CONGRESSO REGIONALE SID-AMD UMBRIA 2024

RITORNO AL FUTURO

DIABETE TIPO 1 E RISCHIO CARDIOVASCOLARE: COSA CI STIAMO PERDENDO

MA DAVVERO I FARMACI CARDIO E NEFRO-PROTETTIVI NON POSSONO ESSERE UTILIZZATI NEL DM1?

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Università degli Studi di Perugia

Disclosure

Il sottoscritto Dr. Michelantonio De Fano dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Eli-Lilly
- Novo Nordisk
- Astra Zeneca
- Guidotti
- Sanofi
- Savio Pharma

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

In fede, Michelantonio De Fano

L'IMPORTANZA DEL DCCT

The New England
Journal of Medicine

Volume 329 SEPTEMBER 30, 1993 Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

Abstract *Background.* Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). We examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

Methods. A total of 1441 patients with IDDM — 726 with no retinopathy at base line (the primary-prevention cohort) and 715 with mild retinopathy (the secondary-intervention cohort) were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional therapy with one or two daily insulin injections. The patients were followed for a mean of 6.5 years, and the appearance and progression of retinopathy and other complications were assessed regularly.

Results. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76 percent (95 percent confidence interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe nonproliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥40 mg per 24 hours) by 39 percent (95 percent confidence interval, 21 to 52 percent), that of albuminuria (urinary albumin excretion of ≥300 mg per 24 hours) by 54 percent (95 percent confidence interval, 19 to 74 percent), and that of clinical neuropathy by 60 percent (95 percent confidence interval, 38 to 74 percent). The chief adverse event associated with intensive therapy was a two-to-threefold increase in severe hypoglycemia.

Conclusions. Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM. (N Engl J Med 1993;329:977-86.)

INSULIN-dependent diabetes mellitus (IDDM) is accompanied by long-term microvascular, neurologic, and macrovascular complications. Although the daily management of IDDM is burdensome and the specter of metabolic decompensation ever-present, long-term complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease, have caused the most morbidity and mortality since the introduction of insulin therapy.[1,2] The prevention and amelioration of these complications have been major goals of recent research.

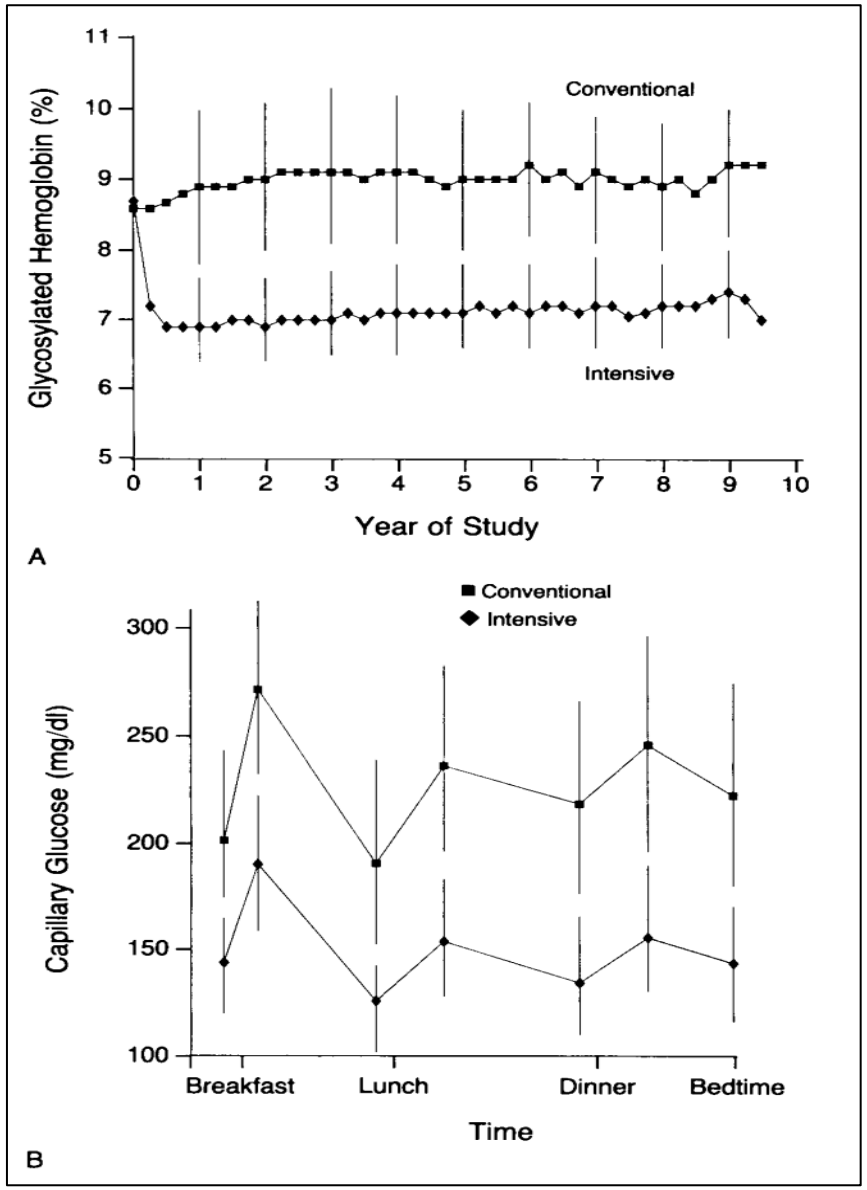
Although studies in animal models of diabetes[3-5] and epidemiologic studies[6-8] implicate hyperglycemia in the pathogenesis of long-term complications, previous clinical trials have not demonstrated a consistent or convincing beneficial effect of intensive therapy on them.[9-11] A recent publication from the Stockholm Diabetes Intervention Study demonstrated a more uniform beneficial effect of intensive therapy in patients with established complications, despite the apparent crossover of most conventionally treated patients to intensive therapy during the trial.[12]

The Diabetes Control and Complications Trial was a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy with regard to their effects on the development and progression of the early vascular and neurologic complications of IDDM.[13-15] The intensive-therapy regimen was designed to achieve blood glucose values as close to the normal range as possible with three or more daily insulin injections or treatment with an insulin pump. Conventional therapy consisted of one or two insulin injections per day. Two cohorts of patients were studied in order to answer two different, but related, questions: Will intensive therapy prevent the development of diabetic retinopathy in patients with no retinopathy (primary prevention), and will inten-

Address reprint requests to the DCCT Research Group, Box NDIC/DCCT, Bethesda, MD 20892.

Supported under cooperative agreements and a research contract with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases and by the National Heart, Lung, and Blood Institute, the National Eye Institute, the National Center for Research Resources, and various corporate sponsors (listed in *Diabetes Care* 1987;10:1-19).

*A complete list of the persons and institutions participating in the Diabetes Control and Complications Trial Research Group appears in the Appendix.



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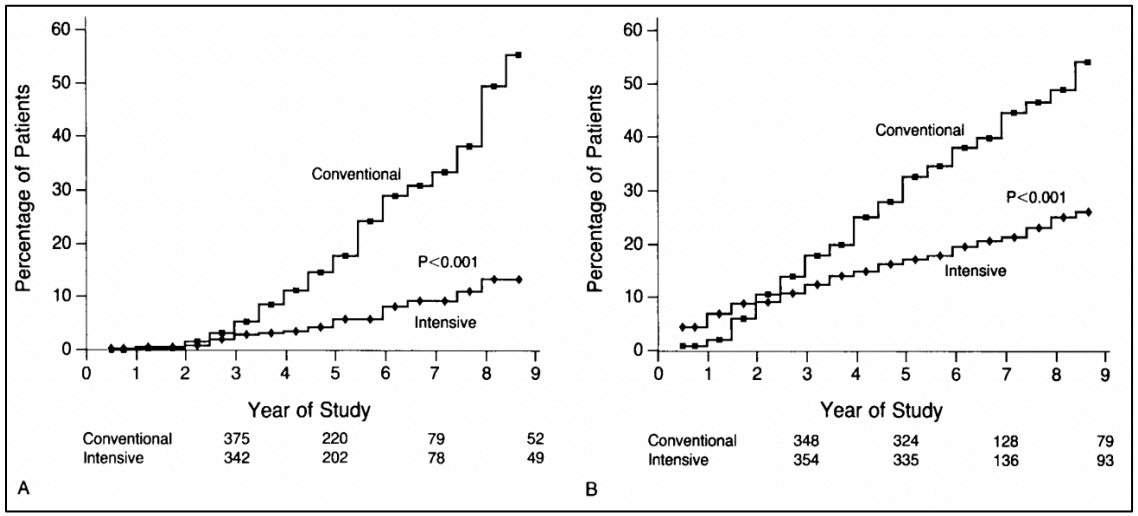
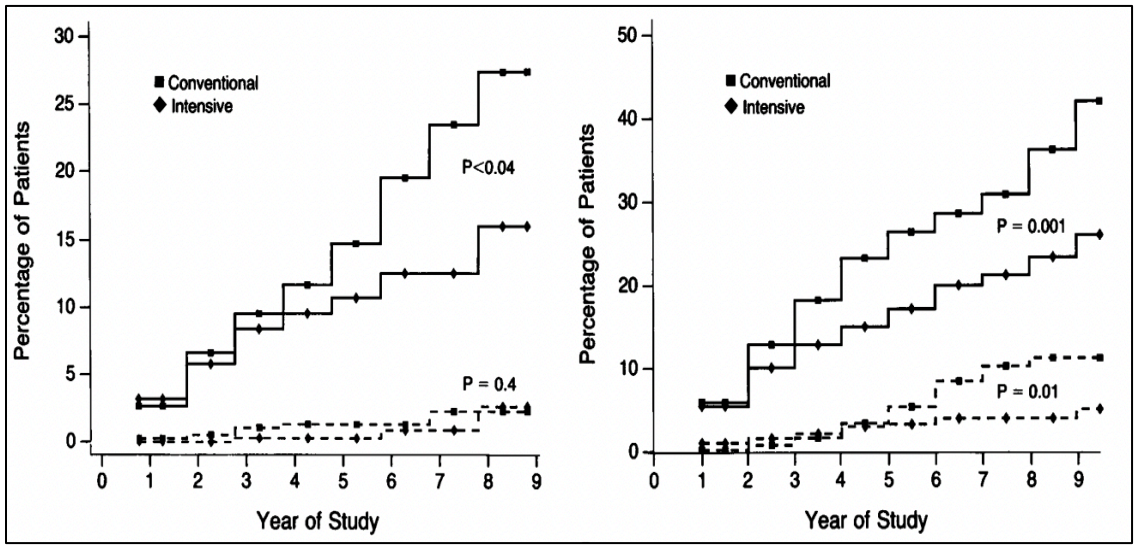
The Diabetes Control and Complications Trial Research Group, N Eng J Med. 1993, 329:977-986

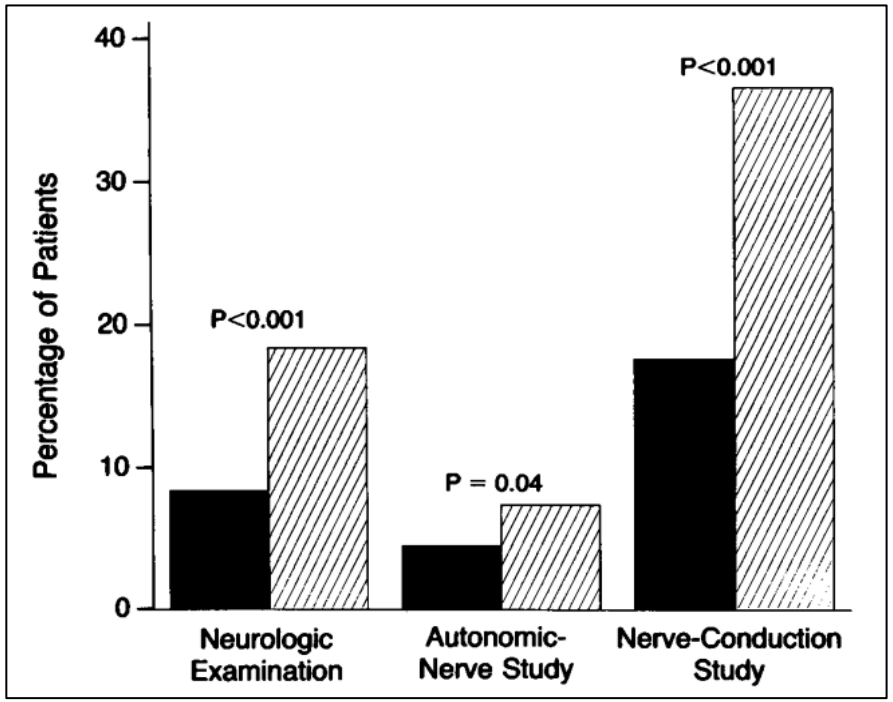
«THE GLUCOSE HYPOTHESIS»



RETINOPATIA DIABETICA



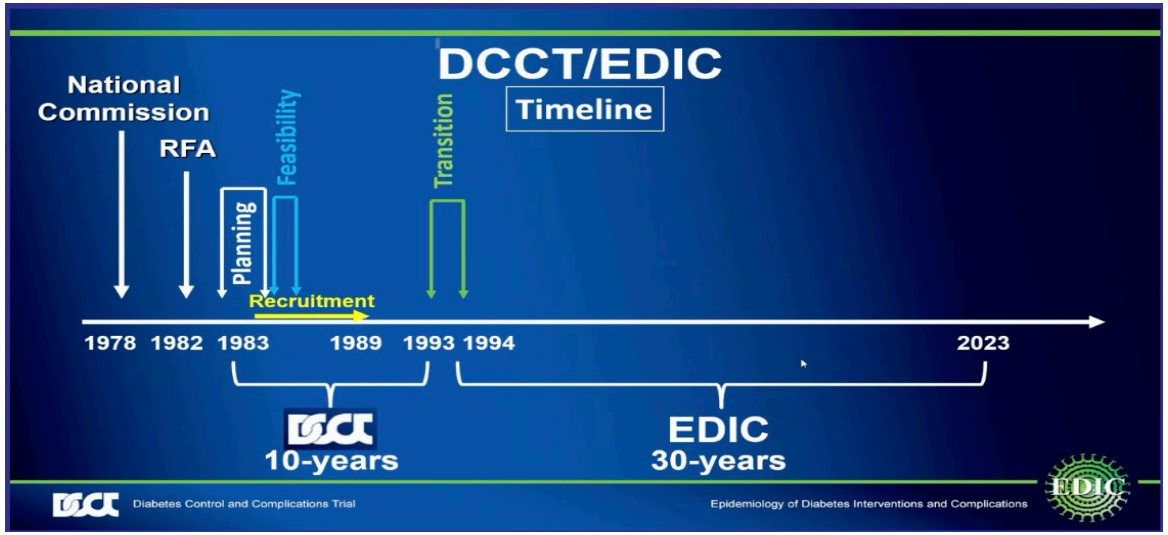
COMPARSA DI MICRO O MACROALBUMINURIA

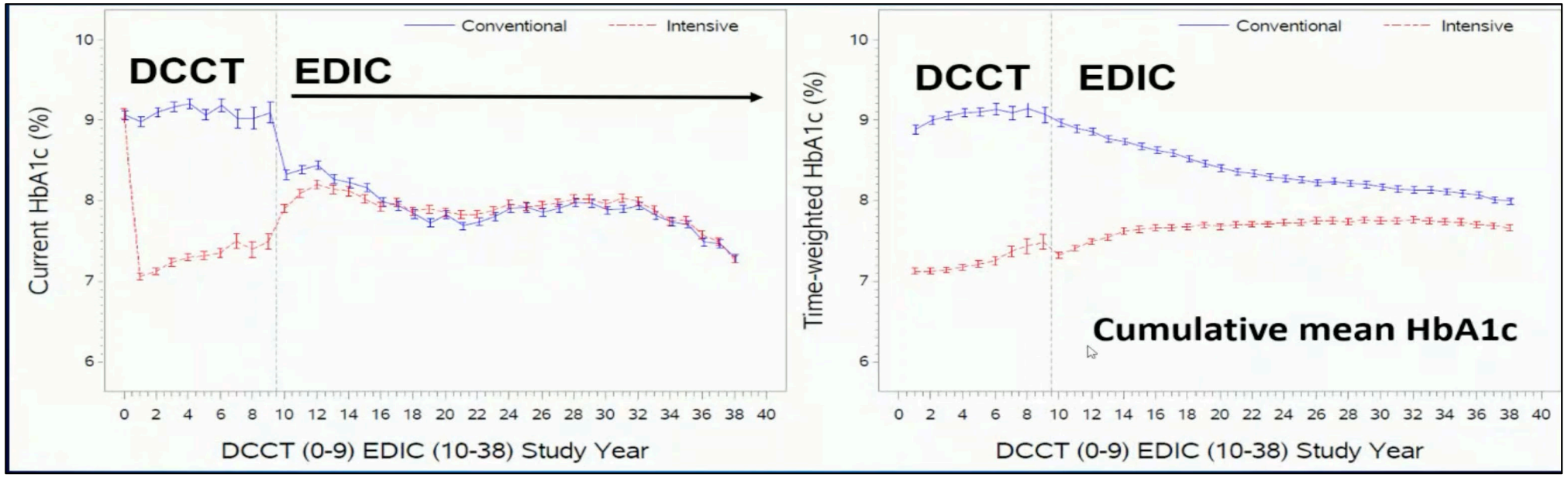


NEUROPATIA DIABETICA

The Diabetes Control and Complications Trial Research Group, N Eng J Med. 1993, 329:977-986

EDIC STUDY


DCCT/EDIC
Timeline
National Commission
RFA
Planning
Feasibility
Transition
Recruitment
1978 1982 1983 1989 1993 1994 2023
DCCT
10-years
EDIC
30-years
Diabetes Control and Complications Trial
Epidemiology of Diabetes Interventions and Complications
EDIC


Conventional
Intensive
DCCT
EDIC
Current HbA1c (%)
10
9
8
7
6
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
DCCT (0-9) EDIC (10-38) Study Year
Conventional
Intensive
DCCT
EDIC
Time-weighted HbA1c (%)
Cumulative mean HbA1c
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
DCCT (0-9) EDIC (10-38) Study Year

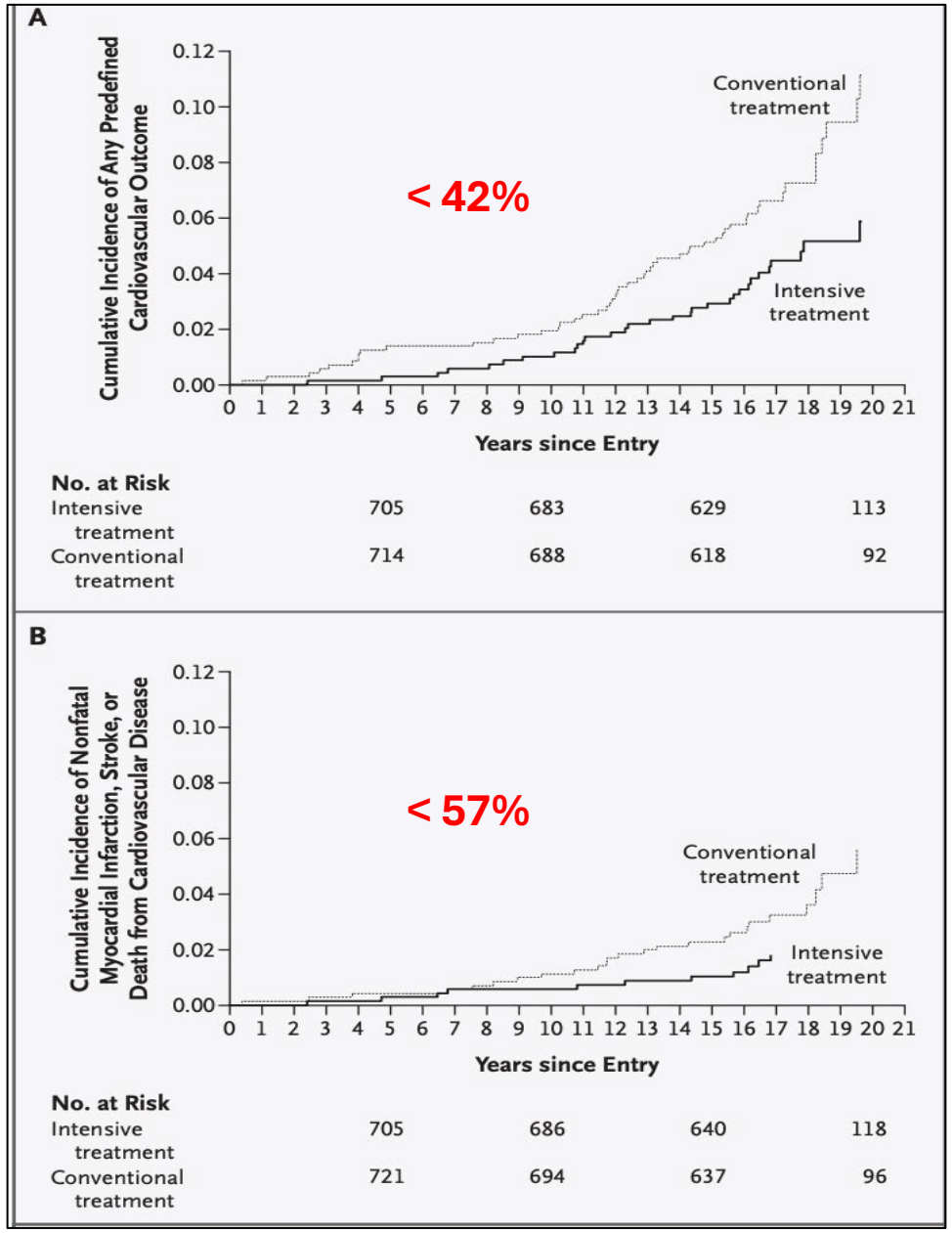


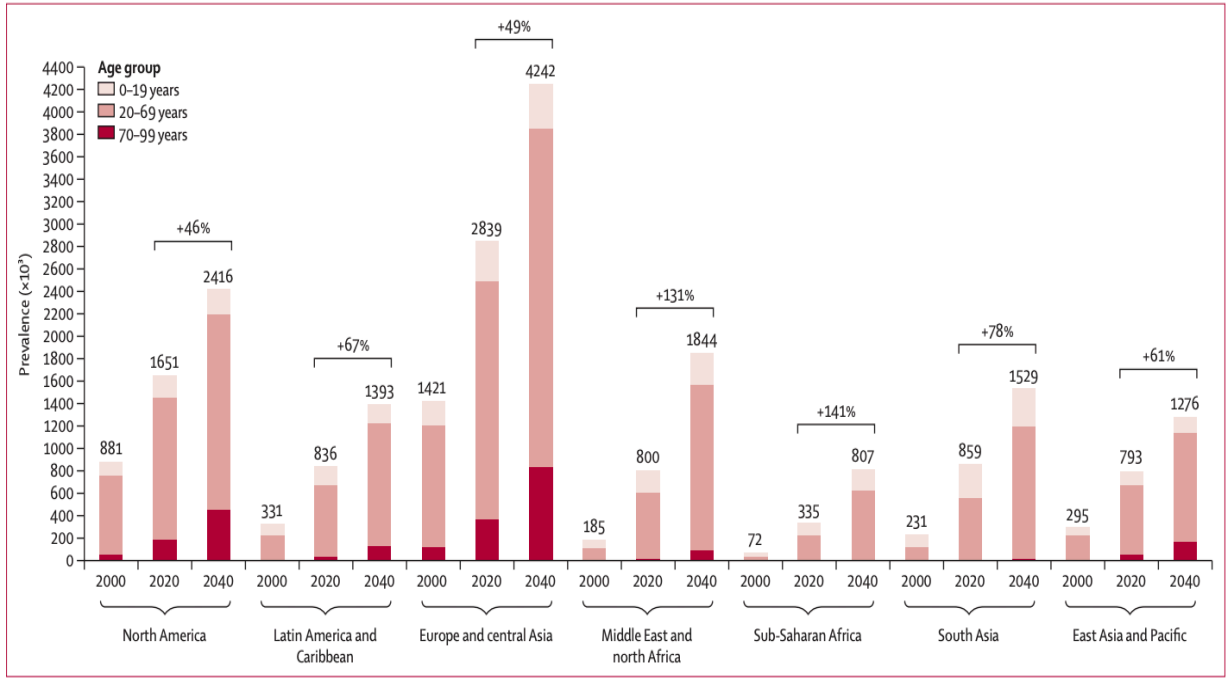
Table 4. Clinical Characteristics of EDIC Participants at Baseline in the DCCT According to the Presence or Absence of Cardiovascular Disease over the Course of the DCCT/EDIC Study.*

Characteristic	No Cardiovascular Disease (N=1358)	Cardiovascular Disease (N=83)	P Value
Intensive-treatment group (%)	50	37	0.02
Male sex (%)	53	48	0.39
Retinopathy at baseline (%)	49	63	0.014
Age (yr)	27±7	31±6	<0.001
Duration of diabetes (yr)	6±4	7±5	0.03
Body-mass index	23.3±2.8	24.0±2.8	0.05
Systolic blood pressure (mm Hg)	114±12	116±11	0.10
Diastolic blood pressure (mm Hg)	73±9	73±9	0.43
Serum creatinine (mg/dl)	0.81±0.15	0.78±0.14	0.08
Total cholesterol (mg/dl)	175±33	194±34	<0.001
HDL cholesterol (mg/dl)	51±12	50±13	0.78
LDL cholesterol (mg/dl)	109±29	127±29	<0.001
Triglycerides (mg/dl)	80.9±47.5	87.6±47.2	0.039
Albumin excretion rate (mg/24 hr)	15.7±18.5	19.3±22.8	0.02
Albumin excretion rate ≥40 mg/24 hr (%)	5	8	0.16
Glycoslated hemoglobin value at eligibility (%)	9.0±1.6	9.5±1.8	0.014
Current cigarette smoker (%)	18	33	<0.001
Autonomic nervous system–variation in RR (×1000)	47.9±22.2	43.3±19.0	0.17
Heart rate (beats/min)	68±11	70±12	0.07
Myocardial infarction in parents (%)	15	29	<0.001

Nathan D, et al. N Engl J Med. 2005; 353(25):2643-53. The Diabetes Control and Complications Trial Research Group, Diabetes 2016, 65:1370-1379.

LO SCENARIO ATTUALE

- Prevalenza nel 2021: circa 8.5 milioni di casi
- Incidenza nel 2021: 0.5 milioni di casi
- Aspettativa di vita rimanente per una diagnosi fatta a 10 anni: varia da 13 a 65 anni



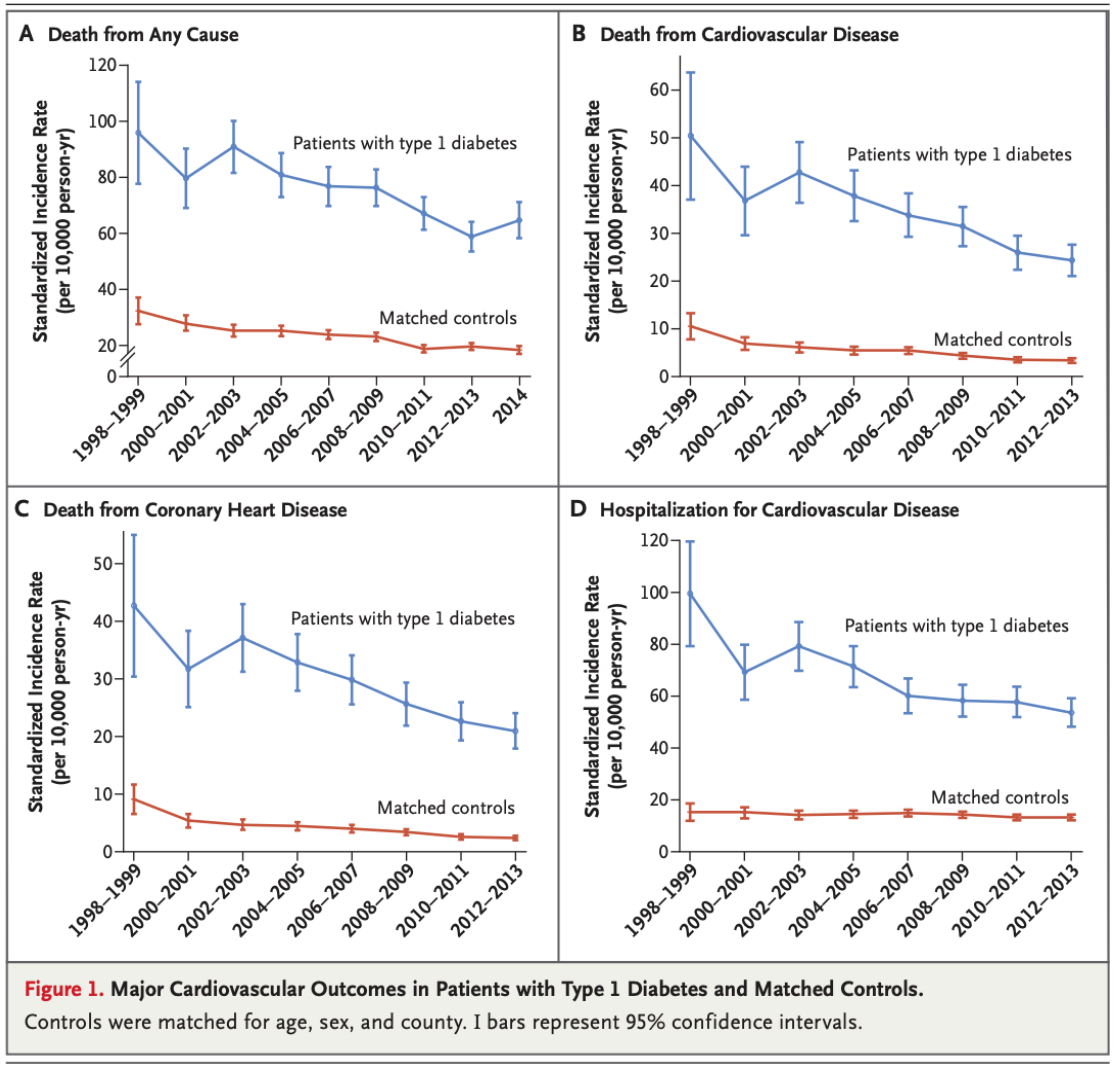
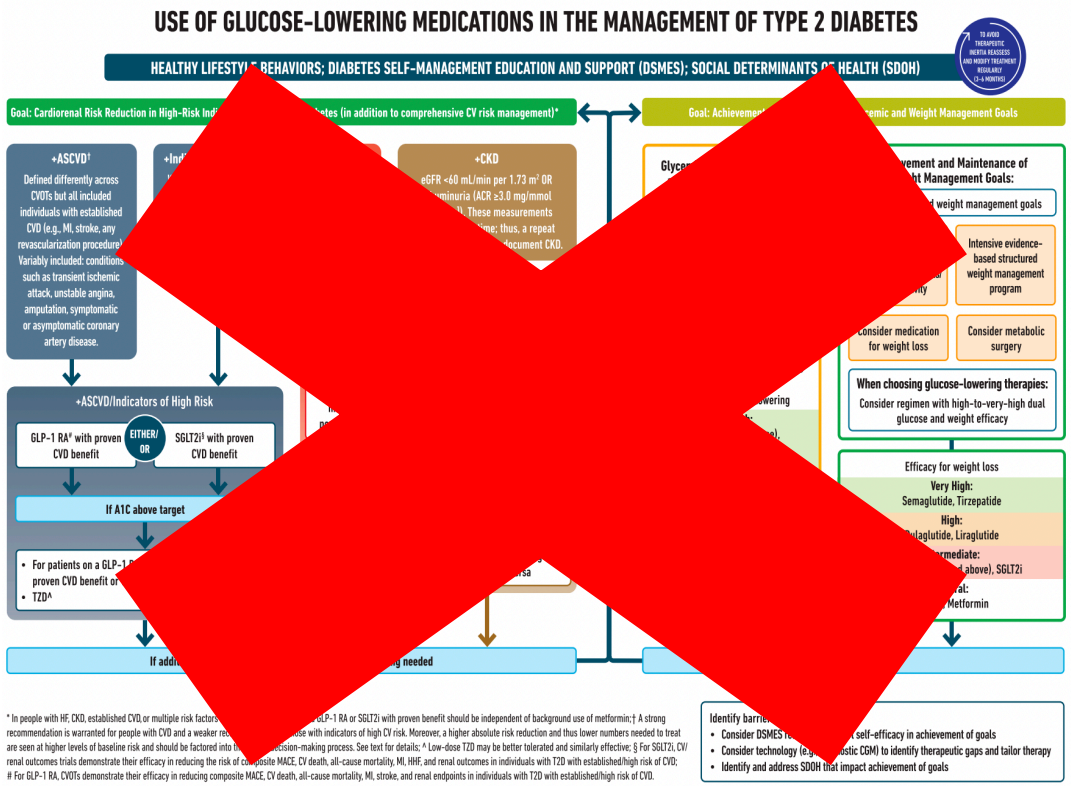


Figure 1. Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

Gregory GA, et al. Lancet Diabetes Endocrinol. 2022; 10:741-60. Rawshani A, et al. N Engl J Med. 2017; 376:1407-1418.

LO SCENARIO ATTUALE



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

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11.1. Cardiovascular risk assessment in type 1 diabetes

With respect to treatment targets and thresholds for other CV risk factors, a critical question is predicting CV risk in patients with T1DM without CVD. Determining ASCVD risk in patients with T1DM is less well studied than in patients with T2DM.

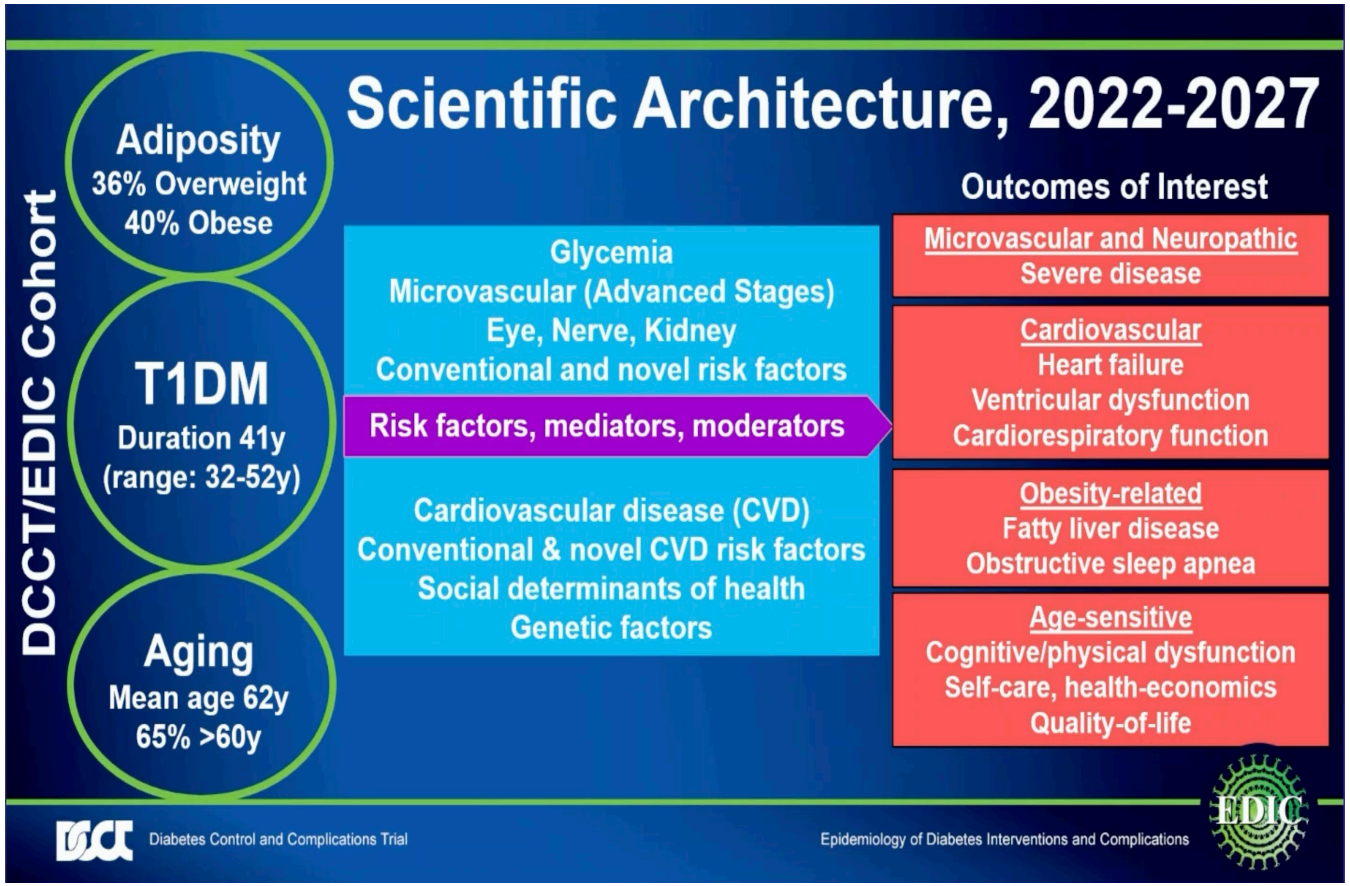
In 2011, an observational study using the data from 3661 patients in the Swedish National Diabetes Register proposed a 5-year CVD risk model for use in patients with T1DM.[789] More recently, the Steno Type 1 Risk Engine was externally validated at 5 years but lacks validation at 10 years.[790] Age at the onset and duration of diabetes are two risk factors that lead the estimation of CV risk. Thus, patients diagnosed with T1DM at an early age show an increased incidence of CVD. In addition, excess mortality in patients diagnosed with T1DM under the age of 10 years, compared with those aged 26–30 years at diagnosis, has been highlighted by a Swedish study.[791] This concept has been underlined by the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, which showed duration of diabetes to be an independent risk factor for MACE.[791,792] Several other risk factors related to diabetes management, including glycaemic control, insulin requirements, smoking, cardiac autonomic neuropathy, dysfunctional immune response, and insulin resistance, are to be taken into account.[788]

A recent risk tool, developed based on the Scottish/Swedish Diabetes Registry and validated in the Swedish National Diabetes Register can provide individualized risk predictions.[793] This 10-year ASCVD risk prediction tool https://diabepi.shinyapps.io/cvdrisk/ could facilitate risk estimation and discussions with patients with T1DM.

2023

American Diabetes Association Professional Practice Committee. Diabetes Care. 2024; 47(Suppl.1):S158-S178. Cosentino F, et al. Eur J Heart. 2020; 41(2):255-323. Marx N, et al. Eur J Heart. 2023; 44(39): 4043-4140

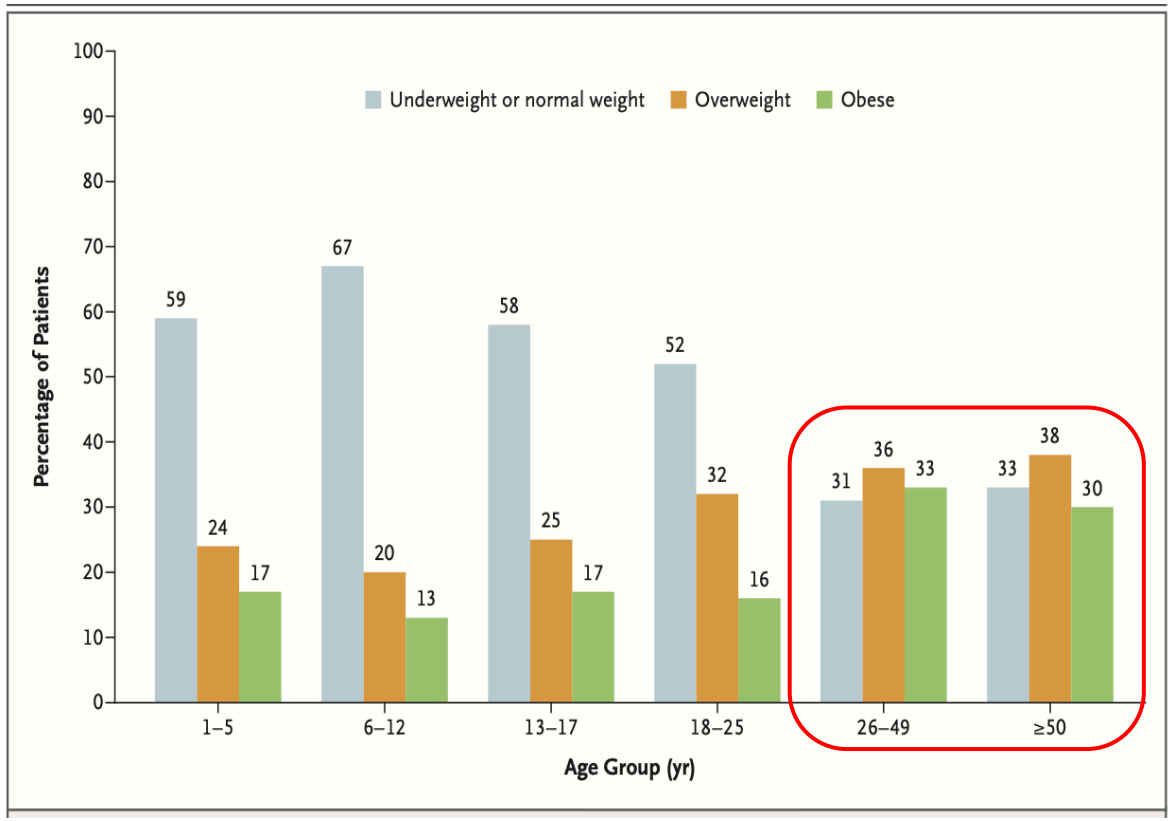
LO SCENARIO ATTUALE:
IL FOLLOW UP DEL DCCT/EDIC STUDY

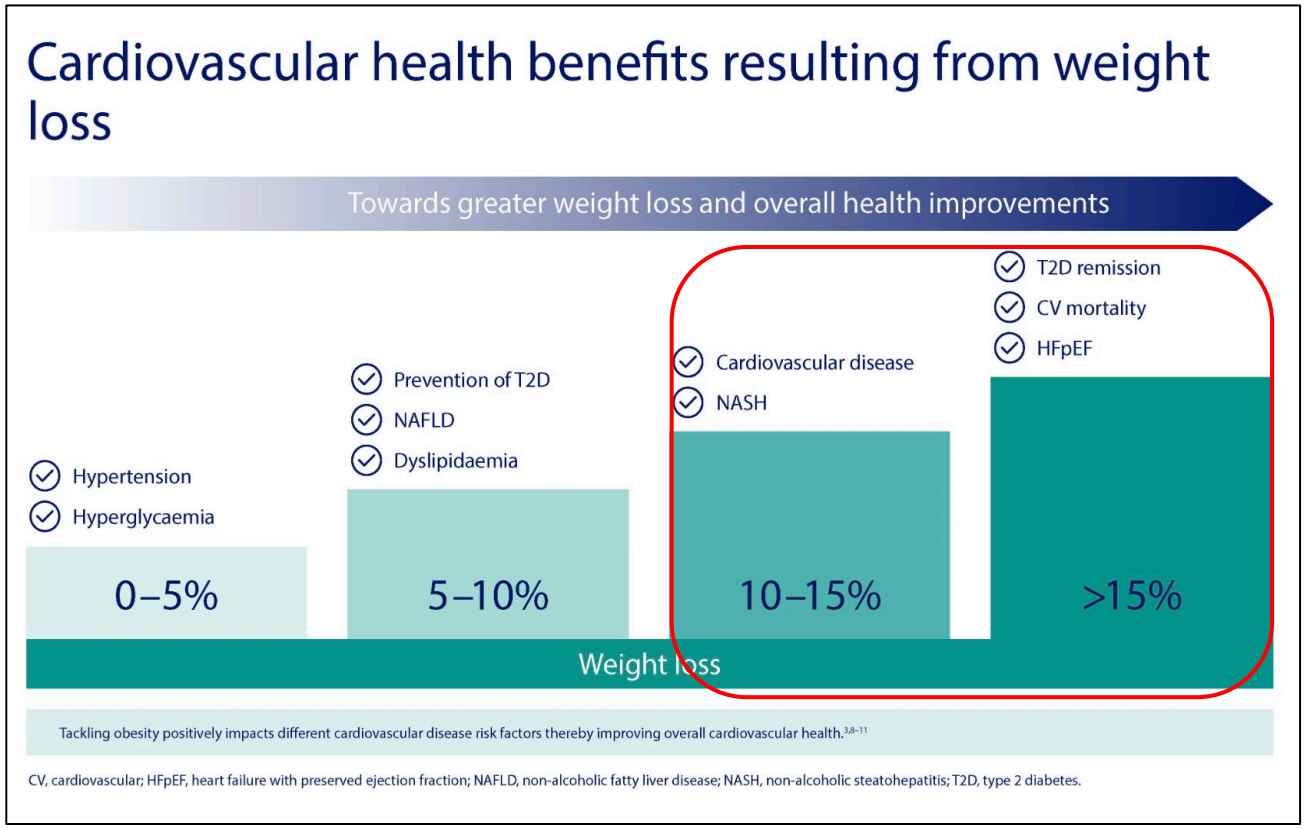


	Females	Males
Mean age (range)	63 (48-78)	64 (48-79)
Age >65 years (%)	38	42
Mean T1D duration (range)	42 (34-54)	41 (34-54)
Mean BMI (kg/m^2)	29.3	29.5
Obese (BMI ≥30) (%)	39	41
Mean HbA1c (%)	7.3	7.2

Mean HbA1c levels over entire course of DCCT/EDIC remain lower in original intensive treatment group.

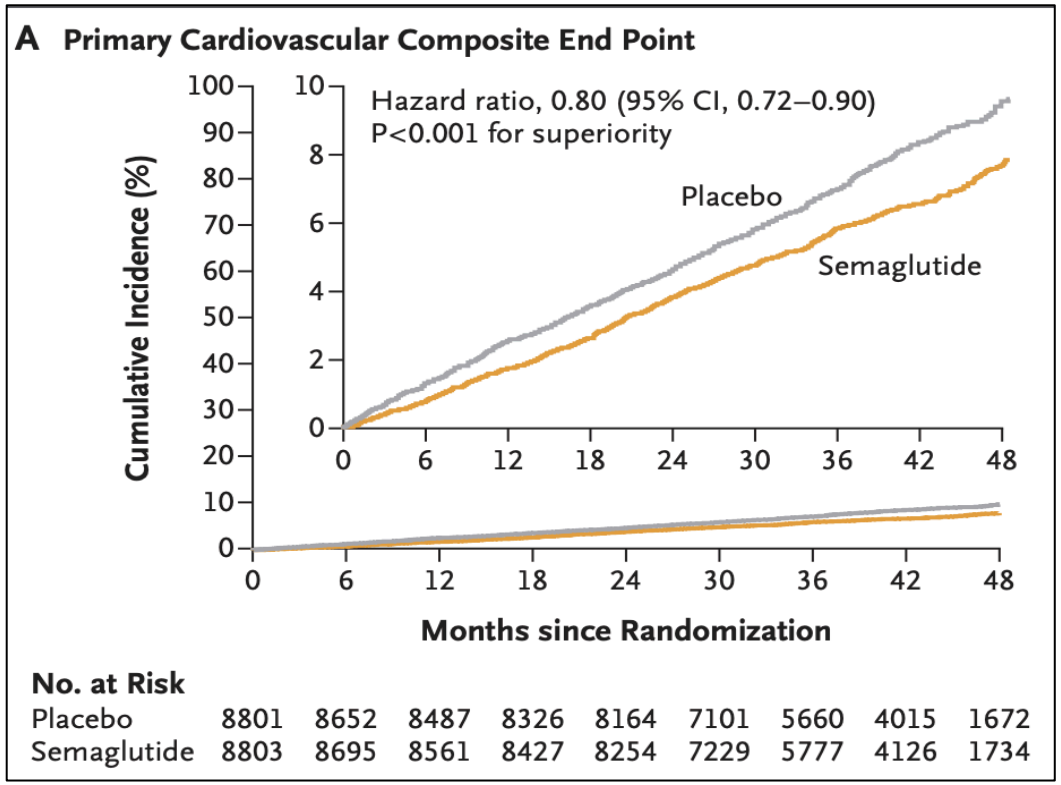
L'IMPATTO DELL'OBESITÀ



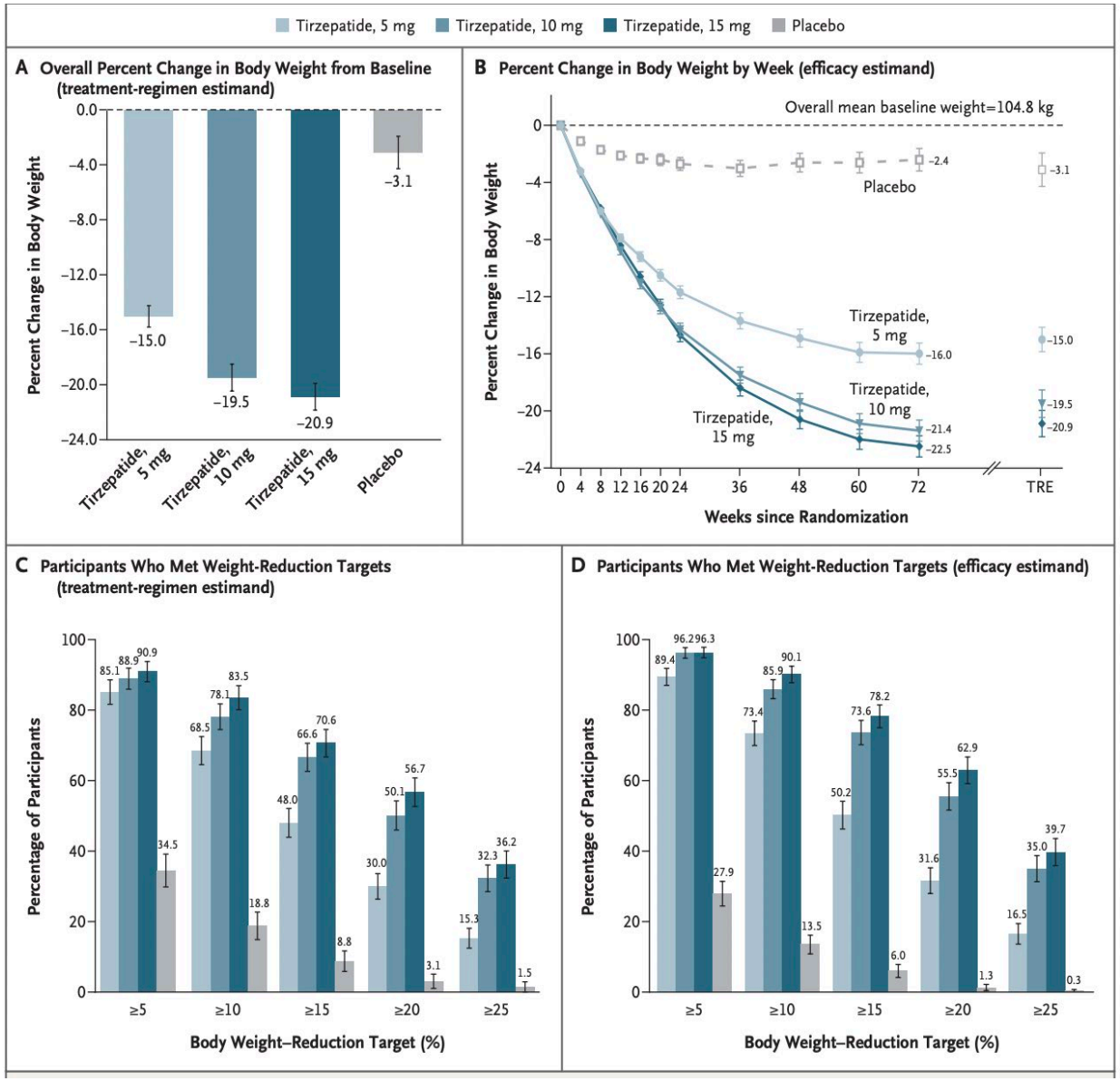


Manrique-Acevedo C, et al. N Engl J Med. 2024; 390:1207-1217

GLP-1 RA e GIP/GLP-1 RA PER IL TRATTAMENTO DELL'OBESITÀ

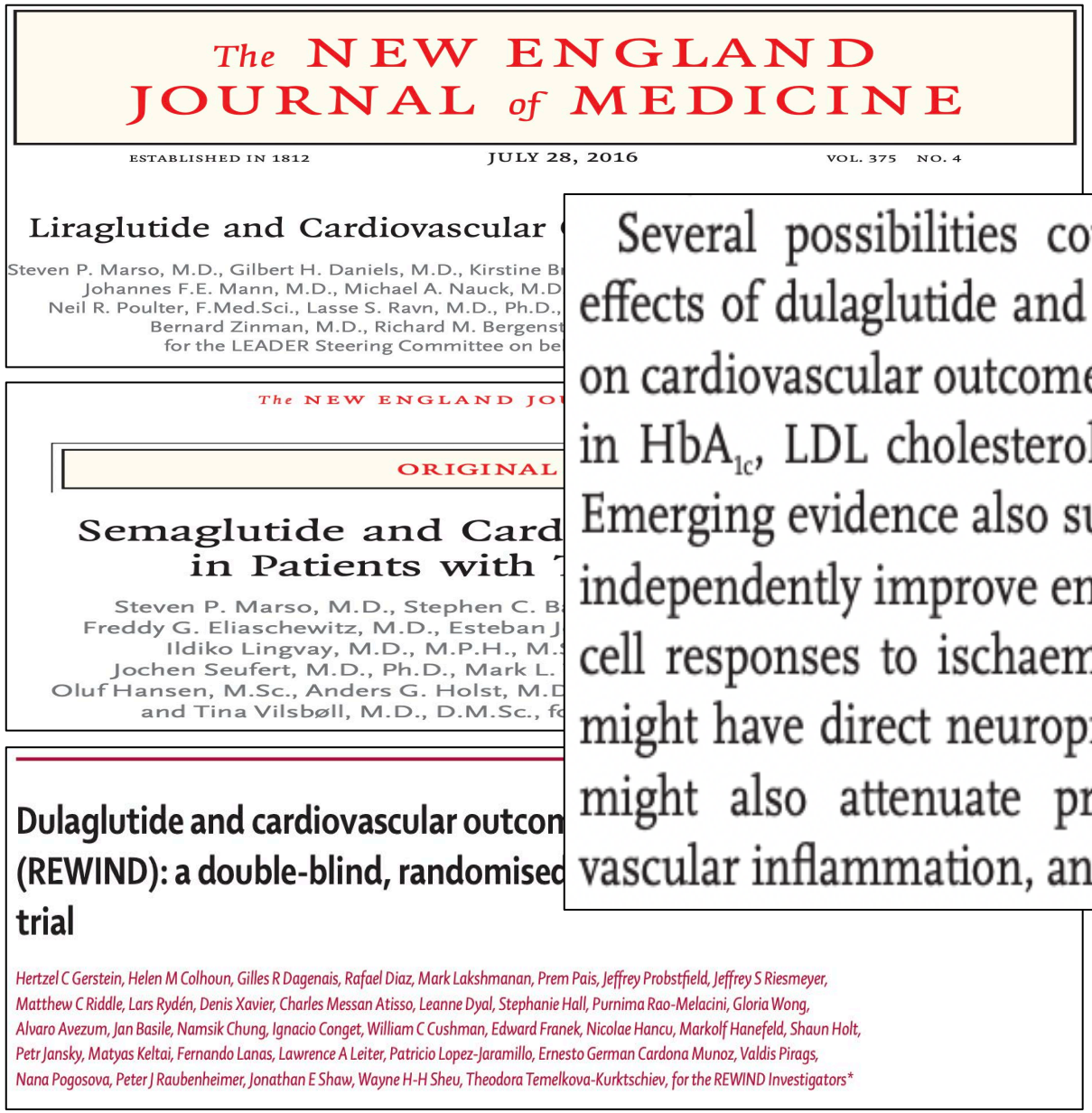


Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)



Lincoff AM, et al. N Engl J Med. 2023; 389:2221-2232. Jastreboff AM, et al. N Engl J Med. 2022; 387:205-16.

MA È SOLO QUESTIONE DI PESO?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine B
Johannes F.E. Mann, M.D., Michael A. Nauck, M.D
Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D.,
Bernard Zinman, M.D., Richard M. Bergenst
for the LEADER Steering Committee on be

The NEW ENGLAND JO

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Semaglutide and Card
in Patients with

Steven P. Marso, M.D., Stephen C. B
Freddy G. Eliaschewitz, M.D., Esteban J
Ildiko Lingvay, M.D., M.P.H., M.
Jochen Seufert, M.D., Ph.D., Mark L.
Oluf Hansen, M.Sc., Anders G. Holst, M.D
and Tina Vilsbøll, M.D., D.M.Sc., f

Dulaglutide and cardiovascular outcon
(REWIND): a double-blind, randomised
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*

Several possibilities could account for the salutary effects of dulaglutide and other GLP-1 receptor agonists on cardiovascular outcomes. These include the reduction in HbA_{1c}, LDL cholesterol, blood pressure, and weight. Emerging evidence also suggests that these drugs might independently improve endothelial function, endothelial cell responses to ischaemia, and platelet function, and might have direct neuroprotective effects.[28] These drugs might also attenuate progression of atherosclerosis, vascular inflammation, and vasoconstriction.[29]

peso:
g

peso:
utide 0.5 mg
utide 1 mg

Perdita di peso:
-3 kg

Marso SP, et al. N Engl J Med. 2016; 375:311-322. Marso SP, et al. N Engl J Med. 2016; 375:1834-1844. Gerstein HC, et al. Lancet. 2019; 394(10193):121-130

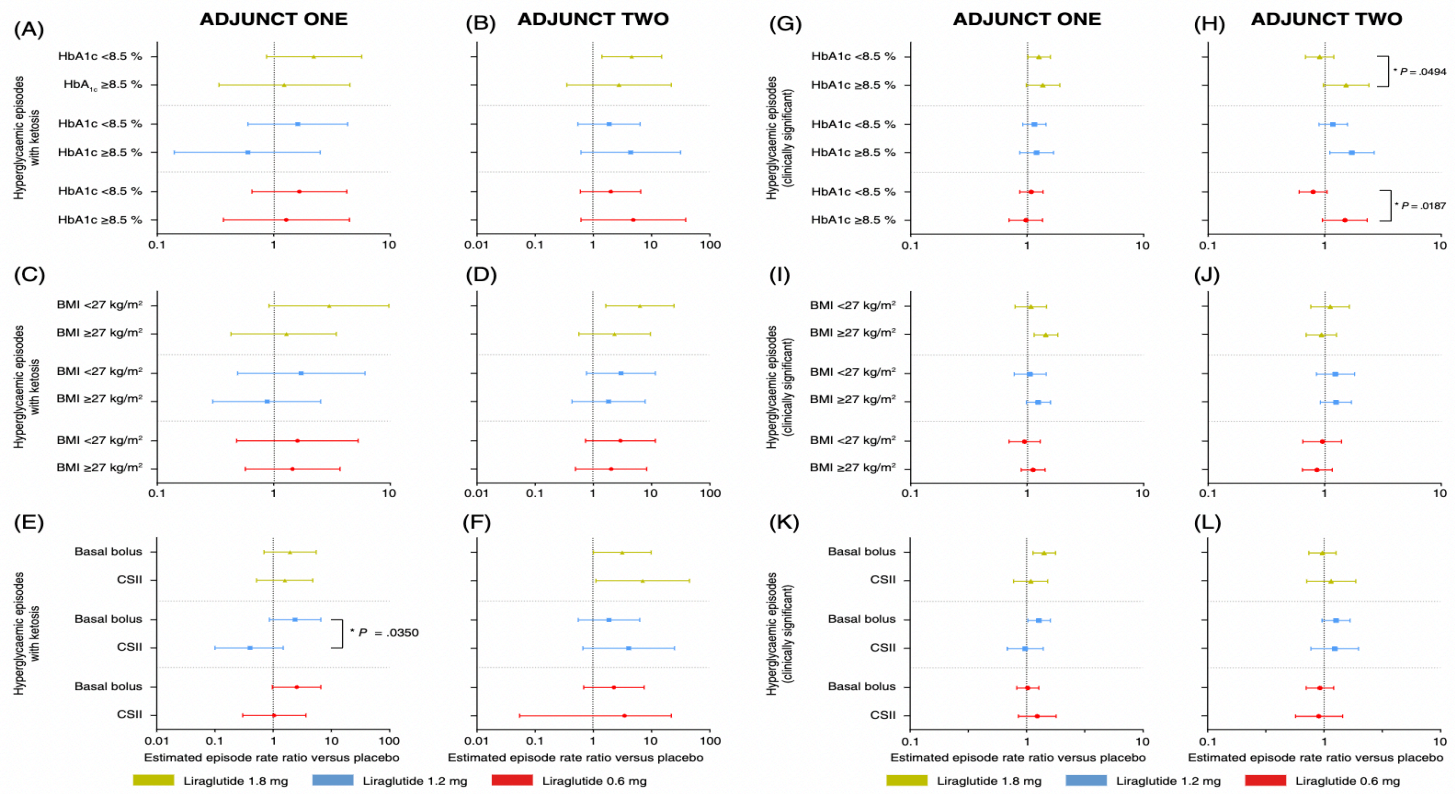
GLP-1 RA NEL DM1

ADJUNCT ONE (52 settimane)

- Riduzione di HbA1c di 0.5%
- Riduzione della dose totale di insulina giornaliera di circa 5 UI
- Riduzione del peso corporeo di circa 4 kg

ADJUNCT TWO (26 settimane)

- Riduzione di HbA1c di 0.3%
- Riduzione della dose totale di insulina giornaliera di circa 10 UI
- Riduzione del peso corporeo di circa 5 kg



Mathieu C, et al. Diabetes Care. 2016; 39(10):1702-1710. Ahrén B, et al. Diabetes Care. 2016; 39:1693-1701. Dejgaard TF, et al. Diabetes Obes Metab. 2021; 23:2752-2762

SGLT2-i NEL DM1

Study	SGLT2 Inhibitor (mg)	Duration (weeks)	HbA1c[a] (%)	Time in range[a] 3.9–10 mmol/L (70–180 mg/dL) (%)	DKA (%)	
					SGLT2 inhibitor	Placebo
Henry et al. [33]	Canagliflozin 100 Canagliflozin 300	18	−0.29 −0.25	–	4.3 6.0	0
DEPICT-1 [34, 40]	Dapagliflozin 5 Dapagliflozin 10	52	−0.33 −0.36	+9.1 +10.7	4.0 3.4	1.9
DEPICT-2 [39, 41]	Dapagliflozin 5 Dapagliflozin 10	52	−0.20 −0.25	+9.0 +10.7	4.1 3.7	0.4
inTandem1 [35]	Sotagliflozin 200 Sotagliflozin 400	52	−0.25 −0.31	+3.0 +10.4	3.4 4.2	0.4
inTandem2 [36]	Sotagliflozin 200 Sotagliflozin 400	52	−0.21 −0.32	+8.4 +13.4	2.3 3.4	0
inTandem3 [37]	Sotagliflozin 400	24	−0.46	–	3.0	0.6
EASE-2 [38]	Empagliflozin 10 Empagliflozin 25	52	−0.39 −0.45	+12.2 +12.5	4.3[b] 3.3[b]	1.2
EASE-3 [38]	Empagliflozin 2.5 Empagliflozin 10 Empagliflozin 25	26	−0.28 −0.45 −0.52	+4.3 +10.7 +7.4	0.8 – –	

SGLT2, sodium-glucose co-transporter-2; HbA1c, glycated haemoglobin; DKA, diabetic ketoacidosis. [a]Relative to placebo. [b]Pooled data for both EASE-2 and EASE-3 studies.

	Weight loss (kg)	Reduction of insulin dose (%)
DEPICT-1	5 mg: -3.0 10 mg: -3.7	5 mg: -8.8% 10 mg: -13.2%
DEPICT-2	5 mg: -3.2 10 mg: -3.7	5 mg: -10.8% 10 mg: -11.1%
inTandem1	200 mg: -2.4 400 mg: -3.5	200 mg: -6.2% 400 mg: -9.7%
inTandem2	200 mg: -2.0 400 mg: -2.6	200 mg: -8.2% 400 mg: -9.5%
inTandem3	400 mg: -3.0	400 mg: -9.7%
EASE-2	10 mg: -2.7 25 mg: -3.3	10 mg: -13.3% 25 mg: -12.7%
EASE-3	2.5 mg: -1.8 10 mg: -3.0 25 mg: -3.4	2.5 mg: -6.4% 10 mg: -9.5% 25 mg: -12.6%

Hropot T, et al. Hormon Res Paediatr. 2023; 96:620-630. Goldenberg RM, et al. Diabetes Obes Metab. 2019; 21:2192-2202

SGLT2-i NEL DM1

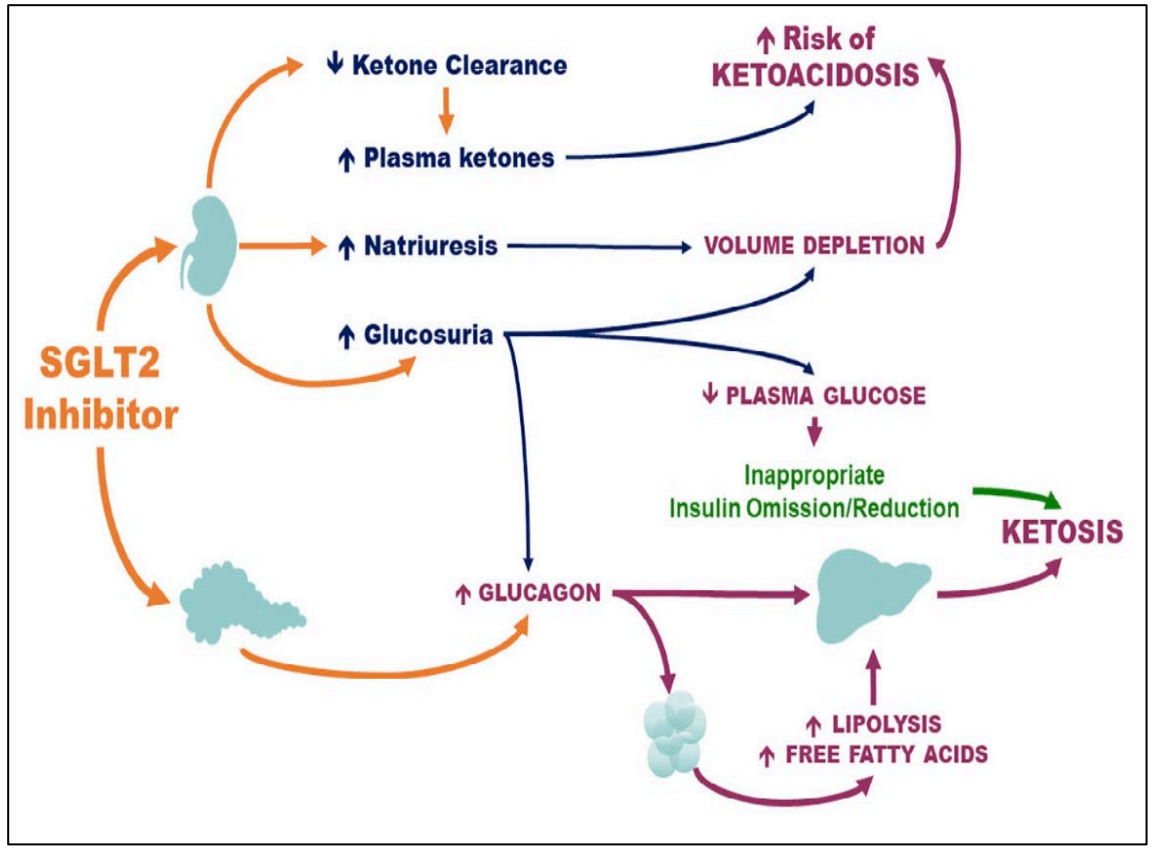


Table 2—Risk factors for DKA associated with SGLT inhibitor therapy

Risk level for DKA	Factor
Moderate/high	• Reduced basal insulin by more than 10–20% • Insulin pump or infusion site failure • Reduced or inconsistent carbohydrate intake • Excessive alcohol use • Use of illicit drugs • Volume depletion/dehydration • Acute illness of any sort (viral or bacterial) • Vomiting
Low/moderate	• Vigorous or prolonged exercise • Reduced prandial insulin dose by more than 10–20% • Travel with disruption in usual schedule/insulin regimen • Insulin pump use
Minimal/low	• Low BMI (<25 kg/m^2) • Inconsistent caloric intake • Moderate alcohol use* • Female sex

*If ketone levels increase from baseline.

Goldenberg RM, et al. Diabetes Obes Metab. 2019; 21:2192-2202.. Danne T, et al. Diabetes Care. 2019; 42(6):1147-1154

SGLT2-i NEL DM1

Individuals with type 1 diabetes who are the most suitable candidates for an SGLT inhibitor as adjunctive therapy

- Age ≥ 18 years
- Require HbA1C lowering and less glycaemic variability
- Adherent to monitoring and insulin administration
- No recent DKA or signs of decompensated diabetes
- No recurrent severe hypoglycaemia or hypoglycaemia unawareness
- Willing to avoid very low carbohydrates, ketogenic diets and excess alcohol consumption
- Females of childbearing potential should not be pregnant or planning pregnancy, and must be willing to use an appropriate family planning method
- Able to understand and implement a protocol with blood ketone and glucose testing for treating symptomatic ketosis (see **STOP DKA** protocol)
- Overweight or obese

This card holder takes diabetes medication that can cause diabetic ketoacidosis without high glucose levels

STOP DKA Protocol

Symptomatic (e.g. lethargy, loss of appetite, nausea, abdominal pain) ➔ **STOP** SGLTi

AND

Test ketones* and glucose every 2-4 hours (even if blood glucose is not elevated)

AND

Oral ingestion of fluid and carbohydrates (250–500 mL fluid every 2 hours and up to 30–60 g of carbohydrates every 2-4 hours)

AND

Protocol instructions for supplemental insulin and carbohydrates (see STOP DKA table)

*Ketosis/DKA may occur without an elevated blood glucose

(B)

STOP DKA Considerations for Bolus Insulin and Carbohydrates

(for moderate or higher ketones, consider increasing basal insulin by 20%–50% until ketones return to normal)

KETONE level (mmol/L) and category (check every 2–4 h)	BLOOD GLUCOSE* (check every 2–4 h) 4·0–8·0 mmol/L (70–150 mg/dL)	8·1–14·0 mmol/L (151–250 mg/dL)	>14 mmol/L (>250 mg/dL)
<1.0 Normal or Mild	• No extra insulin • Give usual bolus to cover carbohydrates plus usual correction	• No extra insulin • Give usual bolus to cover carbohydrates plus usual correction	• 5–10% TDD supplemental insulin or usual correction bolus plus usual bolus to cover carbohydrates
1·0–1·4 Moderate	• 5% TDD supplemental insulin plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 10% TDD supplemental insulin or 1.5x correction bolus plus usual bolus to cover carbohydrates • 30 g carbohydrates every 2–4 h	• 10% TDD supplemental insulin or 1.5x correction bolus plus usual bolus to cover carbohydrates every 2-4h
1·5–2·9 High	• 10% TDD supplemental insulin plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates every 2-4 h
≥3·0 Extreme	• 10% TDD supplemental insulin plus usual bolus to cover carbohydrates • 45–60 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates every 2-4 h

DKA is likely if ketones remain ≥3 mmol/L despite supplemental insulin

If symptoms are ongoing and/or you are unable to ingest fluids, go directly to the emergency department

*Glucose values in mg/dL are not exact conversions from those in mmol/L to allow for round numbers. TDD=total daily insulin dose; usual bolus=usual bolus using insulin:carbohydrate ratio without correction. If supplemental insulin is calculated by both TDD and correction bolus methods, administer the amount that provides the higher dose of insulin.

Sources of 15 g Simple Carbohydrates (Fluid)

- 150 mL (2/3 cup) regular soft drink
- 250 mL (1 cup) of sports drink
- 150 mL (~2/3 cup) of juice
- 125 mL (1/2 cup) of regular gelatin dessert
- 125 mL (1/2 cup) of apple sauce
- 75 mL (1 stick) of popsicle

Sources of Sugar-free Fluids

- Water
- Low or zero calorie drink mix
- Diet soft drink
- Tea
- Clear soup or broth

Goldenberg RM, et al. Diabetes Obes Metab. 2019; 21:2192-2202

EMPAGLIFLOZIN **DAPAGLIFLOZIN**

Scompenso cardiaco

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

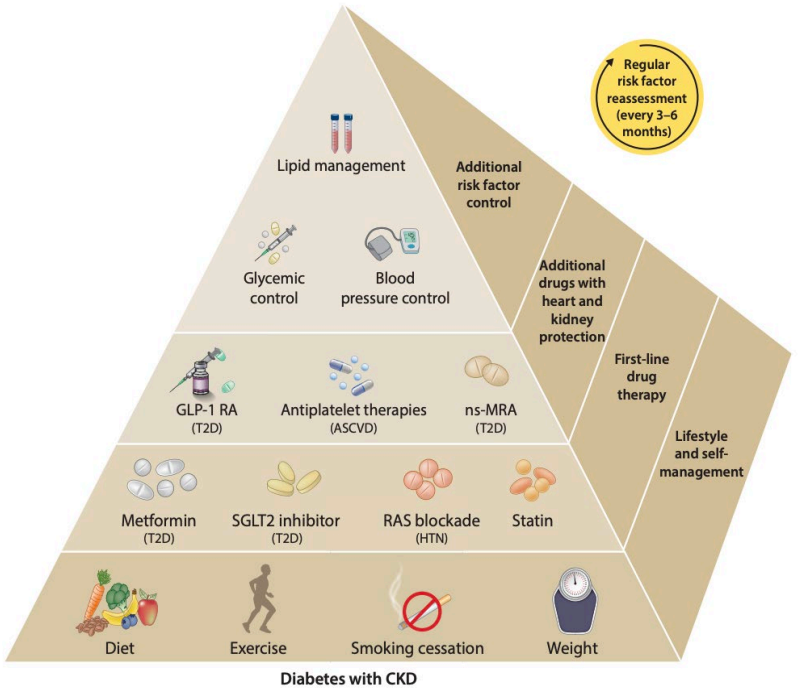
Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

EMPAGLIFLOZIN **DAPAGLIFLOZIN**

Malattia renale cronica

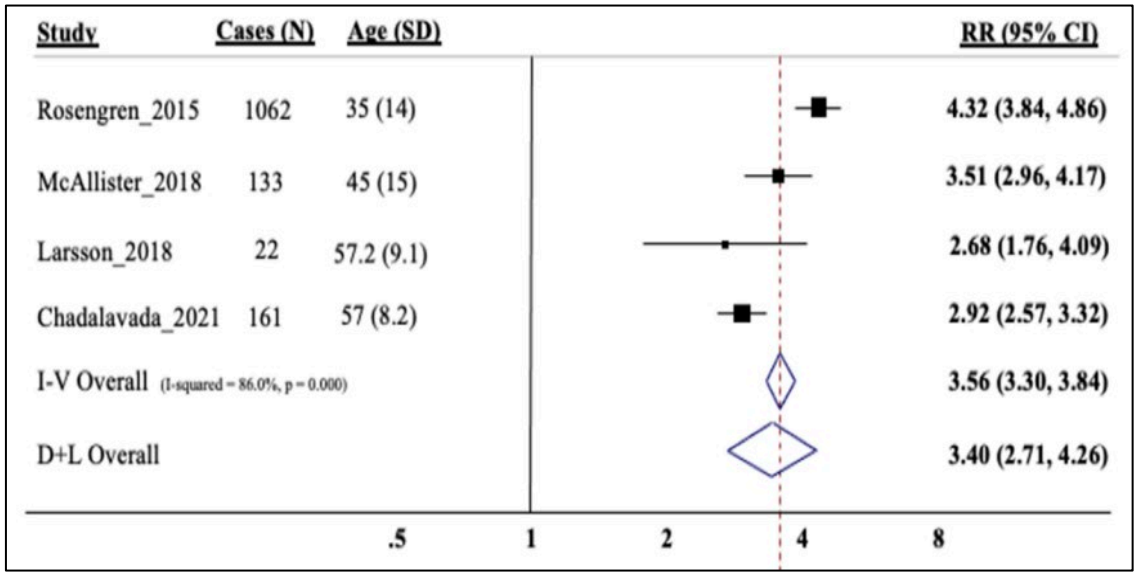
Empagliflozin in Patients with Chronic Kidney Disease

Dapagliflozin in Patients with Chronic Kidney Disease

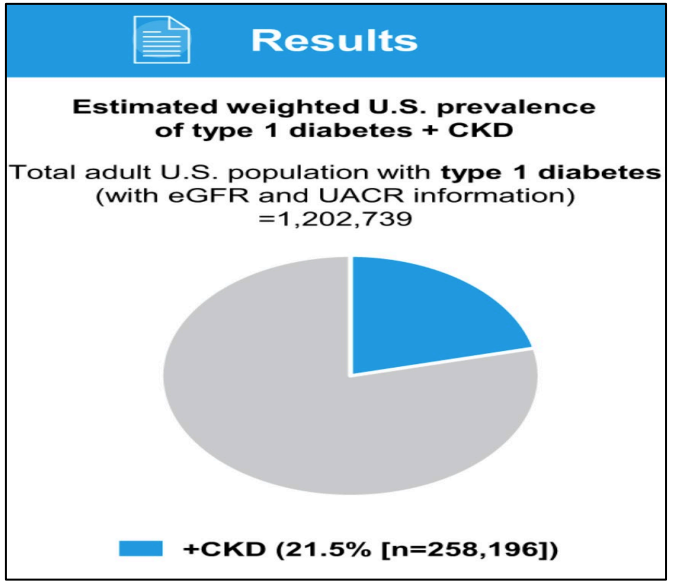


Packer M, et al. N Engl J Med. 2020; 383: 1413-1424. Anker SD, et al. N Engl J Med. 2021; 385: 1451-1461. McMurray JJV, et al. N Engl J Med. 2019; 381(21): 1995-2008. Solomon SD, et al. N Engl J Med. 2022; 387: 1089-1098. McDonagh TA, et al. Eur J Heart. 2021; 42(36):3599-3726. The EMPA-KIDNEY Collaborative Group. N Engl J Med. 2023; 388:117-27. Heersprink HJL, et a. N Engl J Med. 2020; 383: 1436-1446. KDIGO Diabetes Work Group. Kidney Int. 2020; 102(5S):S1-S127.

L'IMPATTO CLINICO DI HF E DKD NEL DM1



This study demonstrates that cardiac autoimmunity, as evidenced by the presence of ≥2 cardiac autoantibodies, is associated with increased LV chamber dimensions, increased LV mass, and lower EF. This dilated (eccentric) LV remodeling phenotype is different from the concentric remodeling previously reported in this cohort in association with glycated hemoglobin and macroalbuminuria[2,3] that is also observed in type 2 diabetes mellitus, but is consistent with the type of remodeling found in other conditions associated with cardiac autoantibodies.[1,4,5]



Variable	*n* (*N* = 258,196)
Age at interview,† median (IQR), years	65 (63–76)
Male, *n* (%)	152,061 (59)
Race/ethnicity,‡ *n* (%)	
Non-Hispanic White	155,929 (60)
Non-Hispanic Black§	47,303 (18)
Mexican American	4,380 (2)
Other Hispanic	18,277 (7)
Other ethnicity§	32,306 (13)
eGFR,‖¶ mean (SD), mL/min/1.73 m^2	57 (4)
UACR,¶ median (IQR), mg/g	89 (8–875)

Haji M, et al. Diabetes Res Clin Pract. 2023; 202:110805. Sousa DR, et al. Circulation. 2020; 141:1107-9. Rossing P, et al. Diabetes Care. 2024; 47(8):1395-1399

COSA MANCA?

- **Dati provenienti da RCTs, disegnati per gli specifici outcomes cardiovascolari e renali.**

Empagliflozin in Patients with Chronic Kidney Disease

METHODS

We enrolled patients with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200. Patients

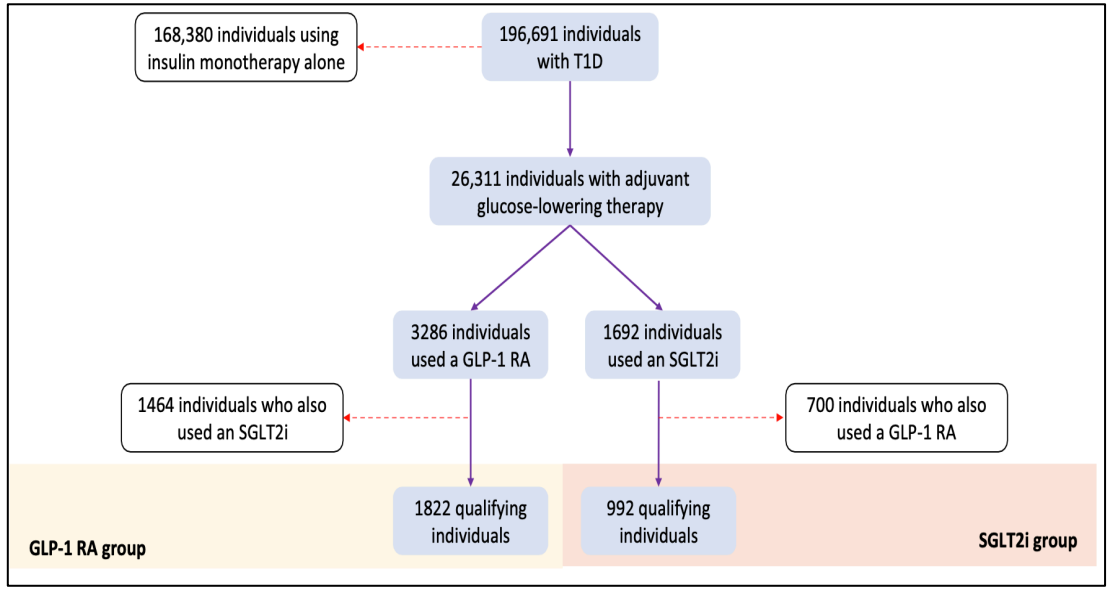
Diabetes type — no./total no. (%)		
Type 1	34/1525 (2.2)	34/1515 (2.2)
Type 2	1470/1525 (96.4)	1466/1515 (96.8)
Other or unknown	21/1525 (1.4)	15/1515 (1.0)

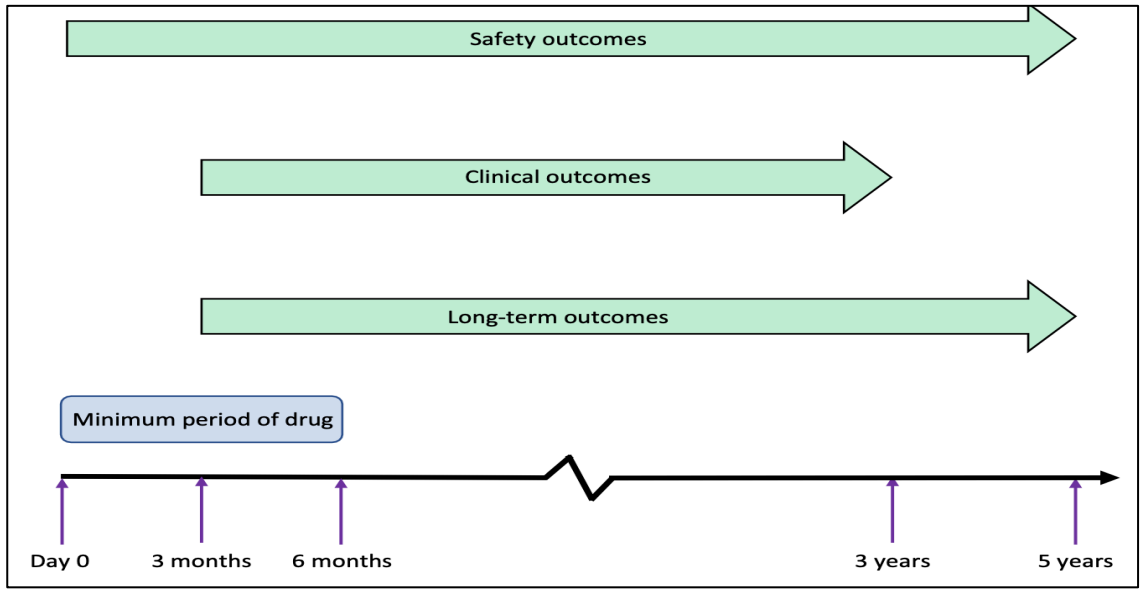
Subgroup	Empagliflozin (*no. of patients with event/total no.*)	Placebo (*no. of patients with event/total no.*)	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)

Ketoacidosis¶	6 (0.2)	0.09	1 (<0.1)	0.02	—

The EMPA-KIDNEY Collaborative Group. N Engl J Med. 2023; 388:117-27

I DATI DI REAL-WORLD





Characteristic	SGLT2i (*n*=992)	GLP-1 RA (*n*=1822)
Age at index event (years)	53.3±15.4	47.1±15.8
Sex (male/female) (%)	53/47	37/63
Race (White/Black or African American/Asian/ Native American/Unknown) (%)	68/7/4/2/19	74/10/1/1/14
Neuropathy (%)	3	3
Retinopathy (%)	4	4
Nephropathy (%)	4	3
Weight (kg)	91.2±21.9	99.3±24.4
BMI (kg/m^2)	30.2±6.6	33.5±7.1
Systolic BP (mmHg)	130±20	129±18
Diastolic BP (mmHg)	75±11	77±10
eGFR (ml/min per 1.73 m^2)	79.9±28.6	87.7±29.6
Cholesterol (mmol/l)	4.4±1.1	4.6±1.1
HbA_{1c} (mmol/mol)	65.0±20.9	62.8±19.8
HbA_{1c} (%)[a]	8.1±1.9	7.9±1.8
DKA history (%)	3	3
Heart failure (%)	10	3
Primary hypertension (%)	28	25
IHD (%)	18	11
CKD (%)	5	3

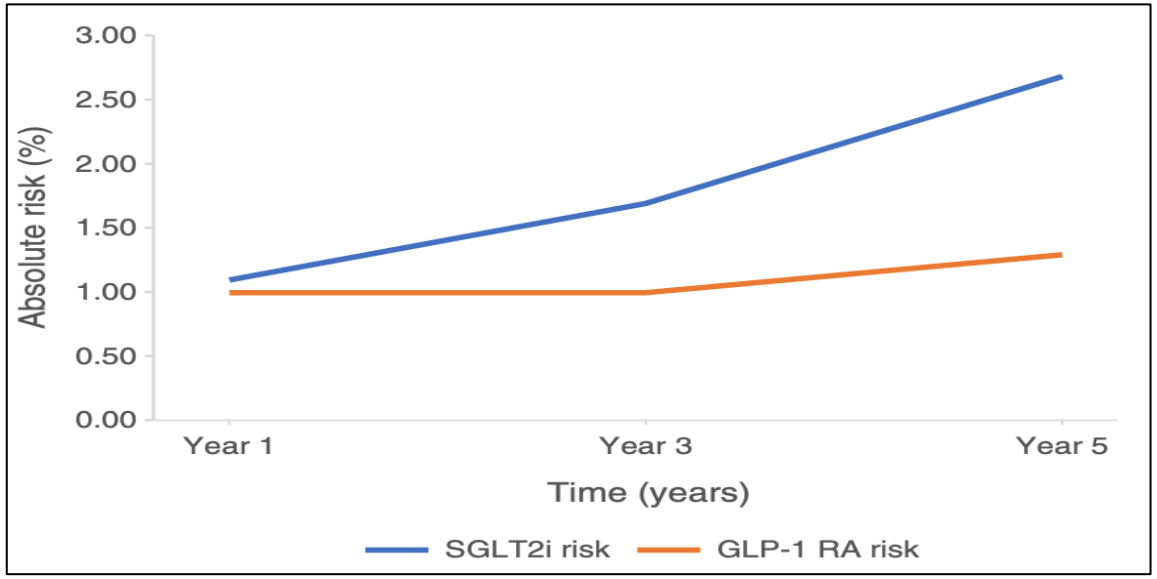
Anson M, et al. Diabetologia. 2023; 66:1869-1881

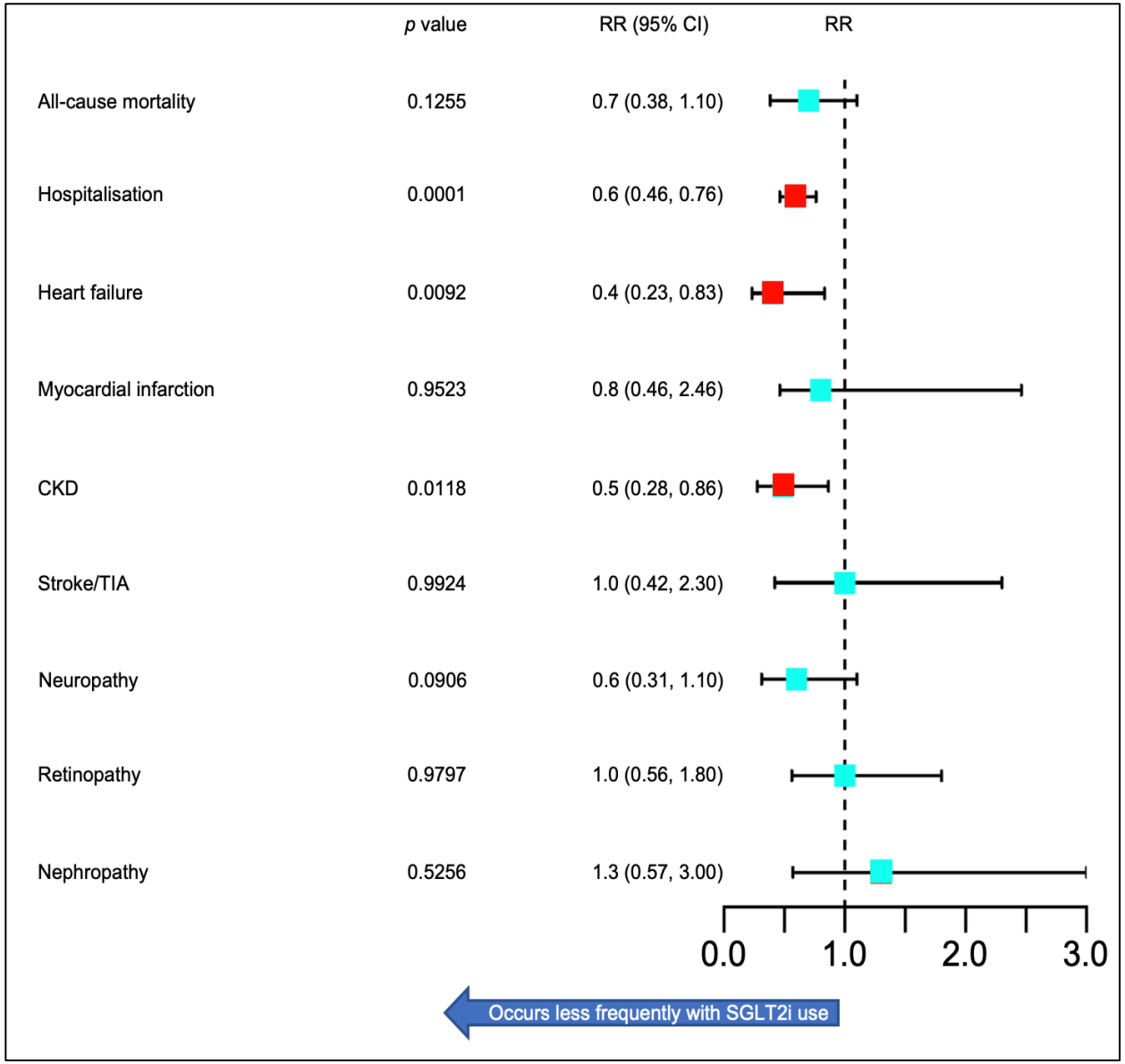
I DATI DI REAL-WORLD

Characteristic	SGLT2i (n=933)			GLP–1 RA (n=933)		
	Baseline	Post initiation	Change	Baseline	Post initiation	Change
HbA_{1c} (mmol/mol)	65.0±20.9	62.8±17.6	−2.6	62.8±19.8	57.4±14.3	−5.4
HbA_{1c} (%)[a]	8.1±1.9	7.9±1.6	−0.2	7.9±1.8	7.4±1.3	−0.5
Weight (kg)	91.2±21.9	88.8±21.4	−2.4	99.3±24.4	100.8±27.0	+1.5
BMI (kg/m^2)	30.2±6.6	30.0±5.9	−0.2	33.1±6.9	33.5±7.1	+0.4
eGFR (ml/min per 1.73m^2)	79.9±28.6	83.4±28.3	+3.5	87.7±29.6	80.5±30.0	−7.2
Cholesterol (mmol/l)	4.4±1.1	4.3±1.1	−0.1	4.6±1.0	4.2±1.6	−0.4

[a]Original HbA_{1c} data presented in DCCT %, with conversion for mean HbA_{1c} in mmol/mol

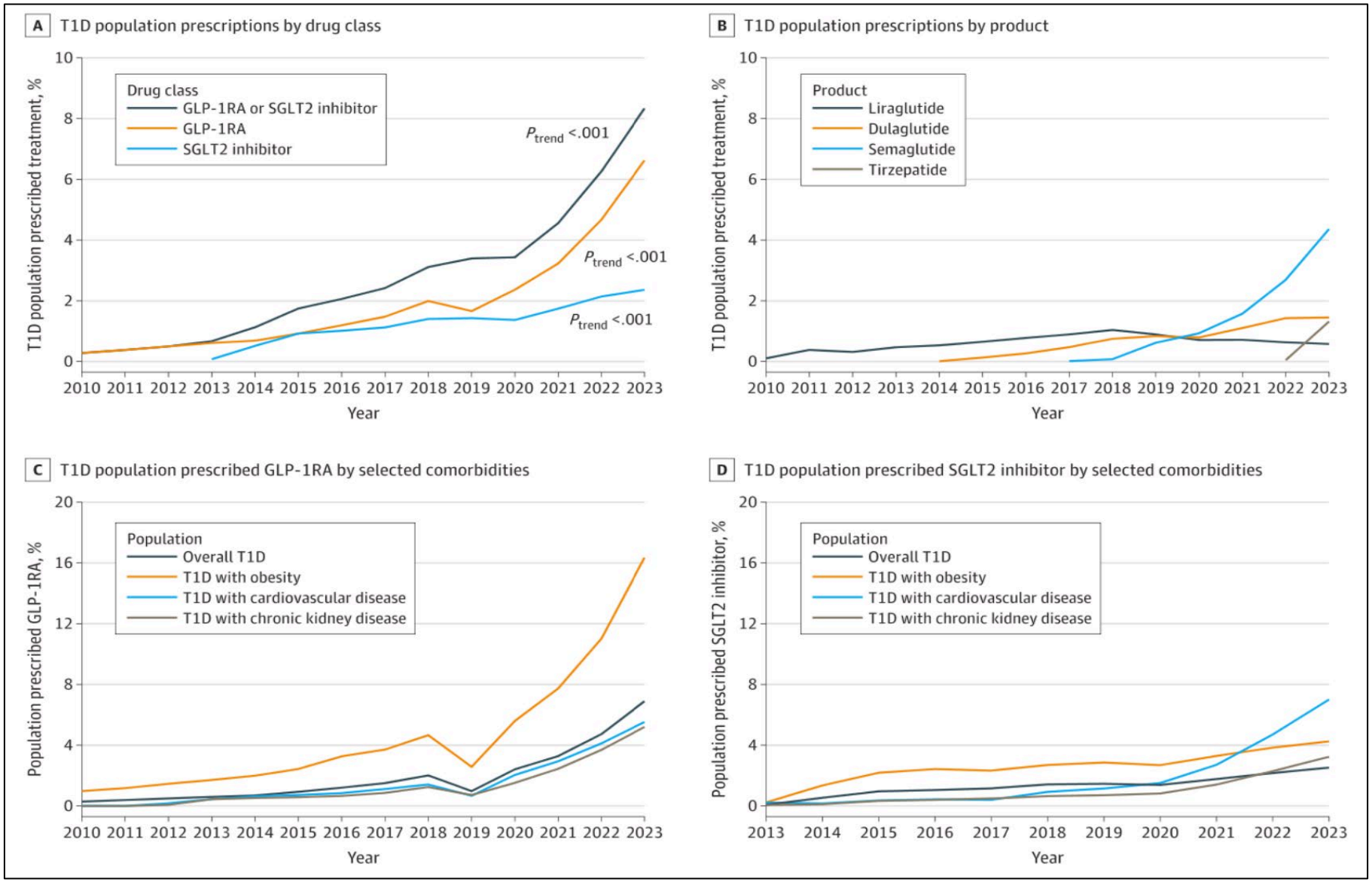
Data expressed as mean ± SD





Anson M, et al. Diabetologia. 2023; 66:1869-1881

I DATI DI REAL-WORLD



Epic Cosmos
2010-2023

- Overall T1D: 405.019
- New GLP-1 RAs prescription: 18.725
- New SGLT2-i prescription: 7.210

Li P, et al. JAMA 2024, October 23

Società Italiana di Diabetologia

1964-2024

https://www.siditalia.it/clinica/moduli-scaricabili/send/14-moduli-scaricabili/1343-consenso-informato-per-la-prescrizione-di-farmaci-off-label

TAKE HOME MESSAGES

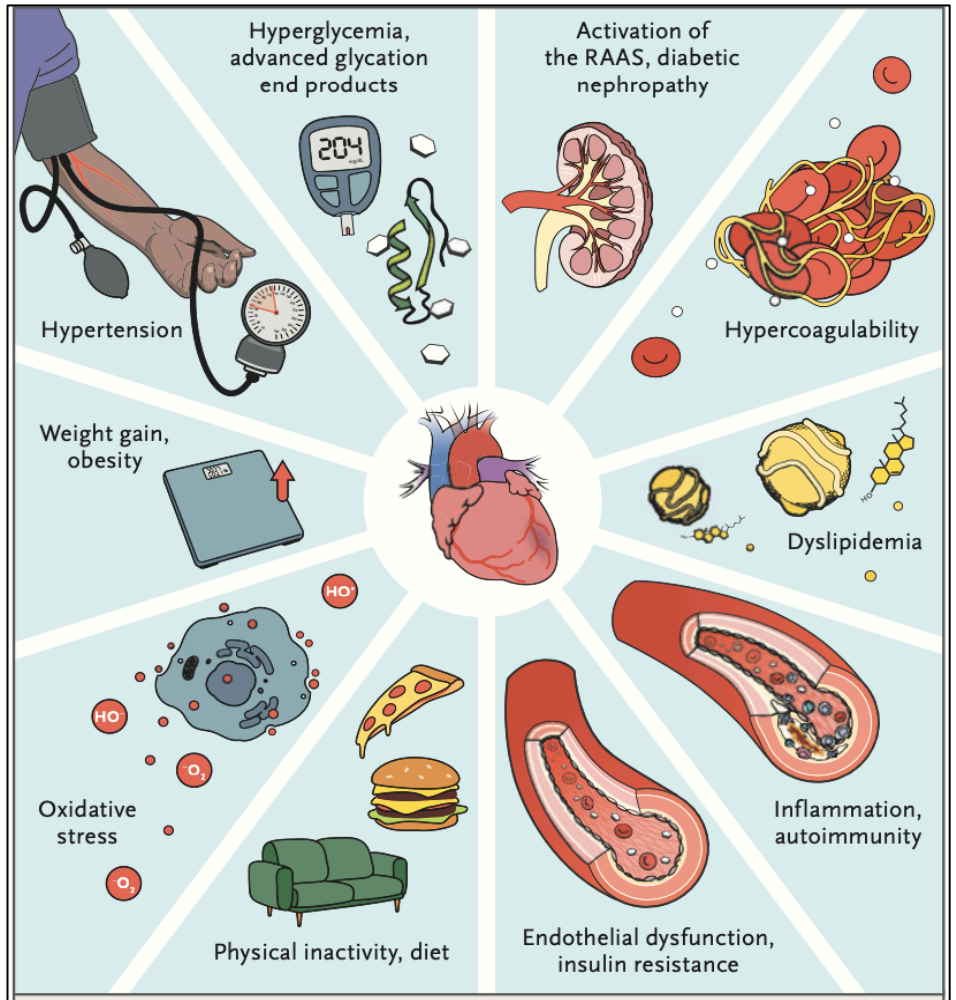


Figure 1. Pathophysiology of Cardiovascular Disease in Patients with Type 1 Diabetes.

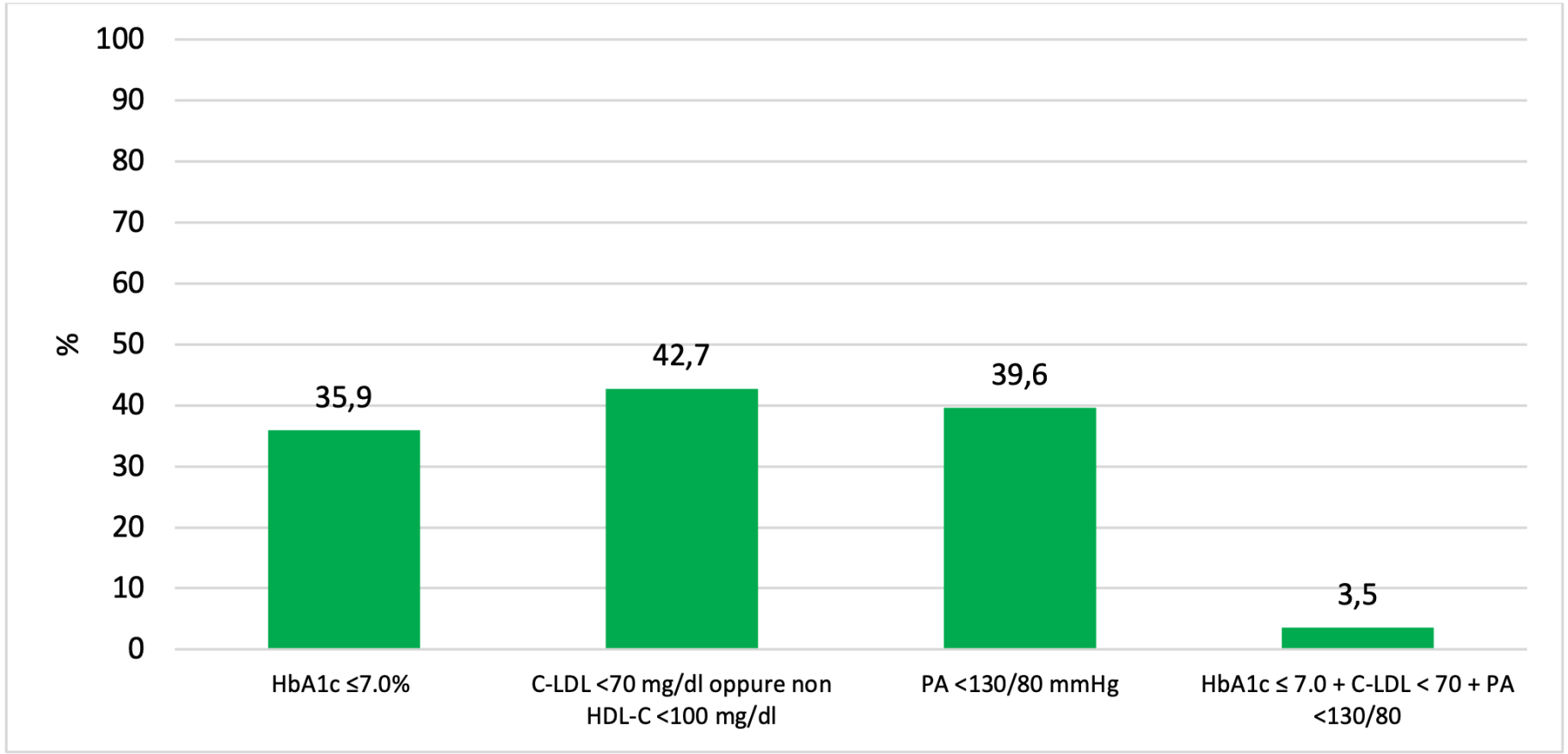
The mechanisms involved in the development of cardiovascular disease in persons with type 1 diabetes are shown.

- L'uso di GLP-1 RAs e SGLT2-i è **NON** consentito nel DM1, ma è doveroso ricordare che due SGLT2-i (Dapagliflozin e Sotagliflozin) sono stati approvati da EMA come terapia aggiuntiva all'insulina nel DM1.
- Le complicazione cardiovascolari e renali presentano una prevalenza significativa nel DM1. Tuttavia mancano RCTs su specifici outcomes cardiovascolari e renali con GLP-1 RAs e SGLT2-i nel DM1.
- I dati di RWE sembrano evidenziare il beneficio extra-glicemico di queste classi anche nel DM1, **MA** le RWE non possono sostituirsi agli RCTs, soprattutto considerando che l'utilizzo di queste classi di farmaci potrebbe esporre le persone con DM1 al rischio di eventi avversi anche severi.
- Tuttavia, valutato il rapporto rischio-beneficio, il clinico può proporne l'utilizzo in regime **off-label** avendo previamente concordato e condiviso la scelta. Si rendono pertanto necessarie la somministrazione e la compilazione del consenso informato.
- L'avvento di nuove tecnologie potrebbe rendere più sicuro l'utilizzo di queste farmaci nel DM1 (es.: sensore per il monitoraggio dei chetoni, farmaci che antagonizzano l'effetto del glucagone nella produzione di corpi chetonici,...).
- **Non bisogna dimenticarci di quello che già possiamo fare per ridurre il rischio CV nella persona con DM1.**

Manrique-Acevedo C, et al. N Engl J Med. 2024; 390:1207-1217

DM1 - Indicatori di esito intermedio

Soggetti con esito intermedio favorevole (%)



GRAZIE PER L’ATTENZIONE

Indicatore	Denominatore	%	Gold standard (25° *percentile*)
Soggetti non trattati con ipolipemizzanti nonostante valori di colesterolo LDL ≥100 mg/dl (%)	Soggetti con colesterolo LDL ≥100 mg/dl (n=12.727)	62,2	53,6
Soggetti con colesterolo LDL ≥100 mg/dl nonostante il trattamento con ipolipemizzanti (%)	Soggetti trattati con ipolipemizzanti (n=16.505)	29,2	25,5
Soggetti non trattati con antiipertensivi nonostante valori pressori ≥140/90 mmHg (%)	Soggetti con valori pressori ≥140/90 mmHg (n=11.400)	53,0	45,7
Soggetti con valori pressori ≥130/80 mmHg nonostante il trattamento con antiipertensivi (%)	Soggetti trattati con antiipertensivi (n=11.233)	24,9	17,7
Soggetti non trattati con ACE-inibitori/Sartani nonostante la presenza di micro/macroalbuminuria (%)	Soggetti con micro/macroalbuminuria (n=5.731)	58,4	45,5
Soggetti con evento cardiovascolare pregresso in terapia antiaggregante piastrinica (%)	Soggetti con evento cardiovascolare pregresso (n=2.144)	82,7	92,3