SGLT2i: oltre la glicemia

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Dichiarazione dei conflitti d'interesse

Gianluca Perseghin dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Honorarium as a speaker in Scientific Events

AstraZeneca
Bayer
Boheringer Ingelheim
Daiichi Sankyo
Lilly
Menarini Diag
MSD
Novartis
Novo Nordisk
PikDare
Roche Diag
Sanofi
Servier

Scientific advisory boards

AstraZeneca
Intercept
Lilly
Merck
Novartis
Novo Nordisk
Pfizer
PikDare
Sanofi

Effetti metabolici, emodinamici, antropometrici, FdR CVD, e CVD/CKD degli SGLT2-i

Metabolici: HbA1c, insulino sensibilità e metabolismo energetico (mitocondrio e stress ossidativo), eritropoietina, corpi chetonici, funzione beta- (e alfa-) cellulare, profilo lipidico

Effetti glucosio indipendenti

Emodinamici: pressione arteriosa, natriuresi, bilancio di attivazione simpatico/parasimpatico

Antropometrici: Massa corporea, grasso viscerale, grasso ectopico (NAFLD/NASH)

FdR CVD non classici: Infiammazione, disfunzione endoteliale, aterogenesi, effetto uricosurico

CVD: riduzione MACE, hHF & new onset HF

CKD: riduzione end-point renale (riduzione proteinuria e rallentamento progressione eGFR)

DeFronzo RA et al Diabetes Obes Metab, 2017

CVD

CVOTs in T2DM

Table 1. Cardiovascular Outcome Trials Involving Patients with Type 2 Diabetes.*

Variable	EMPA-REG OUTCOME	CANVAS Program	CREDENCE	DECLARE–TIMI 58	VERTIS CV	SCORED	All
Drug	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Sotagliflozin	
No. of patients	7020	10,142	4401	17,160	8246	10,584	57,553
Atherosclerotic cardiovascular disease — % of patients	100	65.6	50.4	40.6	100	48.6	63.0
History of heart failure — % of patients	10.1	14.4	14.8	10.0	23.7	31.0	17.0
Outcomes — hazard ratio (95% CI)†							
Major adverse cardiovascular events	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.80 (0.67–0.95)	0.93 (0.84–1.03)	0.99 (0.88–1.12)	0.77 (0.65–0.91)	0.89 (0.84–0.94)
Cardiovascular death	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.78 (0.61–1.00)	0.98 (0.82–1.12)	0.92 (0.77–1.10)	0.90 (0.73–1.12)	0.86 (0.79–0.93)
Hospitalization for heart failure	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.61 (0.47–0.80)	0.73 (0.61–0.88)	0.70 (0.54–0.90)	0.67 (0.55–0.82)	0.68 (0.62–0.75)

* Data sources for the individual trials are as follows: EMPA-REG OUTCOME, Zinman et al.[14]; CANVAS Program, Neal et al.[15]; CREDENCE, Perkovic et al.[16]; DECLARE–TIMI 58, Wiviott et al.[17]; VERTIS CV, Cannon et al.[18]; and SCORED, Bhatt et al.[19] Data are also based on a meta-analysis by McGuire et al.[20]

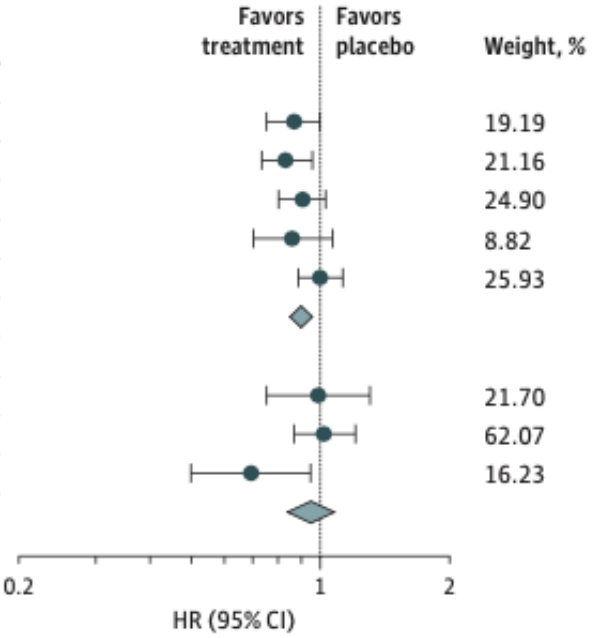
† Hazard ratios are based on a time-to-first event analysis, except for SCORED, which estimated hazard ratios for major adverse cardiovascular events and hospitalization for heart failure on the basis of a total-event analysis. CI denotes confidence interval.

Braunwald E, N Engl J Med, 2022

MACE in CVD PREVENTION

B MACEs by ASCVD status

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



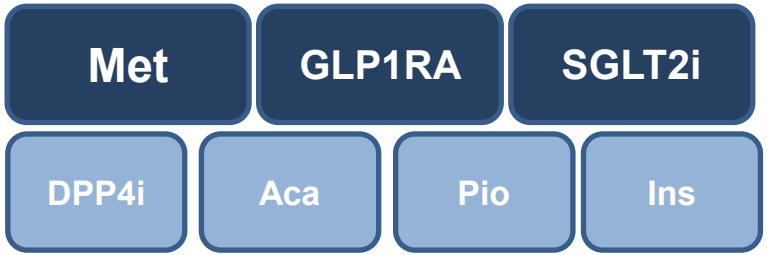
McGuire DK et al, JAMA Cardiol, 2021

Terapia Farmacologica

Quali sono i farmaci di prima, seconda e terza istanza da impiegare per il controllo della glicemia nei pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari?

Si raccomanda l'uso di metformina, SGLT-2i e GLP-1 RA come farmaci di prima scelta per il trattamento a lungo termine in pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari e senza scompenso cardiaco.

Pioglitazone, DPP-4i, acarbosio ed insulina dovrebbero essere considerati farmaci di seconda scelta.



Forza della raccomandazione: forte. Qualità delle prove: moderata.

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ (6 luglio 2021)

hHF

CVD death or hHF

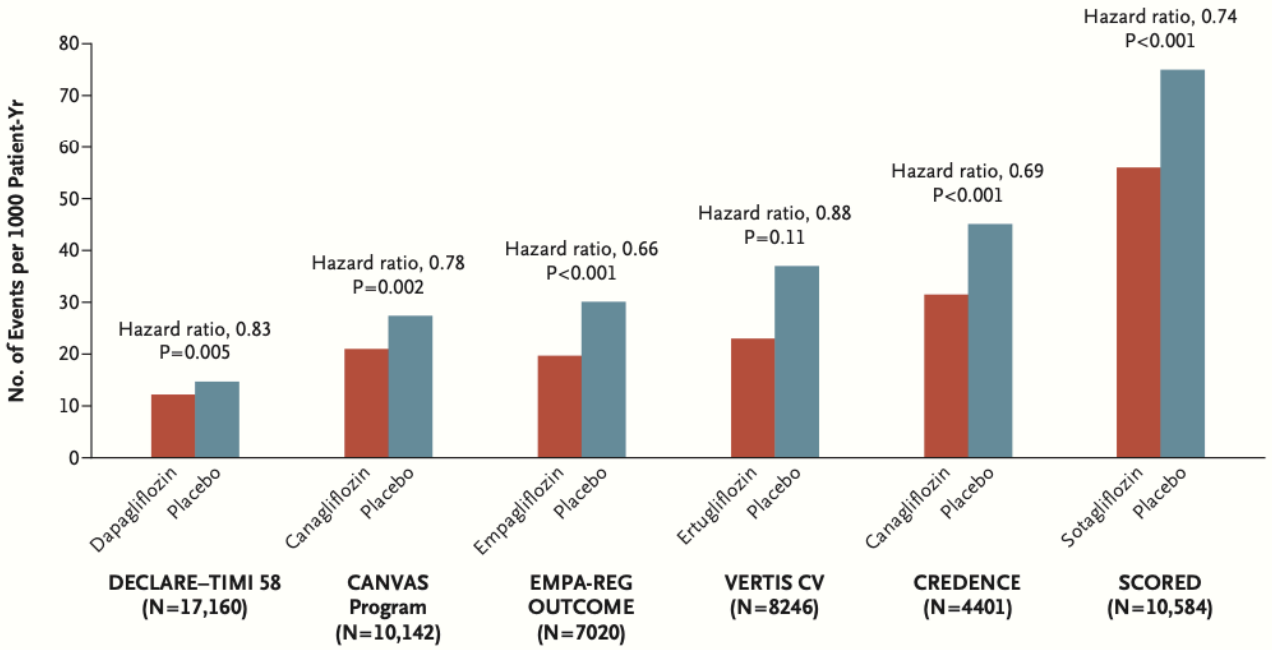


Figure 1. Cardiovascular Death or Hospitalization for Heart Failure among Patients with Type 2 Diabetes Enrolled in Six Treatment Trials.

Outcomes are shown in ascending order of frequency from left to right. Data sources for the six trials are as follows: DECLARE–TIMI 58, Wiviott et al.[17]; CANVAS Program, Young et al.[21]; EMPA-REG OUTCOME, Zinman et al.[14]; VERTIS CV, Cannon et al.[18]; CREDENCE, Perkovic et al.[16]; and SCORED, Bhatt et al.[19]

Braunwald E, N Engl J Med, 2022

CVOTs in HF

Table 2. Cardiovascular Outcome Trials Involving Patients with Heart Failure.*

Variable	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	SOLOIST-WHF
Drug	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
No. of patients	4744	3730	5988	1222
Type 2 diabetes — % of patients	41.7	49.8	49.1	100
LVEF — %	31.1	27.4	54.3	35
Median NT-proBNP — pg/ml	1437	1907	970	1864
Mean eGFR — ml/min/1.73 m^2	65.7	62.0	60.6	49.9
Outcomes — hazard ratio (95% CI)				
Cardiovascular death or hospitalization for heart failure	0.74 (0.65–0.85)	0.75 (0.68–0.86)	0.79 (0.69–0.90)	0.67 (0.52–0.85)
Hospitalization for heart failure	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.64 (0.49–0.83)

* Data sources for the trials are as follows: DAPA-HF, McMurray et al.[24]; EMPEROR-Reduced, Packer et al.[25]; EMPEROR-Preserved, Anker et al.[26]; SOLOIST-WHF, Bhatt et al.[27] The abbreviation eGFR denotes estimated glomerular filtration rate, LVEF left ventricular ejection fraction, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

HF Trials
(+/- diabetes)

DAPA-HF
(Dapagliflozin NEJM 2020)

Emperor Reduced
(Empagliflozin NEJM 2020)

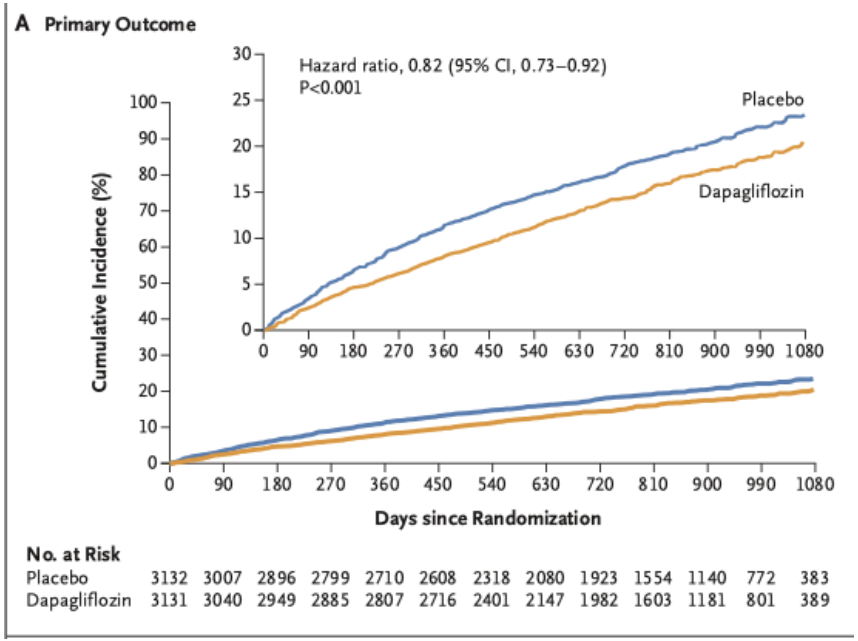
Emperor Preserved
(Empagliflozin NEJM 2021)

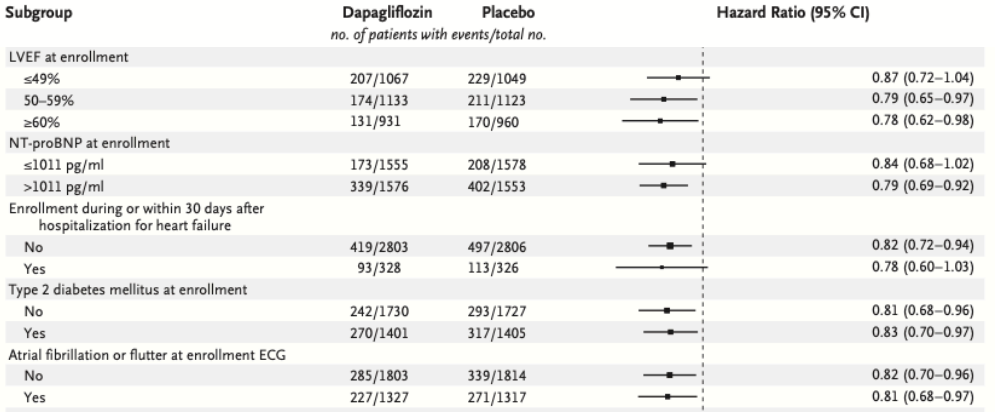
SOLOIST – WHF
(Sotagliflozin NEJM 2021)

DELIVER
(Dapagliflozin NEJM 2022)

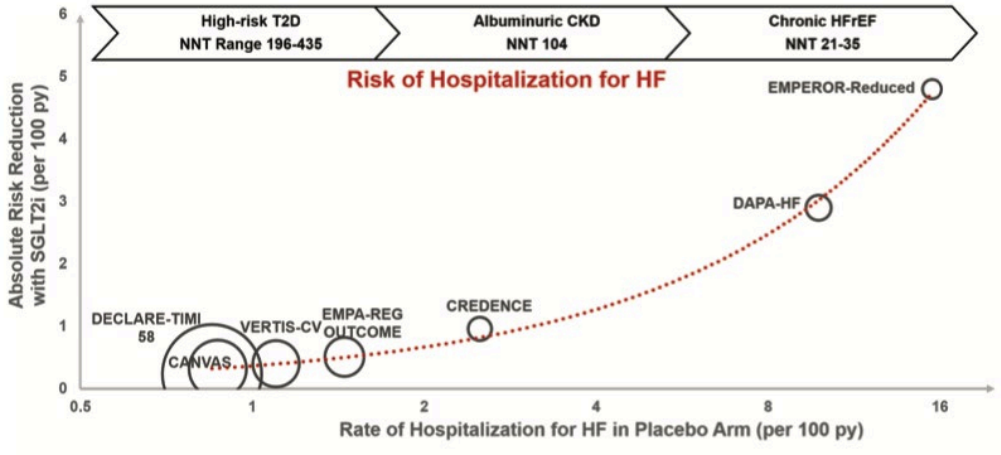
Braunwald E, N Engl J Med, 2022

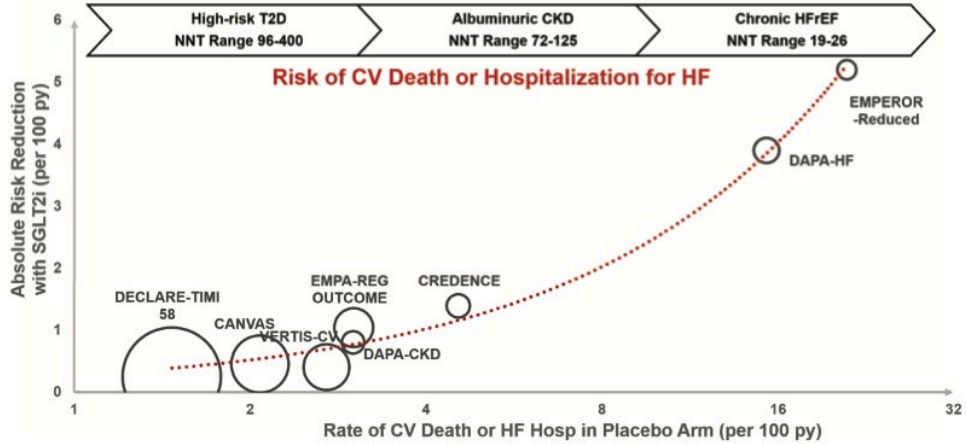
DELIVER





Solomon SD et al, N Engl J Med, 2022





Ongoing trial programmes are further evaluating their role in

myocardial infarction
(EMPACT-MI and DAPA-MI),

acute HF
(EMPULSE-HF, DICTATE-AHF, and DAPA ACT HF-TIMI 68)

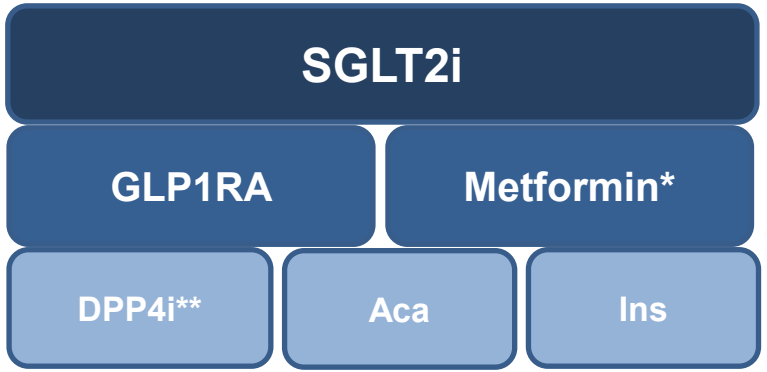
Bathia K et al, Eur J Heart Fail, 2021

Terapia Farmacologica

Quali sono i farmaci di prima, seconda e terza istanza da impiegare per il controllo della glicemia nei pazienti con diabete di tipo 2 con scompenso cardiaco?

Si raccomanda l'uso di SGLT-2i come farmaci di prima scelta per il trattamento a lungo termine di pazienti con diabete di tipo 2 con scompenso cardiaco.

I GLP-1 RA e metformina dovrebbero essere considerati come farmaci di seconda scelta, mentre DPP-4i, acarbosio ed insulina come farmaci di terza scelta.



*La metformina è controindicata in classe NYHA III-IV
**Saxagliptin è associato ad un aumento di ricoveri per scompenso cardiaco

Forza della raccomandazione: forte. Qualità delle prove: moderata.

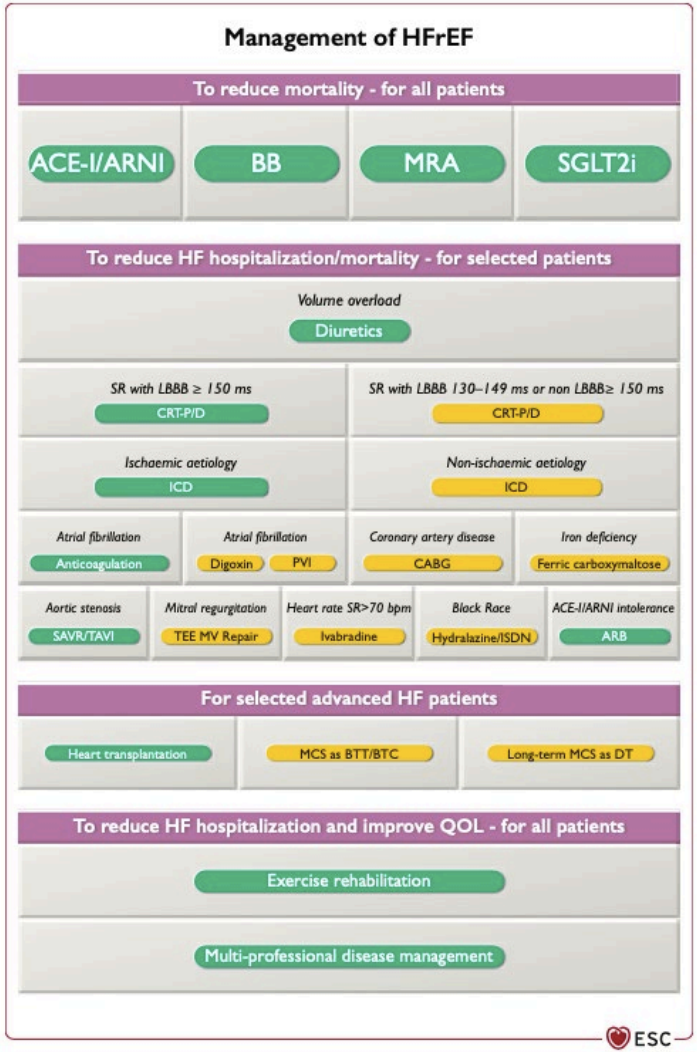
SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ (6 luglio 2021)

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

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

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



Eur Heart J, 2021

hHF

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462/706	244/706	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803/1461	658/1461	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852/1724	872/1724	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225/6314	2089/6314	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992/8681	3689/8681	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730/15 436	7706/15 436	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**

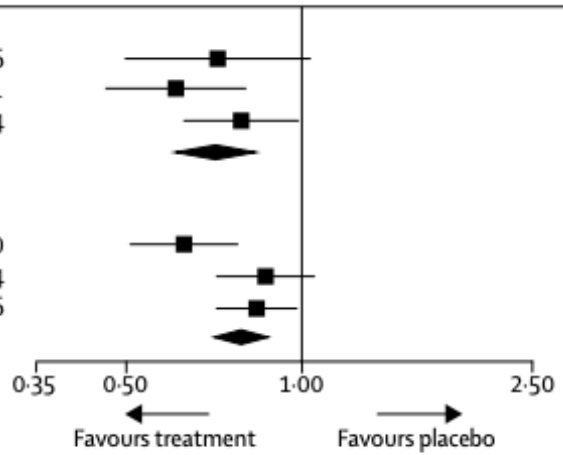
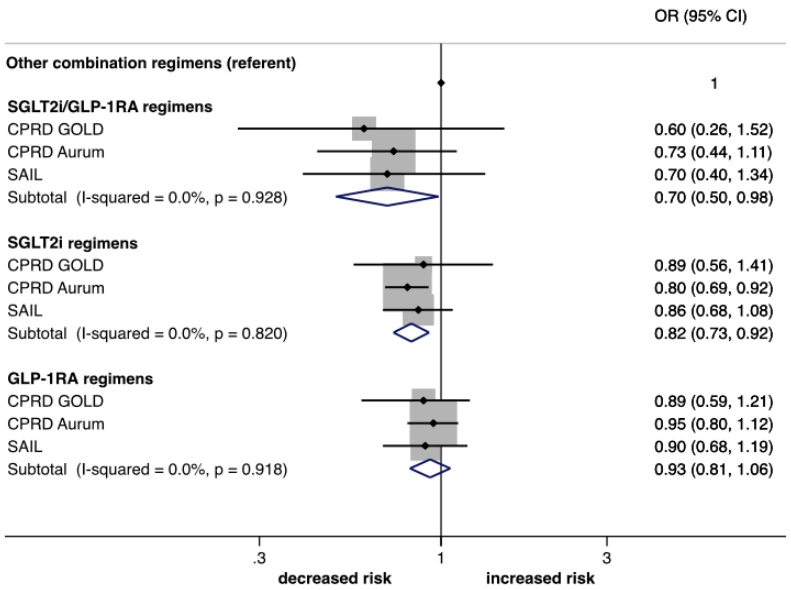


Figure 3: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure**
History of heart failure: Q statistic=2·02, p=0·37, I^2=0·8%; no history of heart failure: Q statistic=5·89, p=0·0527, I^2=66%. The p value for subgroup differences was 0·51. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

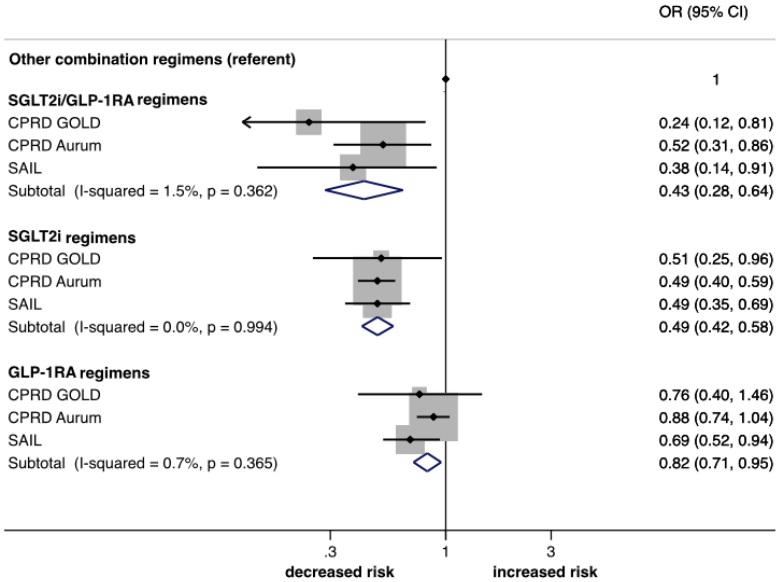
Zelnicker TA et al, Lancet, 2019

Real-world data in UK - primary prevention

MACE



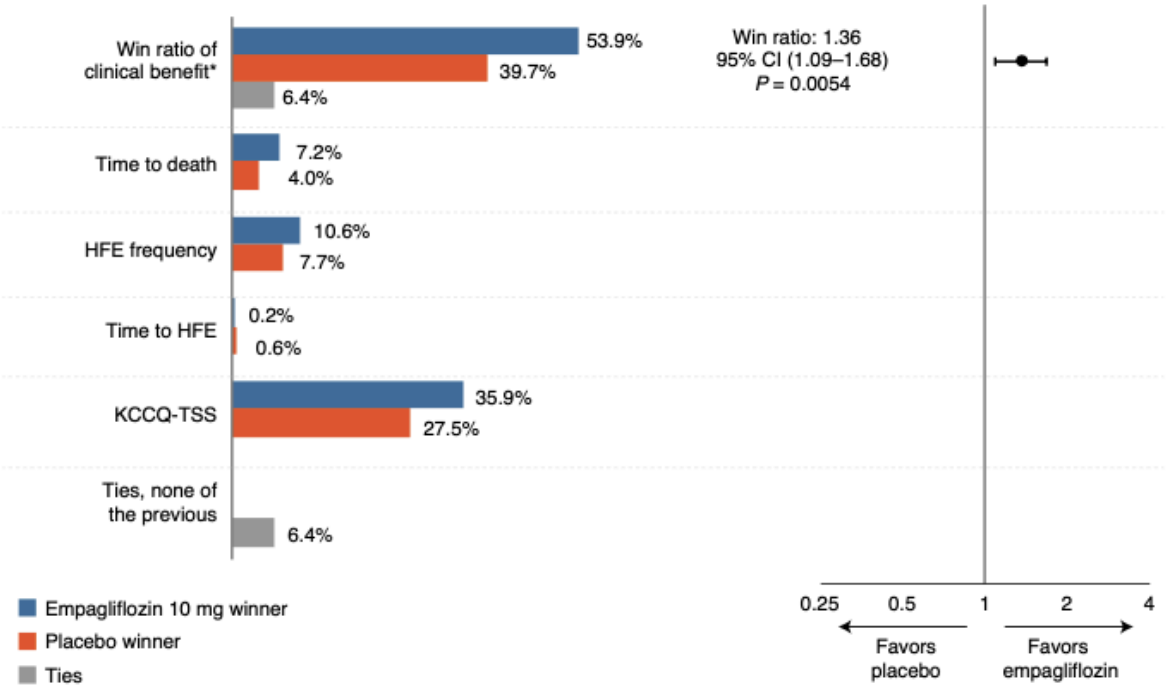
hHF



Wright AK et al, Diabetes Care, 2022

hHF in the acute setting

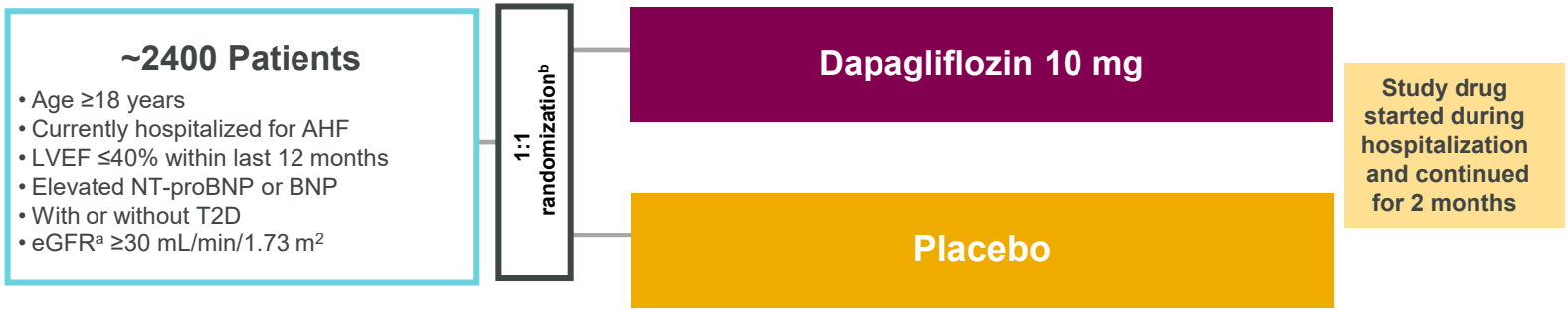
Acute HF Empulse



Primary end-point of clinical benefit (hierarchical composite of all-cause death, heart failure events, and a 5-point or greater difference in KCCQ Total Symptom Score [TSS] change from baseline to 90 days)

Voors AA et al, Nat Med, 2022

DAPA ACT HF-TIMI 68



Primary Endpoint

- Time to first occurrence of CV death or worsening HF

Secondary Endpoints

- Time to first occurrence of composite of CV death, rehospitalization for HF or urgent HF visit
- Time to first occurrence of composite of CV death or rehospitalization for HF
- Time to first occurrence of rehospitalization for HF or urgent HF visit
- Readmission within 30 days of hospital discharge
- Time to CV death
- Time to death

Estimated Primary Completion: Q1 2023

DAPA ACT HF-TIMI 68 is an externally sponsored collaborative research study (Sponsor: The TIMI Study Group).

[a]Calculated using the CKD-EPI equation; [b]Eligible patients will be randomized during hospitalization no earlier than 24 hours and up to 7 days after presentation once stabilized (no increase in the dose of IV diuretics during the 24 hours prior to randomization or no use of IV vasodilators or inotropes during the 24 hours prior to randomization).

Study NCT04363697. ClinicalTrials.gov website.

CKD

Kidney outcomes using generally consistent definitions: Sustained ≥40% decline in eGFR, ESKD or renal death

	Kidney composite outcomes	HR (95% CI)
EMPA-REG OUTCOME[1]	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.55** (0.41–0.73)
CANVAS Programme[2]	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.60** (0.47–0.77)
DECLARE-TIMI 58[3]	Sustained ≥40% decrease in eGFR to <60 mL/min/1.73 m^2 and/or end-stage renal disease and/or renal death	**0.53** (0.43–0.66)
VERTIS CV*	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.66** (0.50–0.88)

*Pre-specified exploratory, intention-to-treat analysis set, 95.0% CI.
CV, cardiovascular; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio. [1]Post-hoc exploratory, Perkovic V et al. *Nephrol Dial Transplant* (2019) 1–9; [2]Pre-specified exploratory, Neal B et al. *N Engl J Med* 2017;377:644-657; [3]Pre-specified secondary, Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

Renal Outcomes Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

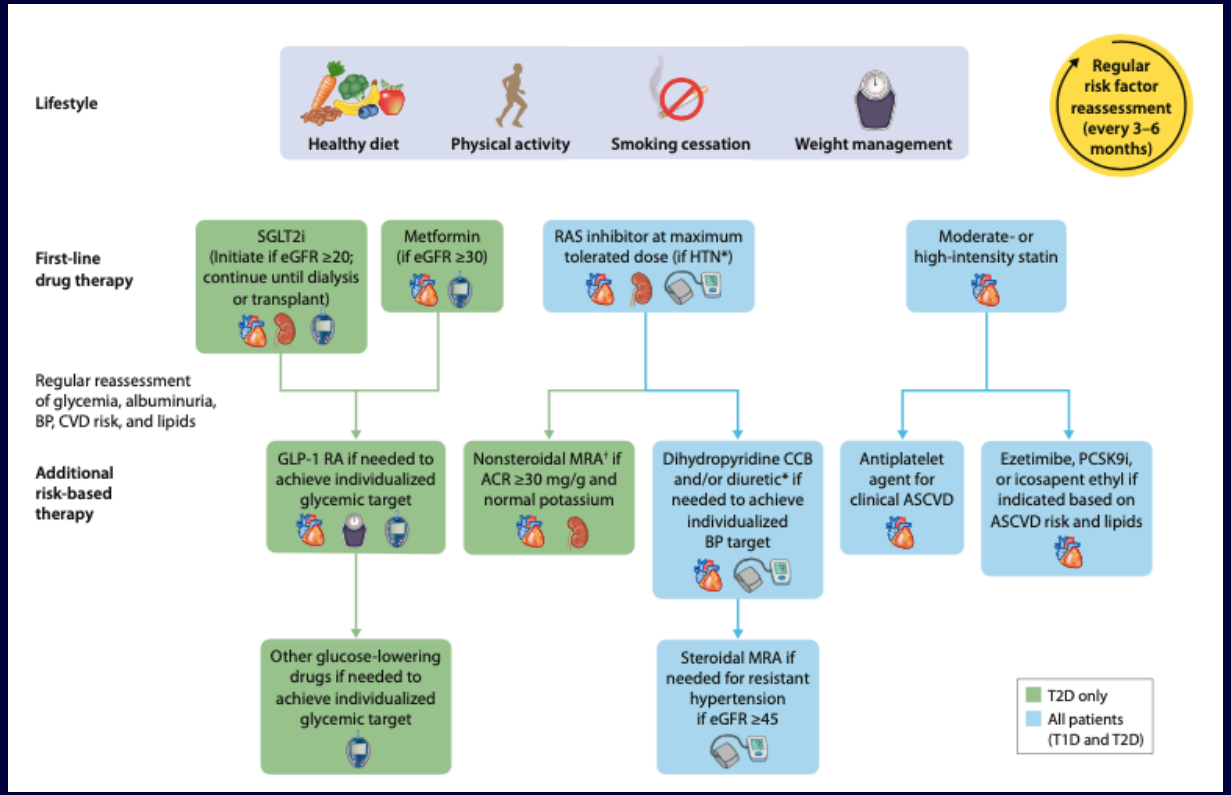
Dapagliflozin in Patients with Chronic Kidney Disease

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*

CKD Trial

(+/- diabetes)

Consensus ADA KDIGO



de Boer IH et al, Diabetes Care, 2022

Pharmacological Research 166 (2021) 105530

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Sodium-glucose transporter 2 inhibitors for renal and cardiovascular protection in US adults with type 2 diabetes: Impact of the 2020 KDIGO clinical practice guidelines

Stefano Ciardullo [a,b,1], Roberto Trevisan [b,c], Gianluca Perseghin [a,b,*,2]

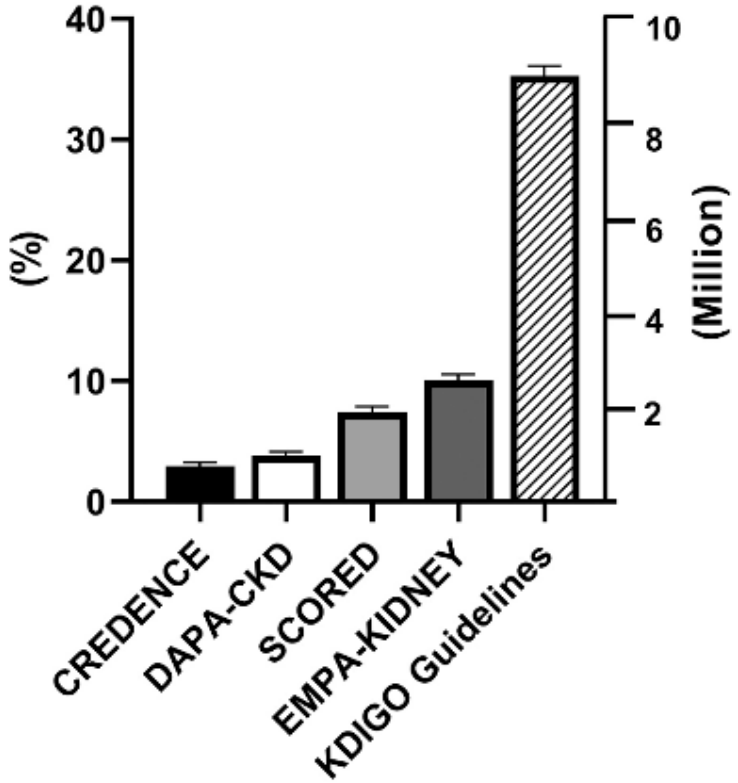
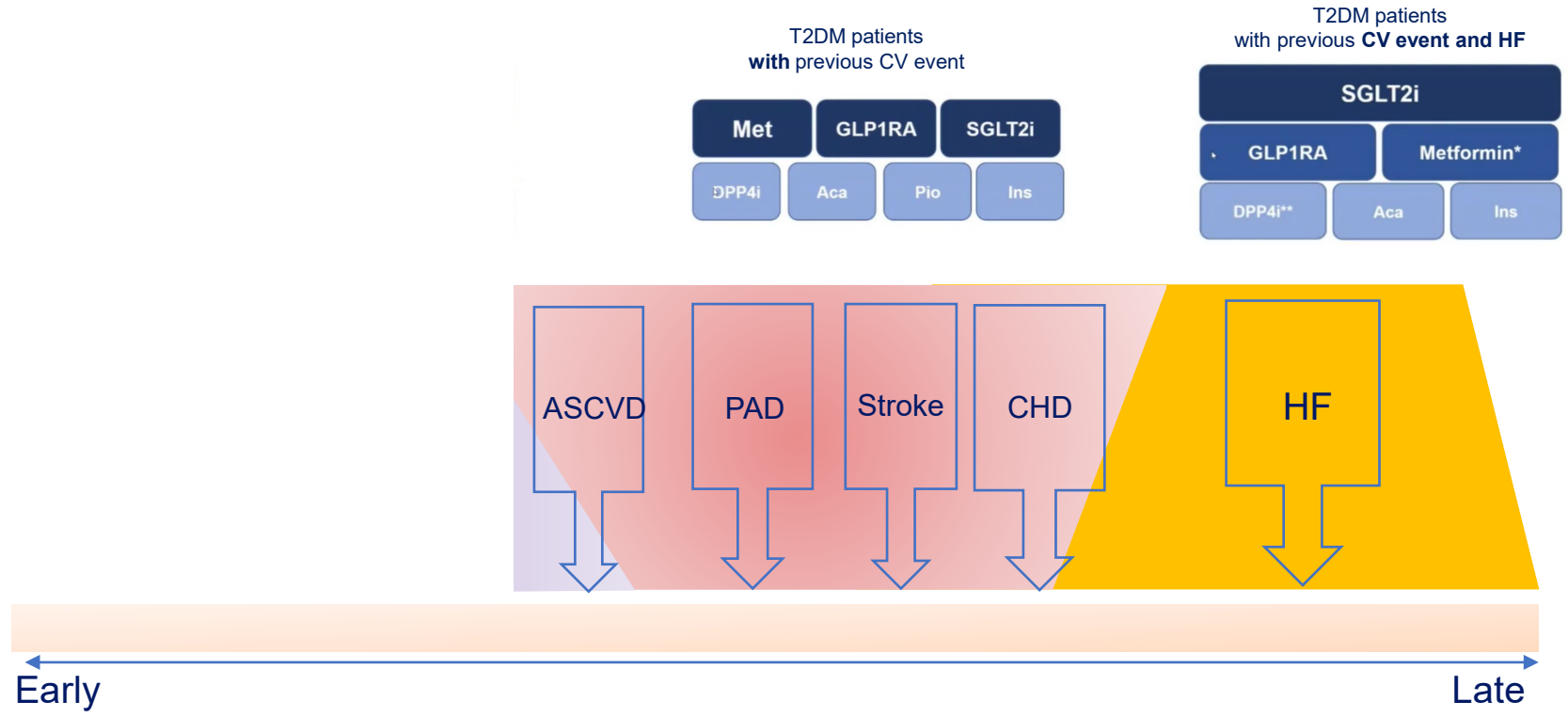


Fig. 1. Proportion of subjects meeting inclusion criteria for randomized clinical trials or guidelines recommendation. Data are expressed as weighted proportions (± Standard Error (SE)).

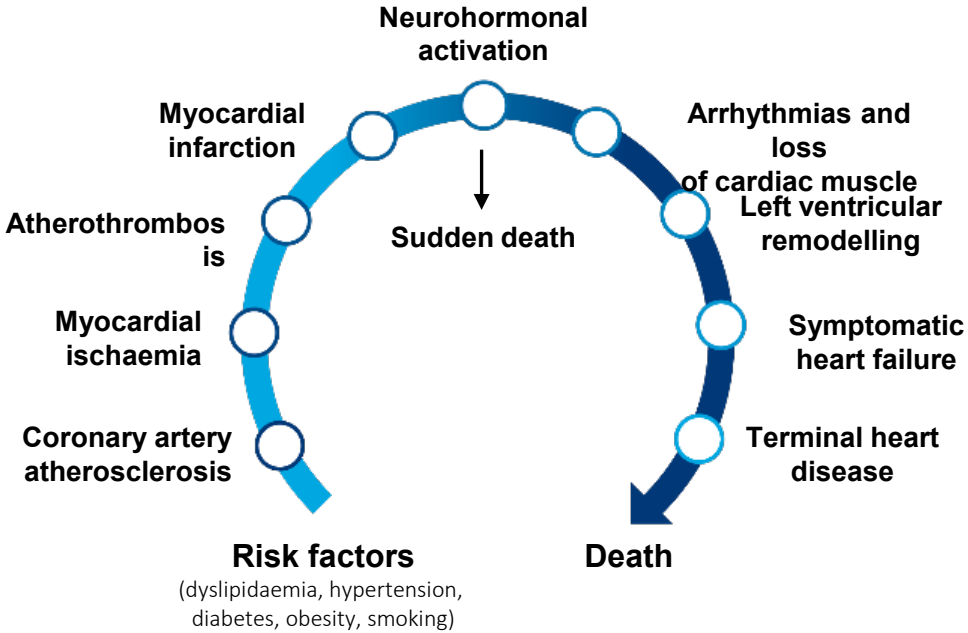
Italian Guidelines

New Paradigm of Management of the **Cardiometabolic Continuum**



Conclusion

CKD/
ASCVD

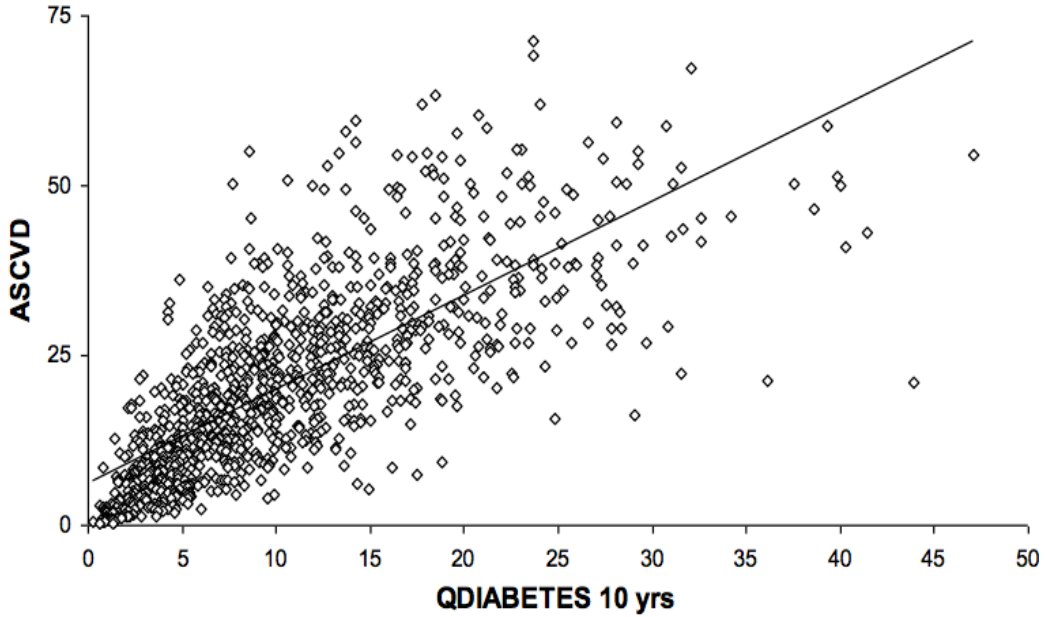


CKD
prot/
HF

?

Dzau VJ et al Circulation, 2006

Rischio ASCVD e rischio SCC



Coefficiente di correlazione lineare di Pearson (r) = 0.743 ($p < 0.001$)
Coefficiente di correlazione per ranghi di Spearman (ρ) = 0.797 ($p < 0.001$).

Cannistraci R et al, (in preparation)

Treatment effectiveness ?

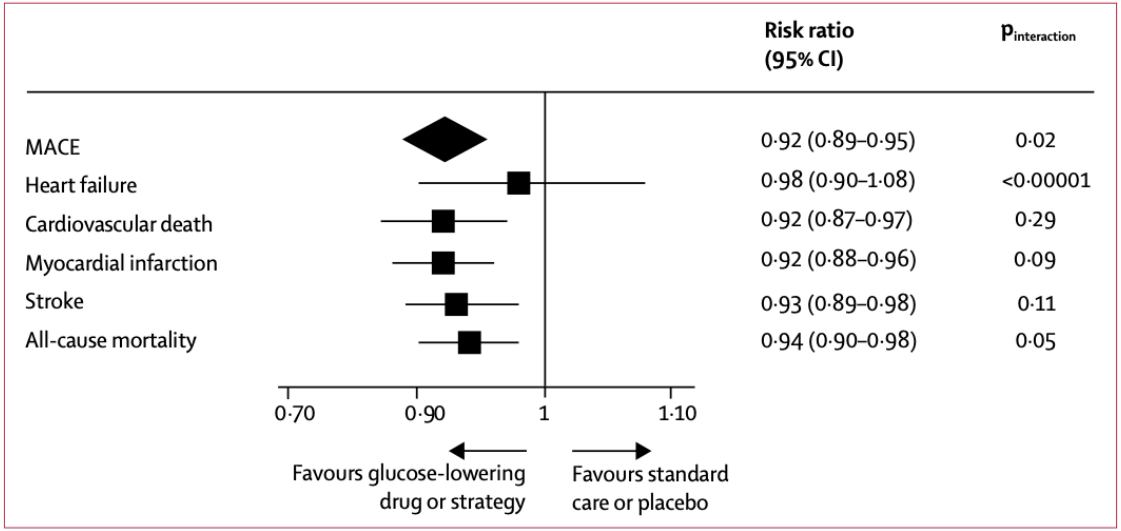


Figure 3: **MACE and individual cardiovascular events comparing glucose-lowering drugs or strategies versus standard care or placebo**

Risk ratios were calculated from an inverse-variance random-effects model. Heterogeneity among diabetes drug class or strategy subgroups was assessed with an interaction term representing treatment effect by therapy category. The findings for myocardial infarction and stroke represent all (fatal and non-fatal) events. MACE=major adverse cardiovascular events.

Ghosh-Swaby OR et al Lancet Diabetes & Endocrinol, 2020

DIABETES RESEARCH AND CLINICAL PRACTICE 180 (2021) 109035

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Comparing medication persistence among patients with type 2 diabetes using sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists in real-world setting

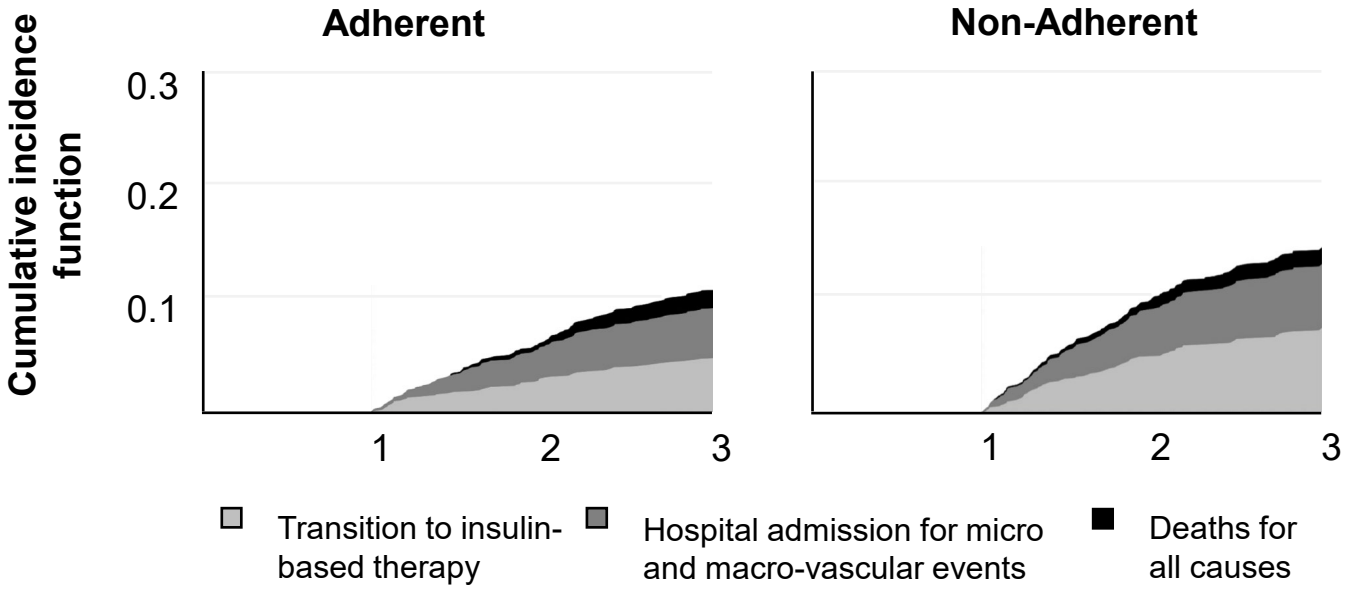
Federico Rea [a,b,1], Stefano Ciardullo [c,d,1], Laura Savaré [a,b,*], Gianluca Perseghin [c,d,2], Giovanni Corrao [a,b,2]

Rea F, Ciardullo S et al Diabetes Res Clin Pract, 2021

		Treatment discontinuation		RR (95% CI)
		GLP1-RA	SGLT2-I	
Overall		24.1%	28.8%	0.85 (0.75 to 0.97)
Sex	Male	23.7%	26.7%	0.94 (0.79 to 1.11)
	Female	24.7%	32.4%	0.79 (0.65 to 0.97)
Age	40-64 yrs	23.3%	29.4%	0.81 (0.69 to 0.95)
	≥65 yrs	25.7%	27.5%	1.00 (0.79 to 1.26)
CV disease	Yes	24.2%	29.1%	0.80 (0.65 to 1.00)
	No	24.0%	28.6%	0.87 (0.78 to 0.97)

Fig. 2 – Adjusted risk ratio (RR), and 95% confidence intervals (CI), of treatment discontinuation with the drug started at the index date (i.e., GLP1-RA or SGLT2-I) in the whole cohort and according to sex, age and cardiovascular (CV) disease.

Outcomes in relazione all'aderenza terapeutica in Regione Lombardia



Ciardullo S et al submitted