

22 – 23  
SETTEMBRE 2023

MEDICINA  
INTERNA 2.0:

la quiete dopo  
la tempesta?

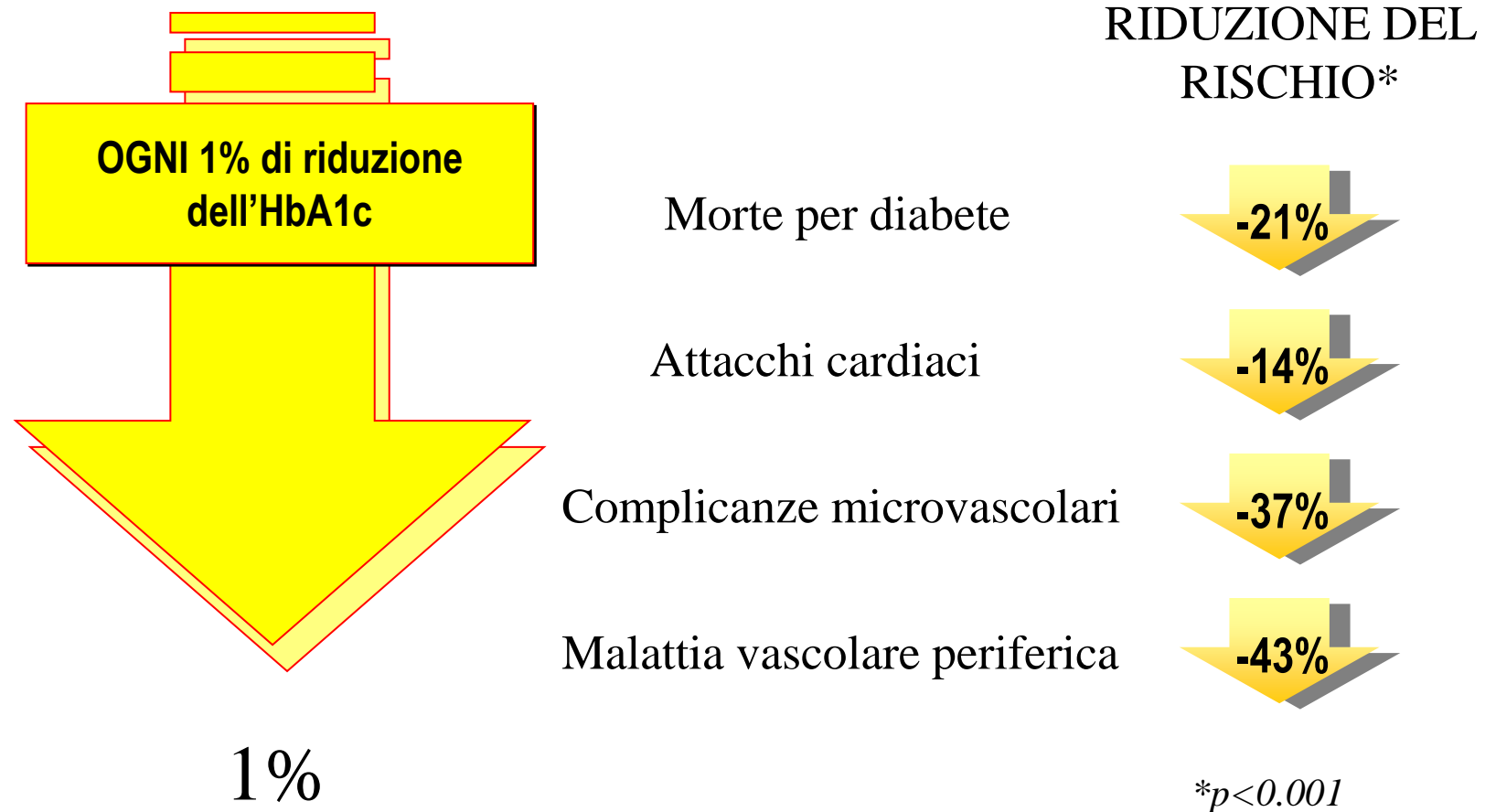
# Il Diabete Mellito di Tipo 2: dal controllo glicemico alla prevenzione del danno d'organo

Dott.ssa Valentina Todisco

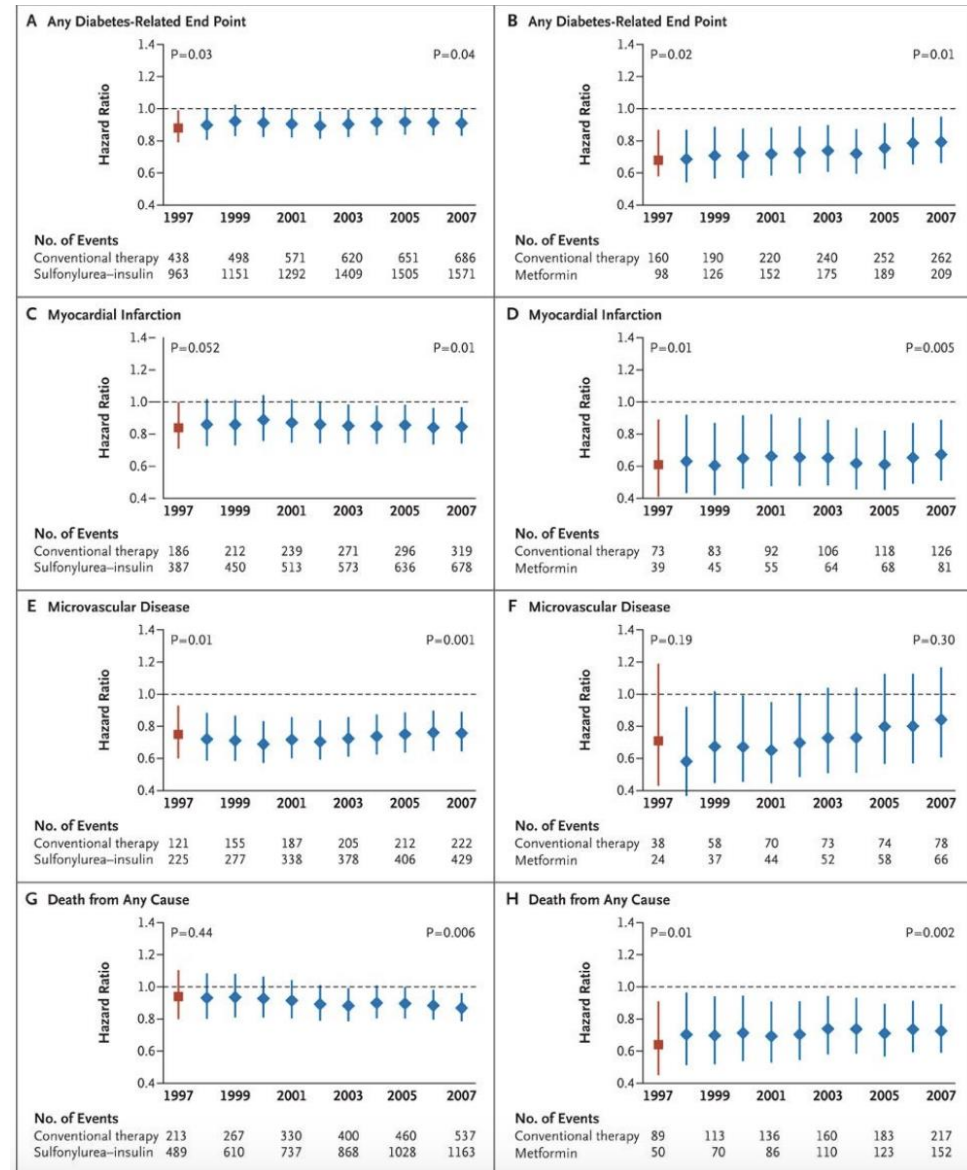
Responsabile UOSD di Endocrinologia,  
Mal. Metaboliche, Dietetica e  
Nutrizione Clinica - Ospedale «A.  
Perrino» Brindisi



# UKPDS



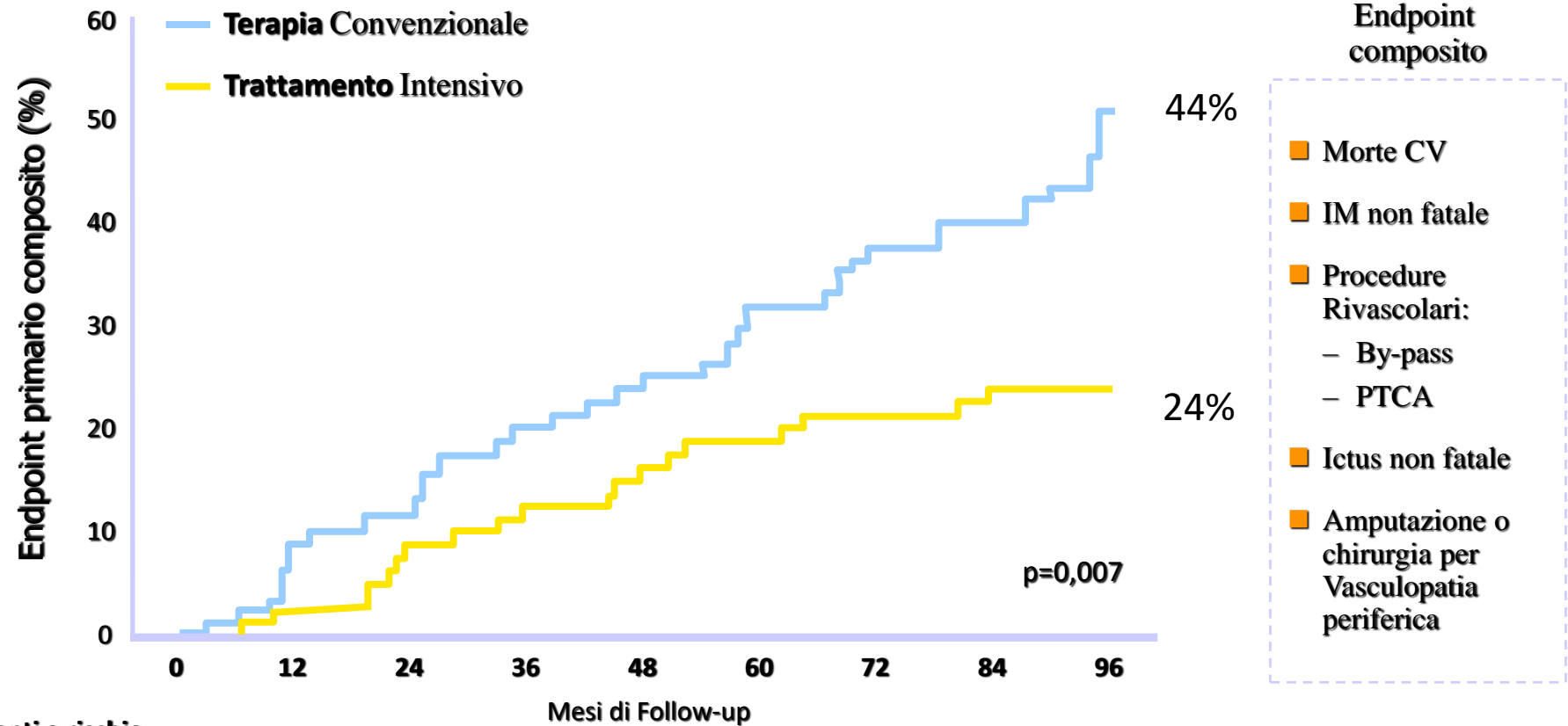
I benefici del trattamento intensivo all'esordio del Diabete mellito tipo 2 si mantengono fino a 10 anni dopo, anche se non si mantiene la differenza in HbA1c



# Studio Steno-2

## Terapia intensiva

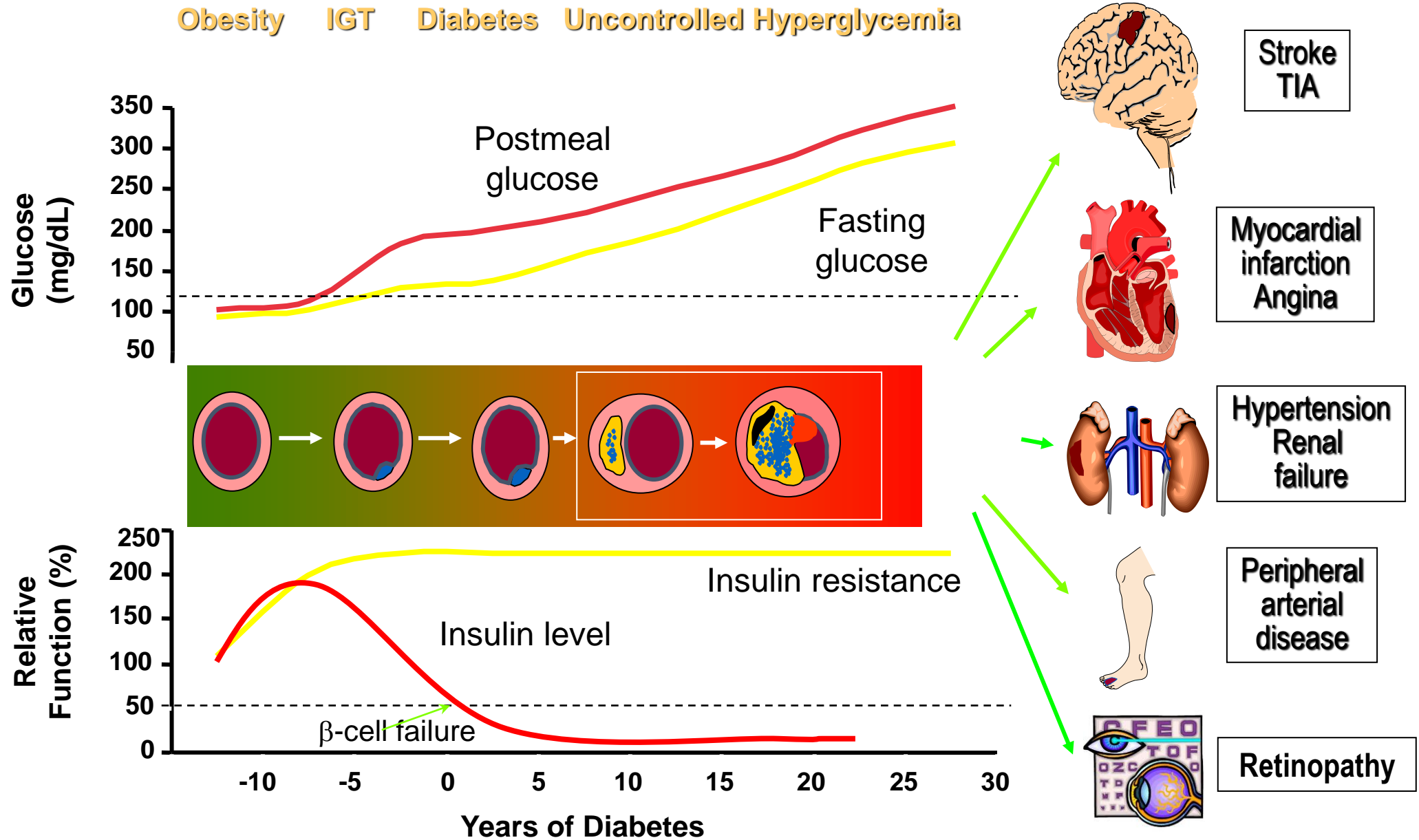
- Introito di grassi inferiore al 30%
- Esercizio fisico > 30 minuti 4 – 5 volte a settimana
- P.A. < 130/80
- Trigliceridi < 150 mg.
- Colesterolo < 175 mg.
- HbA1c < 6,5%



N° pazienti a rischio

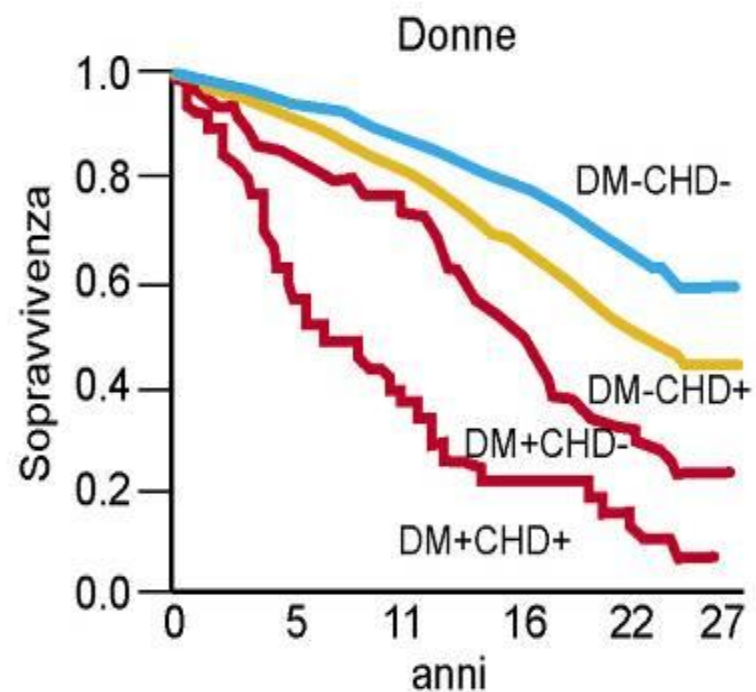
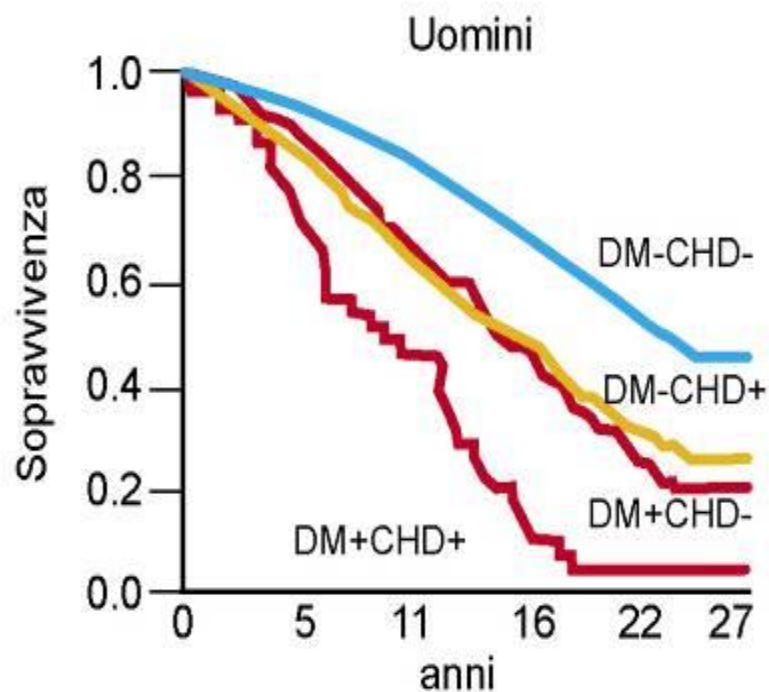
Ter. Convenz.	80	72	70	63	59	50	44	41	13
Ter. Intensivo	80	78	74	71	66	63	61	59	19

# Storia Naturale del diabete tipo 2



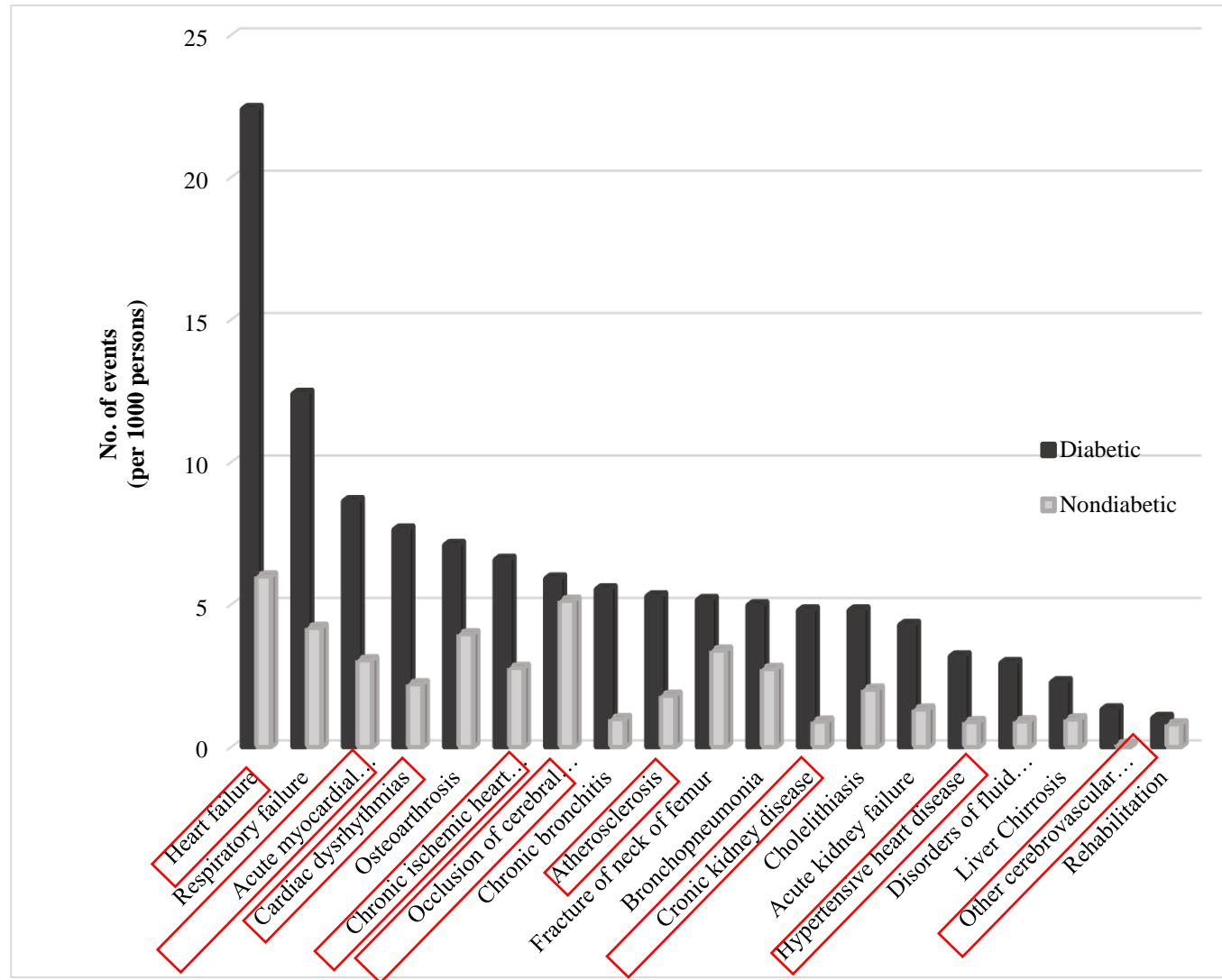
# Il diabete deve essere considerato un equivalente di rischio coronarico?

Risultati del follow-up a 25 anni dello studio Renfrew and Paisley Survey



DM= Diabete mellito  
CHD= Cardiopatia coronarica

# Cause of hospital admission in diabetes in Italy





# Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

\* More or less stringent glycemic goals may be appropriate for individual patients.

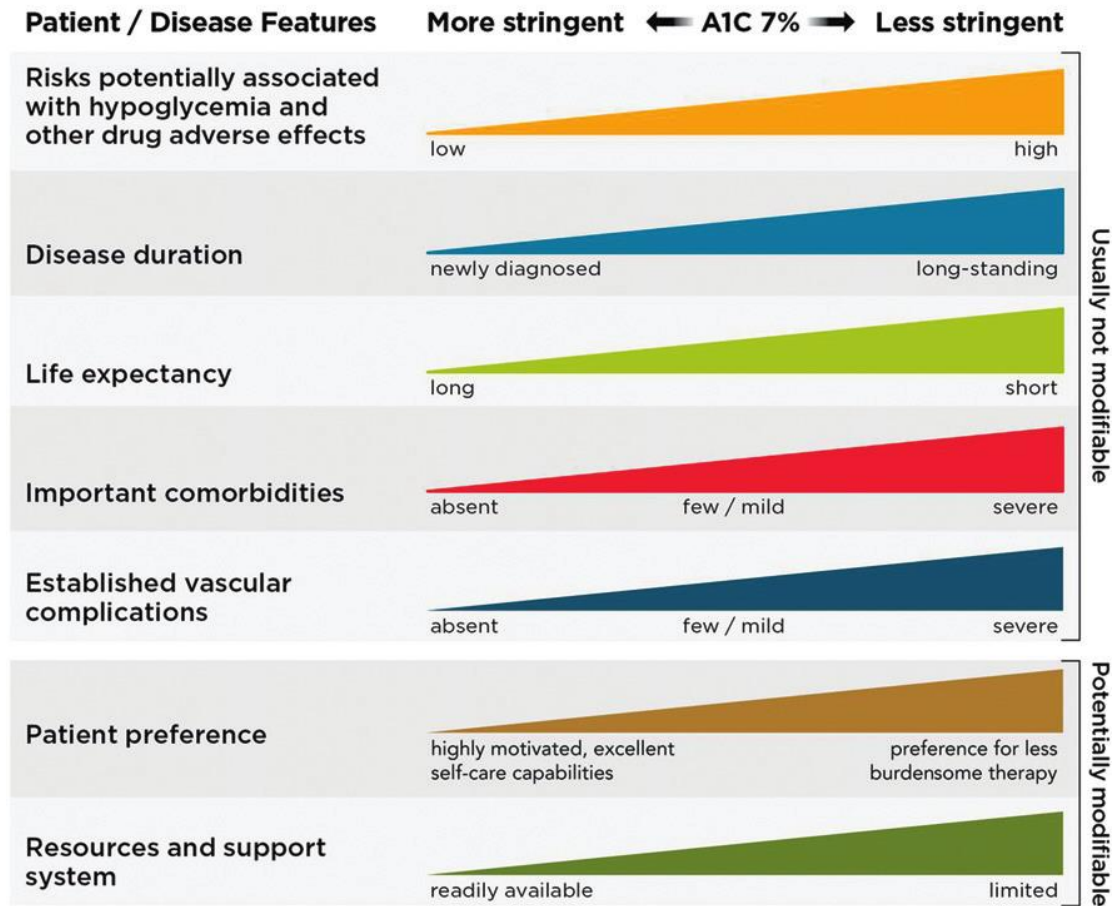
# CGM may be used to assess glycemic target as noted in Recommendation 6.5b and [Fig. 6.1](#).

Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per [Fig. 6.2](#)).

†Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.



## Approach to Individualization of Glycemic Targets



## 1. Obiettivi terapeutici

**1.1** Si raccomanda un target di HbA1c tra 49 mmol/mol (6.6%) e 58 mmol/mol (7.5%) in pazienti con diabete di tipo 2 trattati con farmaci associati ad ipoglicemia.

*Forza della raccomandazione: forte. Qualità delle prove: bassa.*

**1.2.1.** Si raccomanda un target di HbA1c inferiore 53 mmol/mol (7%) in pazienti con diabete di tipo 2 trattati con farmaci non associati ad ipoglicemia.

*Forza della raccomandazione: forte. Qualità delle prove: bassa.*

**1.2.2.** Si suggerisce un target di HbA1c inferiore o uguale a 48 mmol/mol (6.5%) in pazienti con diabete di tipo 2 trattati con farmaci non associati ad ipoglicemia.

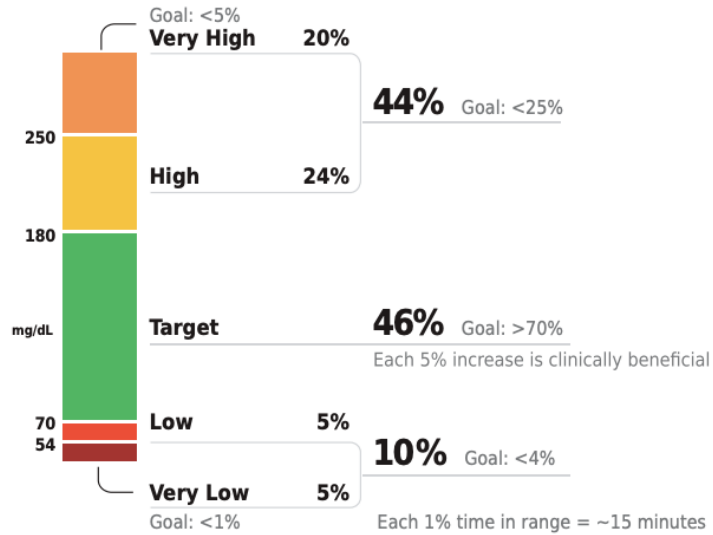
*Forza della raccomandazione: debole. Qualità delle prove: molto bassa.*

# Fattori che influenzano i livelli di HbA1c

- Anemia
- IRC
- Recente trasfusione di emazie
- Deficit di Glucosio 6-fosfato deidrogenasi
- Uso di farmaci che stimolano l'eritropoiesi
- Gravidanza
- Fattori genetici

# AGP Report: Continuous Glucose Monitoring

## Time in Ranges Goals for Type 1 and Type 2 Diabetes



**Test Patient** DOB: Jan 1, 1970

**14 Days: August 8-August 21, 2021**

**Time CGM Active: 100%**

## Glucose Metrics

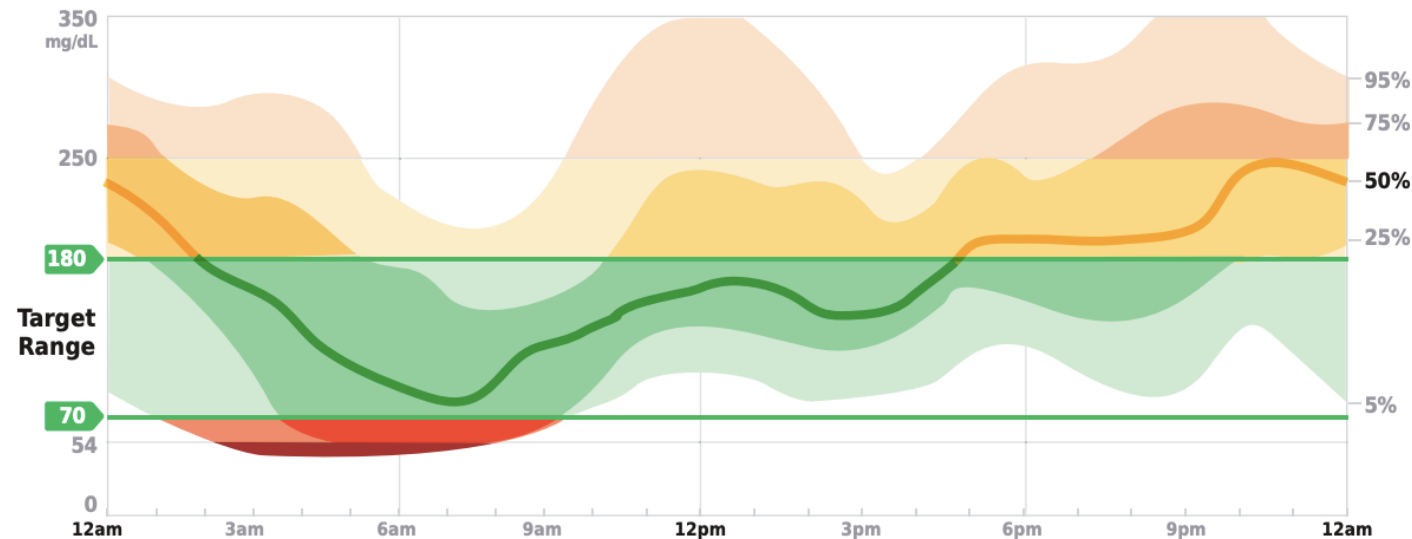
**Average Glucose** ..... **175 mg/dL**  
Goal: <154 mg/dL

**Glucose Management Indicator (GMI)** ..... **7.5%**  
Goal: <7%

**Glucose Variability** ..... **45.5%**  
Defined as percent coefficient of variation  
Goal: ≤36%

## Ambulatory Glucose Profile (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if they occurred in a single day.



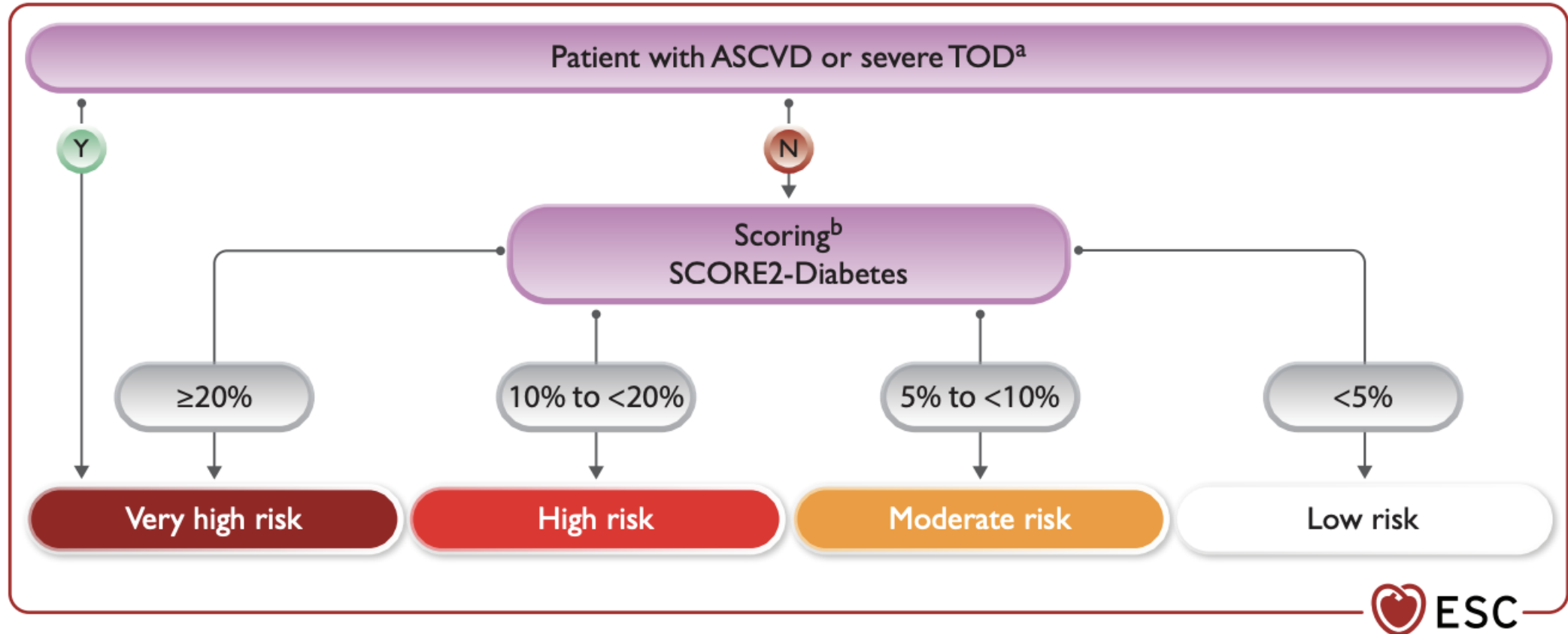
## CV risk categories in patients with DM

Very high-risk	Patients with DM and established CVD or other target organ damage <sup>a</sup> or three or more major risk factors <sup>b</sup> or early onset T1DM of long duration (>20 years)
High-risk	Patients with DM duration $\geq 10$ years without target organ damage plus any other additional risk factor
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors

<sup>a</sup>Proteinuria, renal impairment defined as eGFR < 30mL/min/1.73m<sup>2</sup>, left ventricular hypertrophy, or retinopathy.

<sup>b</sup>Age, hypertension, dyslipidaemia, smoking, obesity

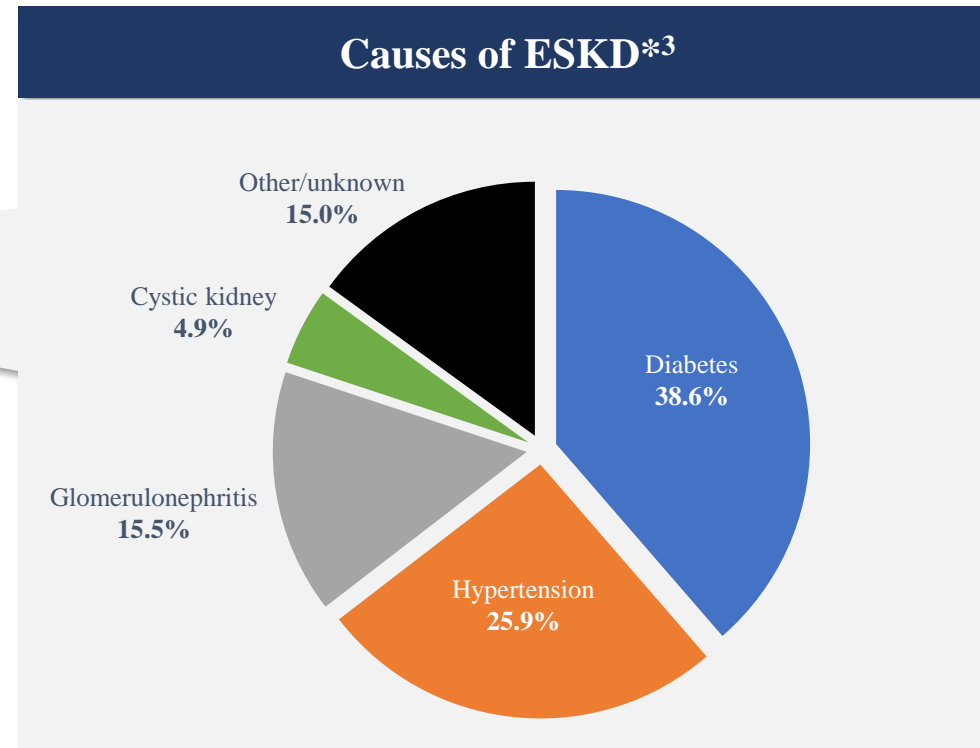
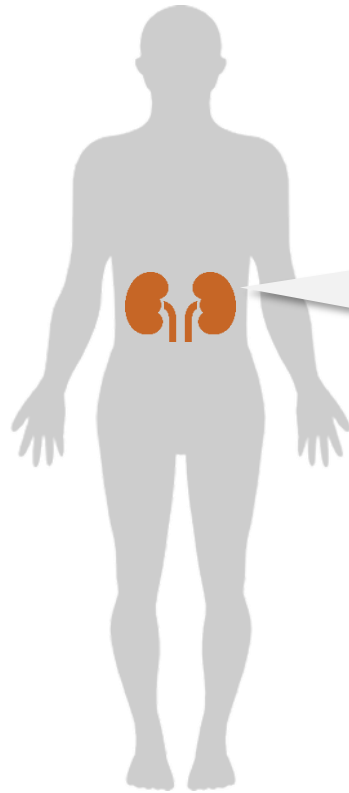
## 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes



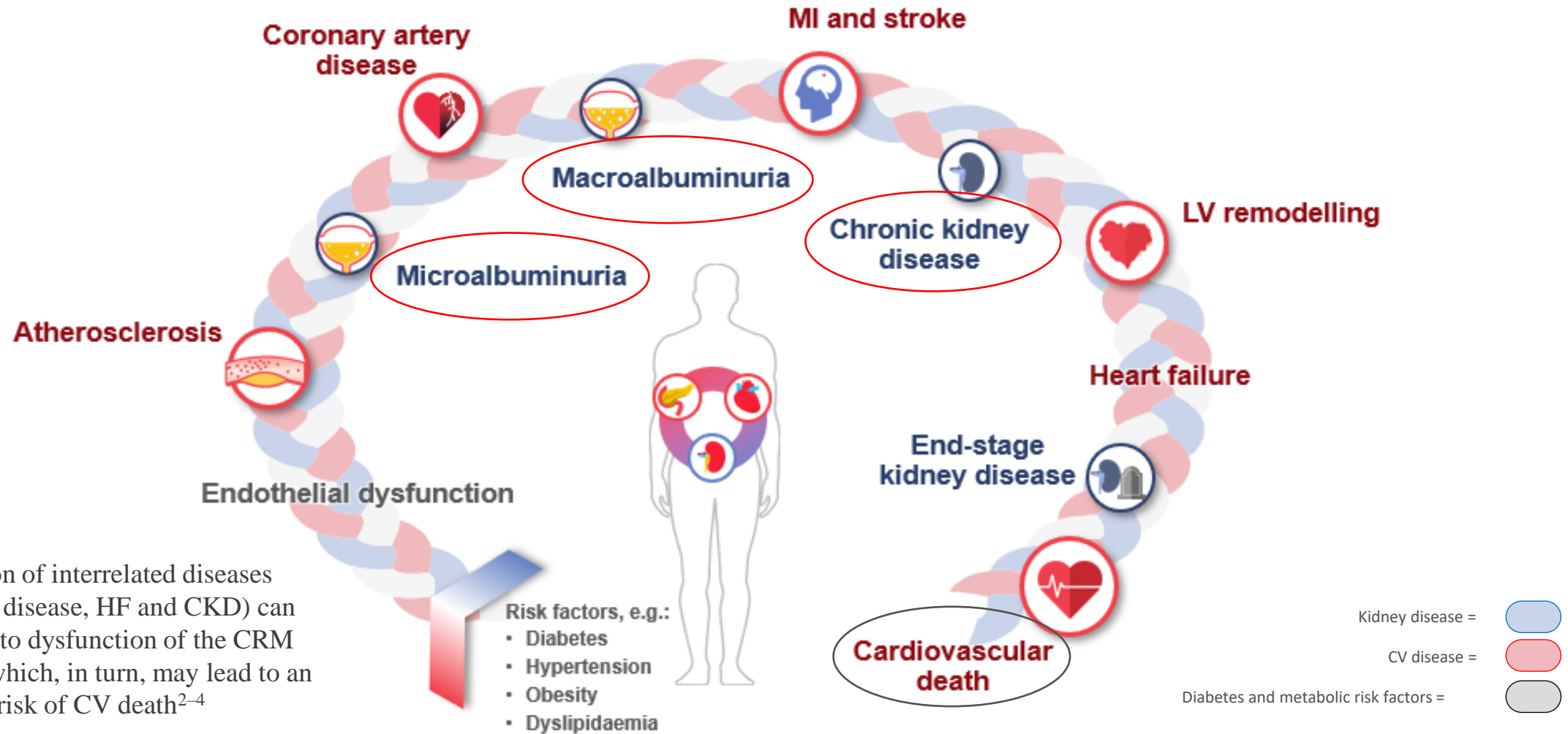
SCORE2: in DM  $\geq 40$  anni, integra informazioni su fattori di rischio CV (fumo, età, Pressione sistolica, HDL colesterolo) con informazioni specifiche sul diabete (età alla diagnosi, HbA1c, eGFR)

# Diabetes is a leading cause of end-stage kidney disease

Approximately 40% of T2D patients develop DKD<sup>1,2</sup>



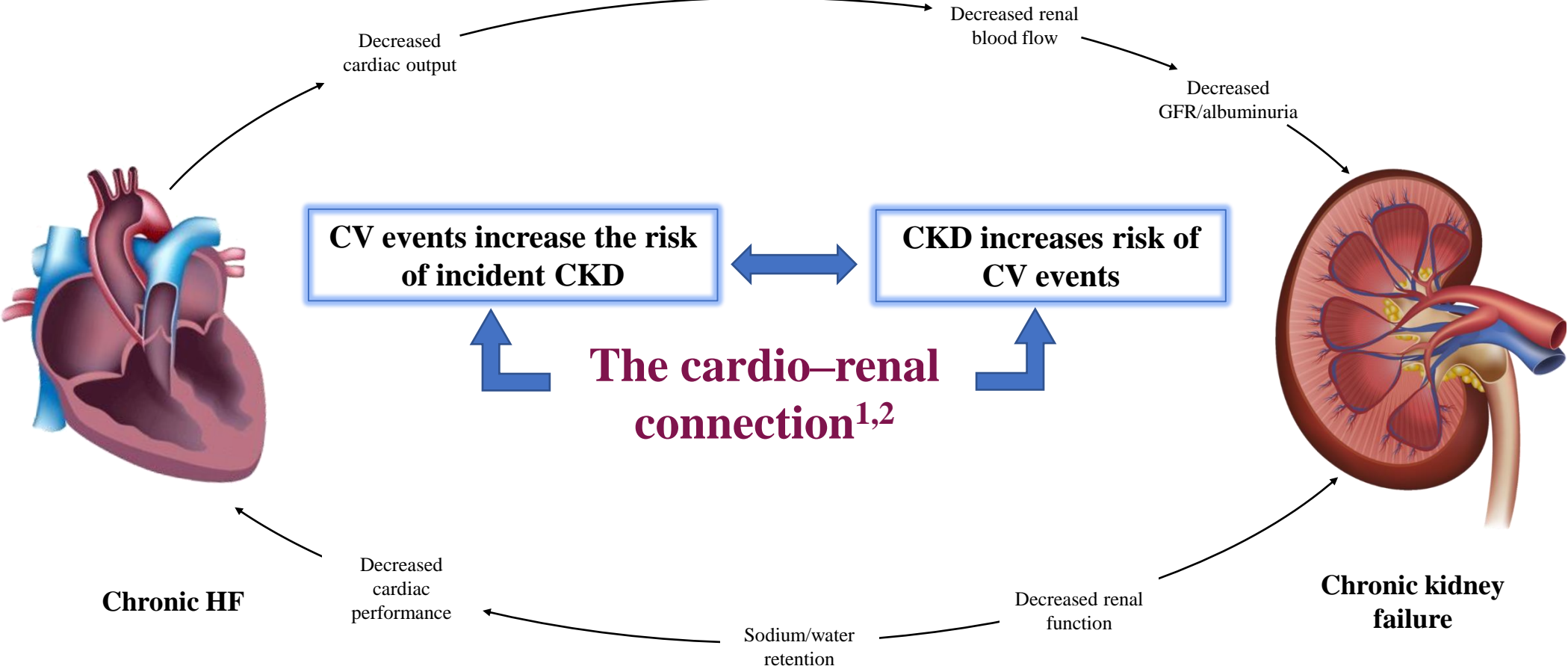
# Continuum Cardio-renale nei pazienti con diabete mellito tipo 2



CRM, cardio-renal-metabolic; T2D, Type 2 Diabetes; CV, cardiovascular; HF, Heart Failure; CKD, Chronic Kidney Disease; MI, Myocardial Infarction; LV, Left Ventricular

Adapted from Dzau VJ *et al. Circulation* 2006;114:2850 - 1. Sarafidis PA *et al. J Cardiometab Syndr* 2006;1:58; 2. Ronco C. *Contrib Nephrol* 2010;164:33; 3. Banerjee S and Panas R. *Hellenic J Cardiol* 2017;58:342; 4. Leon BM and Maddox TM. *World J Diabetes* 2015;6:1246

# Esiste una stretta e specifica associazione fra fisiologia cardiaca e renale

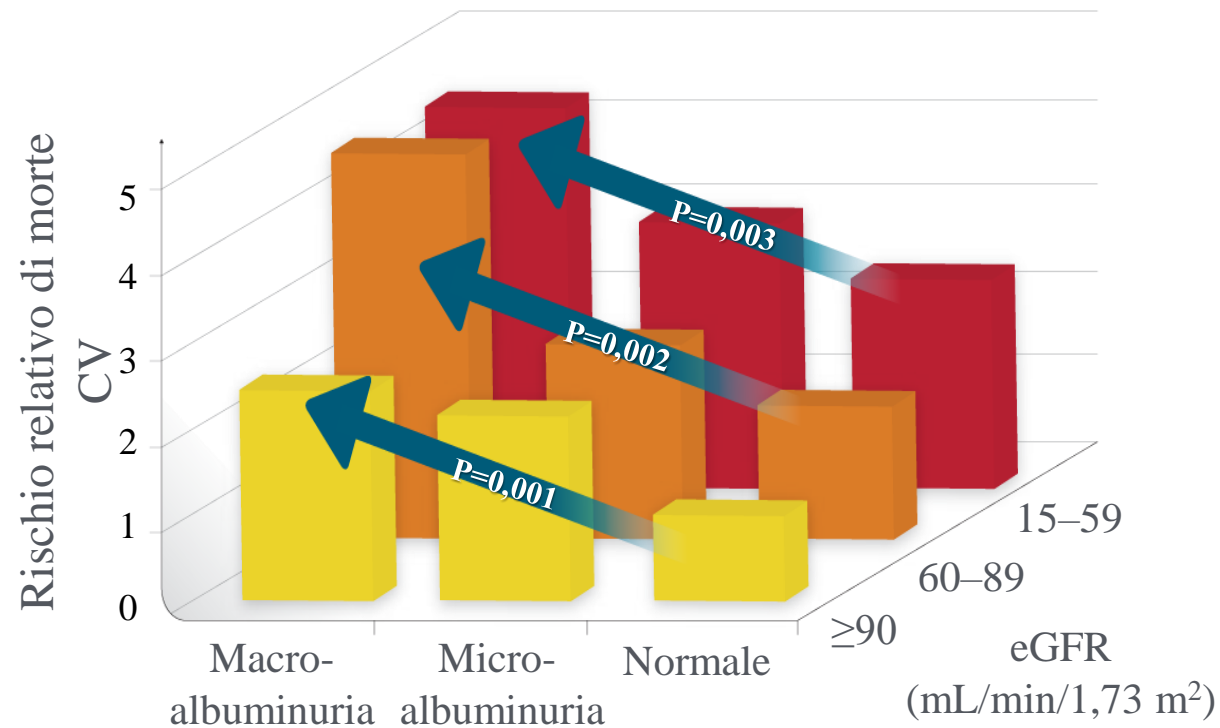
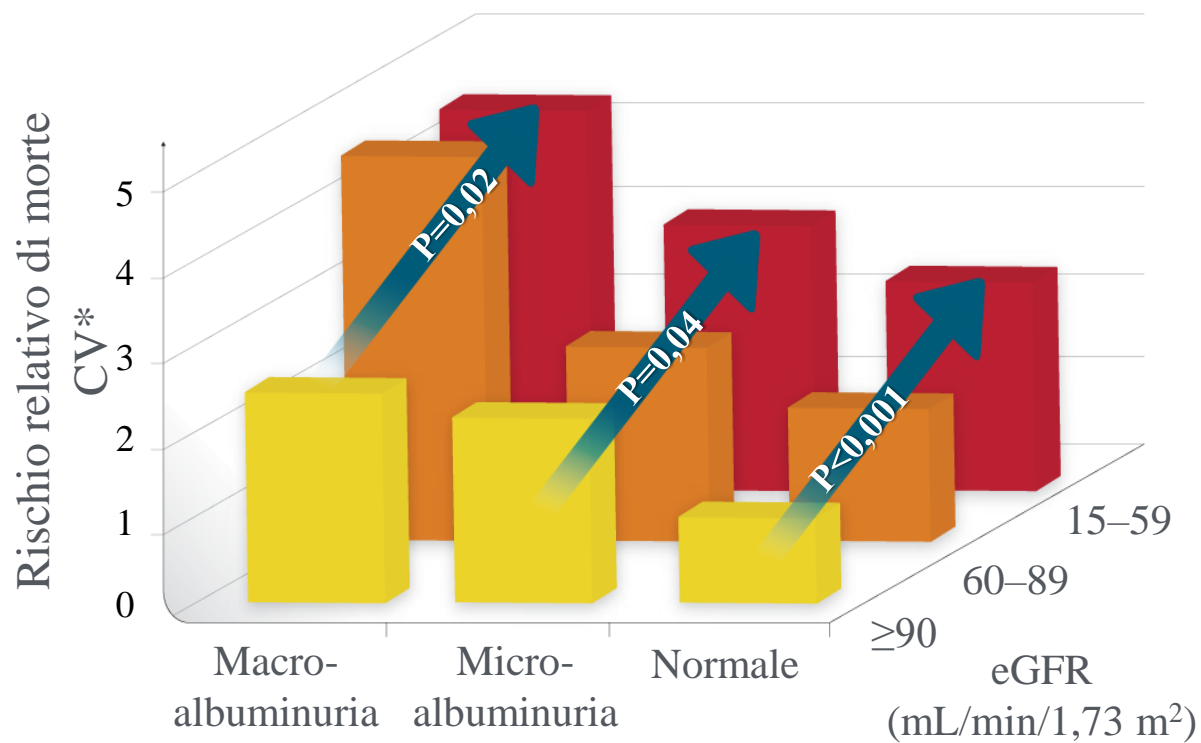


1. Damman K, et al. *J Am Coll Cardiol* 2014;63:853–871  
2. Metra M, et al. *Eur Heart J* 2012;33:2135–2143



# Il rischio di mortalità cardiovascolare (CV) aumenta con il deterioramento della funzionalità renale<sup>1</sup>

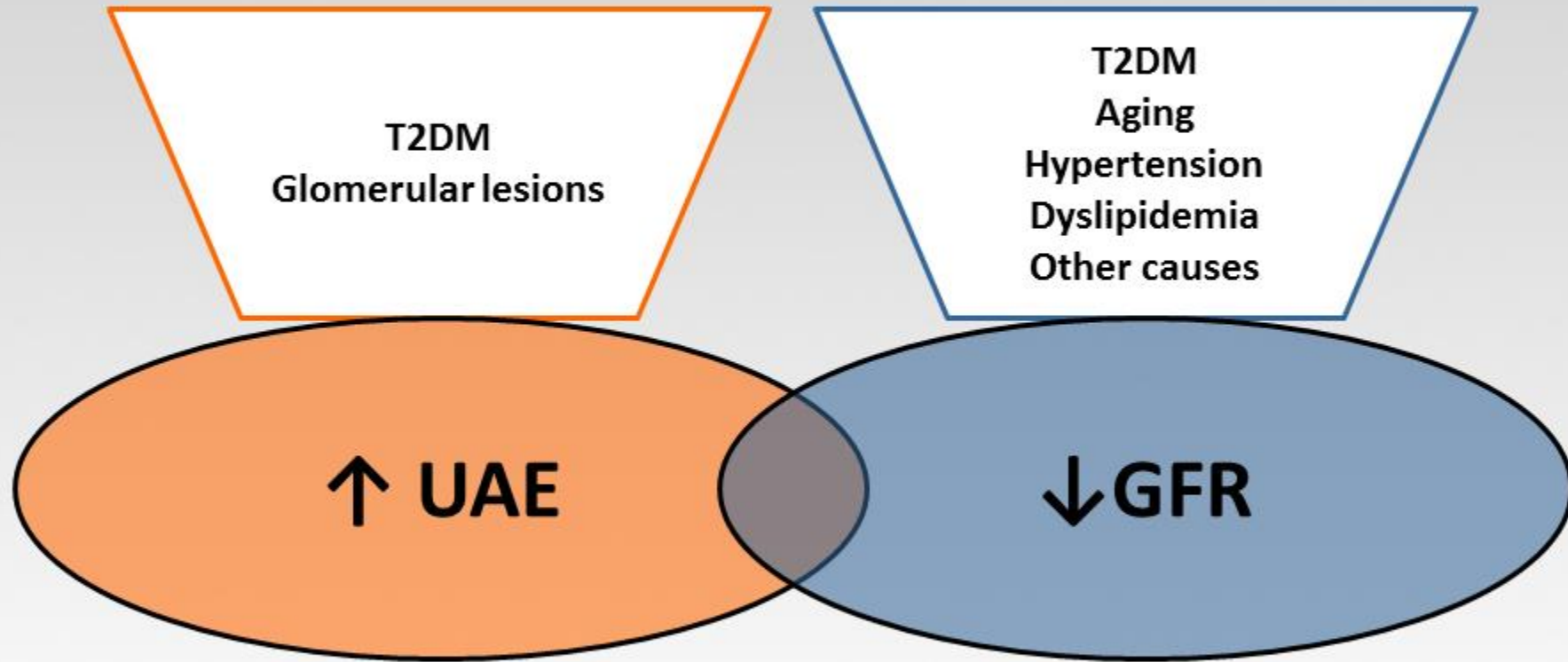
NHANES III 1988–2000



\*Adattato per età, sesso, razza/etnia, storia clinica di malattia CV, categoria di pressione arteriosa, i farmaci antipertensivi, diabete mellito, smoking status, indice di massa corporea, livello di attività colesterolo delle lipoproteine a bassa densità (LDL) e delle lipoproteine ad alta densità (HDL), livelli trigliceridi (log) e categoria della proteina C reattiva.

1. Astor BC, et al. *Am J Epidemiol* 2008;167:1226–34.

# Albuminuria and Reduced GFR: 2 Manifestations of Nephropathy in T2DM

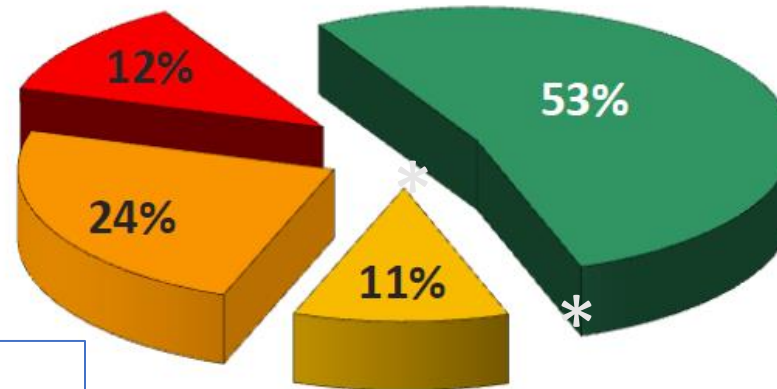


UAE = urinary albumin excretion

# Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Large cohort of patients (120.903) with type 2 diabetes mellitus attending 236 Italian Diabetes Clinics in 2009

- Alb- and low eGFR-    ■ Alb- and low eGFR+
- Alb+ and low eGFR-    ■ Alb+ and low eGFR+



La malattia renale nelle persone con diabete si presenta **NON SEMPRE** con la microalbuminuria come primo segno

**Background.** Kidney dysfunction is a strong predictor of end-stage renal disease and cardiovascular (CV) events. The main goal was to study the clinical correlates of diabetic kidney disease in a large cohort of patients with type 2 diabetes mellitus (T2DM) attending 236 Diabetes Clinics in Italy. **Methods.** Clinical data of 120 903 patients were extracted from electronic medical records by means of an *ad hoc-developed* software. Estimated glomerular filtration rate (GFR) and increased urinary albumin excretion were considered. Factors associated with the presence of albuminuria only, GFR < 60 mL/min/1.73 m<sup>2</sup> only or both conditions were evaluated through multivariate analysis.

De Cosmo (RIACE) for AMD-Annals Study Group, NDT 2014

# La CKD può essere classificata in base al livello di eGFR ed albuminuria<sup>1</sup>

eGFR (mL/min/1,73 m <sup>2</sup> )	Categorie di albuminuria (rapporto albuminuria:creatininuria)		
	A 1 <3 mg/mmol (<30 mg/g)	A 2 3–30 mg/mmol (30–300 mg/g)	A 3 >30 mg/mmol (>300 mg/g)
G1 ≥90	Normal or high	G1 A2	G1 A3
G2 60–89	Mildly decreased	G2 A2	G2 A3
G3a 45–59	Mildly to moderately decreased	G3a A2	G3a A3
G3b 30–44	Moderately to severely decreased	G3b A2	G3b A3
G4 15–29	Severely decreased	G4 A2	G4 A3
G5 <15	Kidney failure	G5 A2	G5 A3

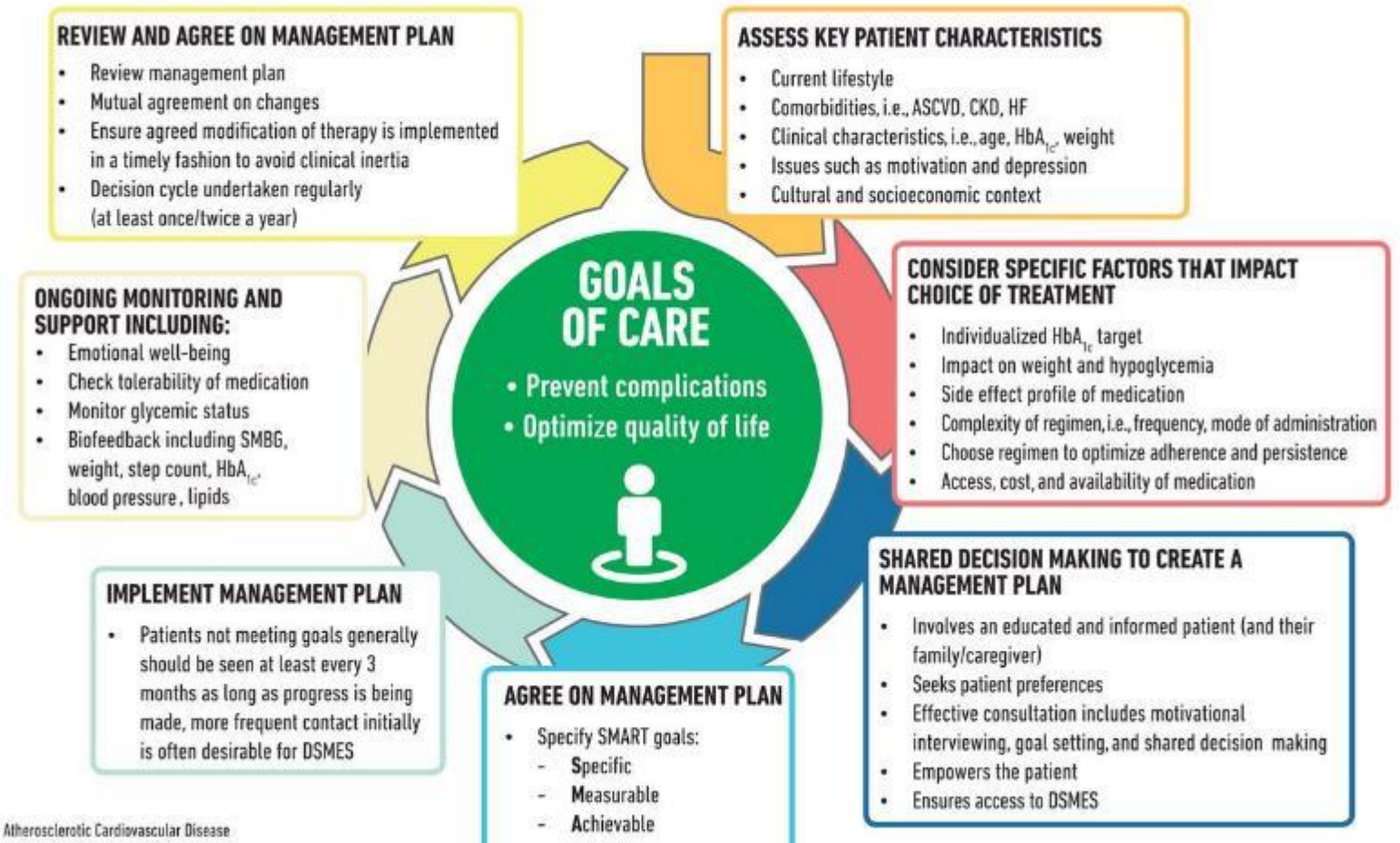


■ Low risk\*    
 ■ Moderately increased risk    
 ■ High risk    
 ■ Very high risk

# 2 obiettivi principali nella cura del DMT2

Prevenzione delle complicanze

Ottimizzazione della qualità di vita



# Consensus Statement ADA/EASD 2022

**FIGURE 1: DECISION CYCLE FOR PERSON-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES**



Comorbilità, Rischio CV, CKD, HF

Impatto su peso e  
Ipoglicemia e protezione CR

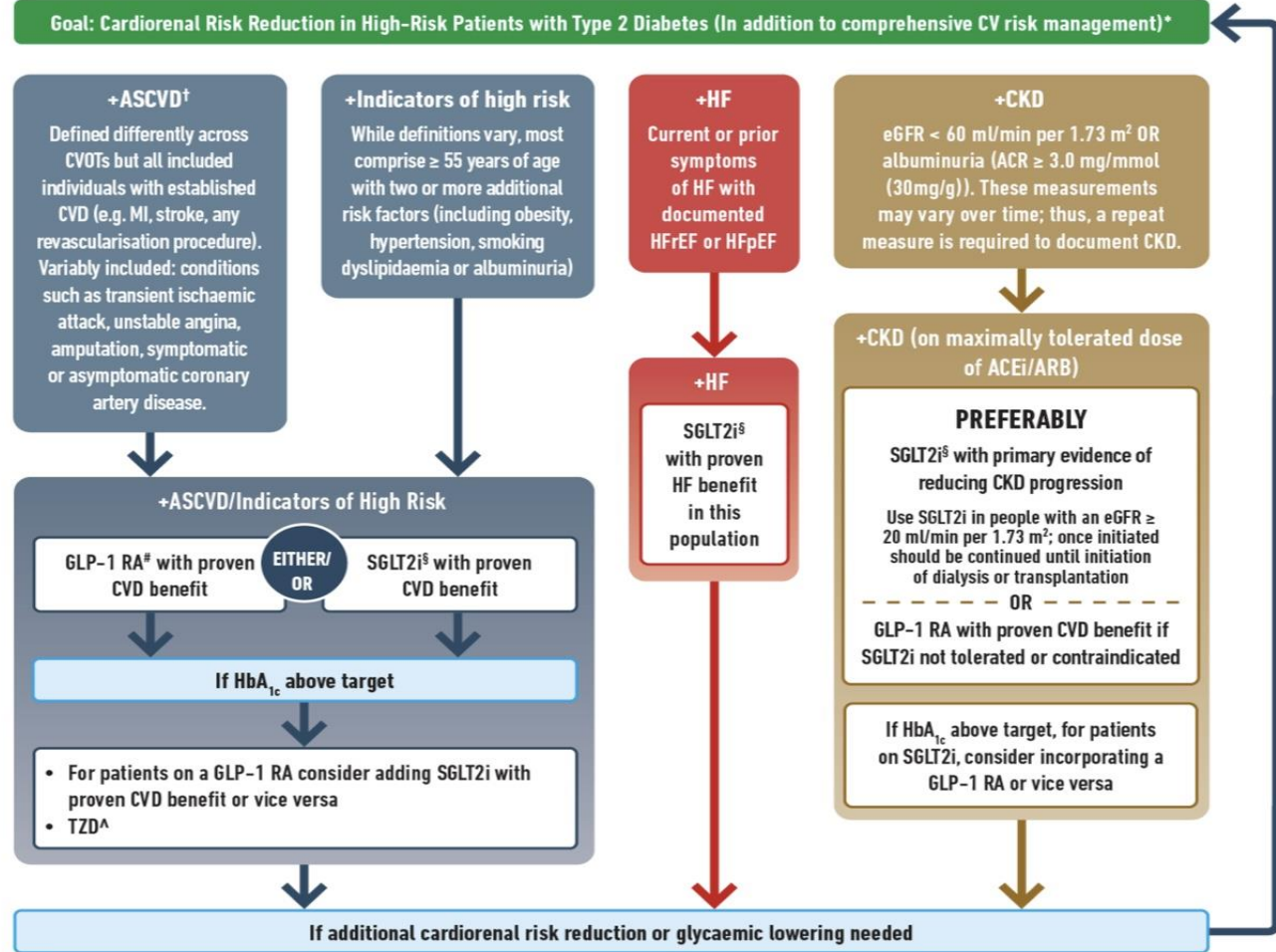
Valutare le preferenze  
del paziente

BGM, Blood Glucose Monitoring; BP, Blood Pressure; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CVD, Atherosclerotic Cardiovascular Disease; DSMES, Diabetes Self-Management Education and Support; HF, Heart Failure.

# FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



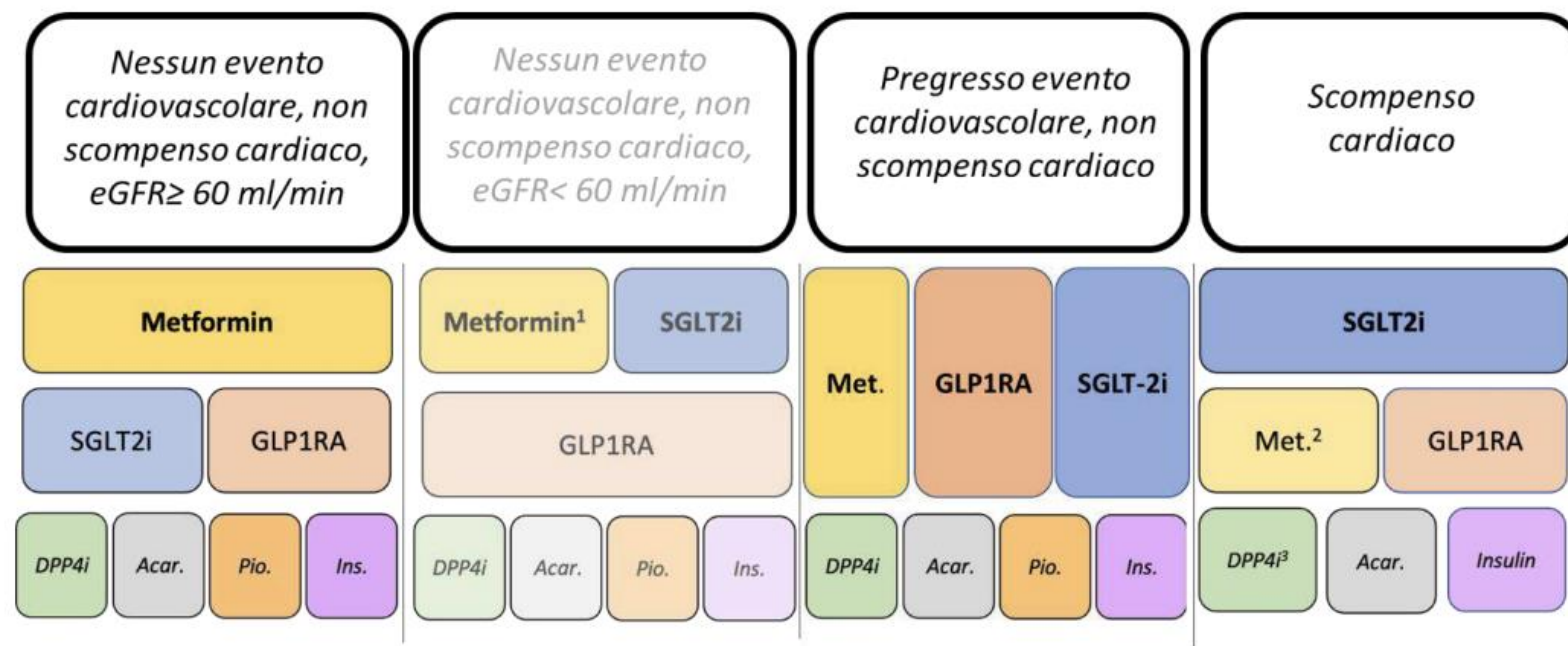
HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with Reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

For people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

## 5. Terapia farmacologica



<sup>1</sup>Se la metformina non è controindicata per ridotto eGFR.

<sup>2</sup>Se la metformina non è controindicata per ridotta funzione cardiaca.

<sup>3</sup>Eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.

La raccomandazione sui pazienti con eGFR < 60ml/min è debole per carenza di studi clinici effettuati su questa popolazione

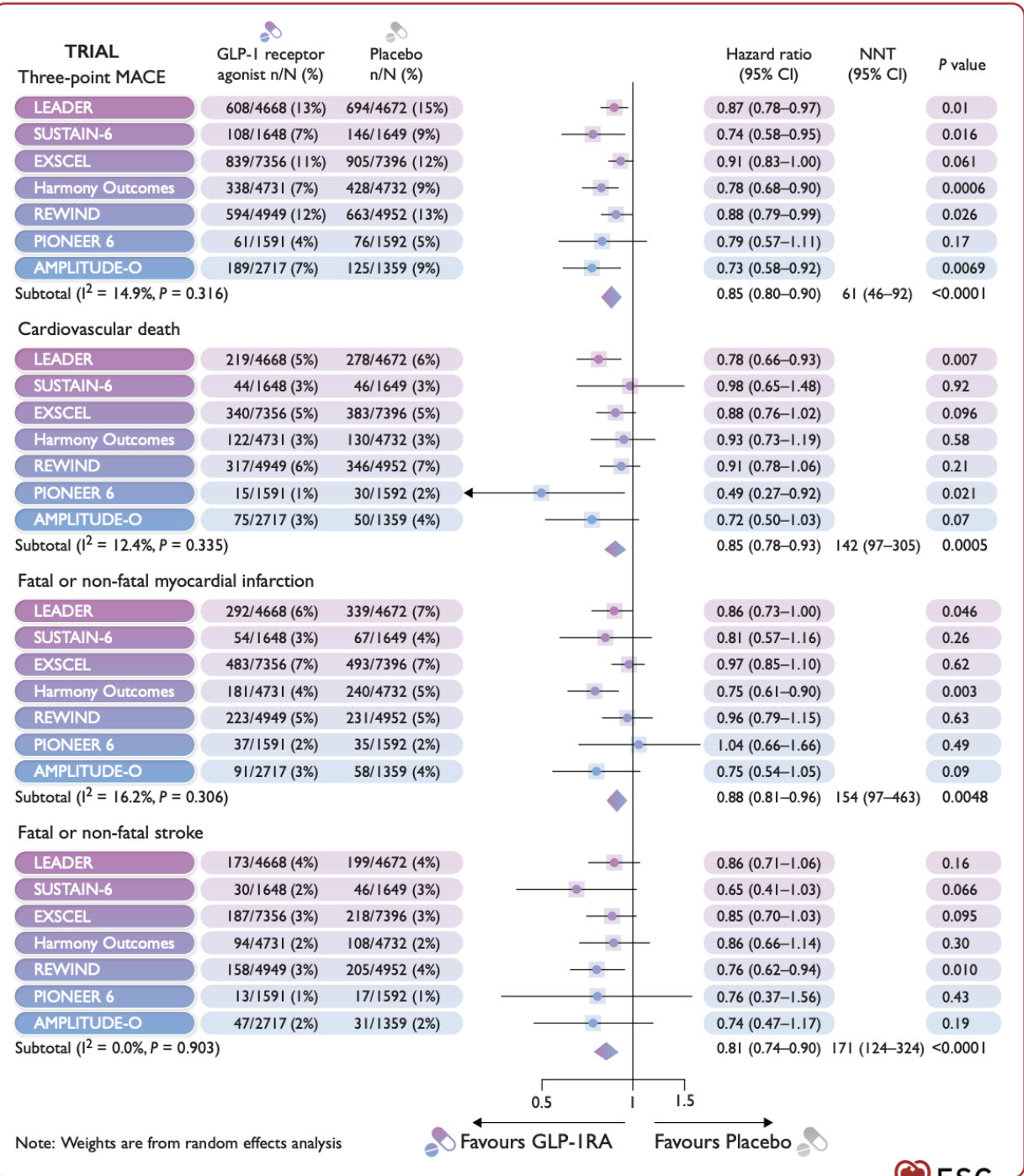
Si raccomanda la deprescrizione di sulfanilurre e glinidi

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

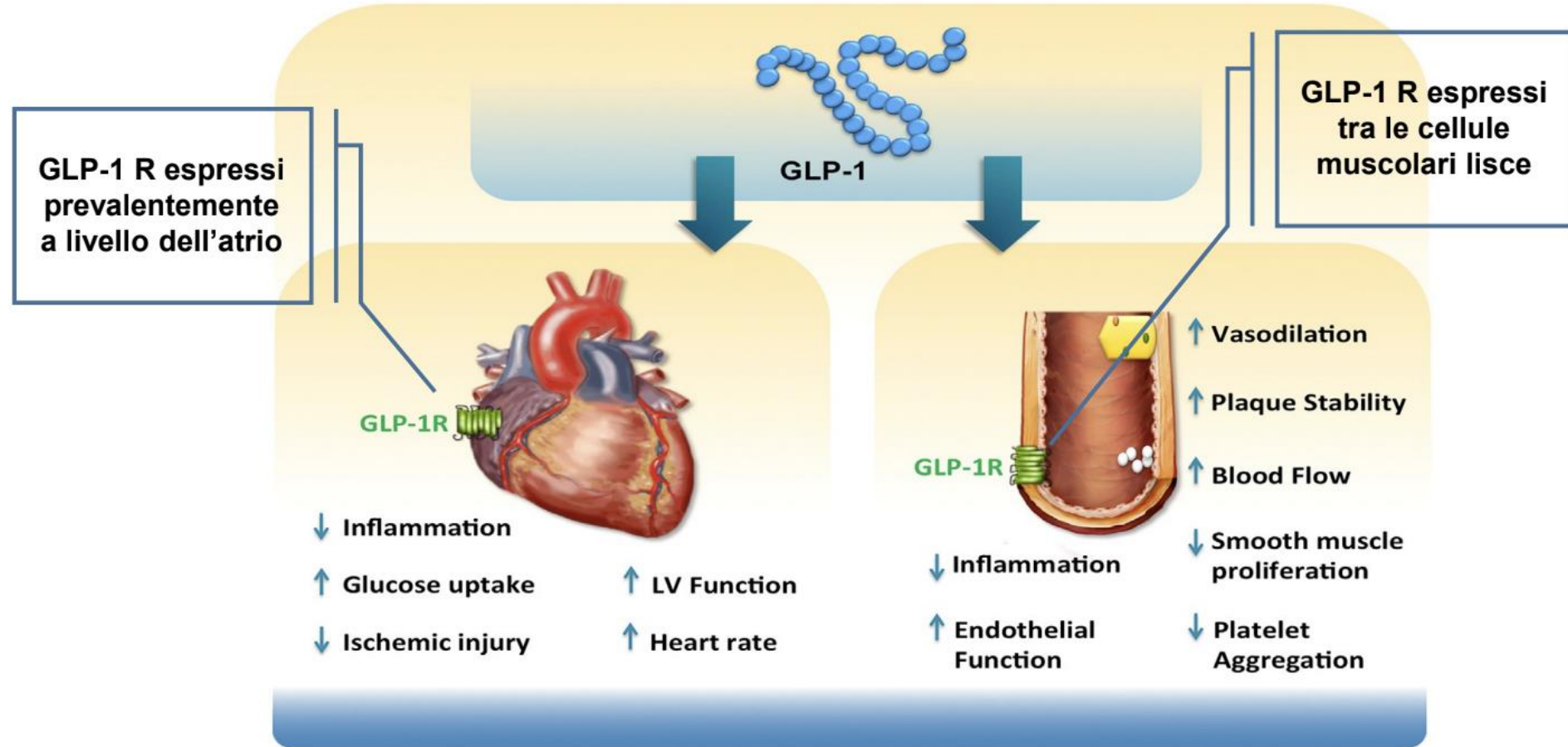


# 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

GLP-1 RA



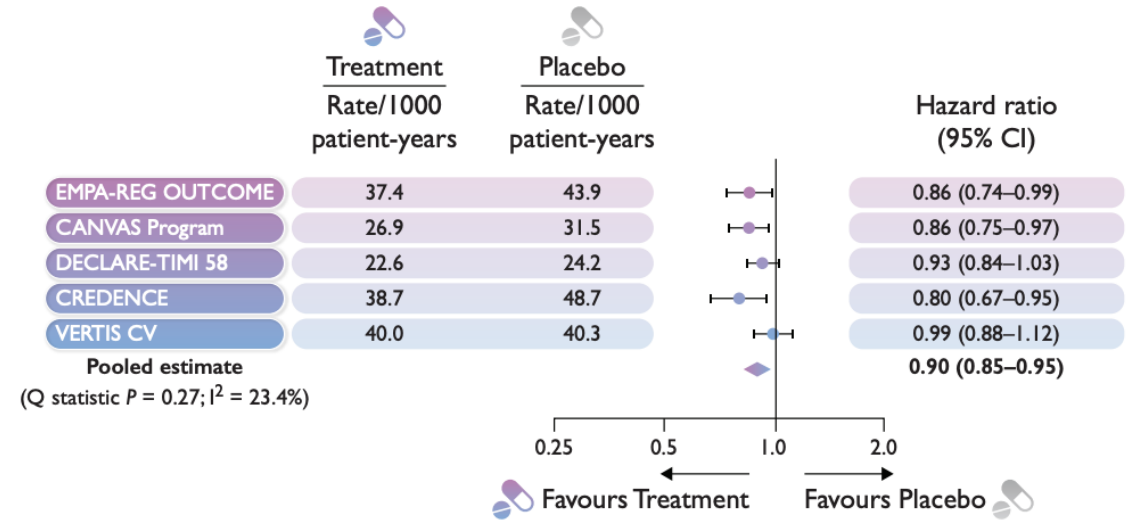
# Effetti cardiovascolari del GLP-1



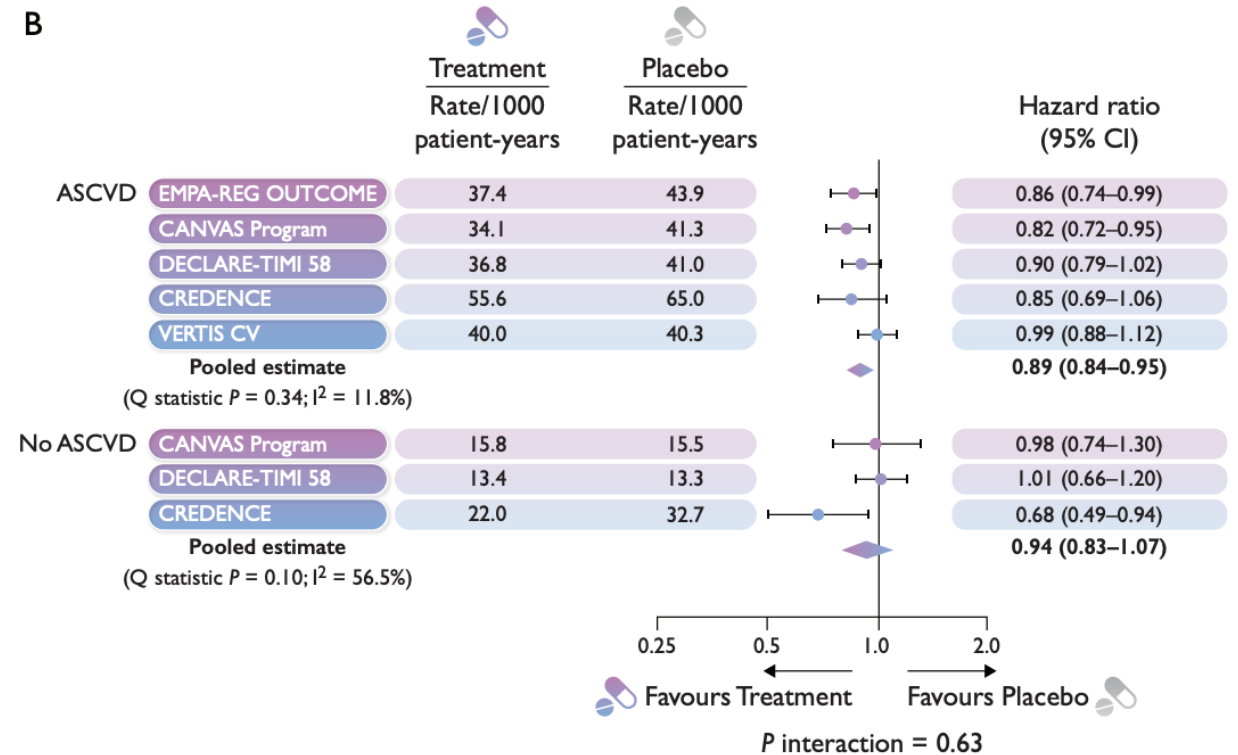
# 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

## SGLT-2 inhibitori

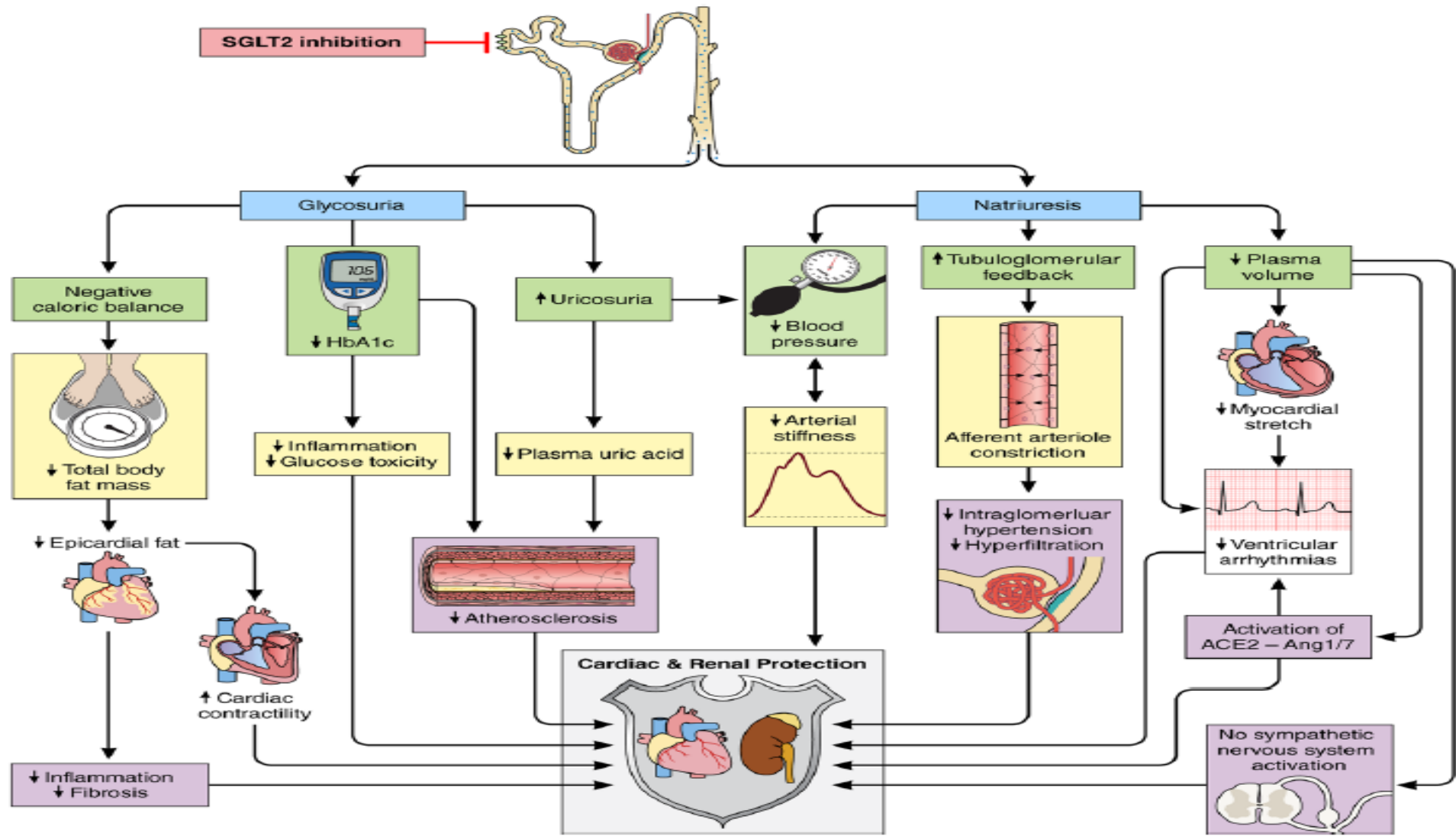
A







B



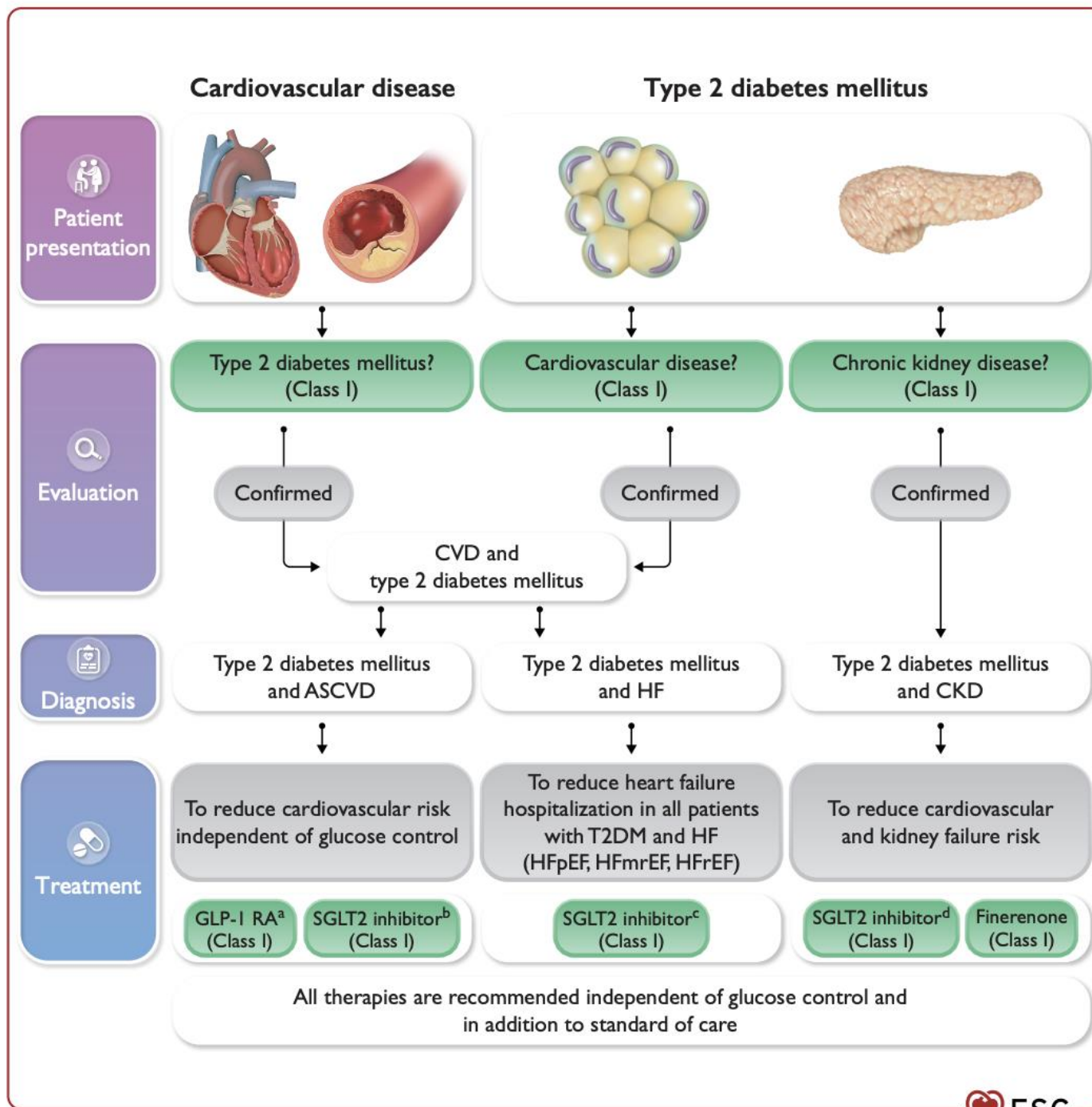
# L'inibizione di SGLT2 ha un effetto pleiotropico di protezione cardiorenale



# Reductions in CV, HF and kidney outcomes observed with SGLT2 inhibitors in patients with T2D: consistent benefits

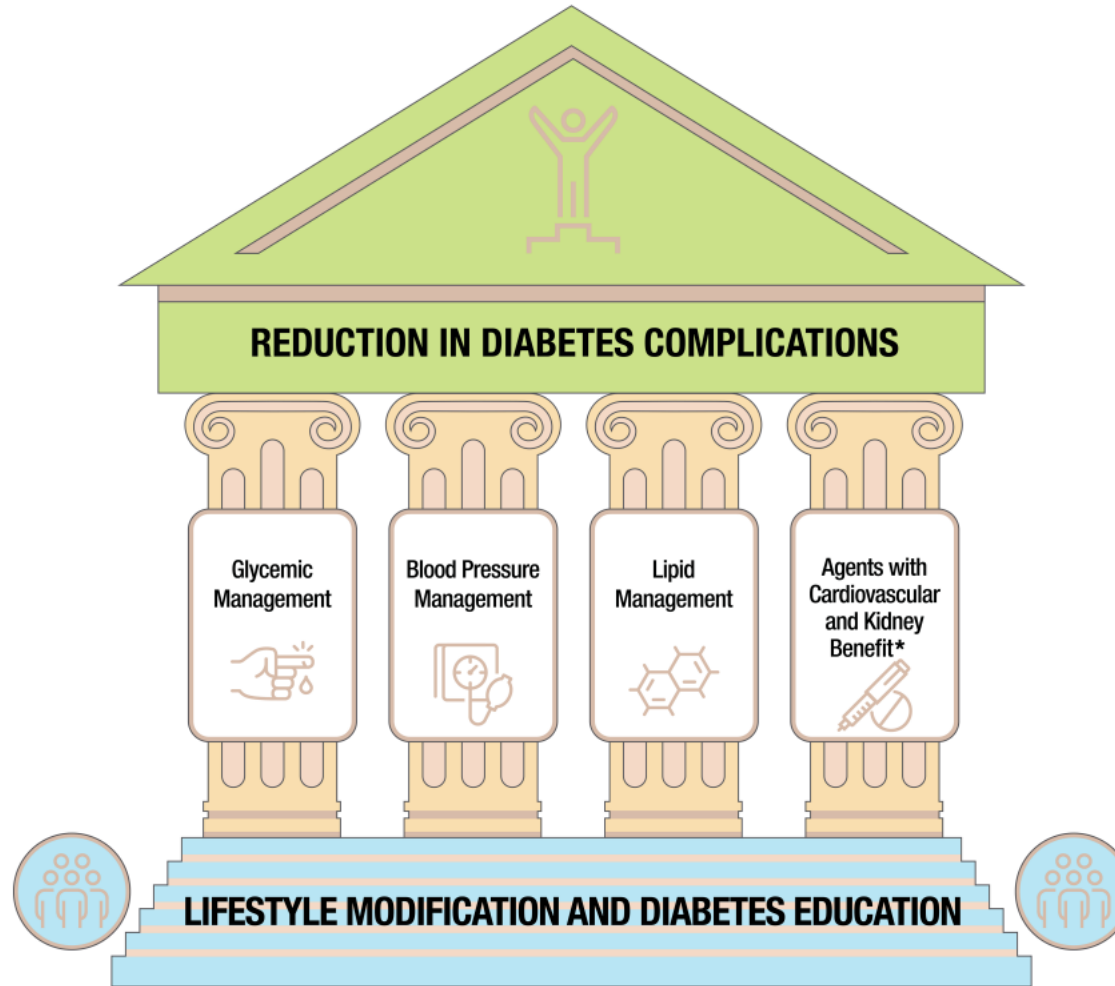
	EMPA-REG OUTCOME <sup>1,2</sup> (empagliflozin)	CANVAS Program <sup>3</sup> (canagliflozin)	DECLARE-TIMI 58 <sup>4</sup> (dapagliflozin)	VERTIS-CV <sup>5,6</sup> (ertugliflozin)	CREDENCE <sup>7</sup> (canagliflozin)
 <b>3P-MACE</b>	▼ 14%*	▼ 14%*	NS	NS <sup>†</sup>	▼ 20%‡
 <b>CV death</b>	▼ 38%‡	NS	NS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

# 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes





## Per ridurre il **RISCHIO CARDIOVASCOLARE GLOBALE** è necessario identificare e trattare **tutti** i fattori di rischio coesistenti nello stesso paziente



**Figure 10.1**—Multifactorial approach to reduction in risk of diabetes complications. \*Risk reduction **interventions** to be applied as individually appropriate.

# Take Home Messages

- Il paziente con Diabete mellito tipo 2 ha un elevato rischio cardio-nefro-vascolare
- E' necessario ottenere e mantenere un buon controllo glicometabolico
- I target glicemici devono essere adattati al paziente
- Nel trattamento dei pazienti con DM2 a rischio di o in presenza di complicanze cardio-nefro-vascolari i farmaci di prima scelta sono SGLT-2i e GLP-1 RA
- Ad ogni visita è importante ricordare che la dieta e l'attività fisica sono alla base del trattamento del diabete
- Nella prevenzione o trattamento delle complicanze cardio-nefro-vascolari si devono trattare tutti i fattori di rischio
- La prevenzione deve essere fatta già nel prediabete, nei pazienti obesi/in sovrappeso e con s. metabolica





**GRAZIE PER L'ATTENZIONE**