SGLT2i e MACE

la riduzione del rischio in prevenzione primaria e secondaria

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CoI

Honorarium as a speaker in Scientific Events

Sigma-Tau	Lilly	AstraZeneca	Takeda	Boheringer Ingelheim
MSD	Novo Nordisk	Sanofi	Menarini Diag	Daichii Sankyo
Roche Diag	Novartis	Servier	Bayer	

Grant support

Novo Nordisk (Investigator-Initiated-Study Grant)
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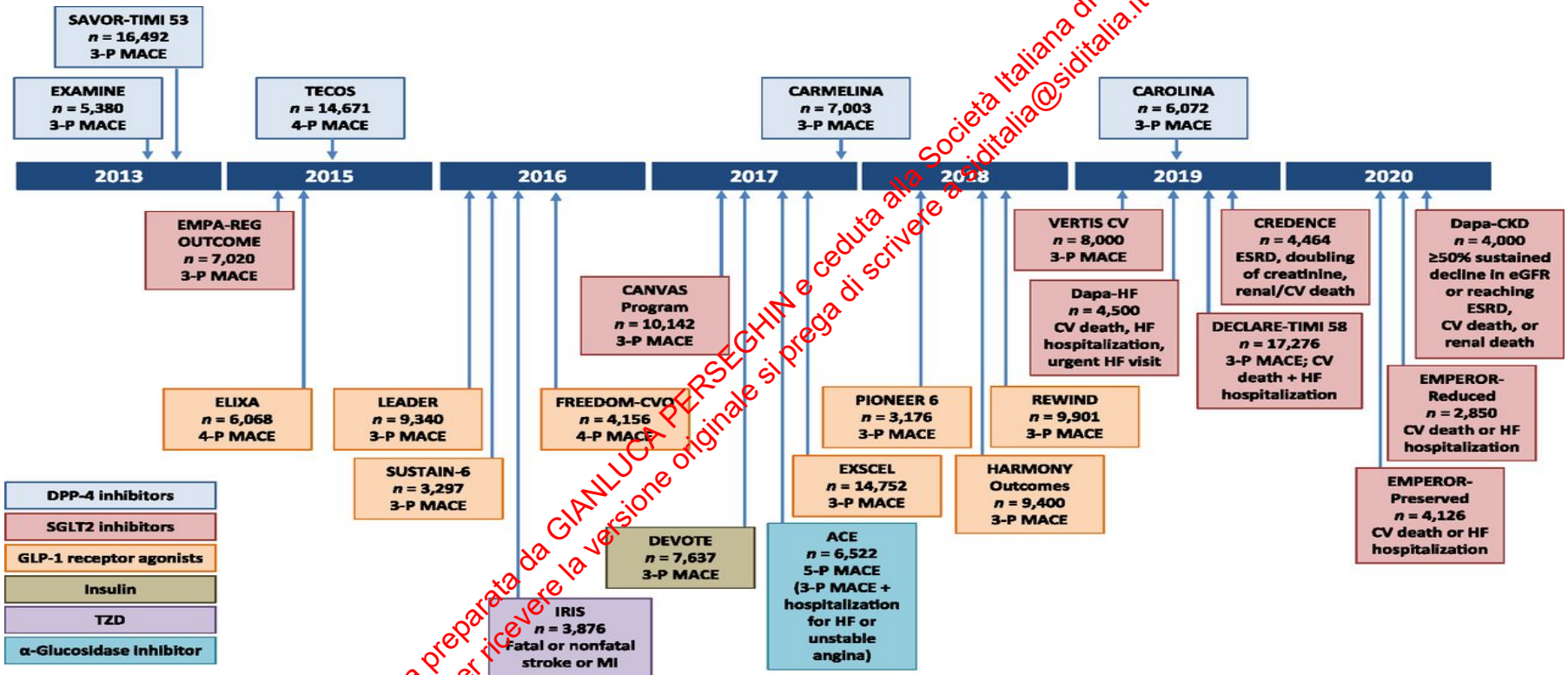
(Travel grants)

Scientific advisory boards

Novo Nordisk, AstraZeneca, Lilly, Sanofi, Merck, Pfizer, Intercept, Novartis, PikDare

EBM: CVOTs e Linee Guida



Cefalu WT Diabetes Care 2018

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 (0.52–0.85)	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.

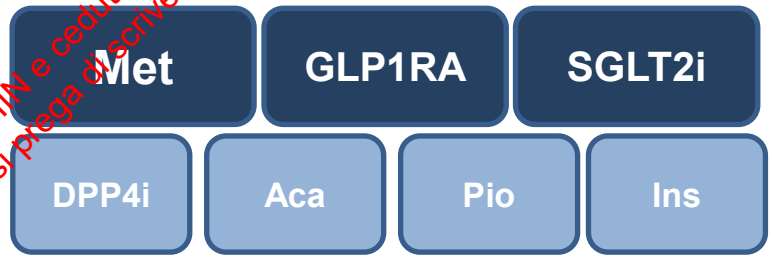
Braunwald E, N Engl J Med, 2022

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)

CVD death or hHF

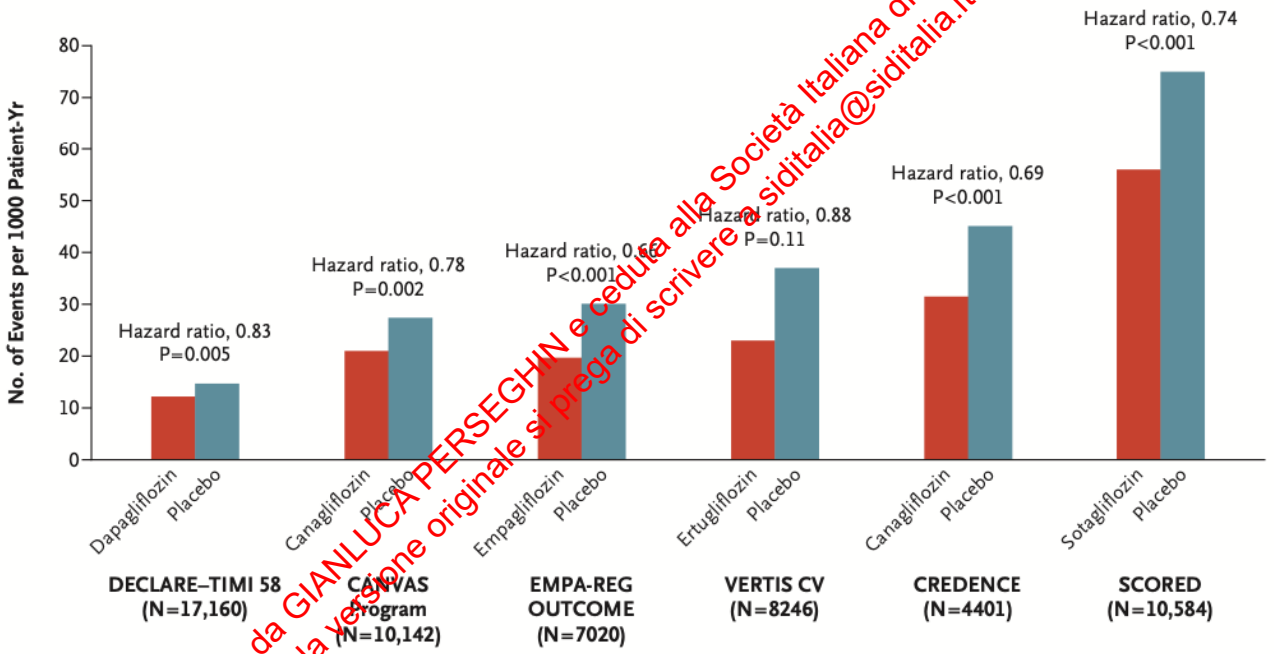


Figure 1. Cardiovascular Death or Hospitalization for Heart Failure among Patients with Type 2 Diabetes Enrolled in Six Treatment Trials.

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

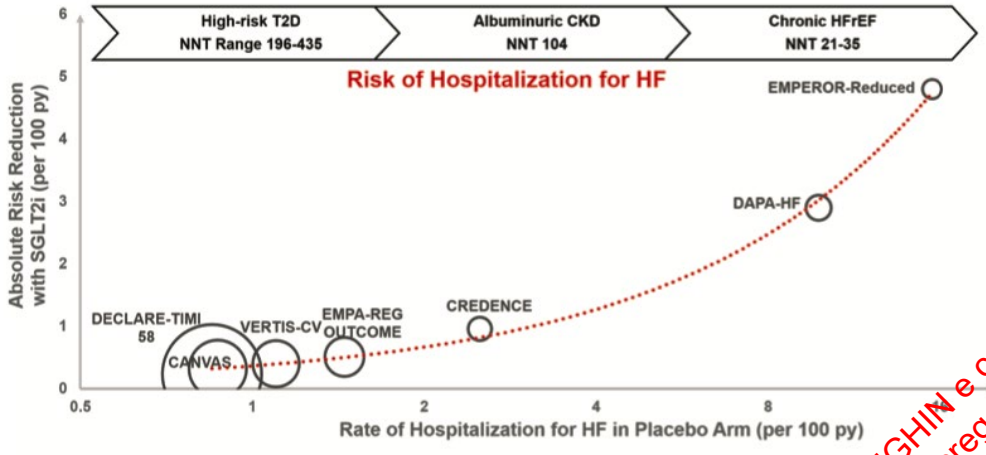
CVOTs in HF

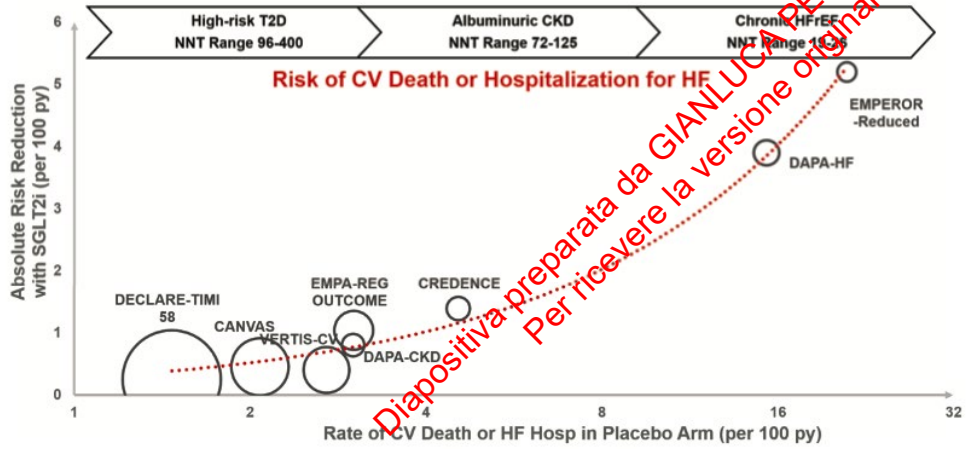
Table 2. Cardiovascular Outcome Trials Involving Patients with Heart Failure.*

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.

Braunwald E, N Engl J Med, 2022





Ongoing trial programmes are further evaluating their role in myocardial infarction (EMPACT-MI and DAPA-MI), HF with preserved ejection fraction (DELIVER), acute HF (EMPULSE-HF, DICTATE-AHF, and DAPA ACT HF-TIMI 68),

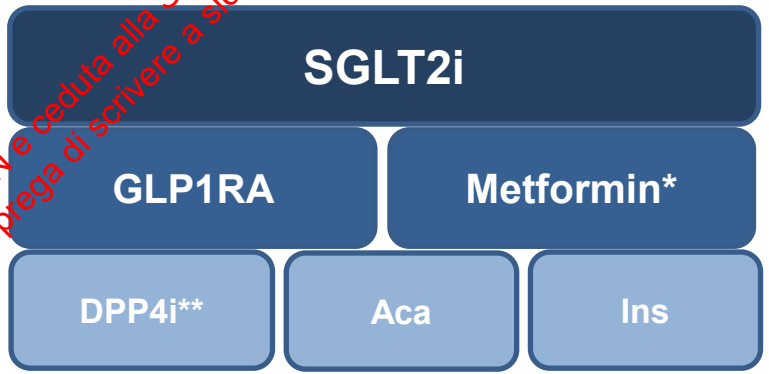
Bathia K et al, Eur J Heart Fail, 2021

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

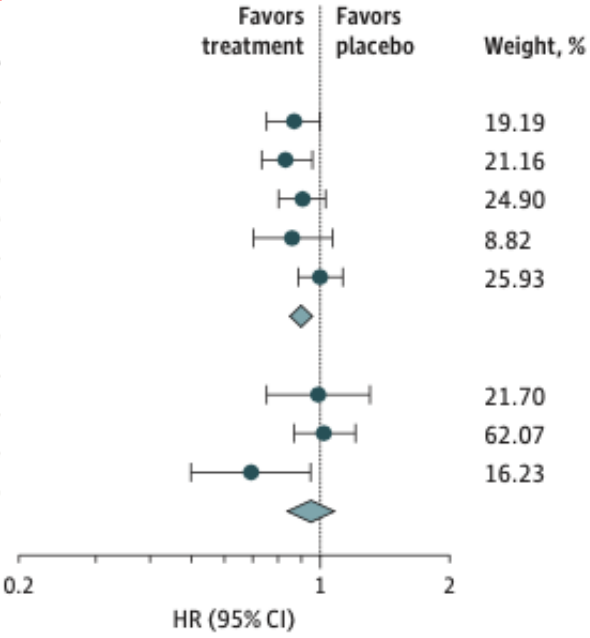
Forza della raccomandazione: forte. Qualità delle prove: moderata.

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

MACE in CVD PREVENTION

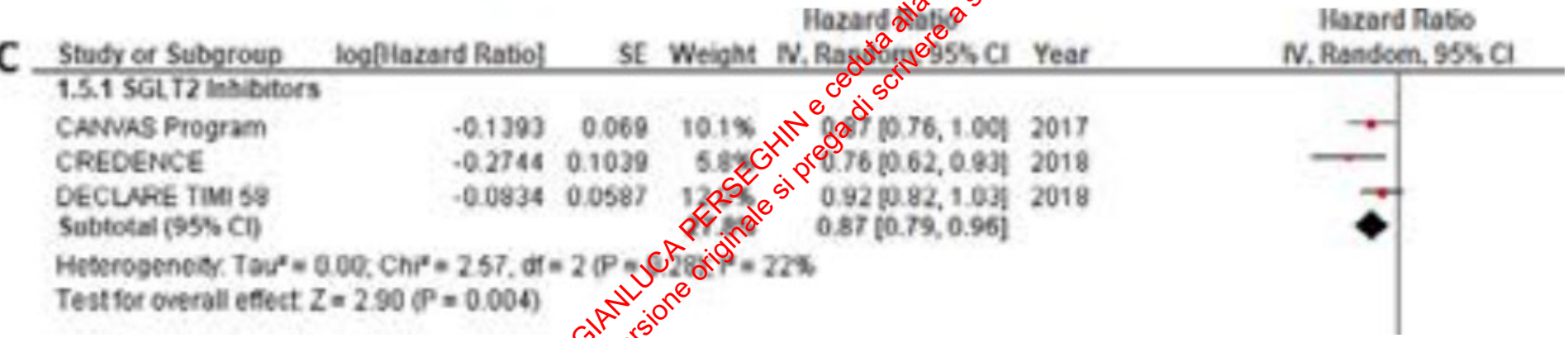
B MACEs by ASCVD status

	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)



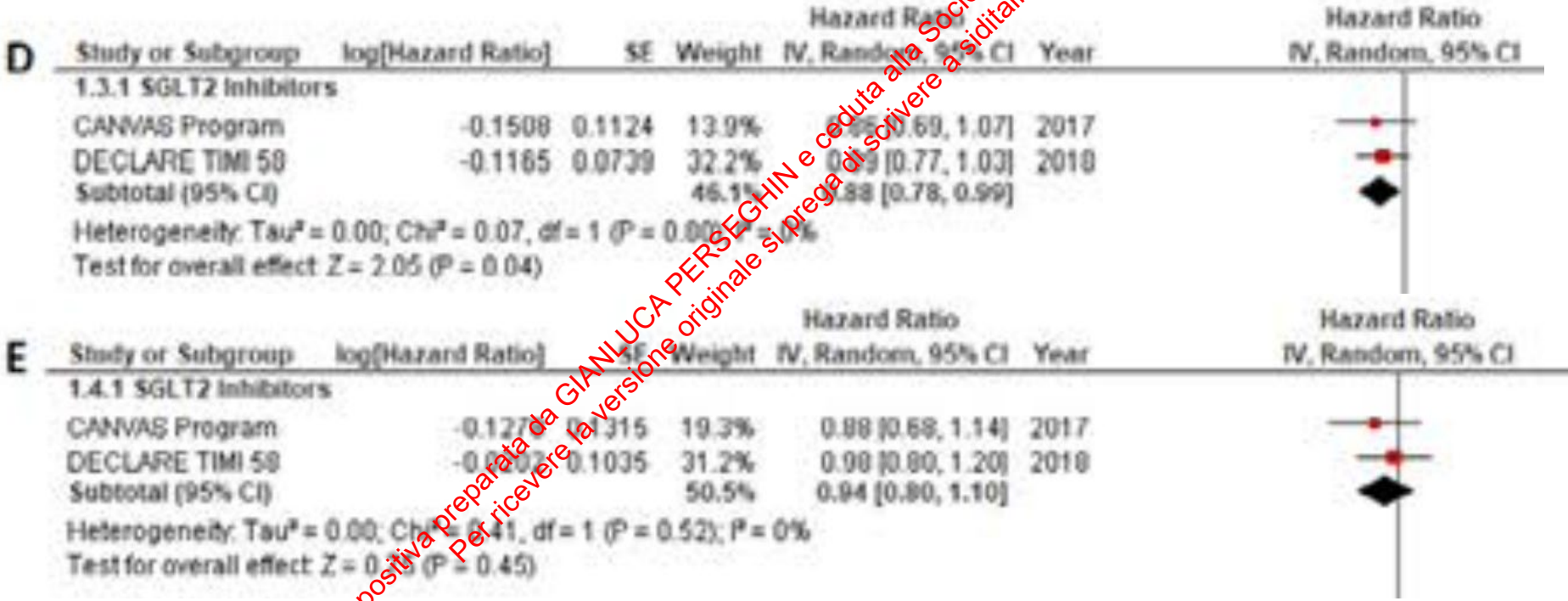
McGuire DK et al, JAMA Cardiol, 2021

MACE
in PRIMARY CVD PREVENTION



Ahmed A et al, Am J Cardiol, 2022

Myocardial infarction and stroke in PRIMARY CVD PREVENTION



Ahmed A et al, Am J Cardiol, 2022

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	30·4		0·63 (0·51–0·78)
CANVAS Program	4992/8681	3689/8681	449	13·6	15·6	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)**

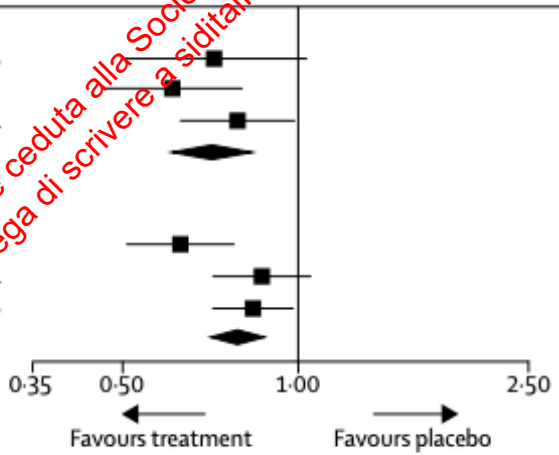


***Figure 3*: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure**

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

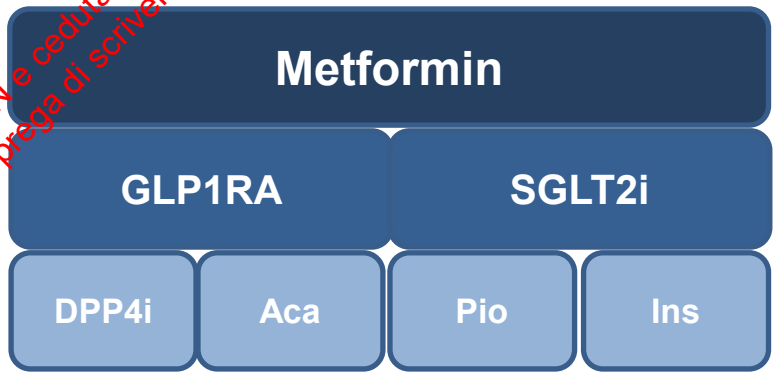
Terapia Farmacologica

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

Si raccomanda l'uso di metformina come farmaco di prima scelta per il trattamento a lungo termine in pazienti con diabete di tipo 2 senza pregressi eventi cardiovascolari.

SGLT-2i e GLP-1 RA sono raccomandati come farmaci di seconda scelta.

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

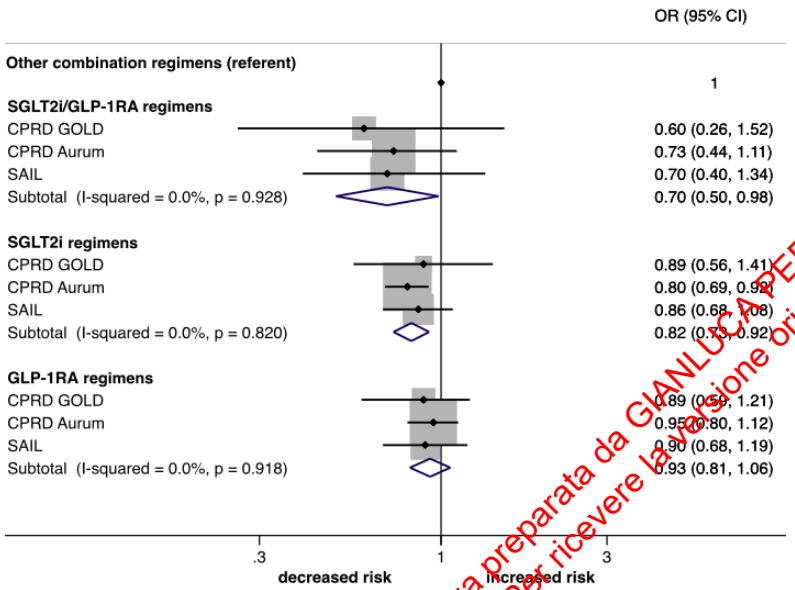


Forza della raccomandazione: forte. Qualità delle prove: moderata.

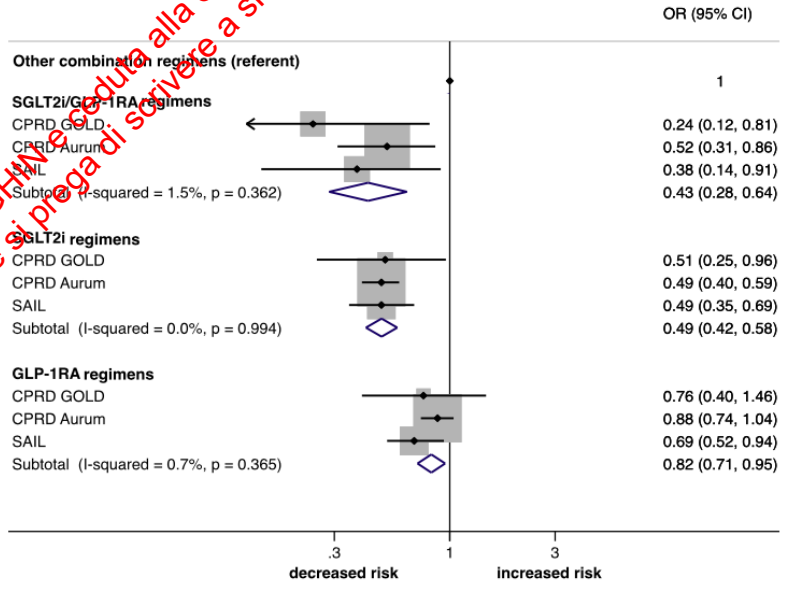
SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ (6 luglio 2021)

Real-world data in UK - primary prevention

MACE



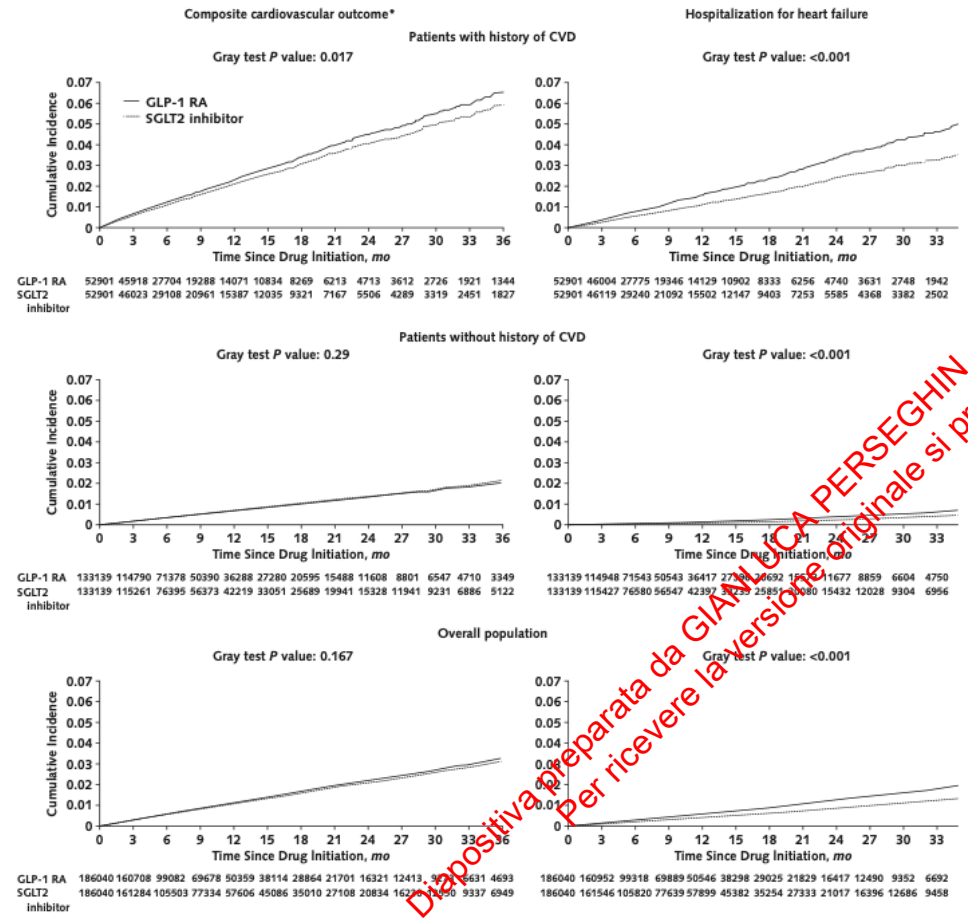
hHF



Wright AK et al, Diabetes Care, 2022

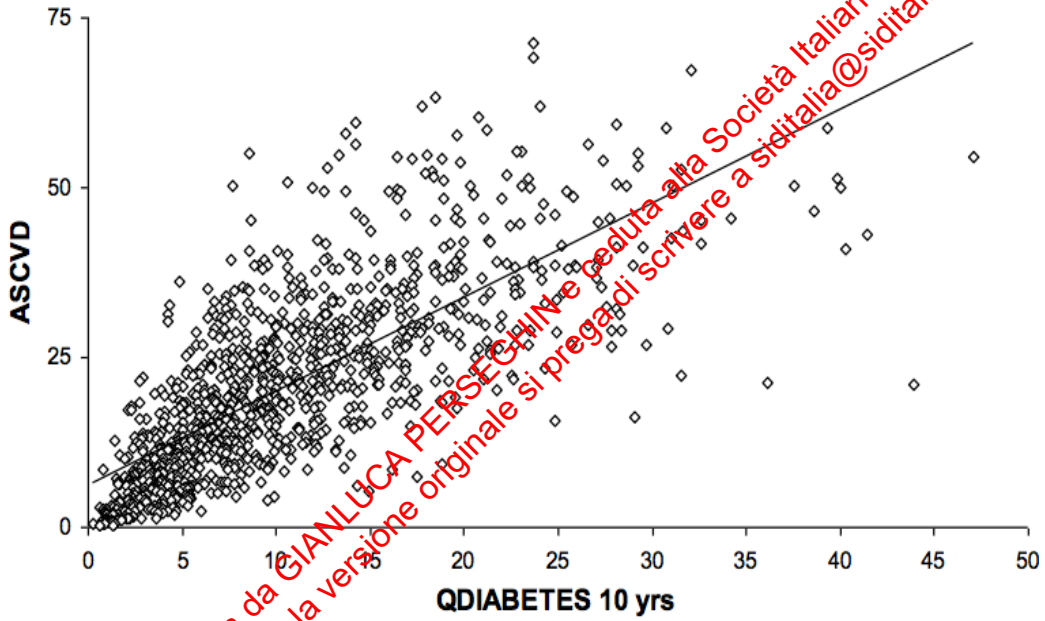
Real-world data in USA primary & secondary prevention

Figure 1. Cumulative incidence function plots for primary outcomes comparing propensity score-matched patients initiating SGLT2 inhibitor versus GLP-1 RA therapy, by history of CVD, and overall.



Patorno E et al, Ann Int Med, 2022

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)

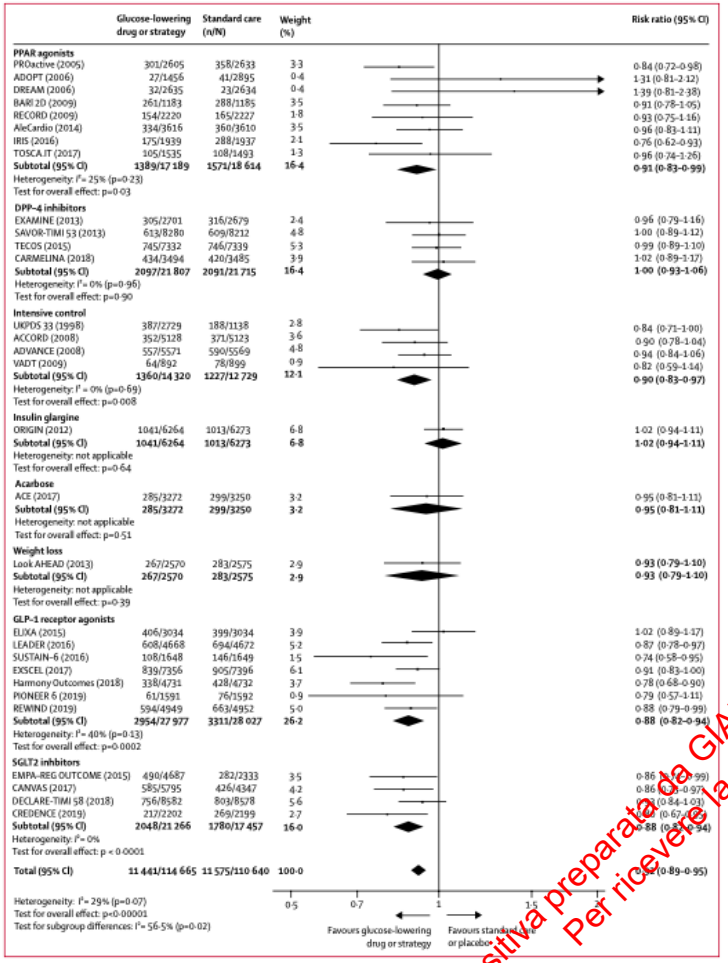


Figure 2: Risk of atherosclerotic major adverse cardiovascular events comparing glucose-lowering drugs or strategies with standard care or placebo, stratified by strategy or drug class

Risk ratios were calculated from an inverse-variance random-effects model. Heterogeneity among drug class or strategy subgroups was assessed with an interaction term representing treatment effect by therapy category. PPAR=peroxisome proliferator-activated receptor.

ASCVD

TZDs	+++
DPP4-i	o
Intensification	+++
Insulin	o
Acarbose	o
Weight loss	o
GLP1-RA	+++++
SGLT2-i	+++++

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

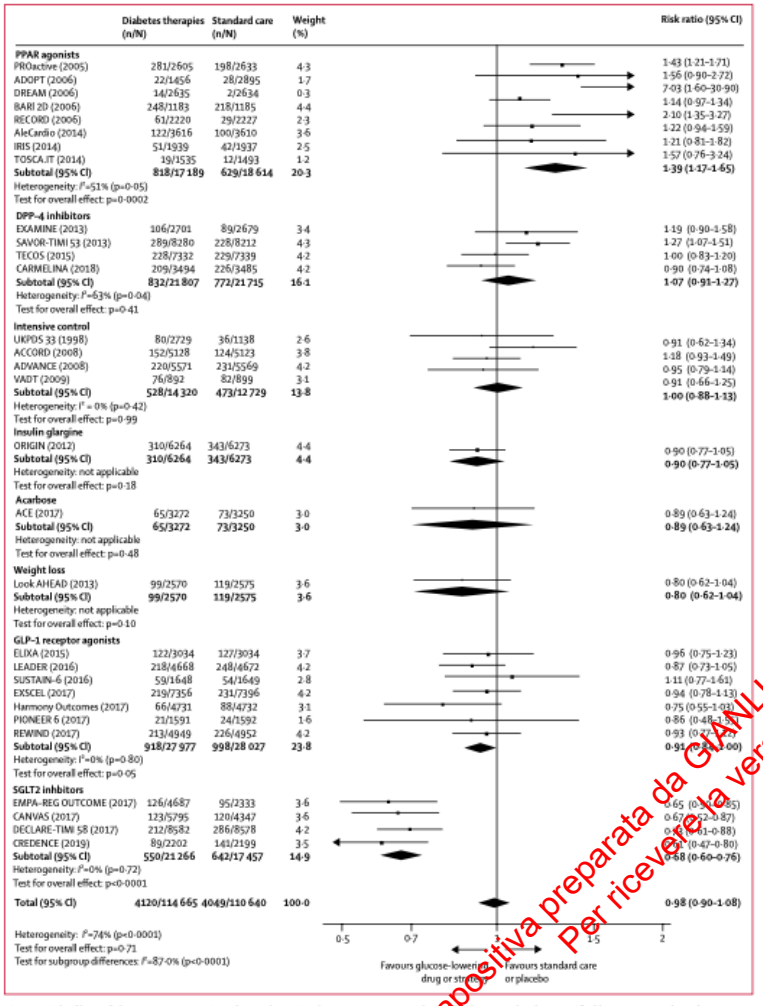


Figure 4: Risk of heart failure events comparing glucose-lowering drugs or strategies with standard care or placebo, stratified by strategy or drug class
Risk ratios were calculated from an inverse-variance random-effects model. Heterogeneity among diabetes drug class or strategy subgroups was assessed with an interaction term representing treatment effect by therapy category. PPAR=peroxisome proliferator-activated receptor.

hHF

TZDs ---

DPP4-i

Intensification o

Insulin o

Acarbose o

Weight loss +

GLP1-RA ++

SGLT2-i +++++

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

Treatment effectiveness ?

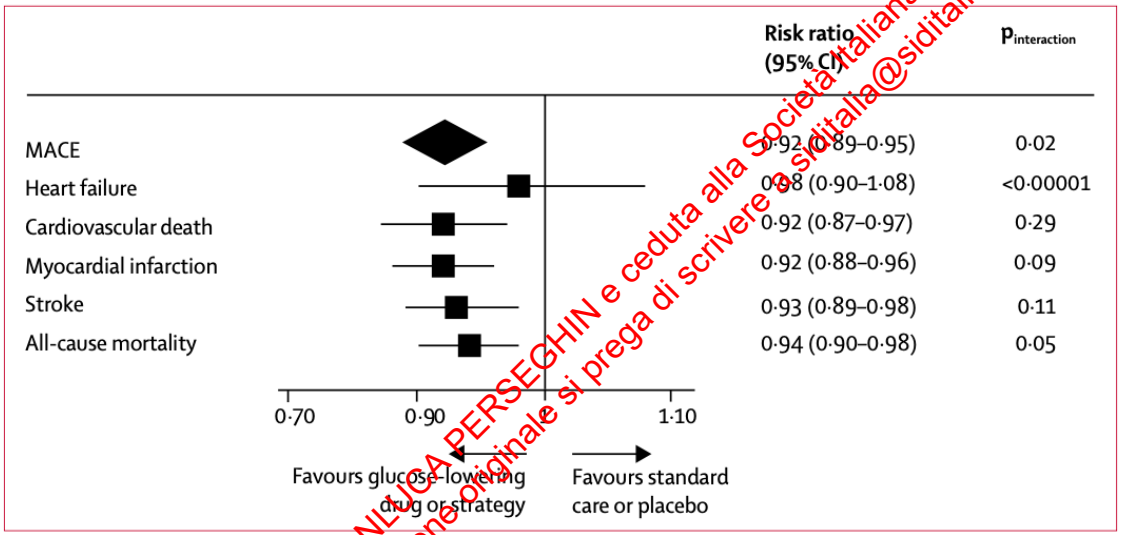


Figure 3: **MACE and individual cardiovascular events comparing glucose-lowering drugs or strategies versus standard care or placebo**

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

Today – Key messages

- **Secondary CVD prevention**

MACE, hHF (& CKD) - RCTs: never seen before +++++

- **Primary CVD prevention**

MACE - RCTs: few data/ RWD: consistent positive data +++

hHF – RCTs: +++++

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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

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*

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, A.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*

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*

ADA 2021 Standard of Medical Care

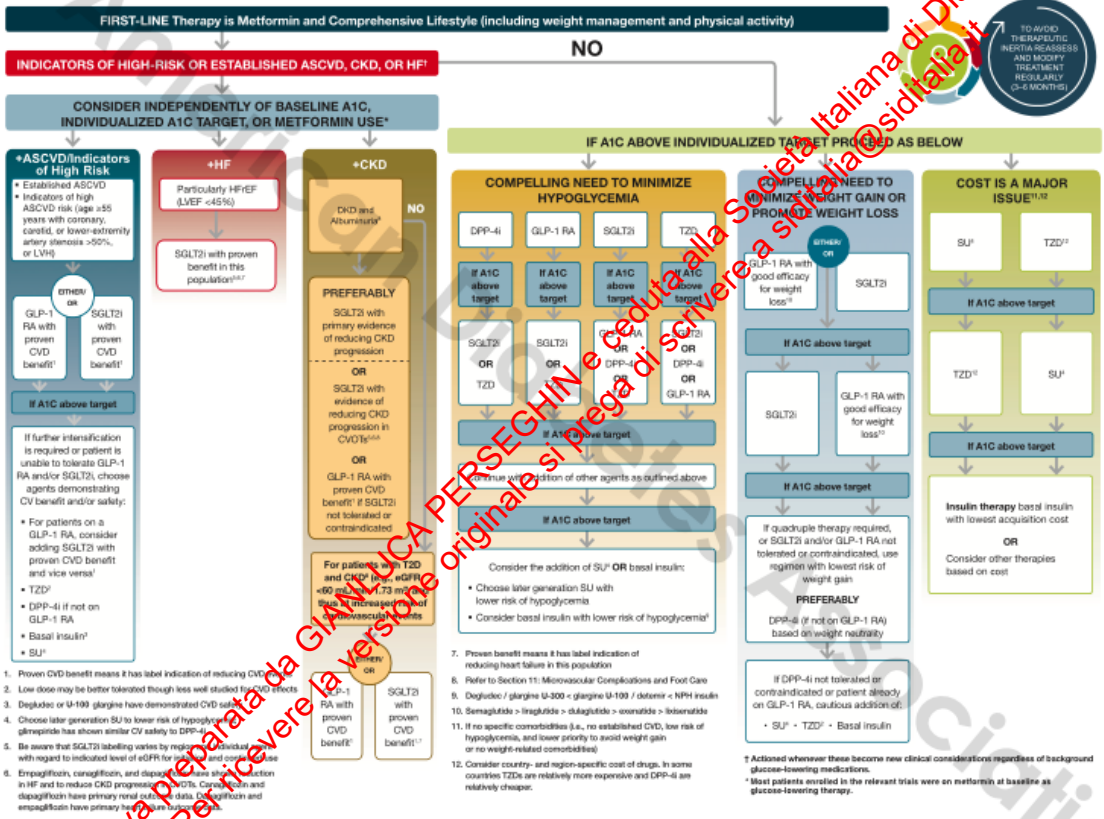
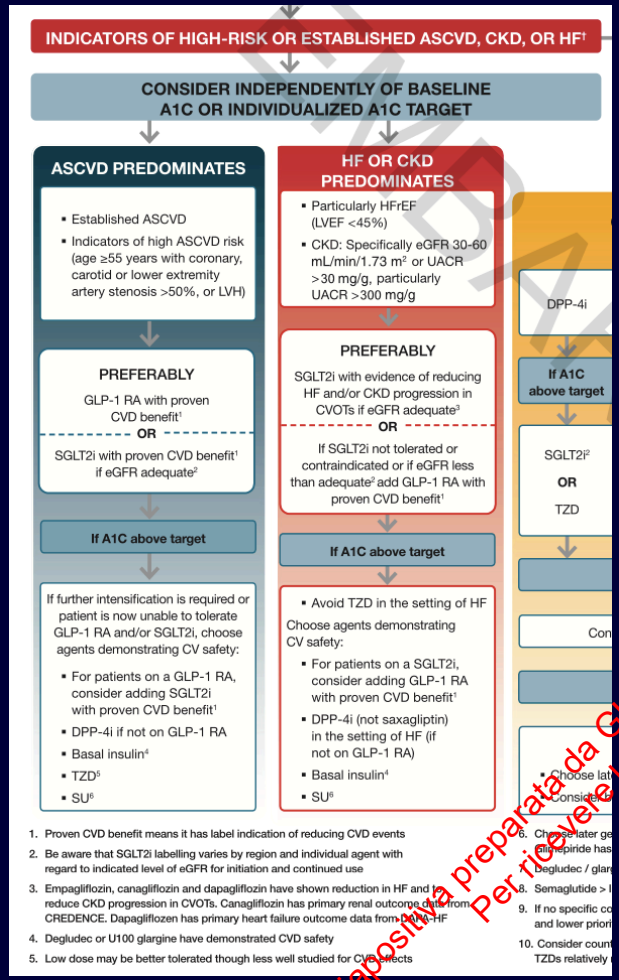


Figure 9.1—Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (35) and Buse et al. (36). For appropriate context, see **Fig. 4.1**. The 2021 ADA PPC adaptation of the **Fig. 9.1** "Indicators of high-risk or established ASCVD, CKD, or HF" pathway has been adapted based on trial populations studied. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SGLT2 i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.



1) Established ASCVD
2) Indicators of high ASCVD risk
   a) patients ≥55 years of age with coronary, carotid, or lower-extremity artery stenosis >50%
   b) left ventricular hypertrophy
   c) heart failure
   d) CKD/altered AER (yes/no)

Independent of A1C, independent of metformin use, and in consideration of patient-specific factors

ADA, Diabetes Care, 2021

ESC EASD Guidelines 2020

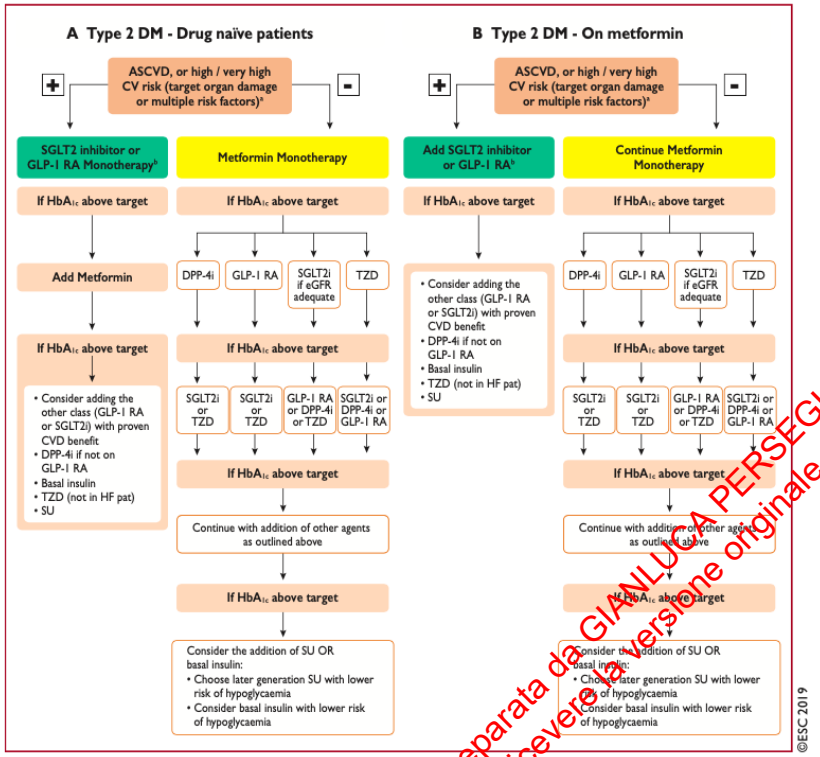


Figure 3 Treatment algorithm in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease, or high/very high CV risk Treatment algorithms for (*A*) drug-naïve and (*B*) metformin-treated patients with diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; GLP1-RA = glucagon-like peptide-1 receptor agonist; HbA1c = haemoglobin A1c; HF = heart failure; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SU = sulphonylureas; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione. [a]See *Table 7*. [b]Use drugs with proven CVD benefit.

Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]
[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.
[c]Age, hypertension, dyslipidemia, smoking, obesity.

Perché?

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

Naveed Sattar, Matthew M Y Lee*, Søren L Kristensen*, Kelley R H Branch, Stefano Del Prato, Nardev S Khurmi, Carolyn S P Lam, Renato D Lopes, John J V McMurray, Richard E Pratley, Julio Rosenstock, Hertzel C Gerstein*

Sattar N et al Lancet Diabetes Endocrinol, 2021

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**
Cardiovascular death					
ELIXA	150/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·21
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	0·72 (0·50–1·03)		0·07
Subtotal (I^2=23·4%, p=0·33)			**0·87 (0·80–0·94)**	**163 (103–353)**	**0·0010**
Fatal or non-fatal myocardial infarction					
ELIXA	270/3034 (9%)	261/3034 (9%)	1·03 (0·87–1·22)		0·71
LEADER	292/4668 (6%)	339/4672 (7%)	0·86 (0·73–1·00)		0·046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0·81 (0·57–1·16)		0·26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0·97 (0·85–1·10)		0·62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0·75 (0·61–0·90)		0·003
REWIND	223/4949 (5%)	231/4952 (5%)	0·96 (0·79–1·15)		0·63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1·04 (0·66–1·66)		0·49
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	0·75 (0·54–1·05)		0·09
Subtotal (I^2=26·9%, p=0·21)			**0·90 (0·83–0·98)**	**175 (103–878)**	**0·020**
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)		0·54
LEADER	173/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)		0·16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)		0·066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)		0·095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0·86 (0·66–1·14)		0·30
REWIND	158/4949 (3%)	205/4952 (4%)	0·76 (0·62–0·94)		0·010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0·76 (0·37–1·56)		0·43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0·74 (0·47–1·17)		0·19
Subtotal (I^2=0·0%, p=0·64)			**0·83 (0·76–0·92)**	**198 (140–421)**	**0·0002**

Figure 2: **Risk of MACE and each of its components**

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

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Sattar N et al Lancet Diabetes Endocrinol, 2021

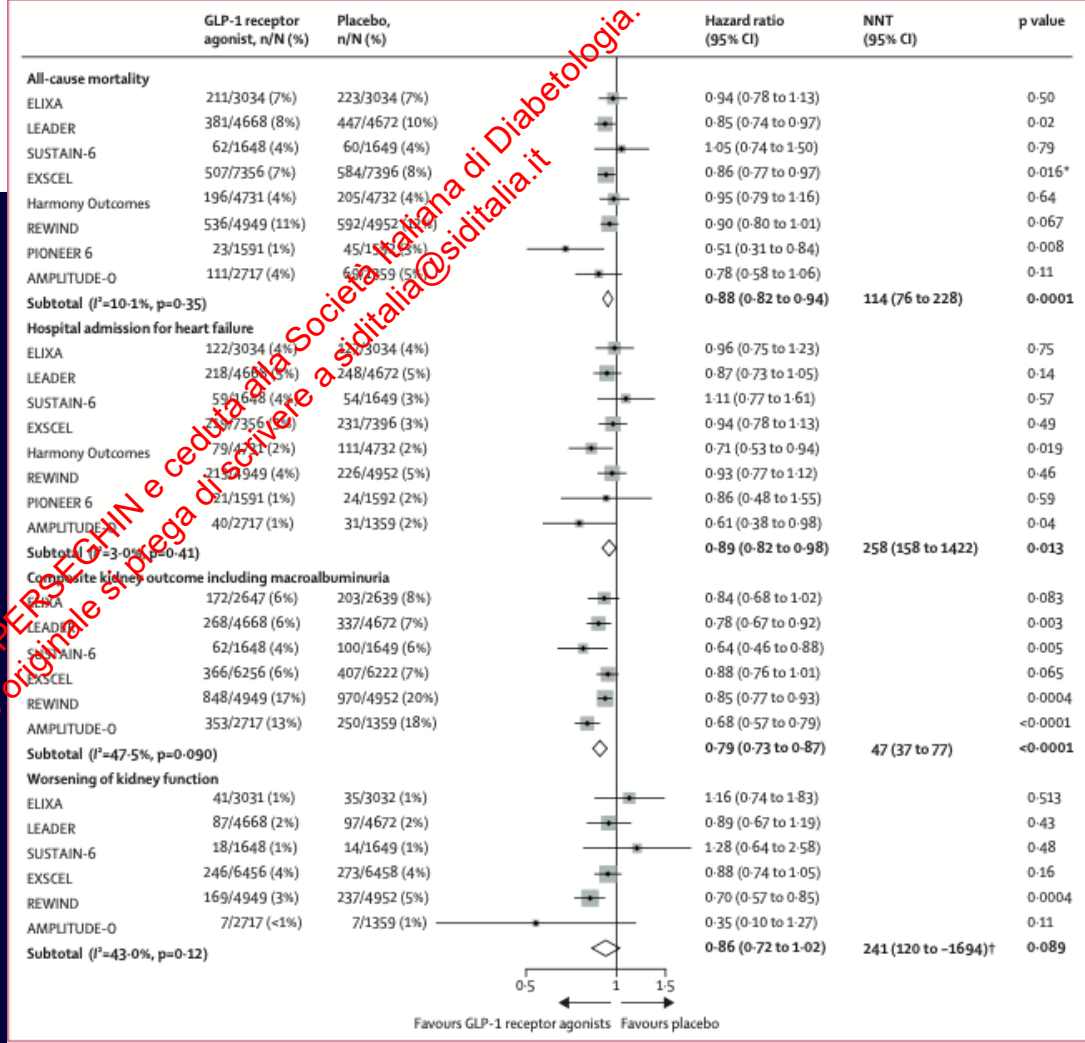
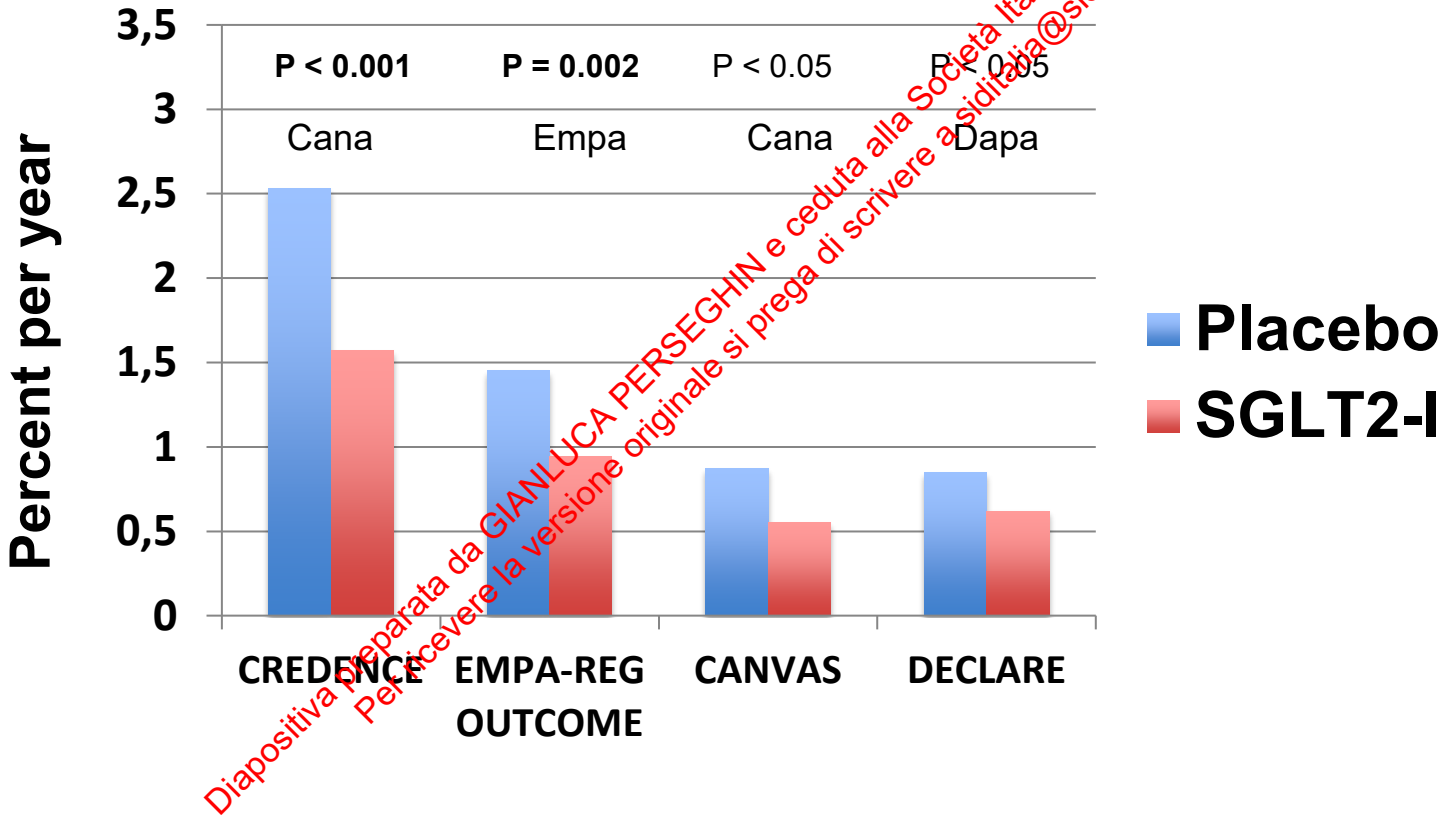


Figure 3: **All-cause mortality, hospital admission for heart failure, and kidney outcomes**

hHF in the CVOTs with SGLT2-inhibitors

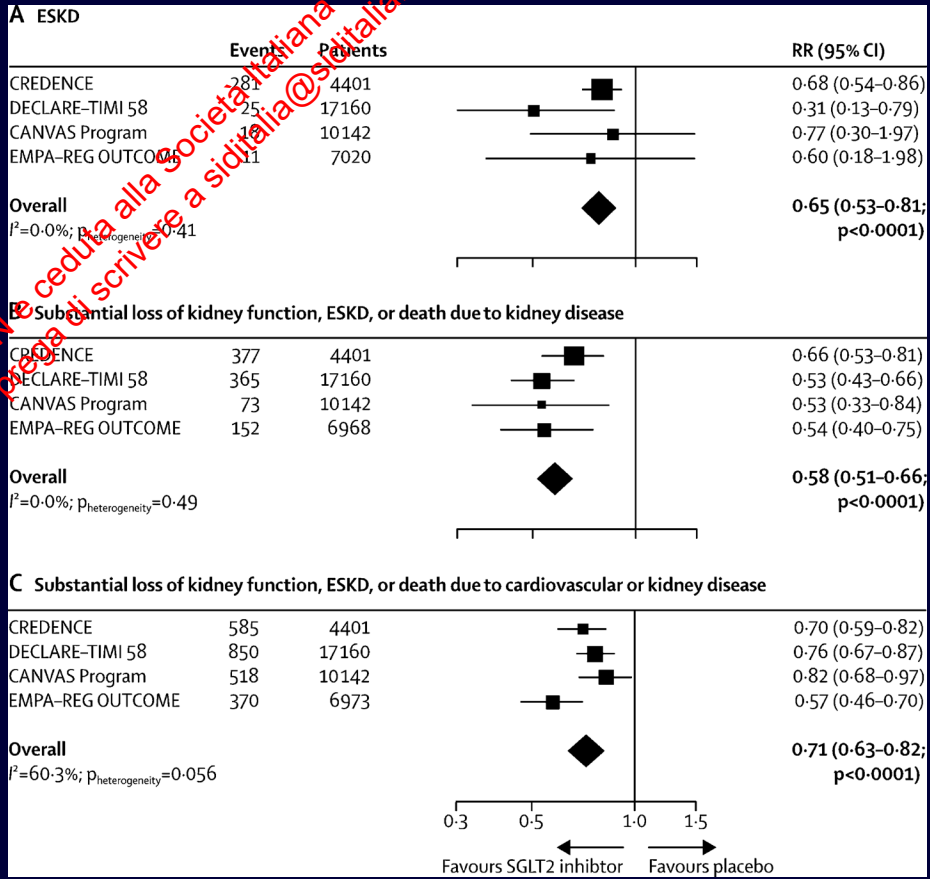


Number of patients to treat to benefit (NNTB) in studies of patients with T2DM

STUDY	CAUSE OF HOSPITALIZATION	NNTB (patient-years)	Hospitalization Rate (% per year)
EMPA-REG (empagliflozin)	All Cause	47	18.3
CANVAS (canagliflozin)	All Cause	81	13.1
EMPA-REG (empagliflozin)	Heart Failure	196	1.45
CANVAS (canagliflozin)	Heart Failure	313	0.87
DECLARE (dapagliflozin)	Heart Failure	435	0.85
CREDENCE (canagliflozin)	Heart Failure	104	2.53
DAPA-HF (dapagliflozin)	Heart Failure	34	9.8

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine



Lancet Diabetes Endocrinol 2019

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Adherence and persistence

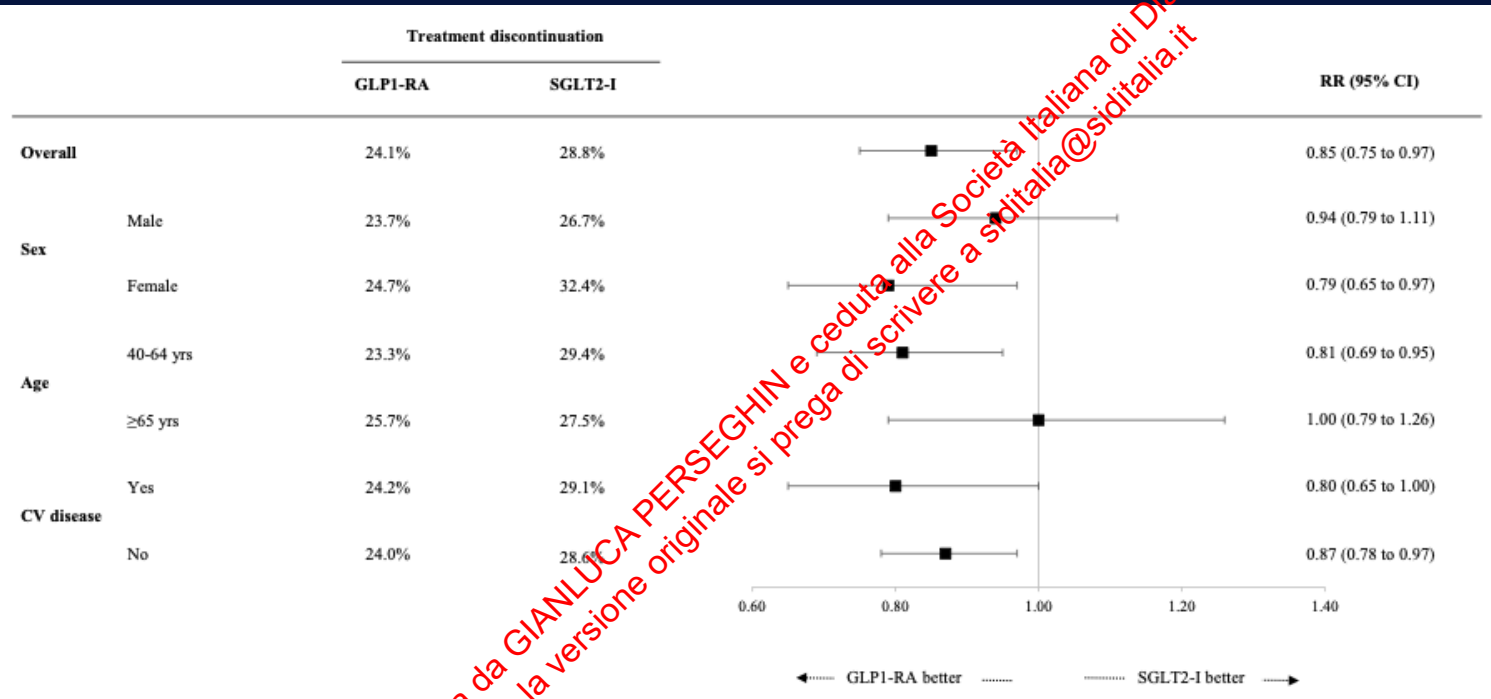
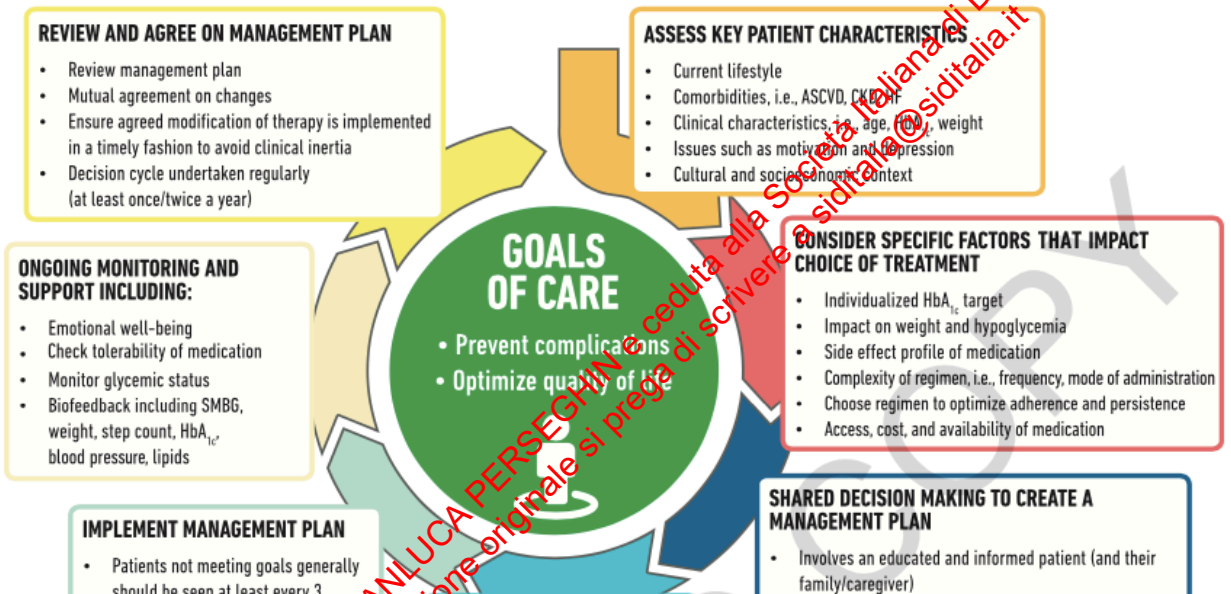


Fig. 2 – Adjusted risk ratio (RR), and 95% confidence intervals (CI), of treatment discontinuation with the drug started at the index date (i.e., GLP1-RA or SGLT2-I) in the whole cohort and according to sex, age and cardiovascular (CV) disease.

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

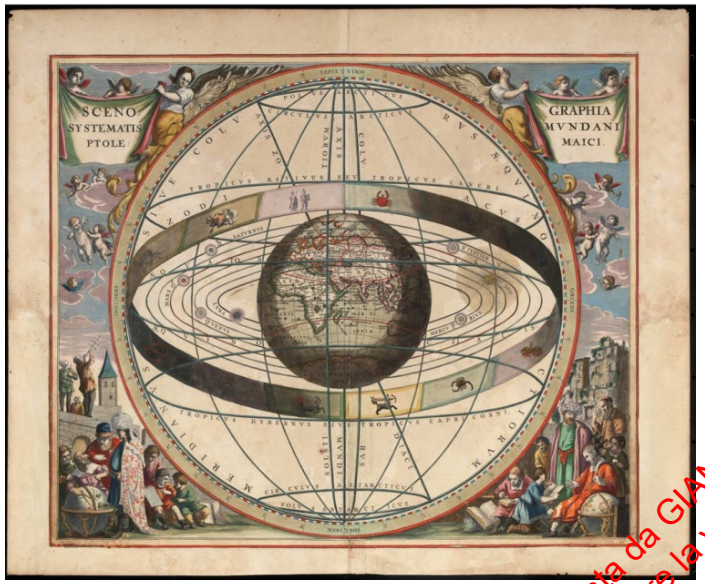
DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

ADA, Diabetes Care, 2020

La rivoluzione culturale in diabetologia



Visione Glucocentrica

DCCT UKPDS CVOTs
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Visione Prognosi centrica