted: 11 July 2023
DOI: 10.1111/dom.15226

REVIEW ARTICLE

WILEY

Cardiovascular prevention with glucose-lowering drugs in type 2 diabetes: An evidence-based approach to the categories of primary and secondary prevention

Edoardo Mannucci MD | Giovanni Antonio Silverii MD



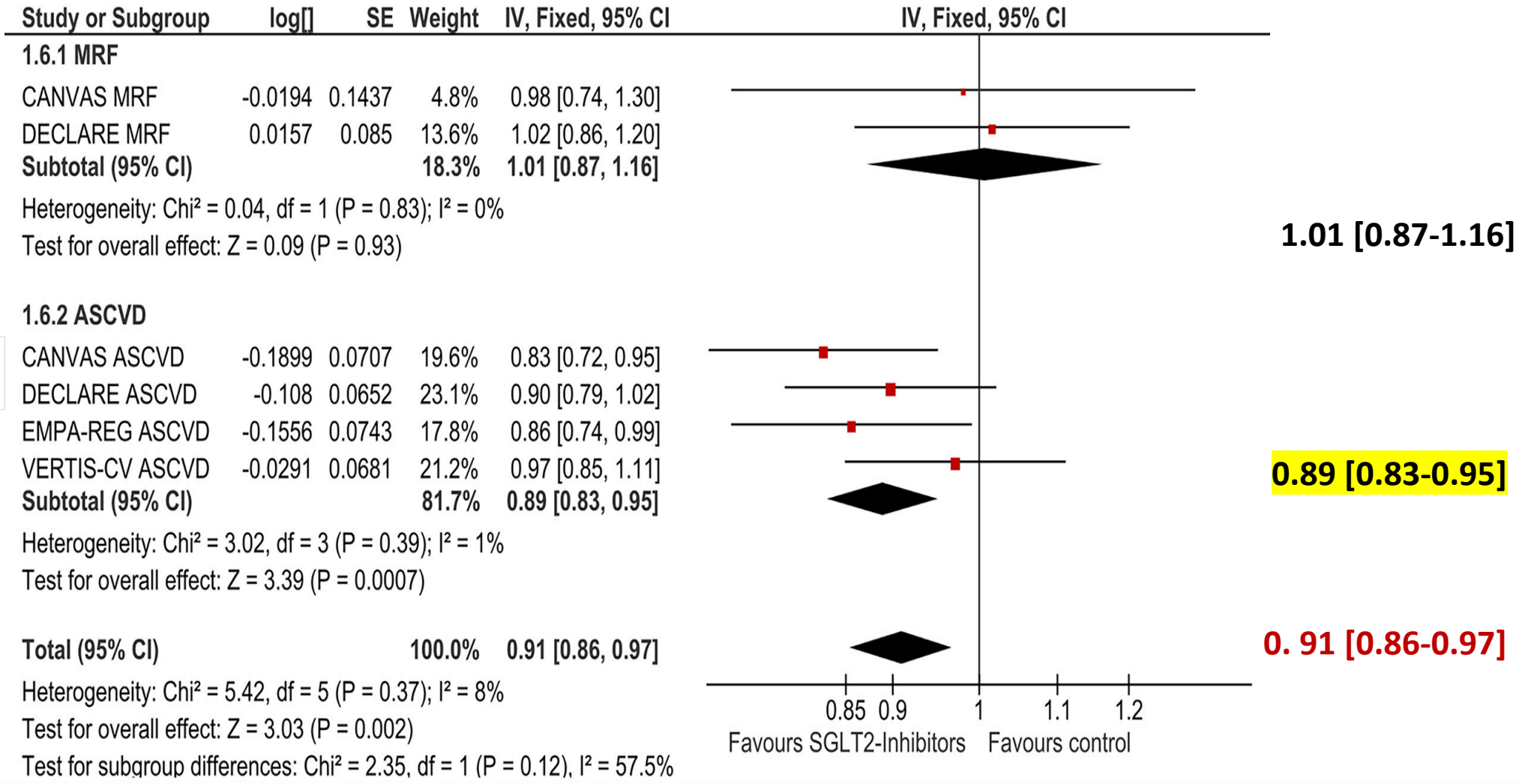
Mannucci E. et al. Diabetes Obesity Metabolism 2023; 25; 3435-3443

Cardiovascular prevention with glucose-lowering drugs in type 2 diabetes: An evidence-based approach to the categories of *primary and secondary prevention*

SGLT2i

Only MRF

AsCVD +



Mannucci E. et al. Diabetes Obesity Metabolism 2023; 25; 3435-3443

Cardiovascular prevention with glucose-lowering drugs in type 2 diabetes: An evidence-based approach to the categories of *primary and secondary prevention*

CONCLUSIONS FROM EVIDENCE AVAILABLE SO FAR

A methodologically rigorous assessment of available evidence leads to the conclusion that, at present, there is no clear demonstration of efficacy for the prevention of MACE in patients with diabetes and without established ASCVD with any class of glucose-lowering drugs.

At the same time, available evidence suggests that, in people with diabetes, there is no major difference in relative risk reduction with GLP-1 RA and SGLT2i between patients with ASCVD and those without ASCVD and with MRF.

On the other hand, baseline absolute risk in cohorts enrolled in clinical trials is much higher in the ASCVD than in the MRF subgroups; consequently, even in the case that relative risk reduction with drug treatment was independent of ASCVD, the expected effect of GLP-1 RA and SGLT2i on absolute risk would be considerably greater in patients with ASCVD.

Mannucci E. et al. Diabetes Obesity Metabolism 2023; 25; 3435-3443

SGLT2i in RWE studies: focus on «*early treatment*»

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)
Obiettivi terapeutici

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Nessun evento cardiovascolare, non scompenso cardiaco, eGFR≥ 60 ml/min	*Nessun evento cardiovascolare, non scompenso cardiaco, eGFR< 60 ml/min*	*Pregresso evento cardiovascolare, non scompenso cardiaco*	*Scompenso cardiaco*
Metformin	**Metformin**[1] + **SGLT2i**	**Met.** + **GLP1RA** + **SGLT-2i**	**SGLT2i**
SGLT2i + **GLP1RA**	**GLP1RA**		**Met.**[2] + **GLP1RA**
DPP4i / *Acar.* / *Pio.* / *Ins.*	*DPP4i* / *Acar.* / *Pio.* / *Ins.*	*DPP4i* / *Acar.* / *Pio.* / *Ins.*	*DPP4i*[3] / *Acar.* / *Insulin*

SGLT2 on IMT, endothelial dysfunction, and arterial stiffness

Hindawi
Journal of Diabetes Research
Volume 2024, Article ID 3212795, 14 pages
https://doi.org/10.1155/2024/3212795

Hindawi

Review Article

Effects of Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors on Intima-Media Thickness: Systematic Review and Meta-Analysis

Interventional and observational studies that provided data on the effects of GLP-1 RAs or SGLT2is on IMT were included.

Eighteen studies examined the effects of GLP-1 RA, and eleven examined the effects of SGLT2i.

GLP-1 RA and SGLT2i significantly decreased IMT :

- **GLP1RAs : (MD = –0 123, 95% CI (-0.170, -0.076), P < 0 0001, I2 = 98%**
- **SGLT2I: MD = – 0 048, 95% CI (-0.092, -0.004), P = 0 031, I2 = 95%**

Conclusions. Treatment with GLP-1 RA and SGLT2i can **lower IMT** in diabetic patients, and GLP-1 RA may be more effective than SGLT2i.

medication (GLP-1 RA: liraglutide and exenatide; SGLT2i: empagliflozin, ipragliflozin, tofogliflozin, and dapagliflozin), randomized clinical trials (RCTs), and diabetic patients. *Results*. The literature search yielded 708 related articles after duplicates were removed. Eighteen studies examined the effects of GLP-1 RA, and eleven examined the effects of SGLT2i. GLP-1 RA and SGLT2i significantly decreased IMT (MD = −0.123, 95% CI (-0.170, -0.076), $P < 0.0001$, $I^2 = 98\%$ and MD = −0.048, 95% CI (-0.092, -0.004), $P = 0.031$, $I^2 = 95\%$, respectively). Metaregression showed that IMT change correlated with baseline IMT, whereas it did not correlate with gender, duration of diabetes, and duration of treatment. *Conclusions*. Treatment with GLP-1 RA and SGLT2i can lower IMT in diabetic patients, and GLP-1 RA may be more effective than SGLT2i.

atherosclerosis

RESEARCH ARTICLE | VOLUME 391, 117490, APRIL 2024

Purchase

Comparative effects of glucose-lowering agents on endothelial function and arterial stiffness in patients with type 2 diabetes: A network meta-analysis

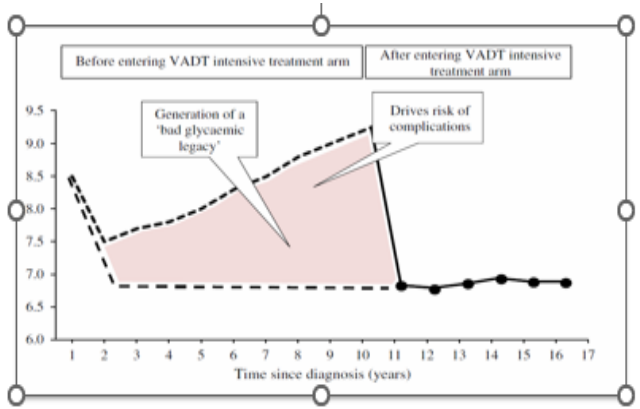
Hayeon Kim • Cheol Ung Choi • Kiyon Rhew • ... Yejee Lim • Myeong Gyu Kim • Kyungim Kim •
Show all authors

- Validated indicators such as **flow-mediated dilation (FMD;** positive value favors) and **pulse wave velocity (PWV**; negative value favors)
- RCTs comparing the effects of GLAs on FMD or PWV with placebo or other GLAs in T2D patients
- **38 RCTs with 2,065 patients**.

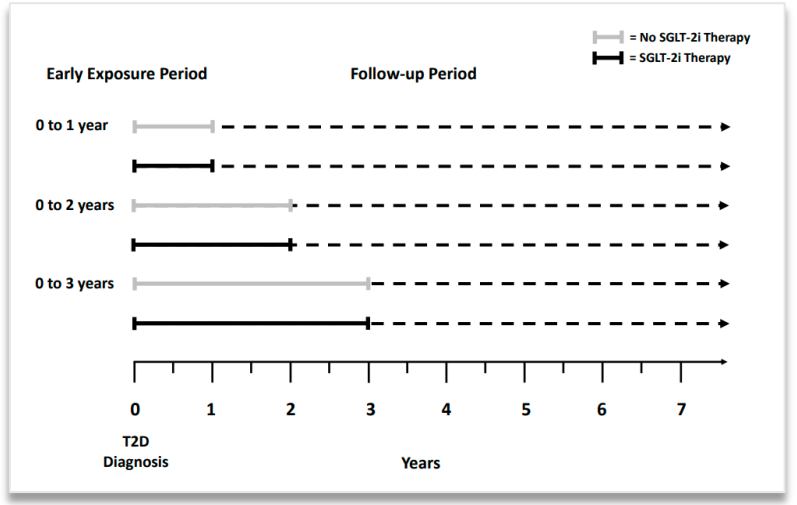
This Network meta-analysis showed more favorable effects of **GLP-1RAs** and **SGLT-2Is** than placebo in improving both **arterial stiffness** and **endothelial function** in patients with T2DM.

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,[j]



We took advantage of a large Italian clinical registry of people with T2D, the AMD Annals Initiative, to extrapolate data from newly-diagnosed patients and free of CVD at baseline, in order to examine the association between attained HbA1c targets in the years following T2D diagnosis and later CVD, *evaluated as a composite of myocardial infarction, stroke, coronary or peripheral revascularization, and coronary or peripheral bypass,* in the whole cohort and then in two populations of patients: those introducing early an SGLT-2i and patients not treated with these drugs during the same period.



251,339 subjects with newly-diagnosed T2D and without CVD at baseline.

Primary Outcome: a composite of myocardial infarction, stroke, coronary or peripheral revascularization, and coronary or peripheral bypass.

The Lancet Regional Health - Europe 2023;31: 100666

Ceriello A., *Russo GT, et al.* Lancet PH Europe, 2023; :31:100666

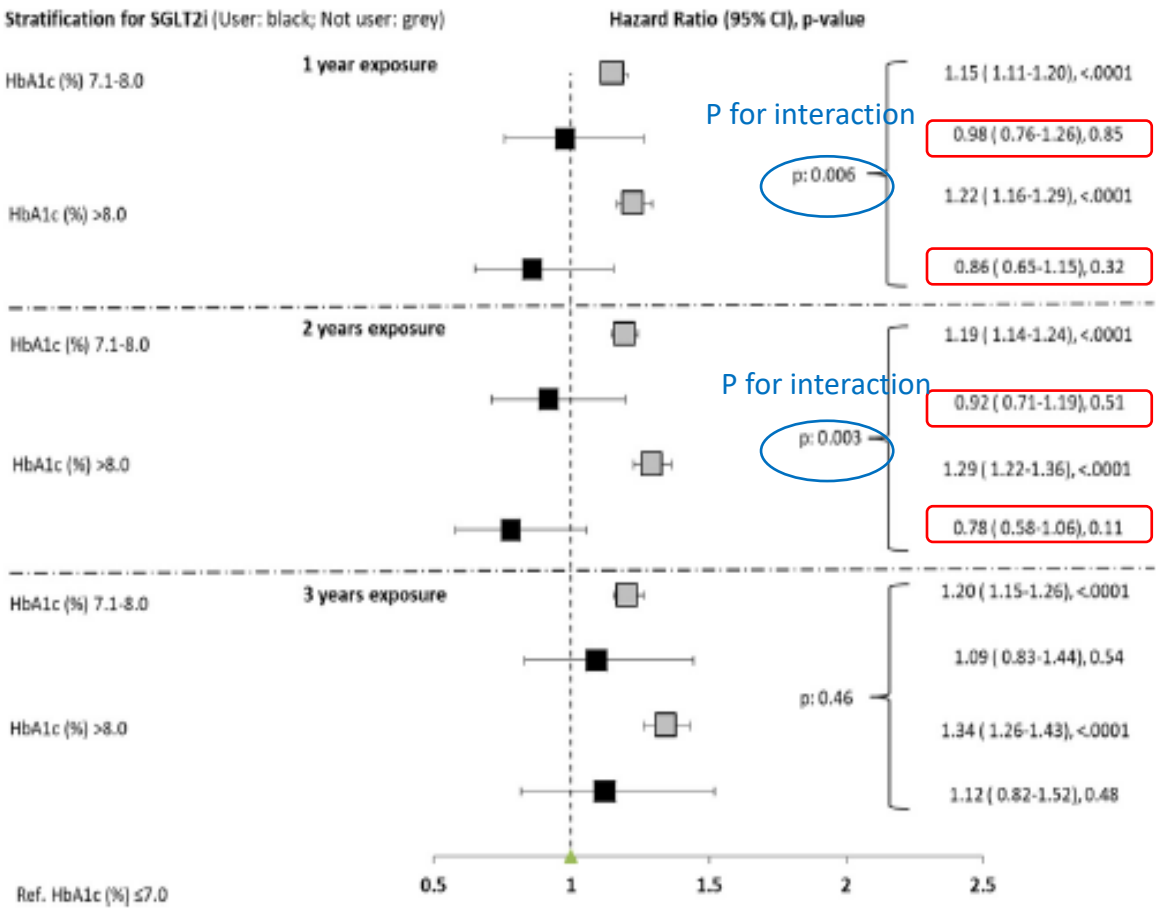


Fig. 4: **Early introduction of SGLT-2i attenuate metabolic memory.** Pseudo-forest plot showing the adjusted hazard ratios (HR) with the relative 95% confidence interval (CI) and the p value, derived from the Cox regression analyses exploring the associations between glycemic control and the risk of the CVD at follow-up in patients stratified according to use of SGLT-2i during the exposure phase or not users, in the three exposure periods assessed. HbA1c ≤ 7% is the reference.

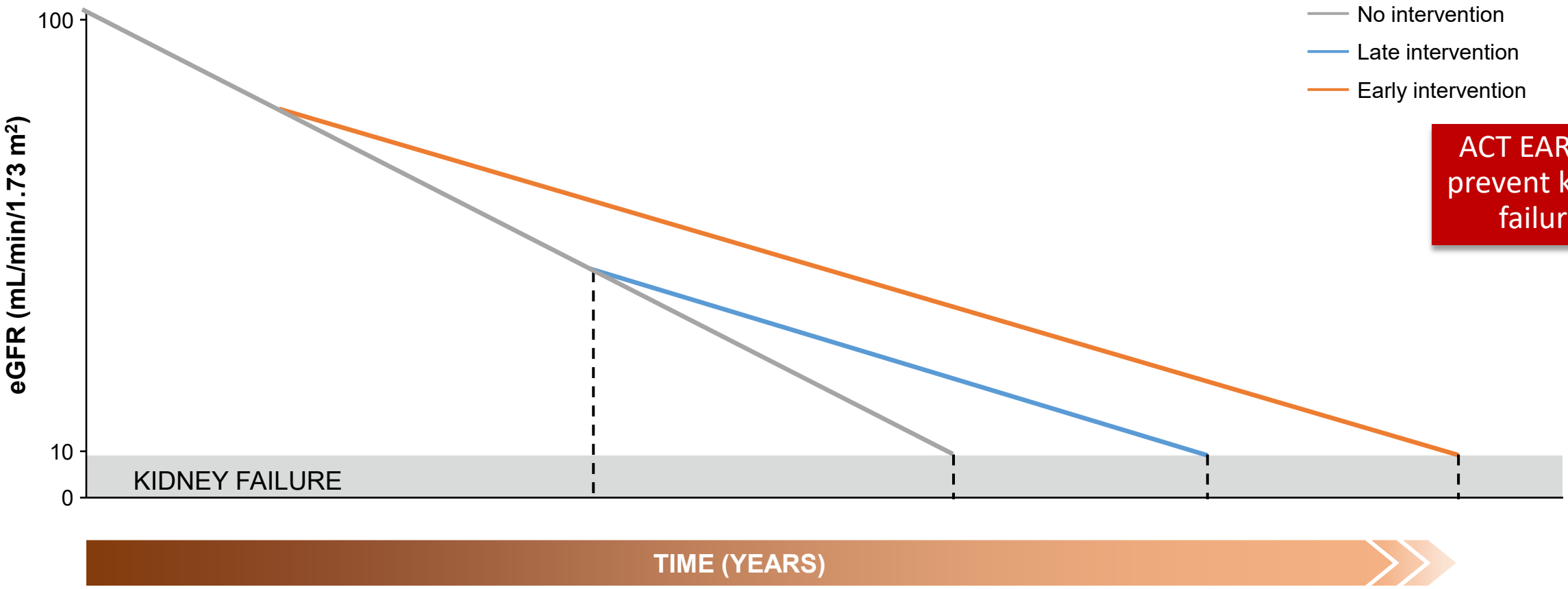
The introduction of SGLT-2i during the exposure periods of 0–1 and 0–2 years eliminated the association between poor glycemic control and the outcome (p for interaction 0.006 and 0.003, respectively, vs. patients with the same degree of glycemic control but not treated with these drugs).

Ceriello A., *Russo GT, et al.* Lancet PH Europe, 2023; :31:100666

Improving diagnosis rates, especially in the earlier stages, is essential for improving outcomes

Early intervention in CKD slows disease progression, preserves kidney function, and improves patient outcomes[1]

Effect of no intervention, late intervention, and early intervention on eGFR decline[2,3]



1. Shlipak MG, et al. Kidney Int 2021;99:34–47; 2. Gansevoort RT, et al. J Am Soc Nephrol 2009;20:465–468

DARWIN-RENAL

Long-term benefits of dapagliflozin on renal outcomes of type 2 diabetes under routine care: a comparative effectiveness study on propensity score matched cohorts at low renal risk

Gian Paolo Fadini,[a,b,f,*] Enrico Longato,[c,f] Mario Luca Morieri,[a] Stefano Del Prato,[d] Angelo Avogaro,[a] and Anna Solini,[e]
DARWIN-Renal Study Investigators

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[b]Laboratory of Experimental Diabetology, Veneto Institute of Molecular Medicine, 35128 Padova, Italy
[c]Department of Information Engineering, University of Padova, 35100 Padua, Italy
[d]Department of Clinical & Experimental Medicine, University of Pisa and Sant'Anna School of Advanced Studies, 56126 Pisa, Italy
[e]Department of Surgical, Medical, Molecular and Critical Area Pathology, University of Pisa, Italy

The Lancet Regional Health - Europe 2024;38: 100847
Published Online xxx
https://doi.org/10.1016/j.lanepe.2024.100847

Summary

Background Despite the overall improvement in care, people with type 2 diabetes (T2D) experience an excess risk of end-stage kidney disease. We evaluated the long-term effectiveness of dapagliflozin on kidney function and albuminuria in patients with T2D.

Methods We included patients with T2D who initiated dapagliflozin or comparators from 2015 to 2020. Propensity score matching (PSM) was performed to balance the two groups. The primary endpoint was the change in estimated glomerular filtration rate (eGFR) from baseline to the end of observation. Secondary endpoints included changes in albuminuria and loss of kidney function.

Findings We analysed two matched groups of 6197 patients each. The comparator group included DPP-4 inhibitors (40%), GLP-1RA (22.3%), sulphonylureas (16.1%), pioglitazone (8%), metformin (5.8%), or acarbose (4%). Only 6.4% had baseline eGFR <60 ml/min/1.73 m^2 and 15% had UACR >30 mg/g. During a mean follow-up of 2.5 year, eGFR declined significantly less in the dapagliflozin vs comparator group by 1.81 ml/min/1.73 m^2 (95% C.I. from 1.13 to 2.48; $p < 0.0001$). The mean eGFR slope was significantly less negative in the dapagliflozin group by 0.67 ml/min/1.73 m^2/year (95% C.I. from 0.47 to 0.88; $p < 0.0001$). Albuminuria declined significantly in new-users of dapagliflozin within 6 months and remained on average 44.3 mg/g lower (95% C.I. from −66.9 to −21.7; $p < 0.0001$) than in new-users of comparators. New-users of dapagliflozin had significantly lower rates of new-onset CKD, loss of kidney function, and a composite renal outcome. Results were confirmed for all SGLT2 inhibitors, in patients without baseline CKD, and when GLP-1RA were excluded from comparators.

Interpretation Initiating dapagliflozin improved kidney function outcomes and albuminuria in patients with T2D and a low renal risk.

Funding Funded by the Italian Diabetes Society and partly supported by a grant from AstraZeneca.

Keywords: Type 2 diabetes; Chronic kidney disease; SGLT2 inhibitors; Prevention; Observational

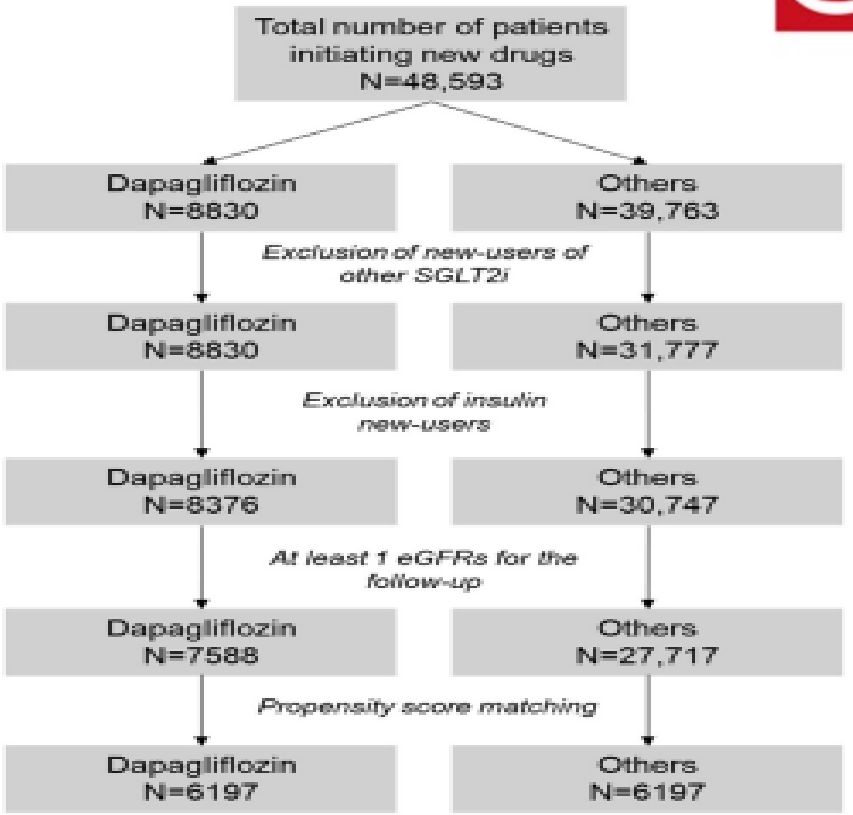


Fig. 1: Study flowchart.

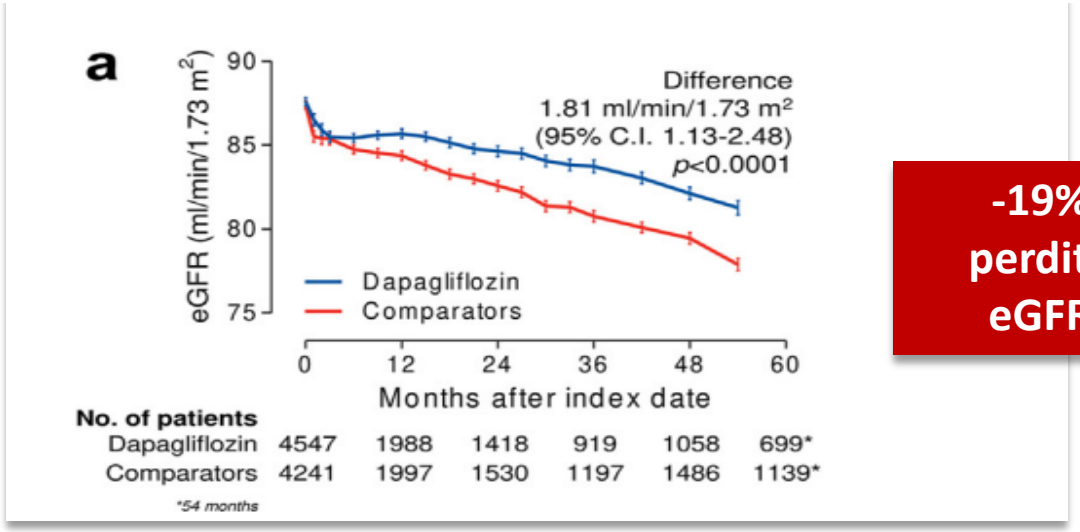
Scopo: valutare efficacia a lungo termine di dapagliflozin sulla malattia renale e albuminuria nei pazienti con DM2

Pazienti senza malattia renale al basale

DARWIN-RENAL

-19% perdita eGFR

albuminuria



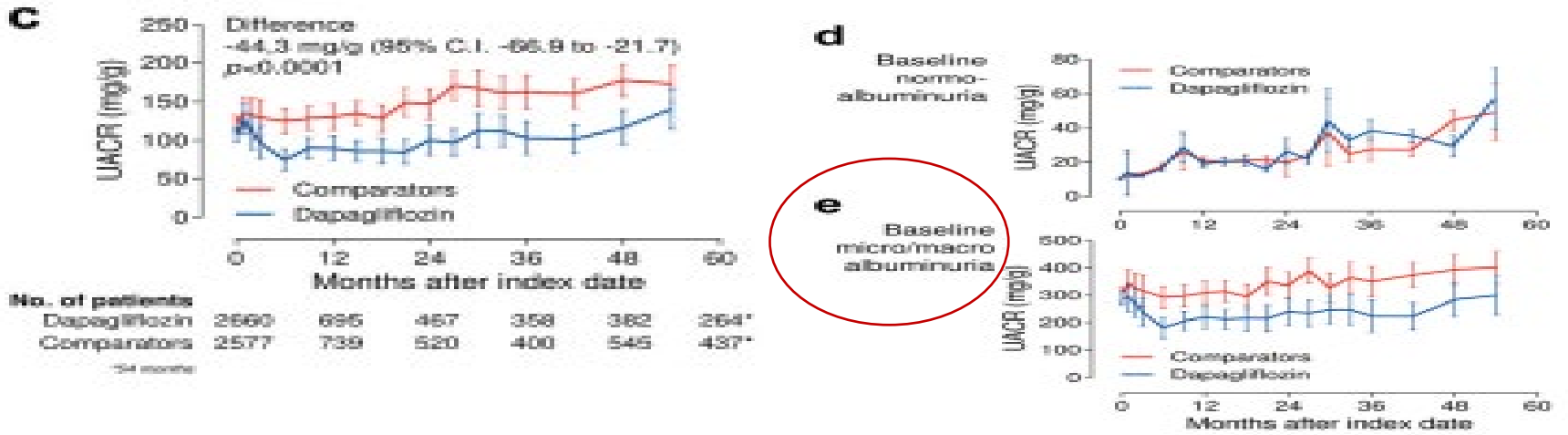


Fig. 2: Change in eGFR and albuminuria in the primary ITT analysis. a) Change in eGFR over time in the two groups (primary outcome). The table at the bottom of the panel shows the number of patients contributing with data at each time point. This is the primary analysis performed, on average on a total of 6197 patients/group contributing with eGFR values, though not all patients had available baseline eGFR. Baseline eGFR was imputed only for PSM, but imputed data were not used for outcome evaluation. b) Total and chronic (6 months on) eGFR slopes in the two groups (bars indicate 95% C.I.). c) Adjusted change in albuminuria (urinary albumin excretion rate, UACR) over time in the two groups and in the split of the population by baseline normo- (d) or micro-macroalbuminuria (e). The table at the bottom of the panel shows the number of patients contributing with data at each time point. The observation period was cut at 54 months.

DARWIN-RENAL

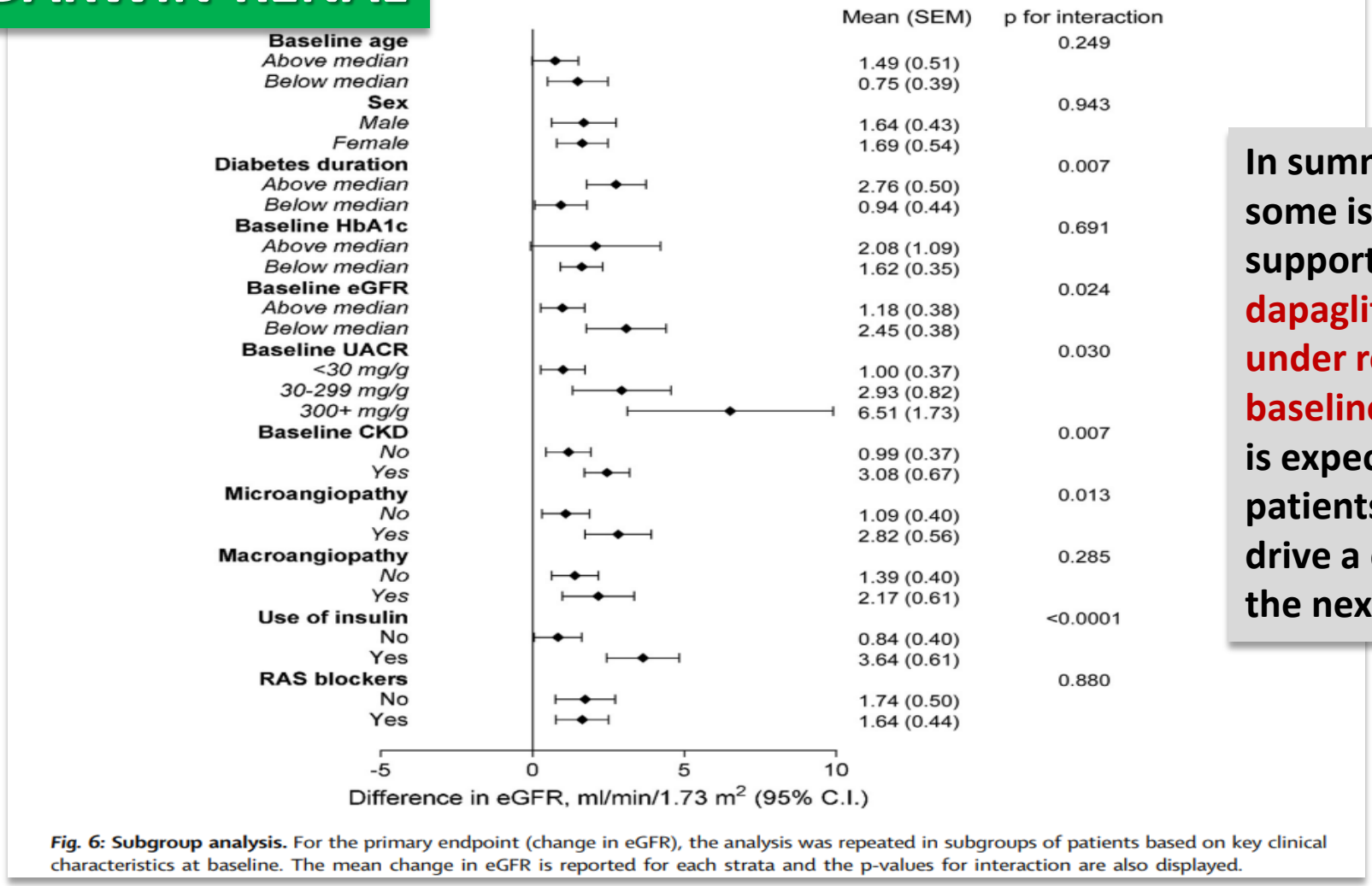
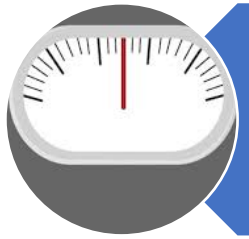
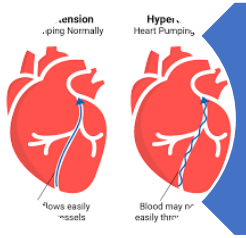


***Fig. 6:* Subgroup analysis.** For the primary endpoint (change in eGFR), the analysis was repeated in subgroups of patients based on key clinical characteristics at baseline. The mean change in eGFR is reported for each strata and the p-values for interaction are also displayed.

In summary, our study, designed to overcome some issues with prior observational research, supports the strong protective effects of dapagliflozin against the loss of kidney function under routine care, even in patients without baseline CKD. Based on real-world evidence, it is expected that broadening the population of patients with T2D who are receiving SGLT2i will drive a change in the epidemiology of ESKD in the next decades.

Hence what do we need in T2D Management?

- Glycemic Control 
- Weight Managemer 
- Managing Comorbidities 
- Safety including low hypoglycemic risk 

SGLT2i effetto metabolico e cardio-nefrovascolare !!


Grazie per l’attenzione

The NEW ENGLAND JOURNAL of MEDICINE

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Empagliflozin in Heart Failure with a Preserved Ejection Fraction

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ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

METHODS

In this double-blind trial, we randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS

Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

CONCLUSIONS

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Anker at the Department of Cardiology and BCRT (Campus CVK), Charité Universitätsmedizin Berlin, 13353 Berlin, Germany, or at s.anker@cachexia.de, or to Dr. Butler at the Department of Medicine, University of Mississippi Medical Center, 2500 North State St., Jackson, MS 39216, or at jbutler4@umc.edu.

*The EMPEROR-Preserved Trial Investigators are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Anker and Butler contributed equally to this article.

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CME at NEJM.org

EMPEROR PRESERVED

NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)

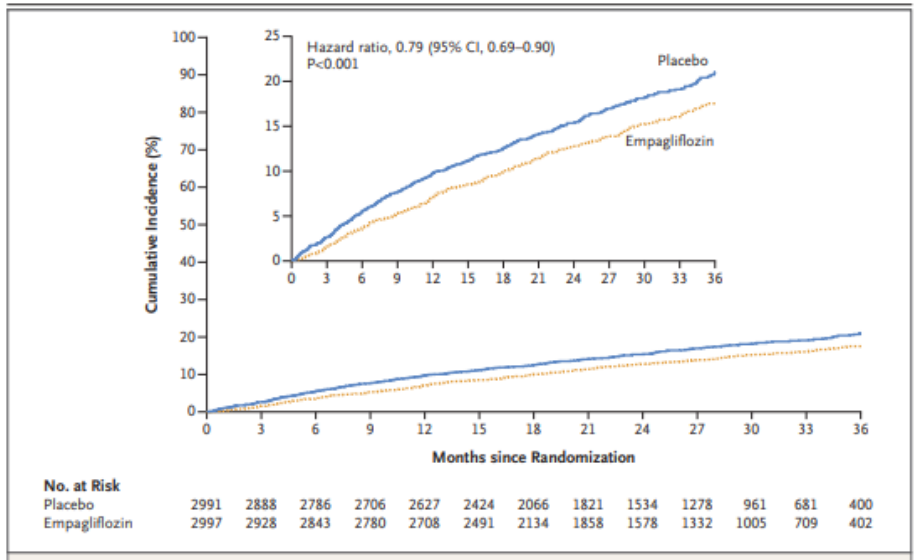

Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

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*

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk c
tion for heart failure and cardiovascular death among patients with
failure and a left ventricular ejection fraction of 40% or less. Whetl
hibitors are effective in patients with a higher left ventricular eje
remains less certain.

METHODS

We randomly assigned 6263 patients with heart failure and a left ve
tion fraction of more than 40% to receive dapagliflozin (at a dose o
daily) or matching placebo, in addition to usual therapy. The primary
a composite of worsening heart failure (which was defined as either
hospitalization for heart failure or an urgent visit for heart failure)
cular death, as assessed in a time-to-event analysis.

RESULTS

Over a median of 2.3 years, the primary outcome occurred in 512 of
(16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5
cebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to
Worsening heart failure occurred in 368 patients (11.8%) in the
group and in 455 patients (14.5%) in the placebo group (hazard rat
CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7
patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05)
and symptom burden were lower in the dapagliflozin group than i
group. Results were similar among patients with a left ventricular eje
of 60% or more and those with a left ventricular ejection fraction of l
and results were similar in prespecified subgroups, including pat
without diabetes. The incidence of adverse events was similar in the

CONCLUSIONS

Dapagliflozin reduced the combined risk of worsening heart failure
cular death among patients with heart failure and a mildly reduced
ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials
NCT03619213.)

DELIVER: The largest and broadest trial to date in patients with LVEF >40%[1]

6263 patients with heart failure and a **left ventricular ejection fraction of more than 40%** to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy.

The **primary outcome** was a composite of **worsening heart failure** (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) **or cardiovascular death**, as assessed in a time-to-event analysis.