QUANDO E COME INIZIARE LA TERAPIA ANTIDIABETICA NEL PAZIENTE CON MULTIPLI FATTORI DI RISCHIO?

PROGETTO Cardialink

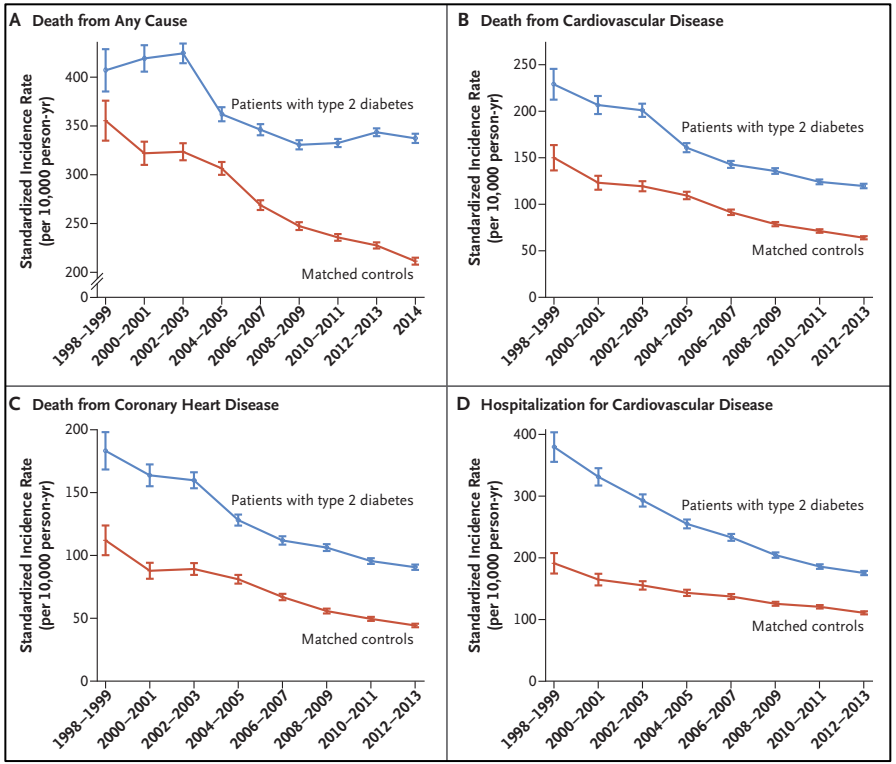
Riccardo Candido

S.S. Centro Diabetologico Distretto 3

Azienda Sanitaria Universitaria Giuliano Isontina

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Naveed Sattar, M.D., Ph.D., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.



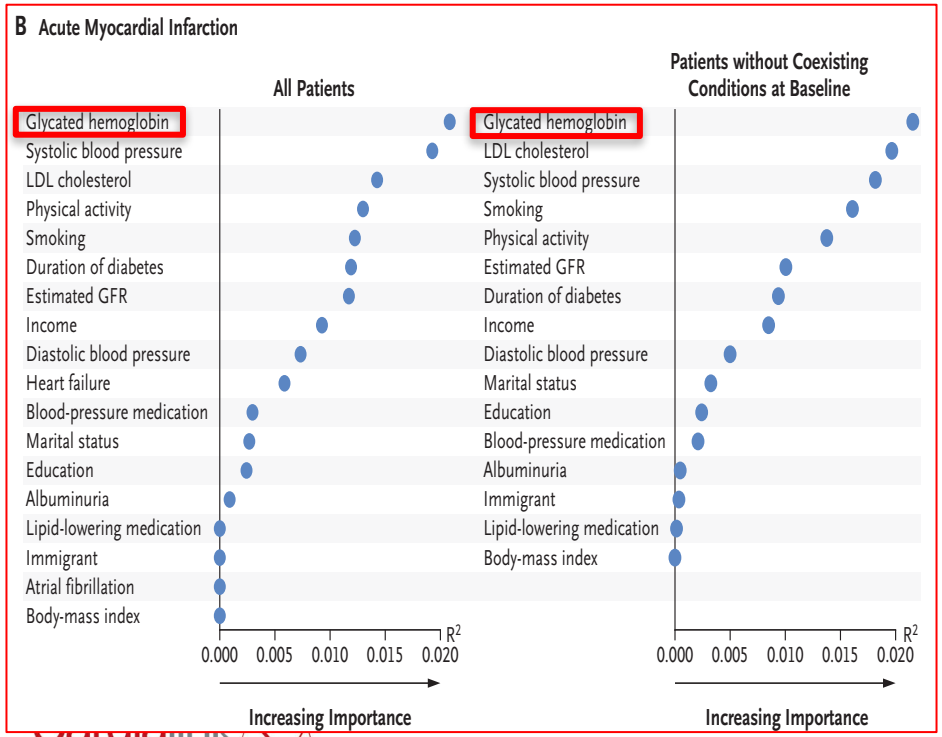
N Engl J Med 2017;376:1407-18

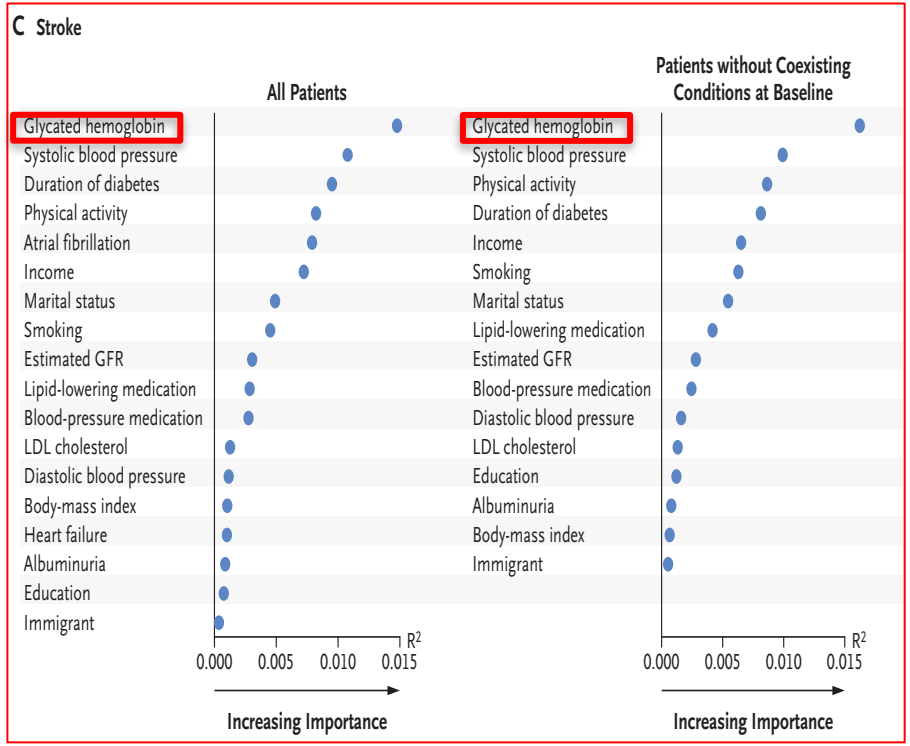
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rawshani A et al. *N Engl J Med* 2018;379:633–644

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes





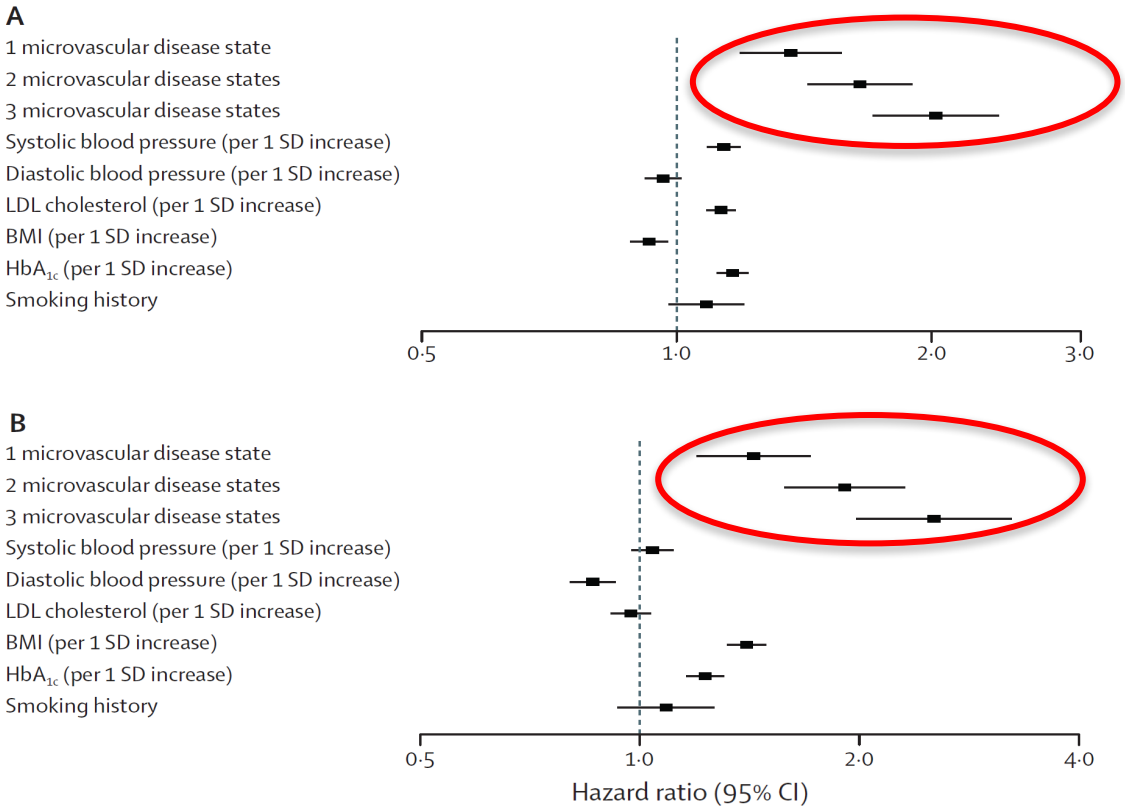
Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study

Lancet Diabetes Endocrinol 2016; 4: 588–97

Jack R W Brownrigg, Cian O Hughes, David Burleigh, Alan Karthikesalingam, Benjamin O Patterson, Peter J Holt, Matthew M Tho Simon de Lusignan, Kausik K Ray, Robert J Hinchliffe**

3-MACE

Heart Failure



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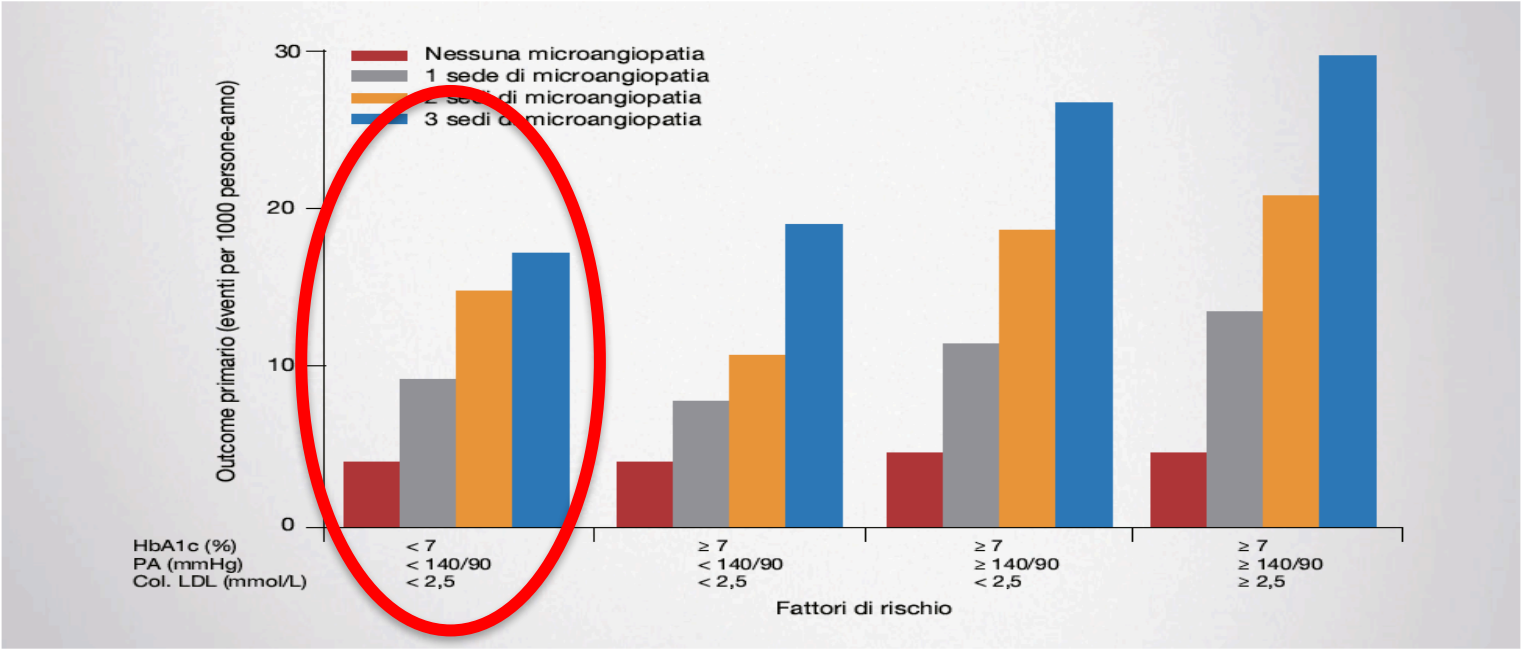
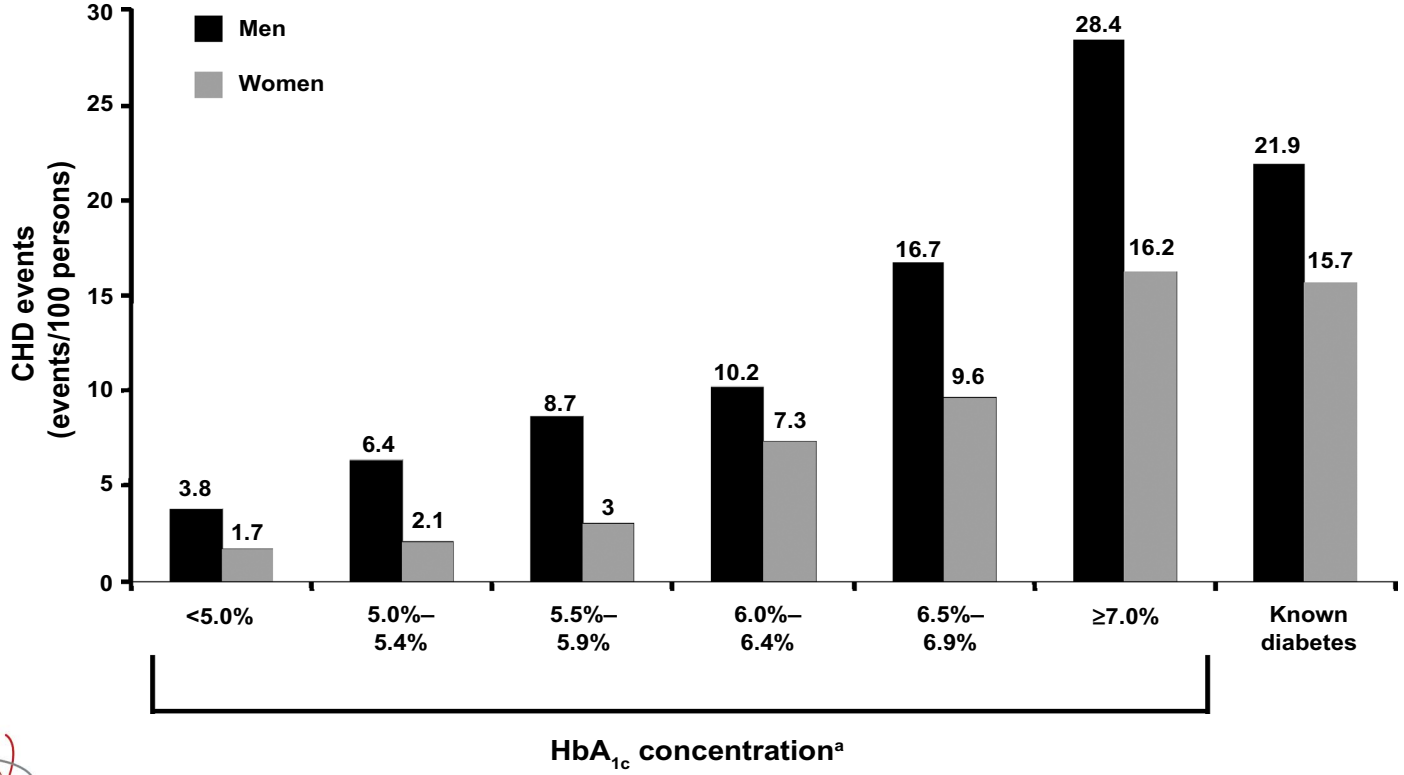
Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study.



Brownrigg JR et al. Lancet Diabetes Endocrinol 2016;4:588-97.

Glycated hemoglobin (HbA1c) and heart disease in type 2 diabetes



PROGETTO Cardialink

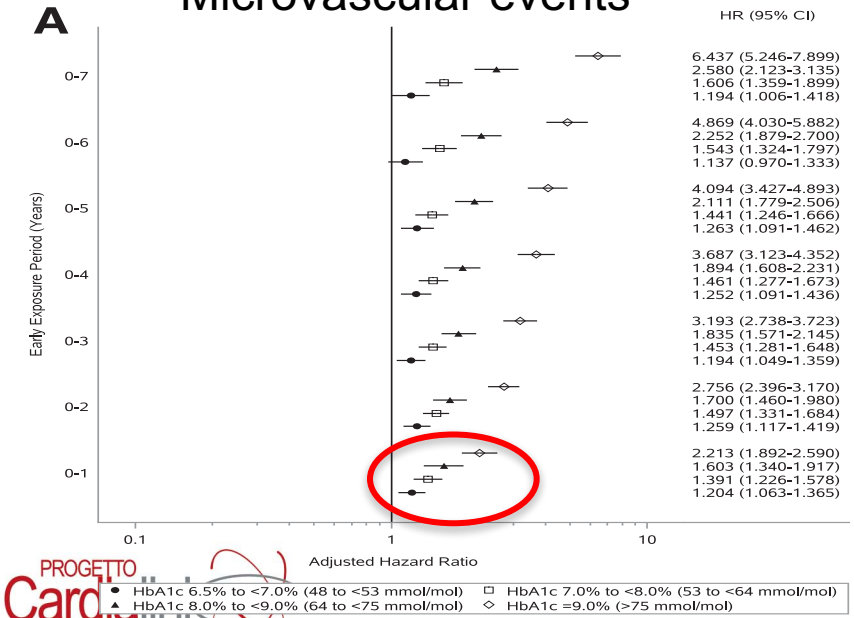
Diabetes Metab Syndr Obes. 2010;3:227-42

The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study)

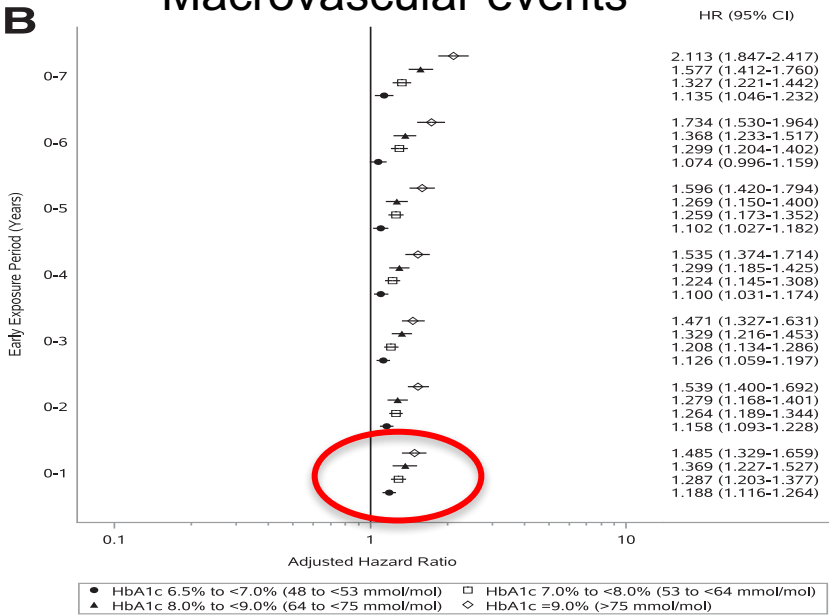
Neda Laiteerapong,[1] Sandra A. Ham,[2] Yue Gao,[1] Howard H. Moffet,[3] Jennifer Y. Liu,[3] Elbert S. Huang,[1] and Andrew J. Karter[3]

Diabetes Care 2019;42:416–426 | https://doi.org/10.2337/dc17-1144

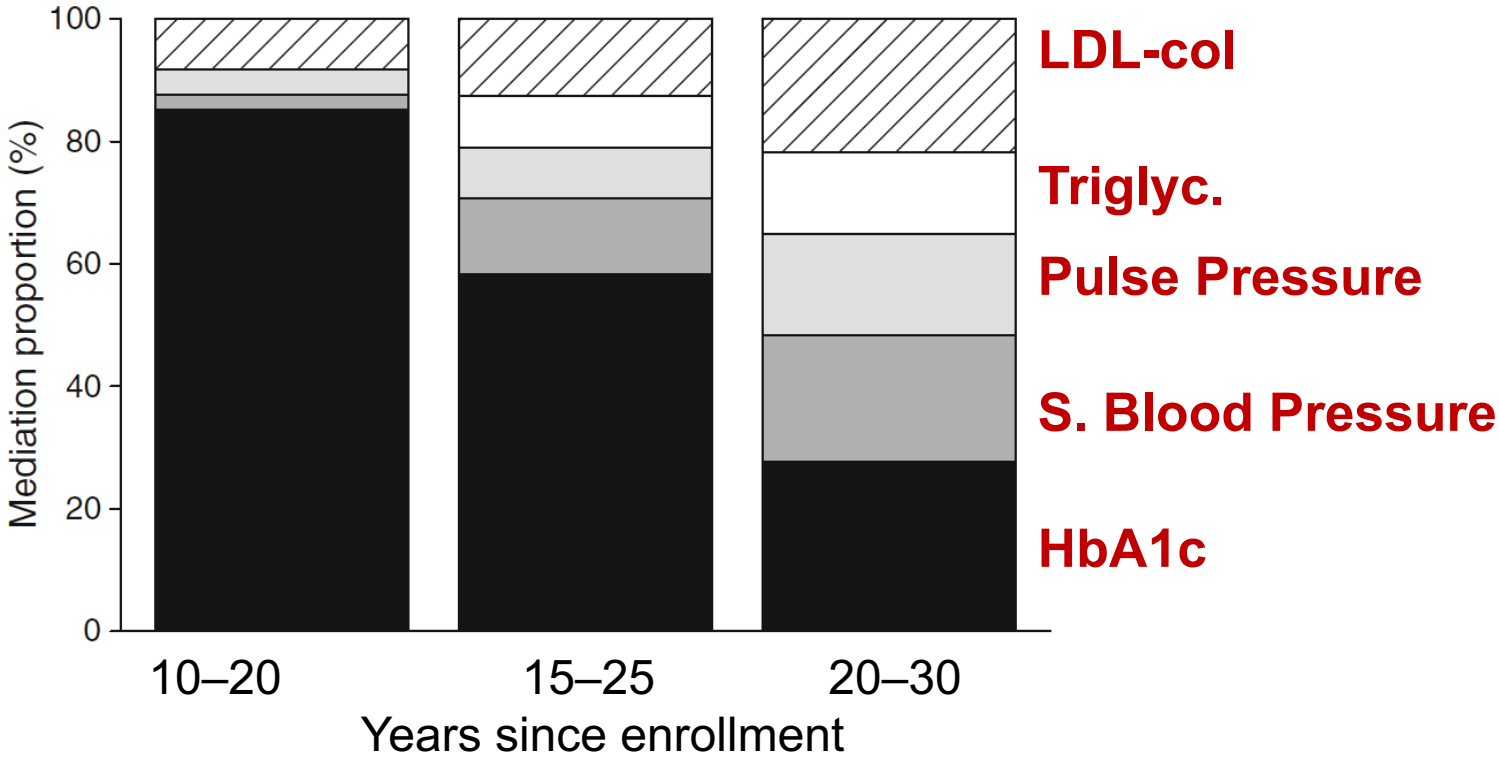
Microvascular events



Macrovascular events



Decomposition of the total effect of HbA1c on CVD risk into the direct and indirect effects



PROGETTO Cardialink

Bebu I et al. Diabetologia 2017; 60:2984-2091

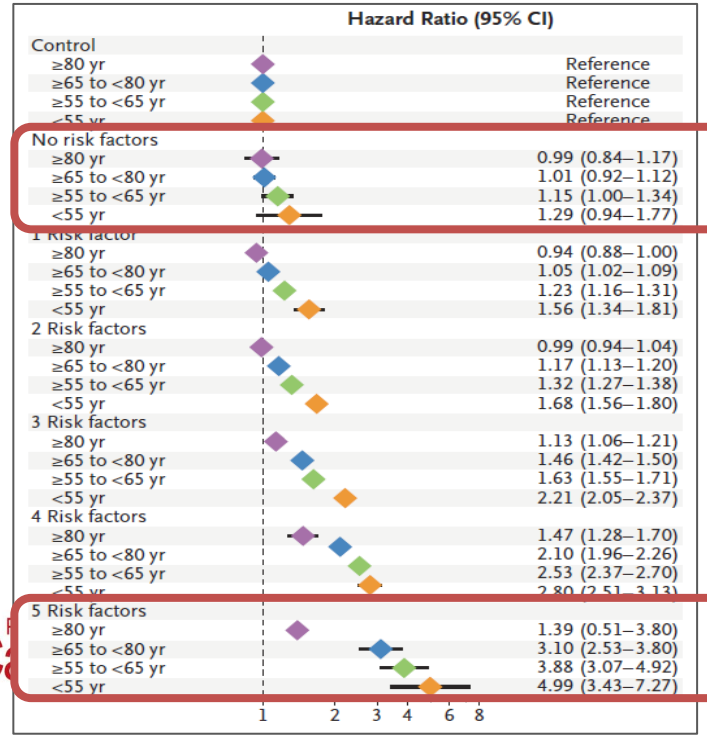
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

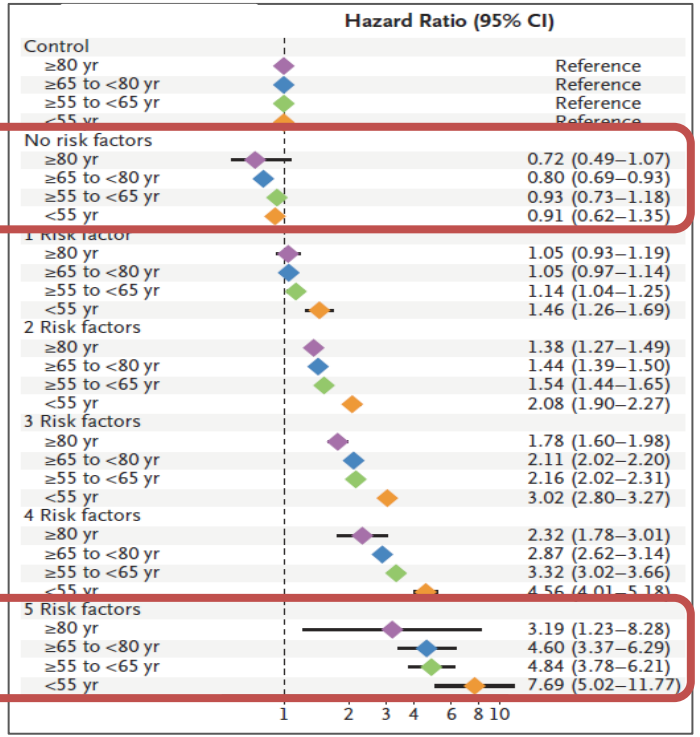
Rawshani A et al. *N Engl J Med* 2018;379:633–644

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mortality



Acute myocardial infarction



ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1—69
doi:10.1093/eurheartj/ehz486

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

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

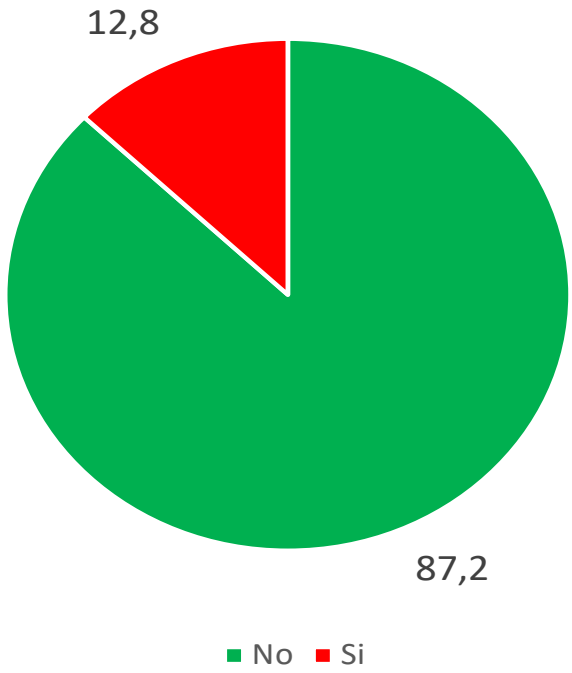
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[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.

Soggetti con storia di malattia CV DMT2- Annali 2018



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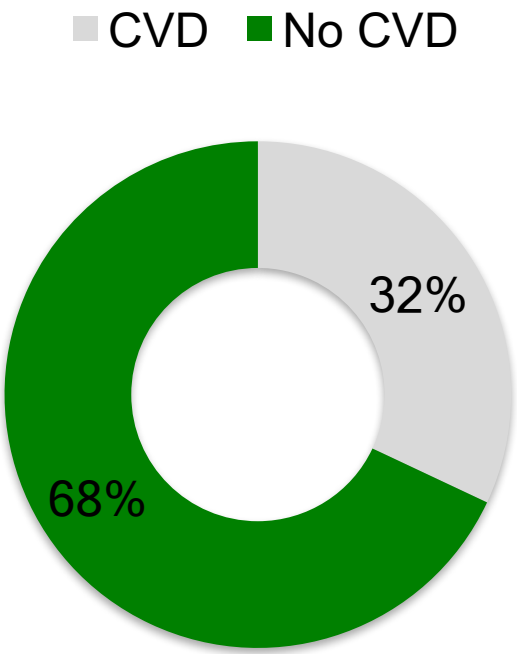
A majority of people with type 2 diabetesdo not have established CVD, most are at risk for a CV event



Einarson et al. Cardiovasc Diabetol (2018) 17:83; ADA. Diabetes Care 2019; 42 (suppl. 1): S103-S123

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

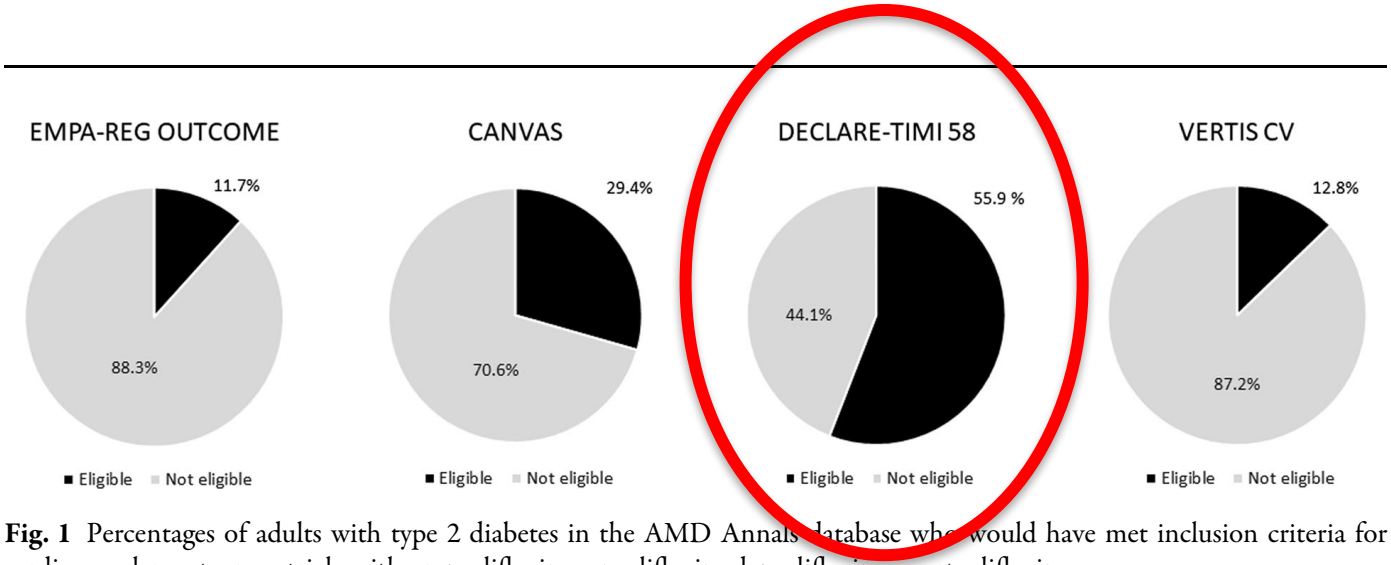
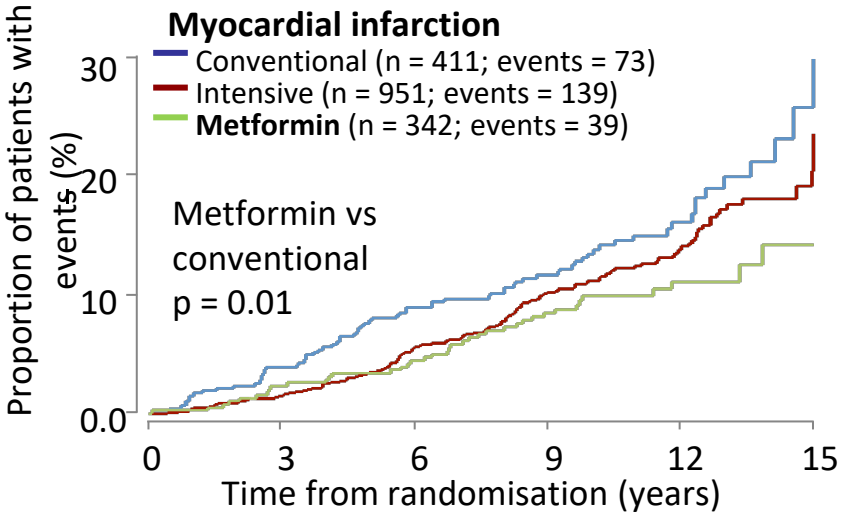


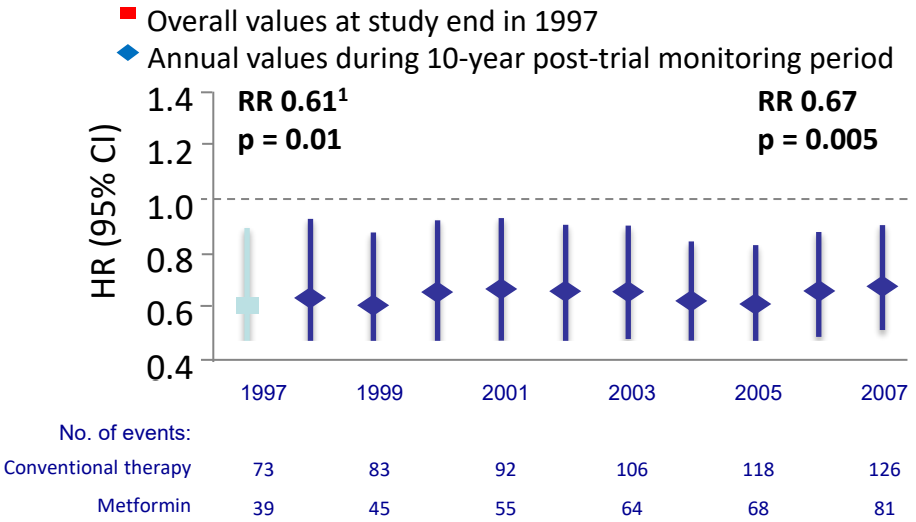
Fig. 1 Percentages of adults with type 2 diabetes in the AMD Annals database who would have met inclusion criteria for cardiovascular outcomes trials with empagliflozin, canagliflozin, dapagliflozin, or ertugliflozin

UKPDS 34 provides some evidence for beneficial CV effects of metformin in overweight patients

Risk of MI is 39% lower with metformin vs conventional therapy in obese patients[1,2]



Significant reduction in MI maintained over 10 years' follow-up[3]

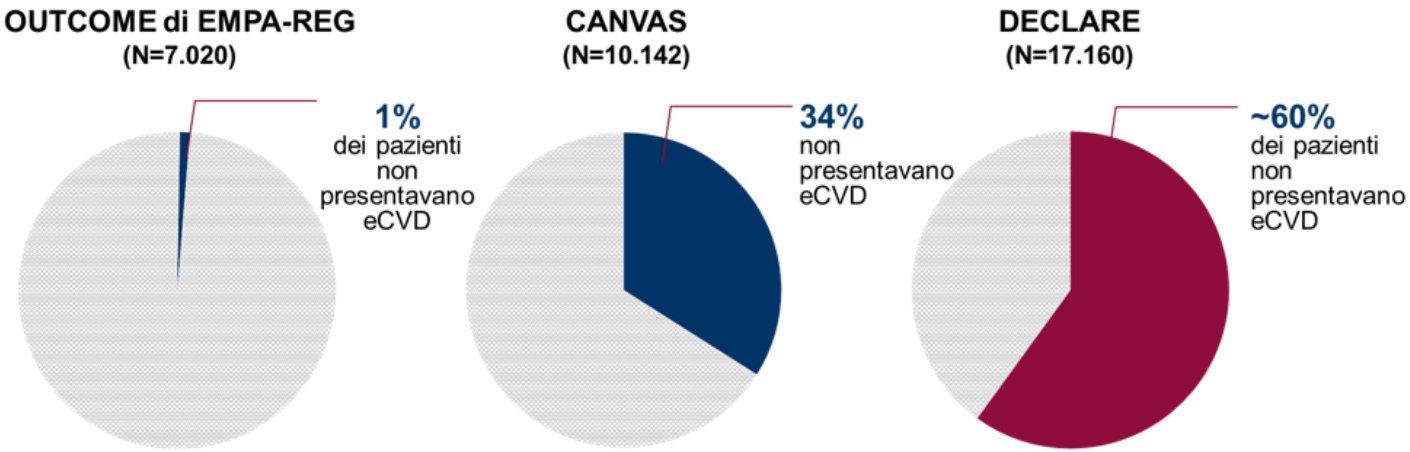


CV, cardiovascular

1. UKPDS 34. *Lancet* 1998;352:854–65. 2. http://www.medicines.org.uk/emc/medicine/23244/SPC. 3. Holman et al. *N Engl J Med* 2008;359:1577–89.

Per gli SGLT2i lo studio DECLARE ha la più alta rappresenzanza di pazienti con DM2 in prevenzione primaria

La percentuale di pazienti che non presentavano patologie CV conclamate varia nell'ambito dei tre studi sugli outcome CV degli SGLT2i

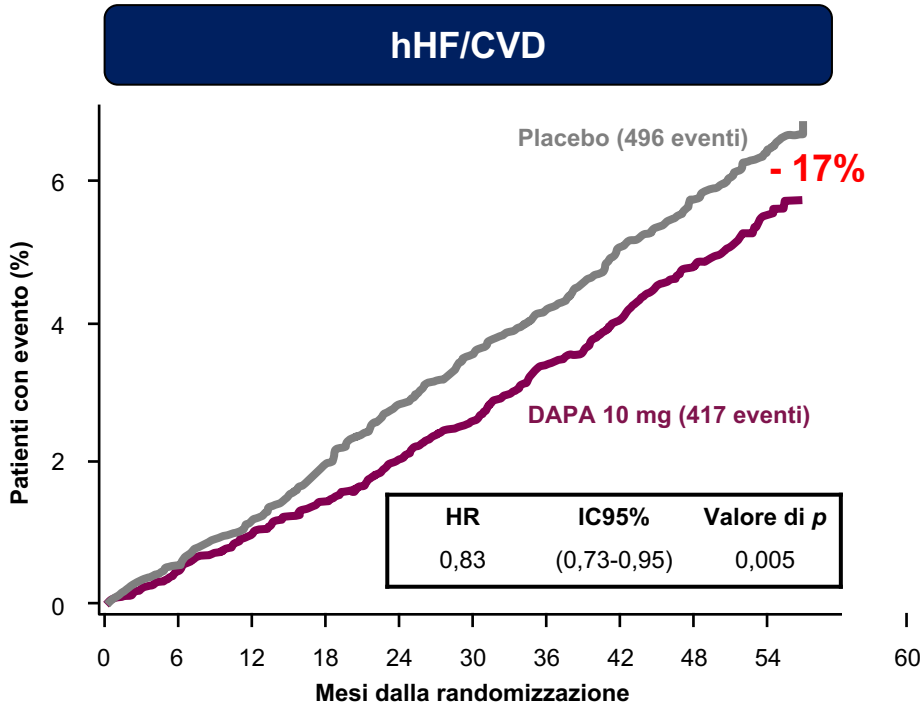


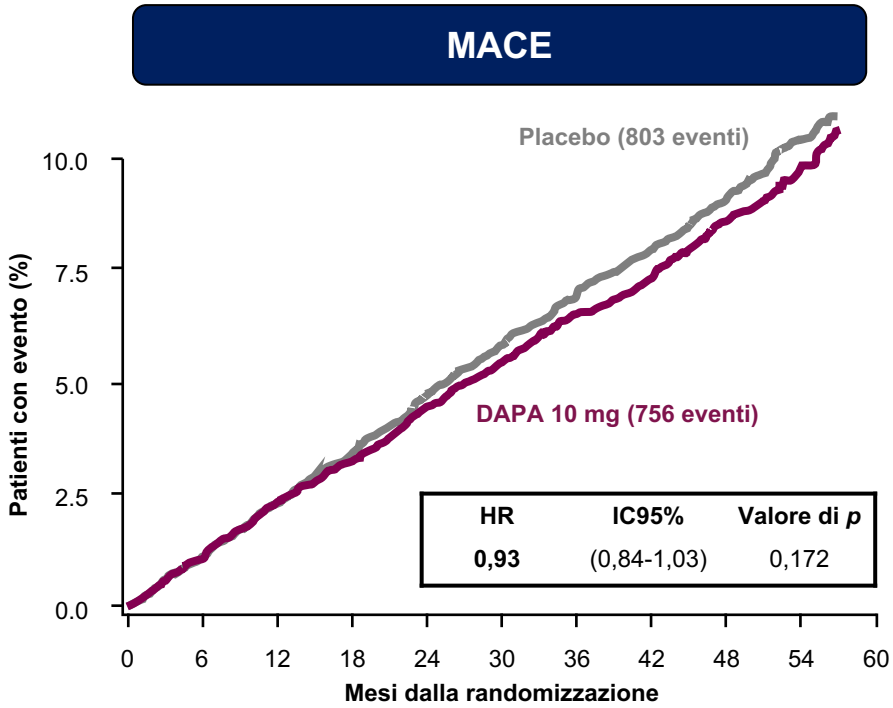
CV, cardiovascolare; SGLT2, cotrasportatore di sodio e glucosio 2; T2D, diabete di tipo 2; eCVD, patologia CV conclamata.

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925;3. Sattar Diabetologia (2013) 56:686–695 4. Raz I, et al. *Diabetes Obes Metab* 2018. http://dx.doi.org/10.1111/dom.13217

PROGETTO Cardialink

In questa popolazione a basso rischio CV, i pazienti trattati con dapagliflozin hanno mostrato una riduzione significativa di hHF/morte CV e un minor numero di eventi MACE rispetto a placebo

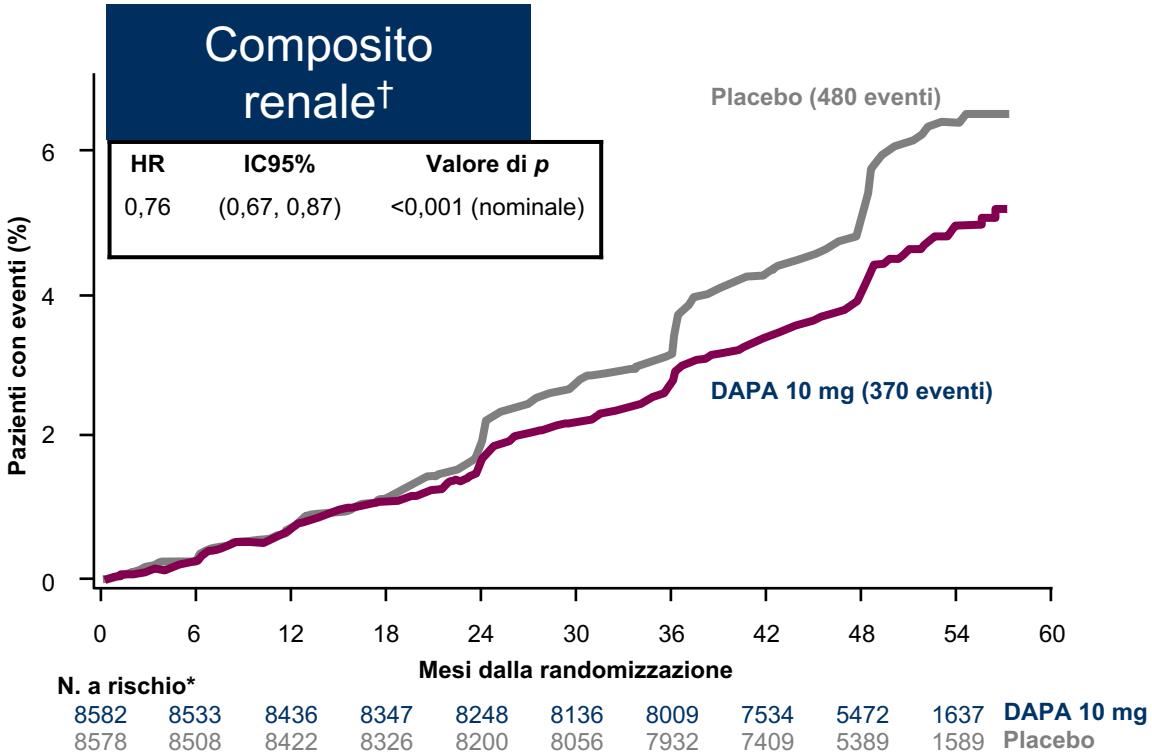




PROGETTO Cardialink

Wiviott SD et al. N Engl J Med. 2019;380(4):347-357

Dapagliflozin ha rallentato la progressione della malattia renale nei pazienti con T2D con una funzionalità renale relativamente buona al basale



PROGETTO Cardialink

Wiviott SD et al. N Engl J Med. 2019;380(4):347-357

Implications of the REWIND Findings

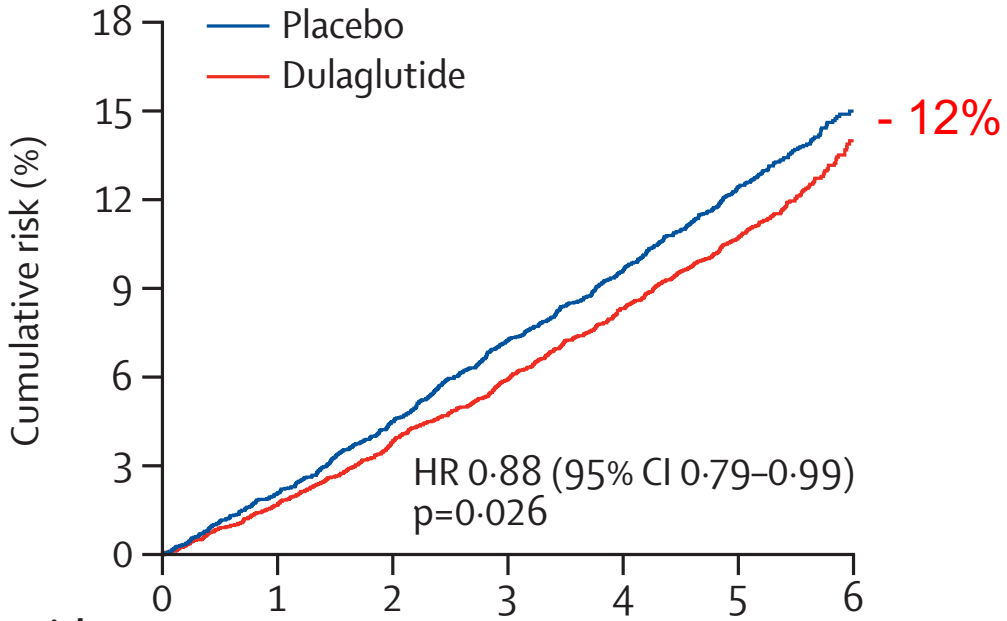
	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY	REWIND
N	6068	9340	3297	14752	9463	9901
Drug Tested	Lixi/d					Dula/wk
Prior CVD	100%					31%
Mean Age	60 y					66 y
Women	30%					46%
Median F/U	2.1 y					5.4 y
DM Duration	9.2 y					10.5 y
Baseline A1c	7.7%					7.3%
Baseline eGFR	76					77
Insulin Use	39%	45%	58%	46%	59%	24%

Participants were similar to the sorts of ambulatory patients with type 2 DM & CV risk factors who are routinely seen in clinical practice

PROGETTO Cardialink

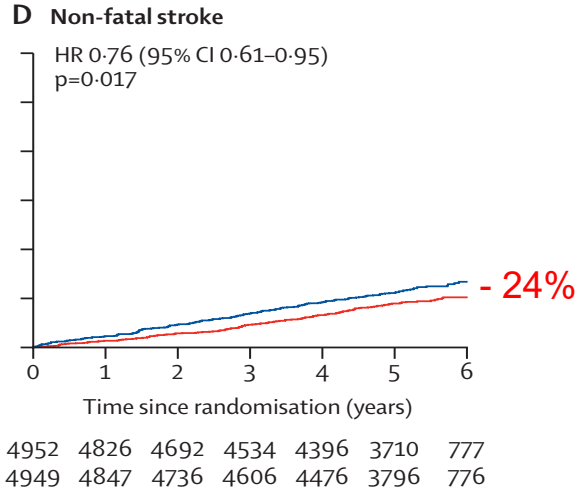
*GLP-1 RA CVOT trials cannot be directly compared due to differences in study design, population and key inclusion/exclusion criteria

Dulaglutide's Effect on the CV Composite Primary Outcome: 1st Occurrence of Nonfatal MI, Nonfatal Stroke, CV Death



Number at risk

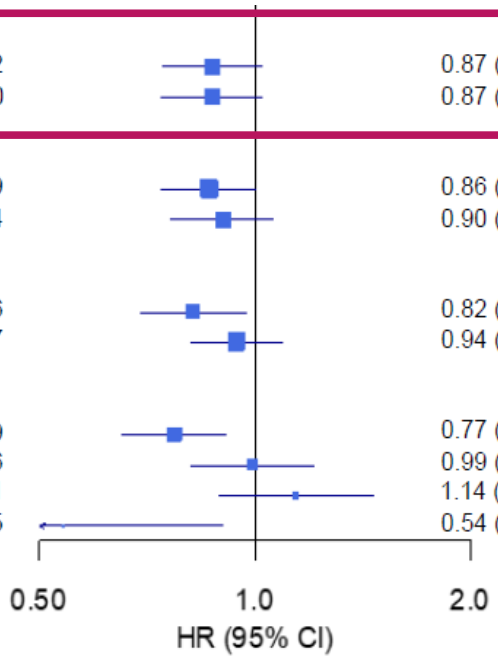
Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741



Gerstein HC et al. Lancet. 2019;394(10193):121-130.

CV Composite in Prespecified Subgroups

Subgroups	Dulaglutide Events/Total (%)	Dulaglutide Rate/100 py	Placebo Events/Total (%)	Placebo Rate/100 py	Hazard Ratio 95% CI	P value for Interaction
History of CVD						
Prior CVD	280 /1560 (17.9)	3.7	315 /1554 (20.3)	4.2	0.87 (0.74-1.02)	
No Prior CVD	277 /3093 (8.9)	1.7	317 /3128 (10.1)	2.0	0.87 (0.74-1.02)	0.970
Baseline HbA1c						
≥ 7.2%	328 /2610 (12.6)	2.5	373 /2603 (14.3)	2.9	0.86 (0.74-1.00)	
< 7.2%	263 /2329 (11.3)	2.2	289 /2334 (12.4)	2.4	0.90 (0.76-1.06)	0.746
BMI (kg/m^2)						
≥ 32	254 /2281 (11.1)	2.1	308 /2302 (13.4)	2.6	0.82 (0.69-0.96)	
< 32	340 /2667 (12.7)	2.5	355 /2650 (13.4)	2.7	0.94 (0.81-1.09)	0.214
Region						
Europe	248 /2174 (11.4)	2.2	315 /2165 (14.5)	2.9	0.77 (0.65-0.90)	
Latin America	191 /1511 (12.6)	2.6	190 /1510 (12.6)	2.6	0.99 (0.81-1.21)	
USA/Canada	132 /1032 (12.8)	2.4	117 /1039 (11.3)	2.1	1.14 (0.89-1.47)	
Asia Pacific	23 / 232 (9.9)	1.9	41 / 238 (17.2)	3.5	0.54 (0.32-0.89)	0.008

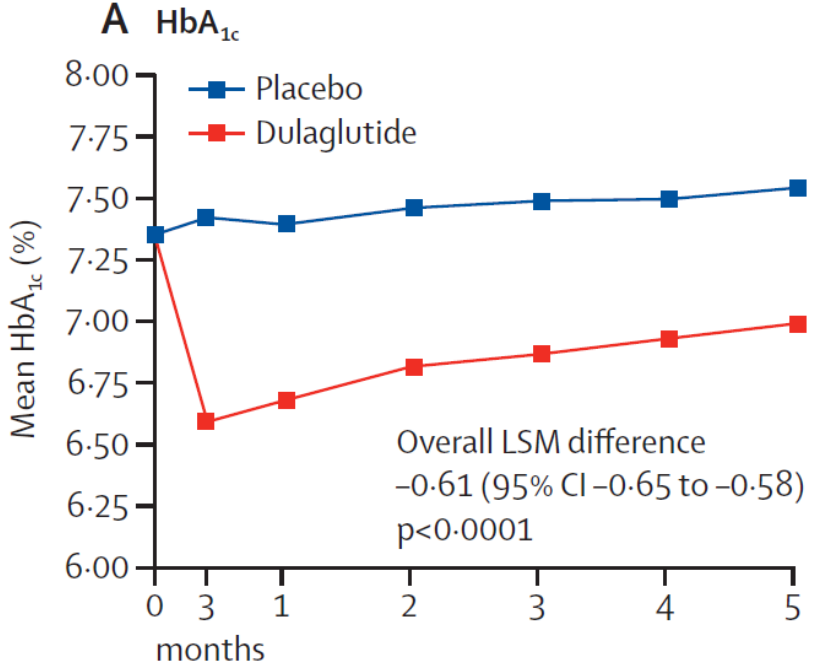


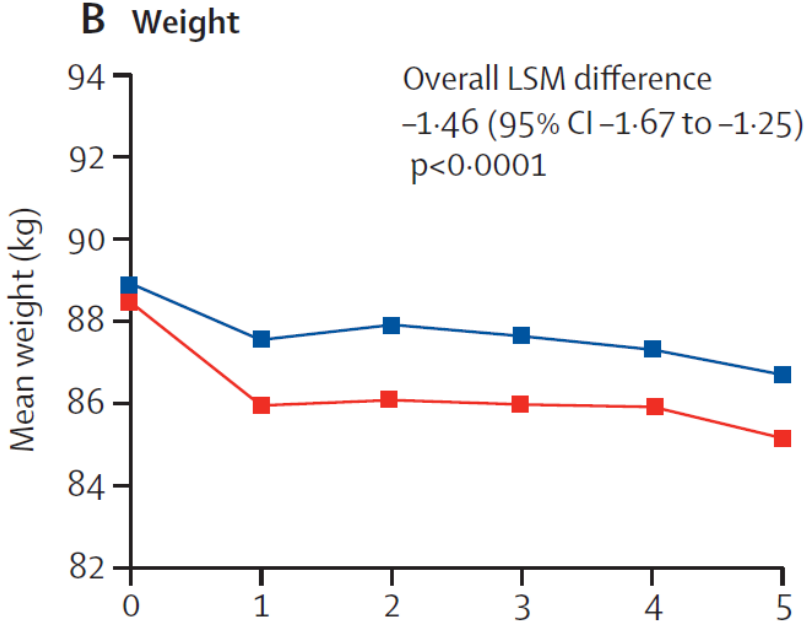
Gerstein HC, et al. *Lancet.* 2019;394(10193):121-130.

REWIND
Dulaglutide CV Outcomes Trial

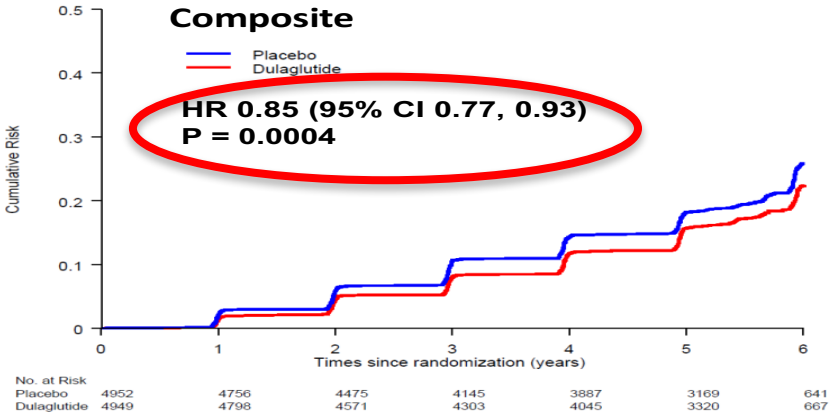
Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

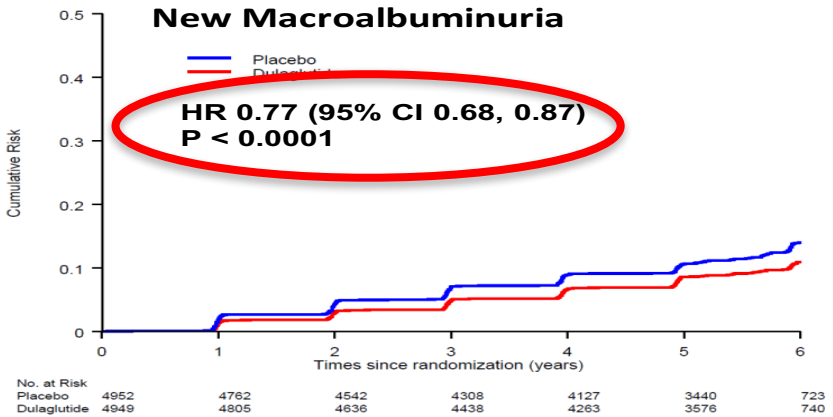
Hertzel C Gerstein, Helen M Colhoun, Gilles R Dagenais, Rafael Diaz, Mark Lakshmanan, Prem Pais, Jeffrey Probstfield, Jeffrey S Riesmeyer, Matthew C Riddle, Lars Rydén, Denis Xavier, Charles Messan Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-Melacini, Gloria Wong, Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, Markolf Hanefeld, Shaun Holt, Petr Jansky, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Ernesto German Cardona Munoz, Valdis Pirags, Nana Pogosova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev, for the REWIND Investigators*

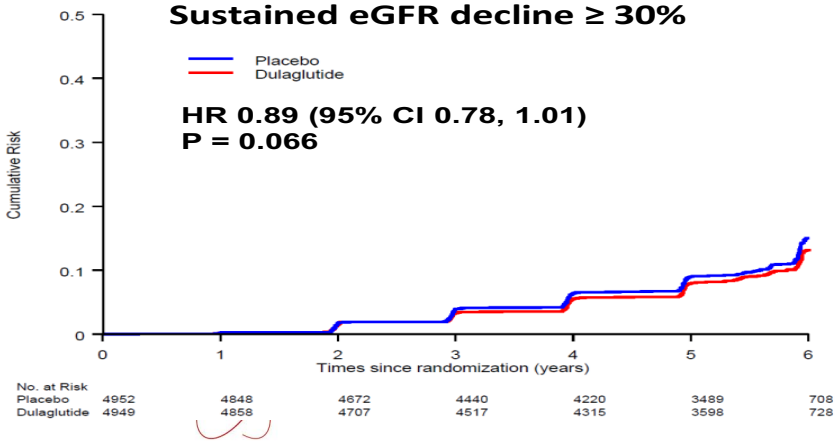


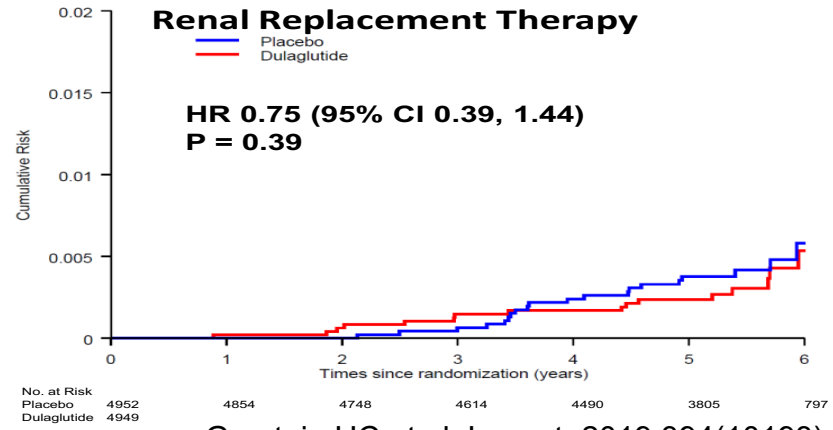


REWIND: Renal Outcomes



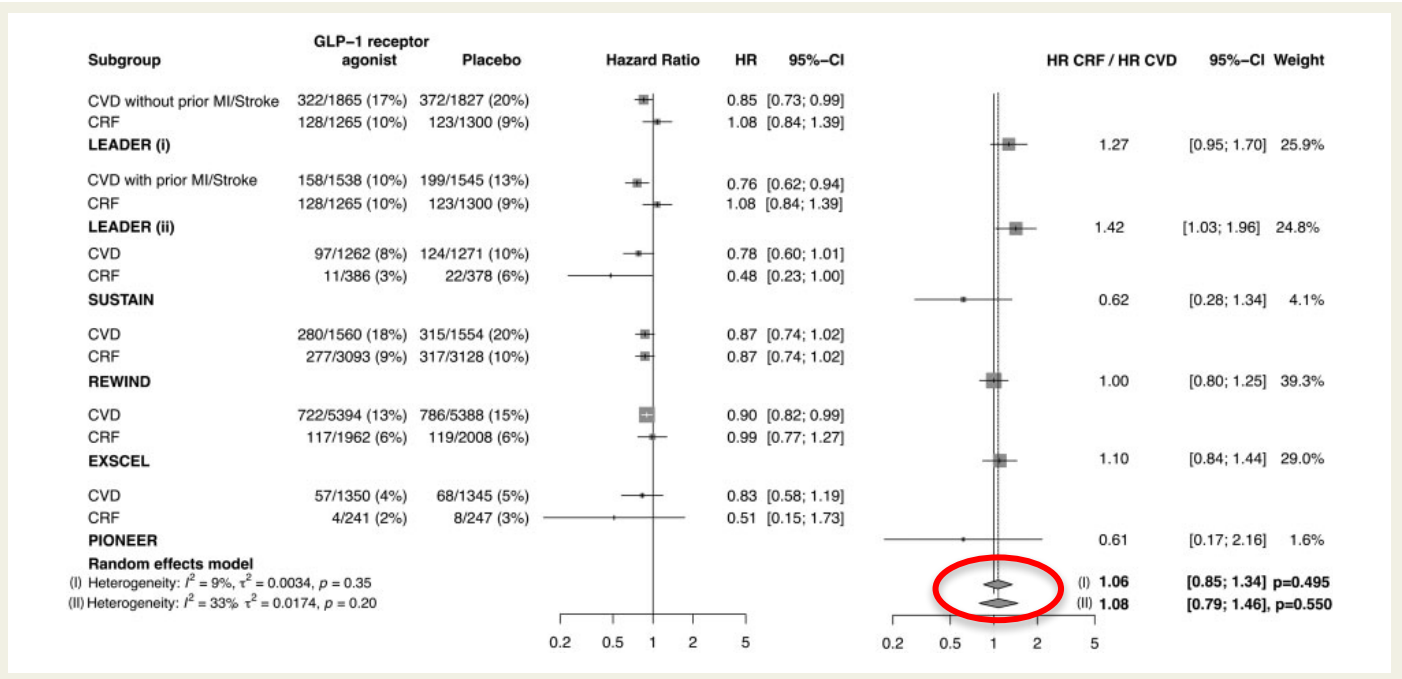




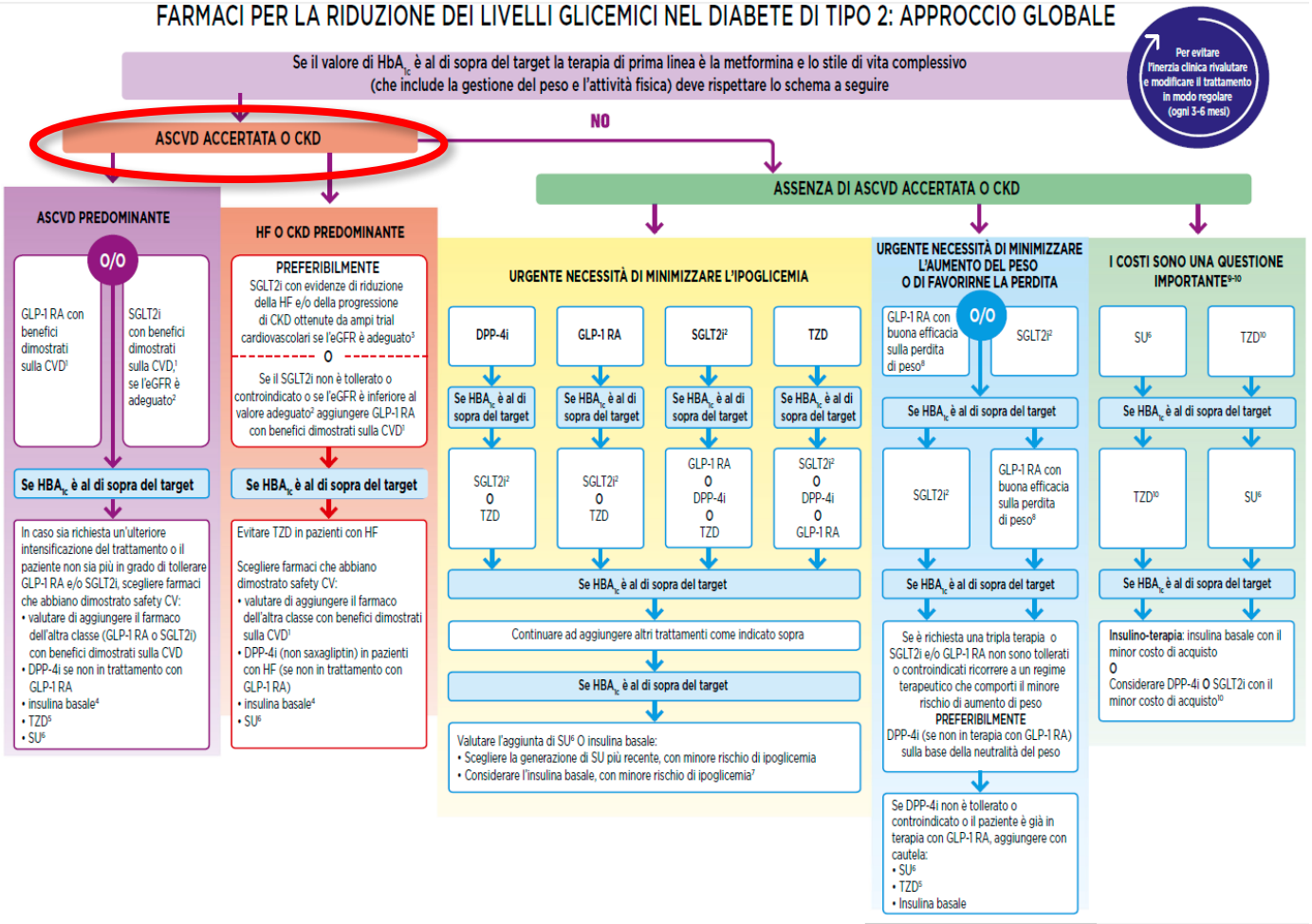


Gerstein HC et al. Lancet. 2019;394(10193):121-130.

Effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events in patients with Type 2 diabetes mellitus with or without established cardiovascular disease: a meta-analysis of randomized controlled trials



Marsico F et al. Eur Heart J. 2020 Feb 20



PROGETTO Cardialink

Diabetologia. 2018 Dec;61(12):2461-2498

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (see below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (see below)

OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

ASCVD predominates

GLP-1 RA with proven CVD benefit[1]

EITHER/ OR

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

HF or CKD predominates

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1,4]

PROGETTO Cardialink

Diabetologia. 2018 Dec;61(12):2461-2498

Diabetologia (2020) 63:221–228
https://doi.org/10.1007/s00125-019-05039-w

CONSENSUS REPORT UPDATE

2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

John B. Buse[1] · Deborah J. Wexler[2,3] · Apostolos Tsapas[4] · Peter Rossing[5,6] · Geltrude Mingrone[7,8,9] · Chantal Mathieu[10] · David A. D'Alessio[11] · Melanie J. Davies[12]

We now also suggest that to reduce risk of MACE, **GLP-1 receptor agonists can also be considered** in patients with **type 2 diabetes without established CVD** with **indicators of high risk, specifically, patients aged 55 years or older** with **coronary, carotid** or **lower extremity artery stenosis >50%, left ventricular hypertrophy**, an **eGFR <60 ml min^{-1} [1.73 m]$^{-2}$** or **albuminuria**.

Diabetologia (2020) 63:221–228
https://doi.org/10.1007/s00125-019-05039-w

CONSENSUS REPORT UPDATE

2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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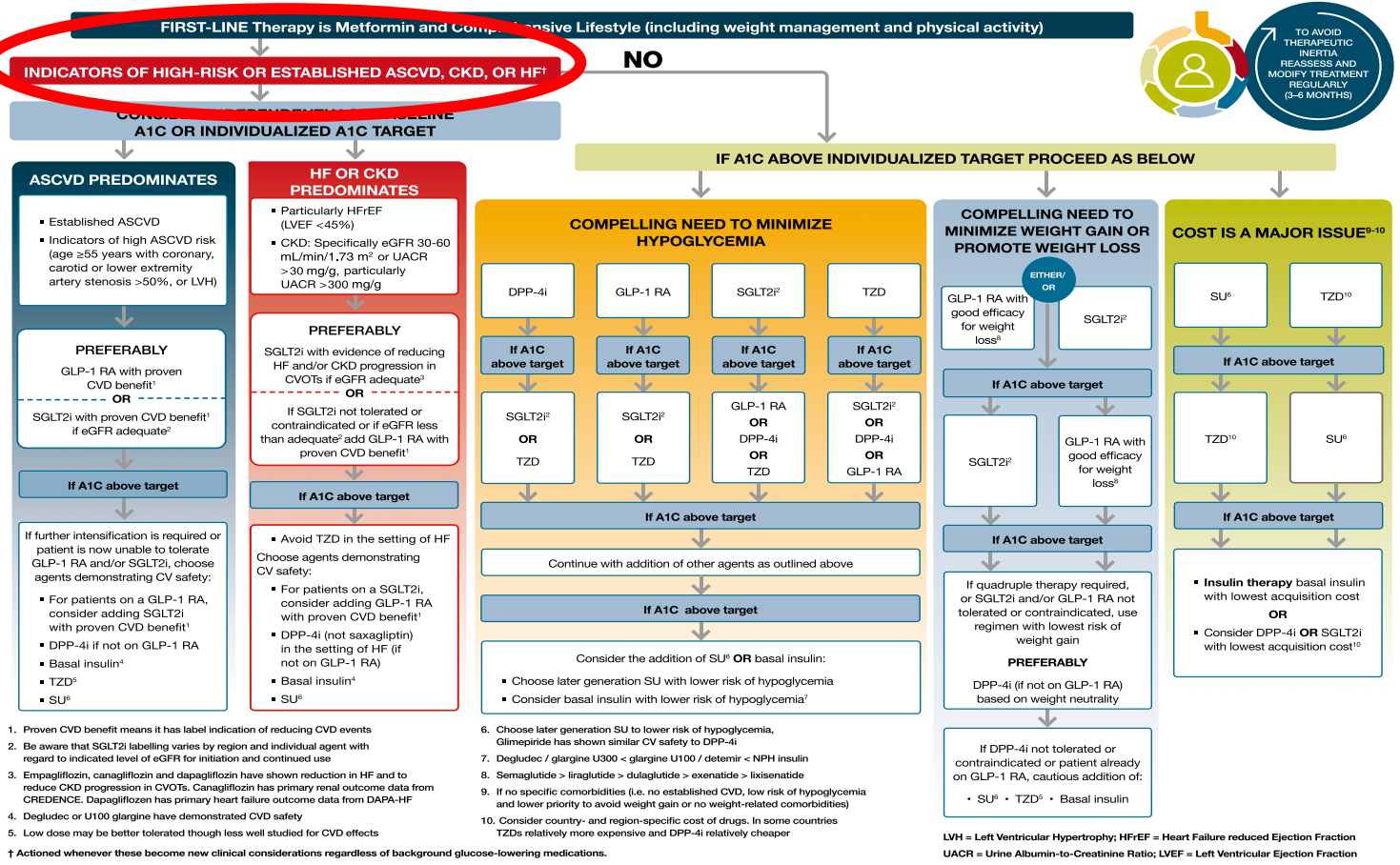
To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention *is strongest for dulaglutide but lacking for other GLP-1 receptor agonists.*

9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2020



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; 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; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

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Decision Algorithm for Prescribing SGLT2 Inhibitors and GLP-1 Receptor Agonists for Diabetic Kidney Disease

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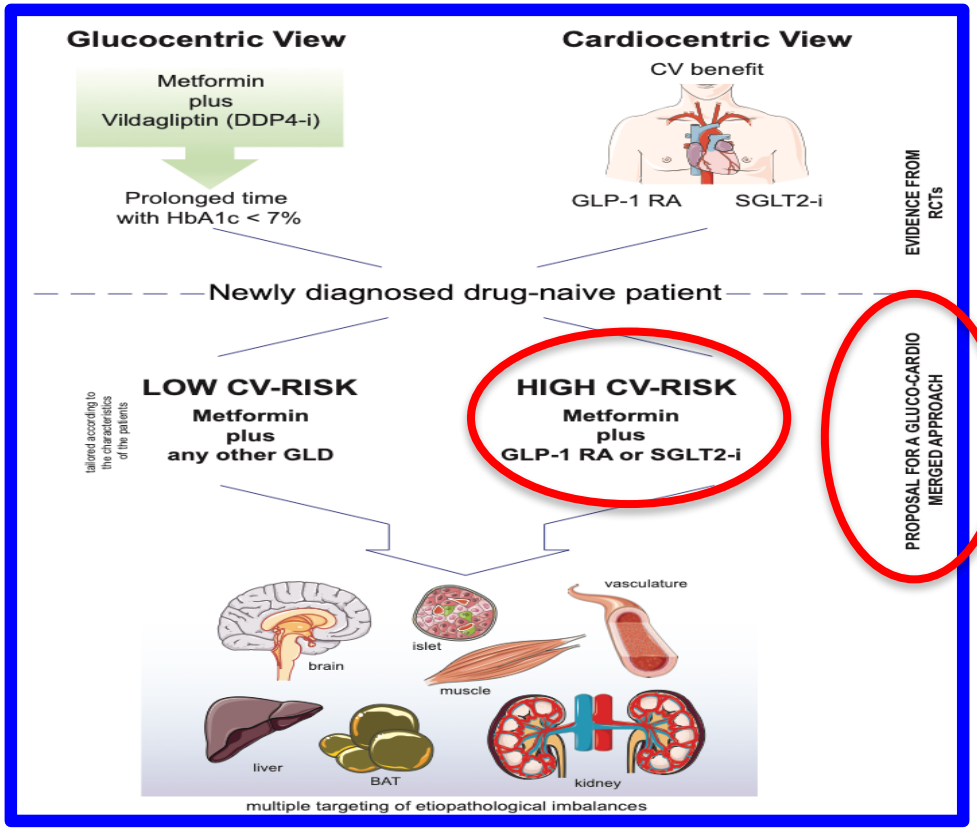
eGFR	UACR <30 mg/g	UACR 30–299 mg/g	UACR ≥300 mg/g
>60 ml/min per 1.73 m^2	SGLT2i or GLP-1 RA[a]	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]	SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
30–60 ml/min per 1.73 m^2	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]		SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
15–29 ml/min per 1.73 m^2	GLP-1 RA (dulaglutide) is preferred. Initiation of SGLT2i is currently contraindicated[d]		

CJASN 15: ●●●–●●●, 2020. doi: https://doi.org/10.2215/CJN.02690320

QUANDO E COME INIZIARE LA TERAPIA ANTIDIABETICA NEL PAZIENTE CON MULTIPLI FATTORI DI RISCHIO?



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