ACCADEMIA di
ALTA FORMAZIONE CLINICA
per MEDICI del TERRITORIO

MILANO | 2023

20 maggio

Inquadrare il diabete

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Highlights

In 2021, IDF estimates show that:

1 in 10

Adults (20-79 years) has diabetes
537 million people

1 in 18

Adults (20-79 years) has impaired fasting glucose
319 million people

3 in 4

People with diabetes live in low and middle-income countries

1 in 2

Adults is undiagnosed
240 million people

1 in 6

Live births (21 million) affected by hyperglycaemia in pregnancy, 80% have mothers with GDM

11.5%

Of global health expenditure spent on diabetes (USD 966 billion)

1 in 9

Adults (20-79 years) has impaired glucose tolerance
541 million people

1.2 million

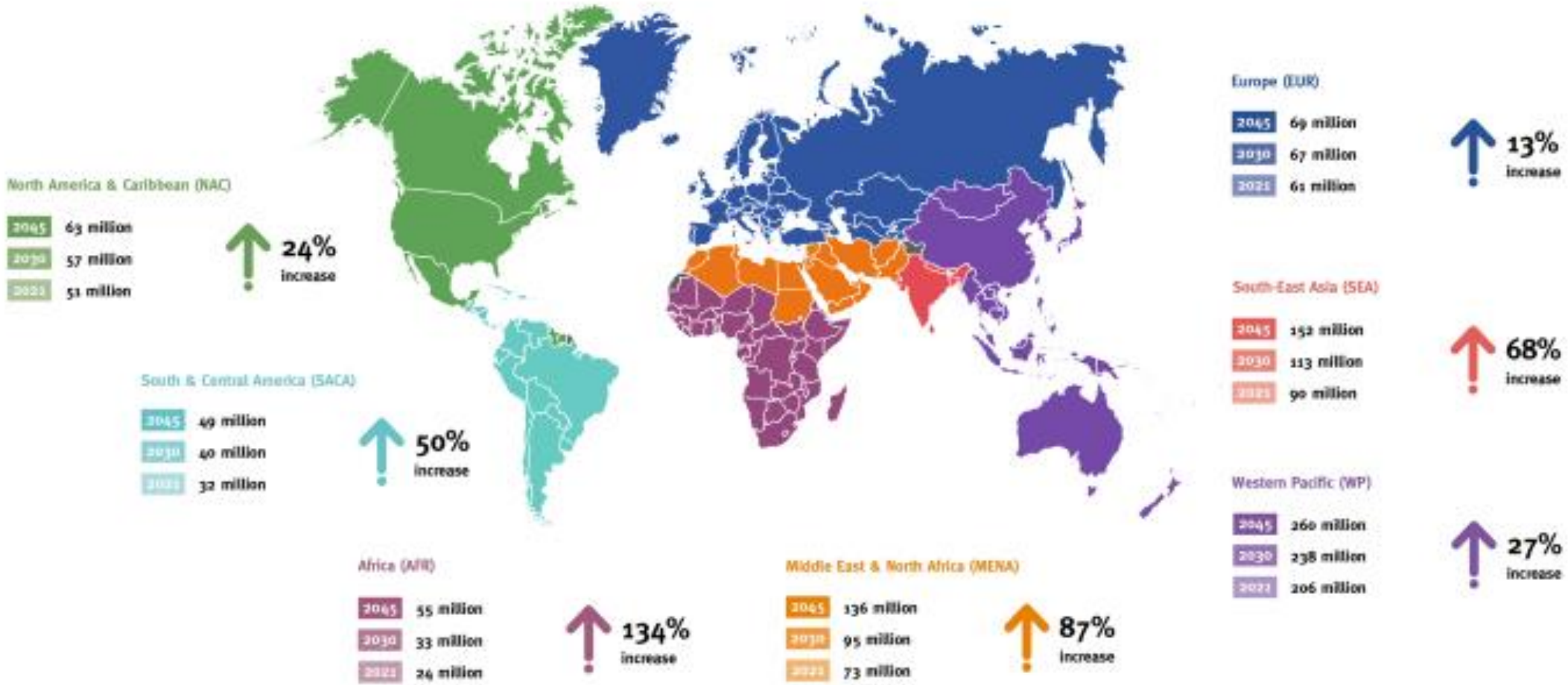
Children and adolescents below 20 years have type 1 diabetes

6.7 million

Deaths attributed to diabetes

Number of people with diabetes

Aged 20–79 years globally and by IDF region



Estimates and projections

Global number of adults (20–79 years) in millions

Estimates of the global prevalence of diabetes in the 20–79 year age group (millions)

Key

151 Number of people with diabetes in millions

Projections of the global prevalence of diabetes in the 20–79 year age group (millions)

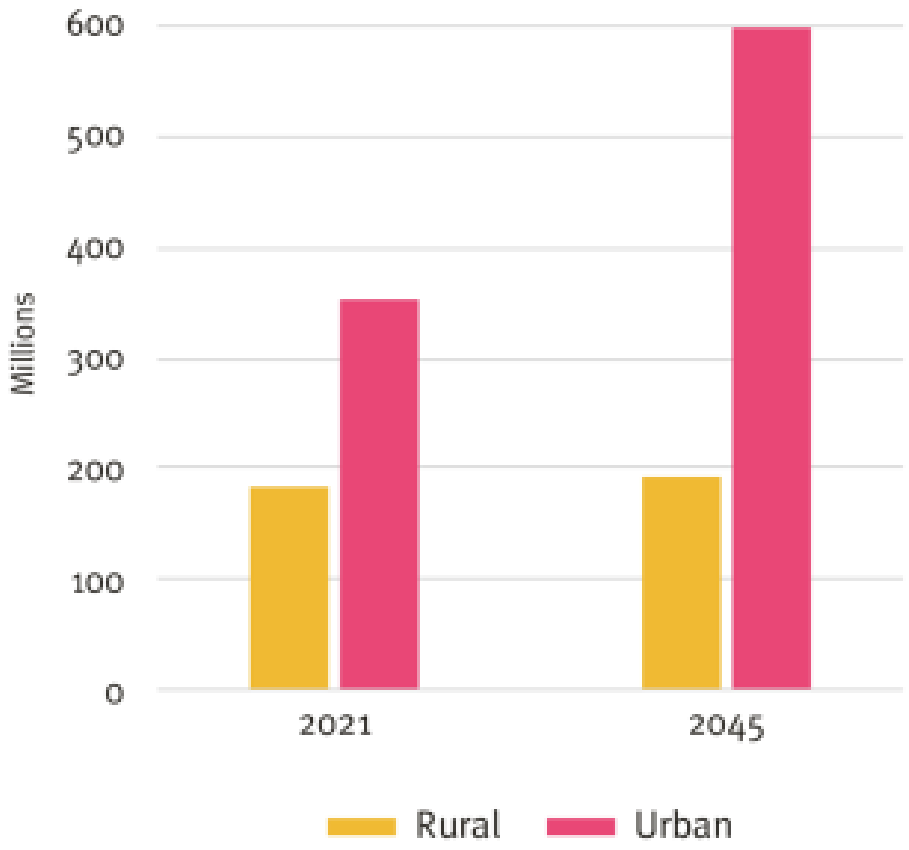
Key

333 Projection in millions

Year projection made

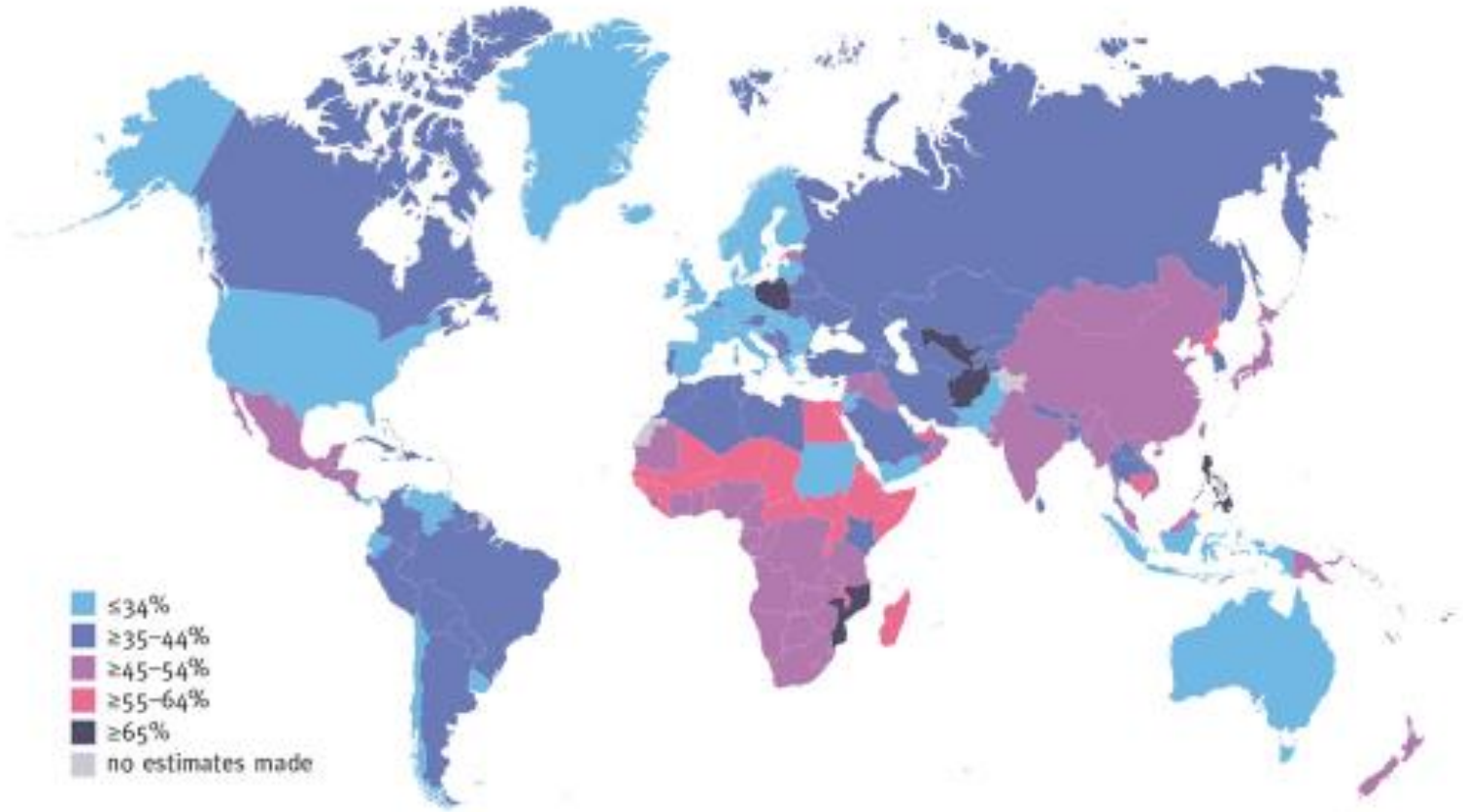
Number of people with diabetes

In adults aged 20–79 years living in urban and rural areas in 2021 and 2045



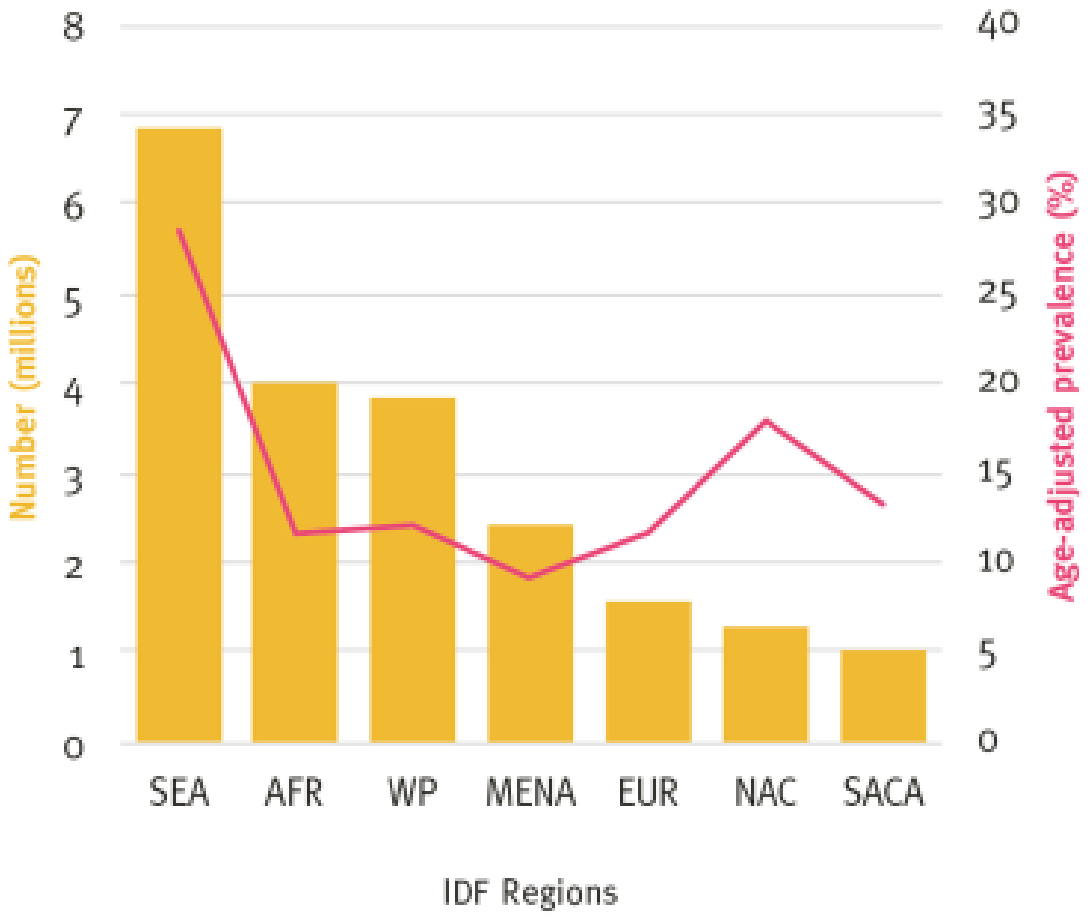
Proportion of adults with undiagnosed diabetes

Aged 20–79 years by country in 2021



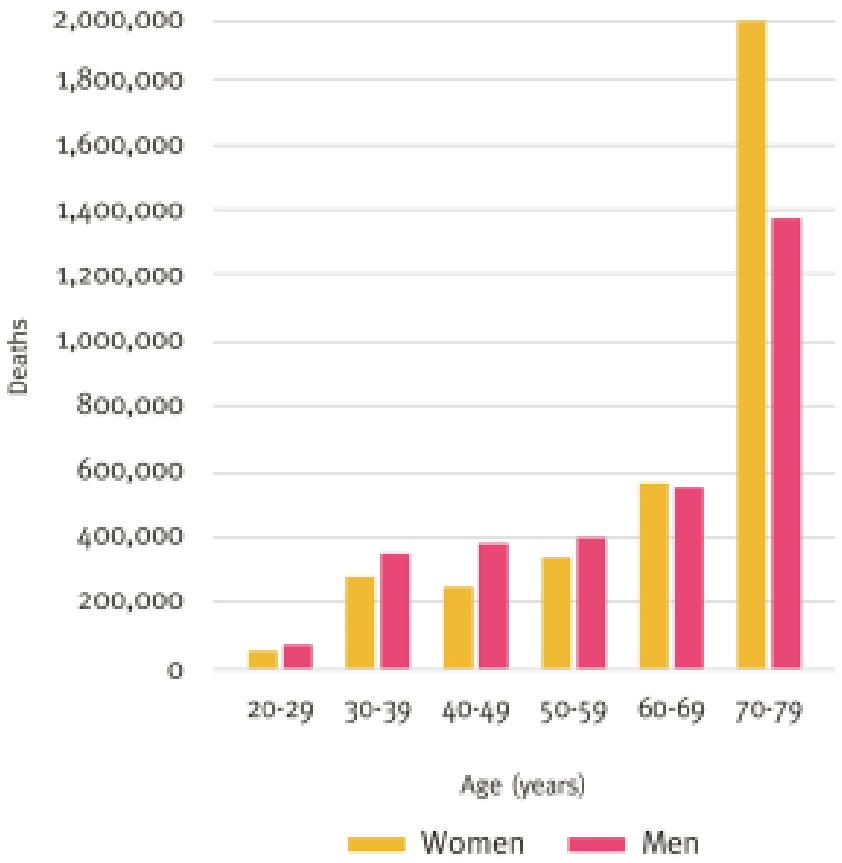
Hyperglycaemia in pregnancy

Per IDF region, 2021



Number of deaths by sex and age

Aged 20–79 years, 2021



Summary

- In 2021, the IDF 10 Edition of the Atlas estimates that 1/10 people aged 20-79 have diabetes
- This equates to 537 million people in the world
- By 2045, this number will increase to 784 million
- There still remain gaps in our estimates due to absent and low-quality data in some parts of the world
- There is a strong need for effective intervention strategies and policies to stall the increase in the number of people developing diabetes

Diabete mellito
una sola definizione tante «storie» di malattia

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki*, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop

Diabete mellito
una sola definizione tante «storie» di malattia

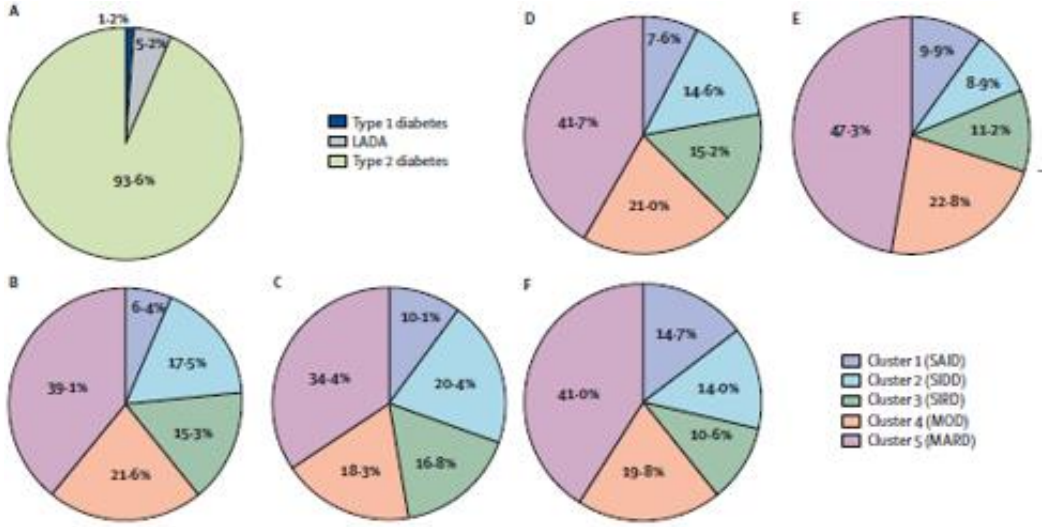


Figure 1: **Patient distribution according to method of classification**
(A) Distribution of ANDIS patients (n=8980) according to traditional classification. (B) Distribution of ANDIS patients (n=8980) according to k-means clustering. (C) Distribution of patients in the Scania Diabetes Registry (n=1466) according to k-means clustering. (D) Distribution of patients in the All New Diabetics in Uppsala cohort (n=844) according to k-means clustering. (E) Distribution of DIREVA patients with newly diagnosed diabetes (n=878) according to k-means clustering. (F) Distribution of DIREVA patients with longer-term diabetes (n=2607) according to k-means clustering. LADA=latent autoimmune diabetes in adults. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes. ANDIS=All New Diabetics in Scania. DIREVA=Diabetes Registry Vaasa.

5 CLUSTERS:

1. SAID: severe autoimmune diabetes
2. SIDD: severe insulin-deficient diabetes
3. SIRD: severe insulin-resistant diabetes
4. MOD: mild obesity-related diabetes
5. MARD: mild age-related diabetes

Diabete mellito tipo 2
una sola definizione tante «storie» di malattia

RESEARCH ARTICLE

WILEY

Pathophysiology-based phenotyping in type 2 diabetes: A clinical classification tool

Jacob V. Stidsen[1] | Jan E. Henriksen[1] | Michael H. Olsen[2] | Reimar W. Thomsen[3] | Jens S. Nielsen[1] | Jørgen Rungby[4,5] | Sinna P. Ulrichsen[3] | Klara Berencsi[3] | Johnny A. Kahlert[3] | Søren G. Friborg[1] | Ivan Brandslund[6] | Aneta A. Nielsen[6] | Jens S. Christiansen[7†] | Henrik T. Sørensen[3] | Thomas B. Olesen[1] | Henning Beck-Nielsen[1]

Coorte di 5813 pazienti danesi con neodiagnosi di diabete mellito.

Sottofenotipizzazione dei pazienti con diagnosi di DM2 secondo la definizione WHO in considerazione **della funzione beta cellulare (HOMA2B)** e dell'**insulino-sensibilità (IS) (HOMA2S)** valutate sulla base dei valori a digiuno di glicemia e peptide-C:

- **Diabete tipo 2 insulinopenico** (alta IS, bassa funzione beta-cellulare)
- **Diabete tipo 2 classico** (bassa IS, bassa funzione beta-cellulare)
- **Diabete di tipo 2 iperinsulinemico** (bassa IS, alta funzione beta-cellulare)

Diabete mellito tipo 2
una sola definizione tante «storie» di malattia

TABLE 1 Prevalence of pathophysiological phenotypes in 5,813 patients with new clinically diagnosed type 2 diabetes in Denmark, 2010-2015

Pathophysiological Phenotypes	Number of Patients, % (95% CI)
Patients with "other specific forms" of diabetes	
Rare subtypes	21, 0.4 (0.2, 0.5)
LADA	164, 2.8 (2.4, 3.2)
Secondary diabetes	43, 0.7 (0.5, 1.0)
Glucocorticoid-associated diabetes	140, 2.4 (2.0, 2.8)
Patients with WHO-defined type 2 diabetes	5,445, 93.8 (93.2, 94.5)
Insulinopenic type 2 diabetes	411, 9.6 (8.7, 10.5)
Classical type 2 diabetes	2,713, 63.3 (61.9, 64.8)
Hyperinsulinemic type 2 diabetes	1,161, 27.1 (25.8, 28.4)

Diabete mellito tipo 2: una sola definizione per tanti fenotipi

Review

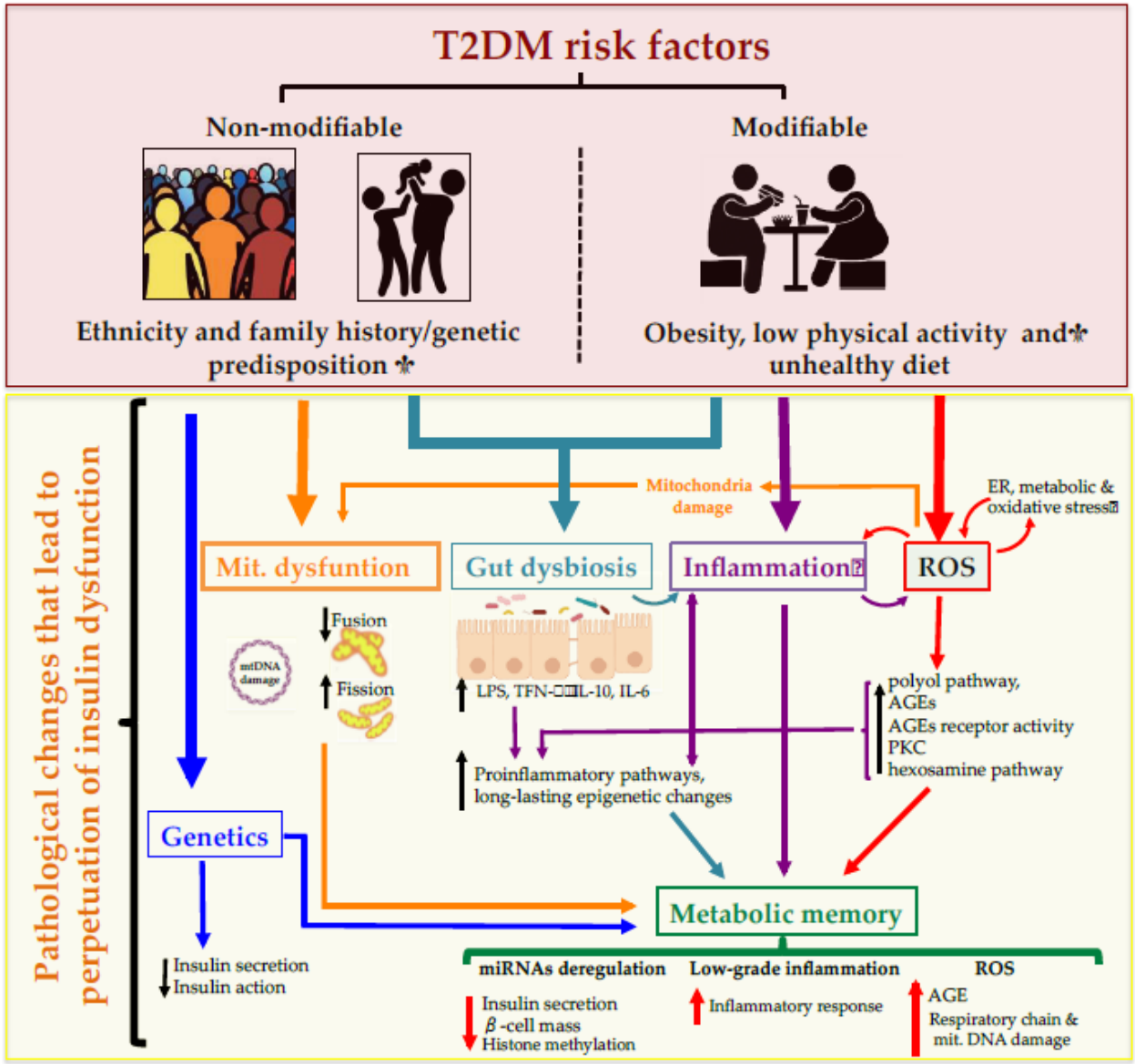
Pathophysiology of Type 2 Diabetes Mellitus

Unai Galicia-Garcia [1,2], Asier Benito-Vicente [2,3], Shifa Jebari [2,3], Asier Larrea-Sebal [1,2], Haziq Siddiqi [4], Kepa B. Uribe [5], Helena Ostolaza [2,3] and César Martín [2,3,*]

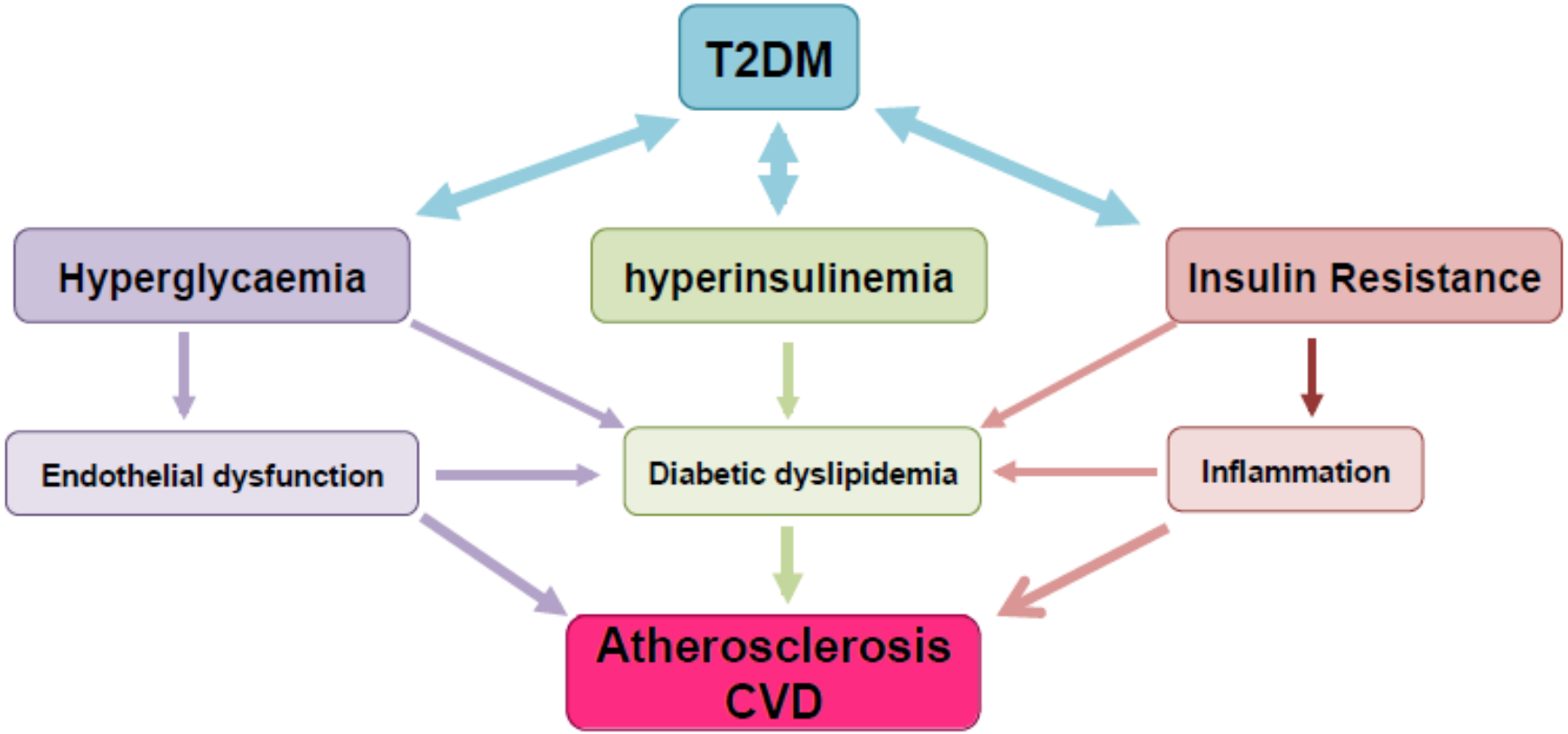
In summary, T2DM is a heterogeneous and progressive disorder that represents a series of metabolic conditions associated with hyperglycemia and caused by defects in insulin secretion and/or insulin action due to a complex network of pathological conditions. There are many different paths, driven by various genetic and environmental factors, that interact and mutually reinforce each other leading to an increased risk of other diseases including heart, peripheral arterial and cerebrovascular disease, obesity and nonalcoholic fatty liver disease, among others. The complex network of pathological conditions leading to T2DM development are summarized in Figure 2.

Int. J. Mol. Sci. **2020**, 21, 6275; doi:10.3390/ijms21176275

Diabete mellito tipo 2: una sola definizione per tanti fenotipi



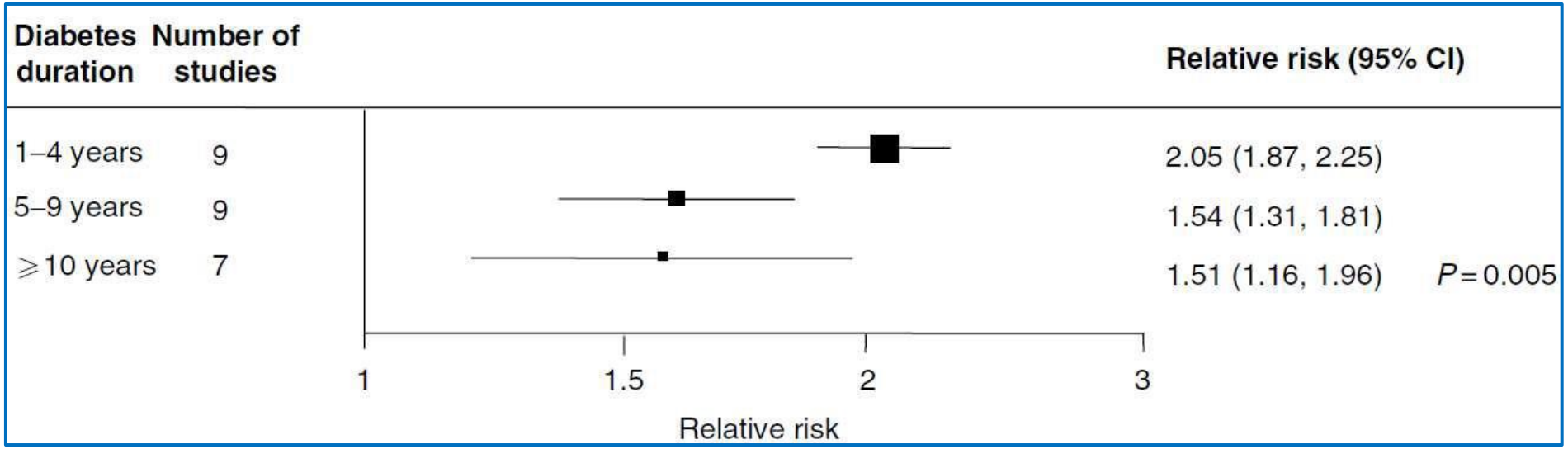
Diabete mellito tipo 2: una sola definizione per tanti fenotipi



Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies

R Huxley*[,1], A Ansary-Moghaddam[1], A Berrington de González[2], F Barzi[1] and M Woodward[1]

Prima il diabete o prima la neoplasia?



greater risk of the malignancy compared with individuals who had diabetes for ⩾5 years (OR 2.1 *vs* 1.5; $P = 0.005$). These results support a modest causal association between type-II diabetes and pancreatic cancer.

British Journal of Cancer (2005) 92, 2076–2083

Insulin Resistance and Cancer-Specific and All-Cause Mortality in Postmenopausal Women: The Women's Health Initiative

Conclusions: High insulin resistance, as measured by HOMA-IR, identifies postmenopausal women at higher risk for cancer-specific and all-cause mortality who could potentially benefit from early intervention.

Kathy Pan, Rebecca A. Nelson, Jean Wactawski-Wende, Delphine J. Lee, JoAnn E. Manson, Aaron K. Aragaki, Joanne E. Mortimer, Lawrence S. Phillips, Thomas Rohan, Gloria Y. F. Ho, Nazmus Saquib, Aladdin H. Shadyab, Rami Nassir, Jinnie J. Rhee, Arti Hurria, Rowan T. Chlebowski

JNCI J Natl Cancer Inst (2020) 112(2): djz069

. Future studies could explore the potential relationship of these findings to the closely related concept of the "metabolically obese, normal weight" or "metabolically unhealthy, normal weight" state, which has also been associated with increased cancer mortality (32).

32. Akinyemiju T, Moore JX, Pisu M, et al. A prospective study of obesity, metabolic health, and cancer mortality. *Obesity (Silver Spring)*. 2018;26(1):193–201.

Mortality after cancer among patients with diabetes mellitus: effect of diabetes duration and treatment

Kristina Ranc · Marit E. Jørgensen · Søren Friis · Bendix Carstensen

Diabetologia 2014

Conclusions/interpretation Our study provides strong evidence that cancer patients with pre-existing diabetes experience higher mortality than cancer patients without diabetes. The higher mortality seen among cancer patients treated with OHAs or insulin is in accordance with the existing evidence that more intensive diabetes treatment reflects a larger degree of comorbidity at the time of cancer diagnosis, and hence poorer survival.

Diabete mellito tipo 1:
una sola definizione per tante storie di malattia

TABLE 1 | Staging of Type 1 Diabetes according to JDRF, the Endocrine Society, and the American Diabetes Association (4).

Stage 1	Stage 2	Stage 3
Beta cell autoimmunity	Beta cell autoimmunity	Beta cell autoimmunity
Normoglycemia	Dysglycemia	Dysglycemia
Presymptomatic	Presymptomatic	Symptomatic

Diabete mellito tipo 1:
una sola definizione per tante storie di malattia

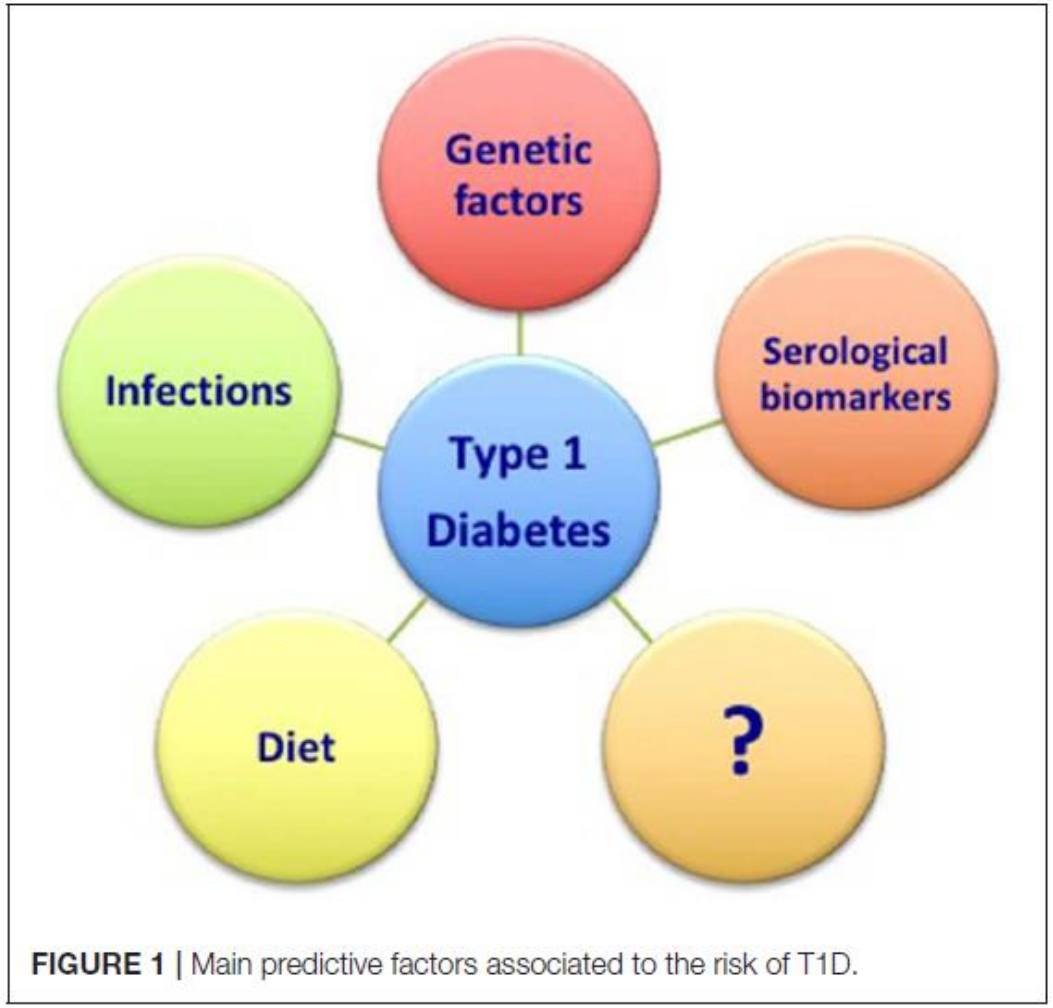


FIGURE 1 | Main predictive factors associated to the risk of T1D.

Molti studi sono in corso per prevenire

sia il Diabete Mellito tipo 1

che il Diabete Mellito tipo 2

Curare il Diabete Mellito

- Educazione alimentare
- Attività fisica
- Precoce identificazione e trattamento farmacologico atto a prevenire lo sviluppo delle complicanze a breve e lungo termine
- Medicina di precisione per identificare sulla base del fenotipo oggi (del genotipo domani ?) le terapia più appropriate sicuramente per il diabete mellito tipo 2 ma forse domani anche per il tipo 1

Curare il
Diabete Mellito tipo 1

Allo stato attuale non esiste una cura

Esiste una terapia complicata che consente al paziente di vivere (bene)

Insulina esogena

Metodi iniettivi:

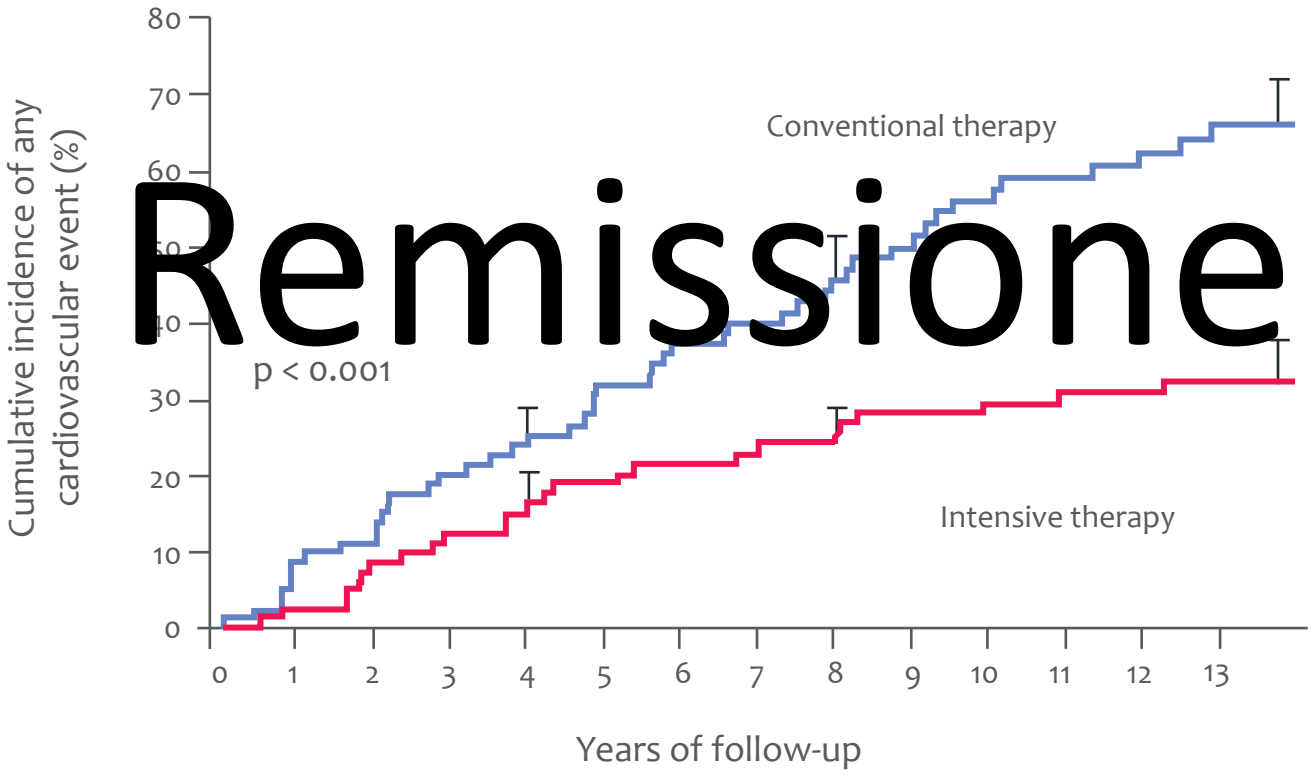
siringhe, penne, microinfusori, hybrid closed loop

In corso tante ricerche per una cura definitiva

Senza di dimenticare dislipidemia, pressione arteriosa, peso corporeo….

Curare il
Diabete Mellito tipo 2

Steno-2: Intensive multifactorial control of CV risk factors continues to reduce CV risk over long-term follow-up

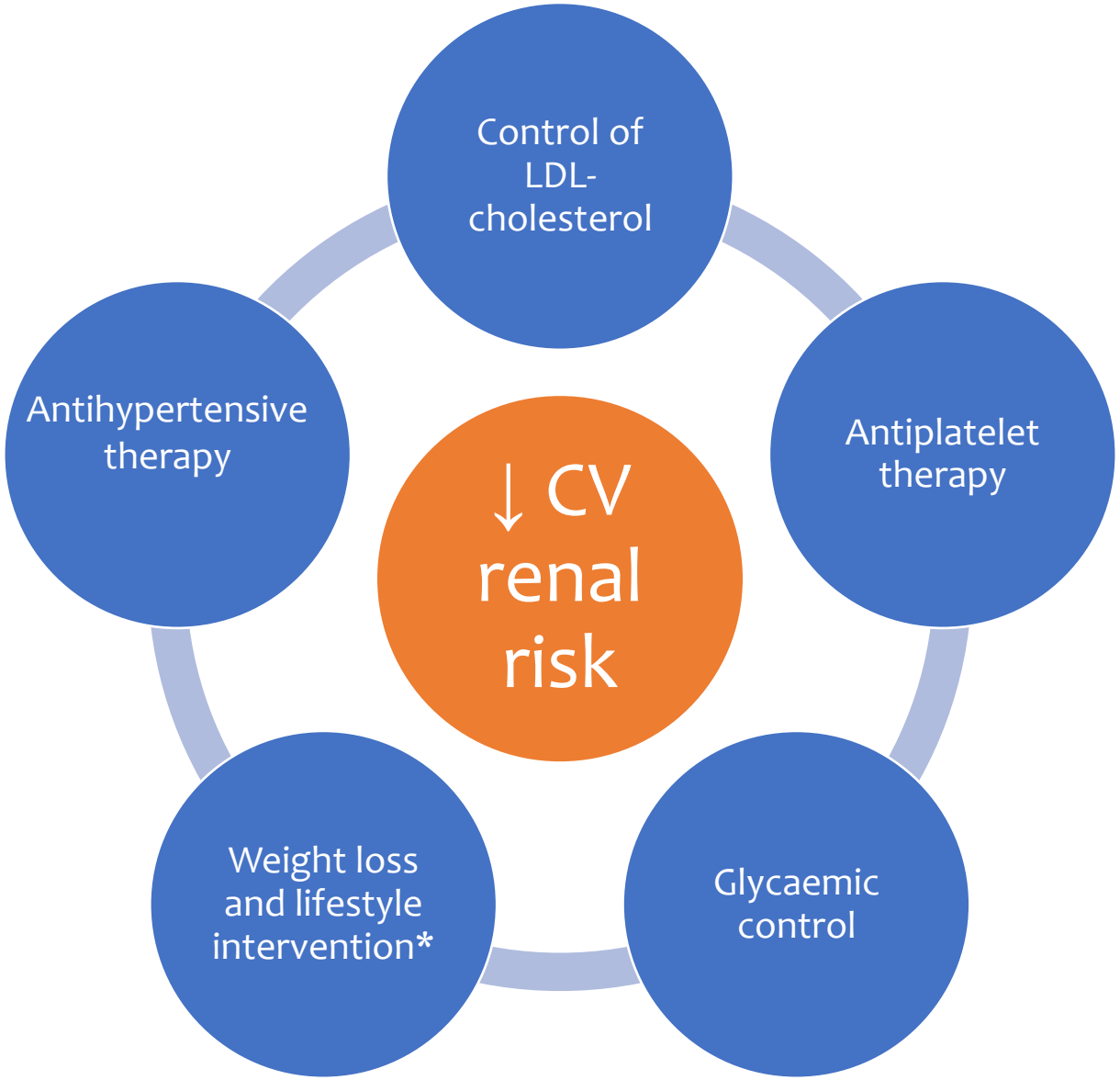


Remissione

-

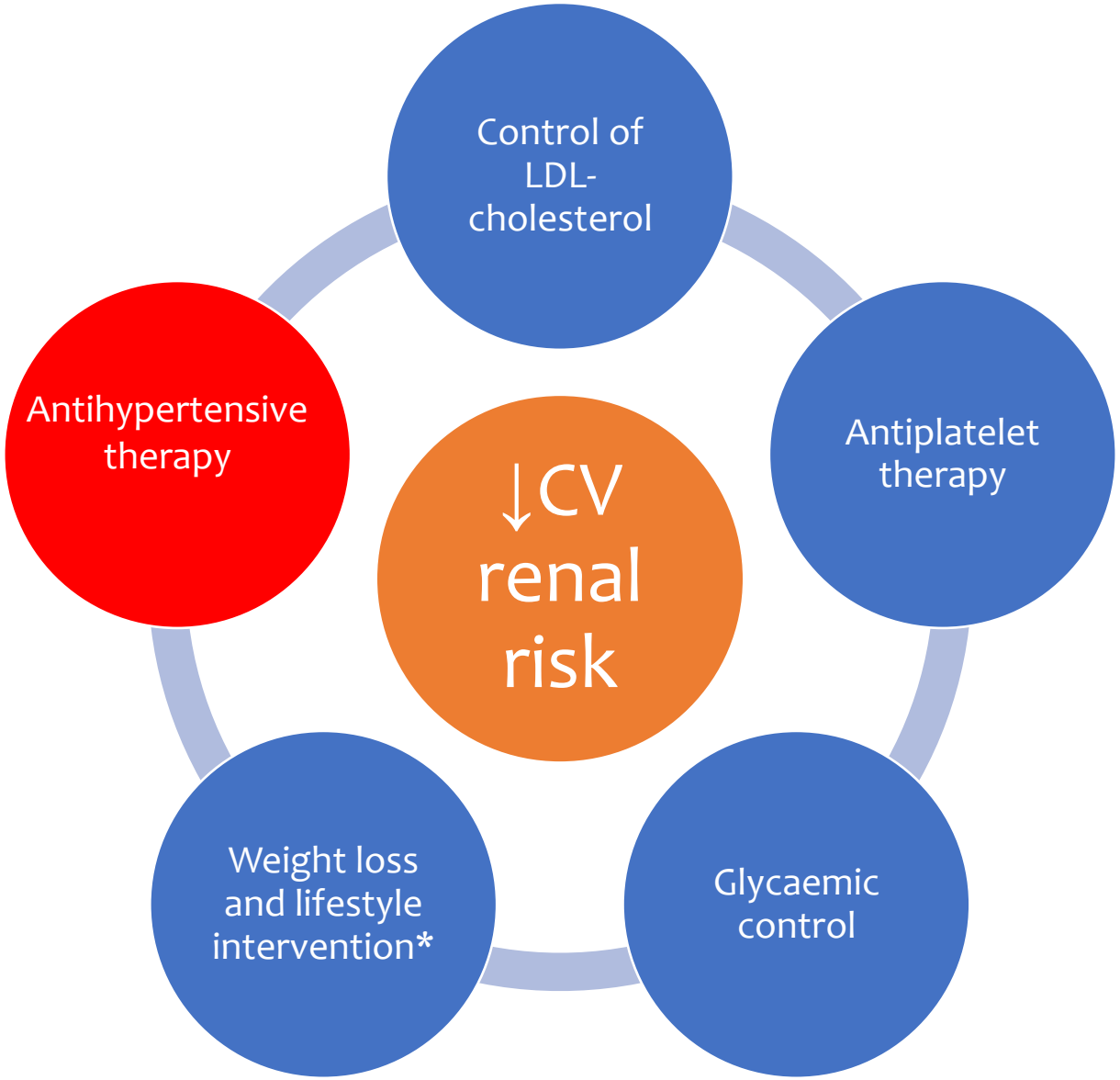
Gaede et al. N Engl J Med 2008;358:580–91.

Gestione del Diabete Mellito tipo 2



- *Includes smoking cessation.
  Rydén et al. Eur Heart J 2013;34:3035–87.

Management of CV renal risk factors



- *Includes smoking cessation.
  Rydén et al. Eur Heart J 2013;34:3035–87.

Controllo della pressione arteriosa

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38

UK Prospective Diabetes Study Group

Clinical end point	Patients with aggregate end points: Tight control (n=758)	Patients with aggregate end points: Less tight control (n=390)	Absolute risk (events per 1000 patient years): Tight control	Absolute risk (events per 1000 patient years): Less tight control	P value	Relative risk for tight control (95% CI)
Any diabetes related end point	259	170	50.9	67.4	0.0046	0.76 (0.62 to 0.92)
Deaths related to diabetes	82	62	13.7	20.3	0.019	0.68 (0.49 to 0.94)
All cause mortality	134	83	22.4	27.2	0.17	0.82 (0.63 to 1.08)
Myocardial infarction	107	69	18.6	23.5	0.13	0.79 (0.59 to 1.07)
Stroke	38	34	6.5	11.6	0.013	0.56 (0.35 to 0.89)
Peripheral vascular disease	8	8	1.4	2.7	0.17	0.51 (0.19 to 1.37)
Microvascular disease	68	54	12.0	19.2	0.0092	0.63 (0.44 to 0.89)

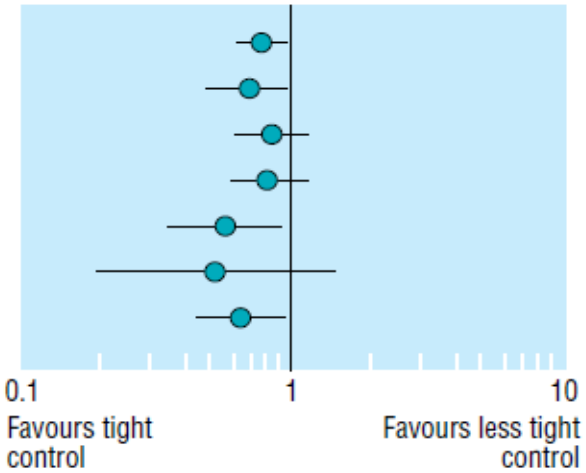


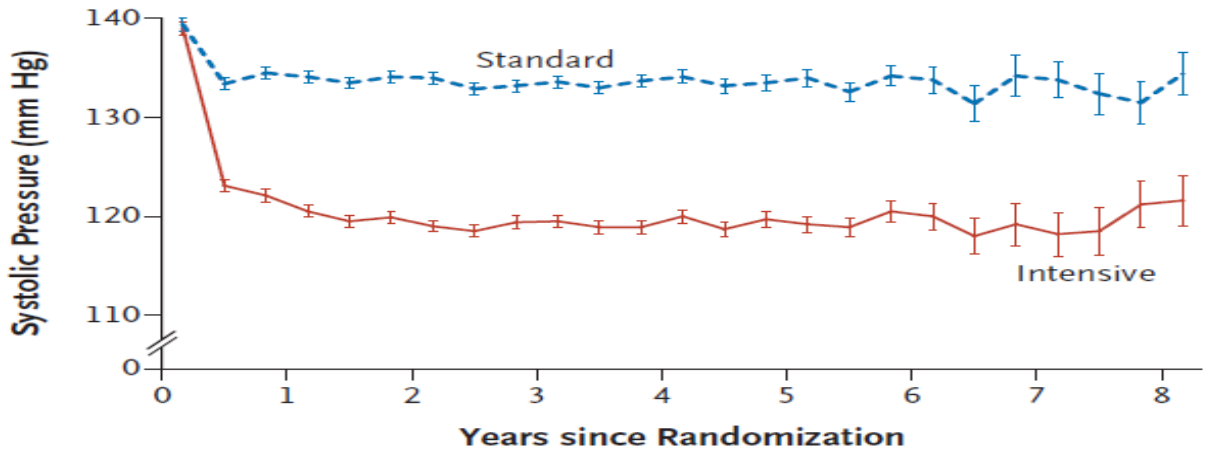
Fig 4 Numbers of patients who attained one or more clinical end points in aggregates representing specific types of clinical complications, with relative risks comparing tight control of blood pressure with less tight control

BMJ 1998;317:703–13

Controllo della pressione arteriosa

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

Figure 1. Mean Systolic Blood-Pressure Levels at Each Study Visit.

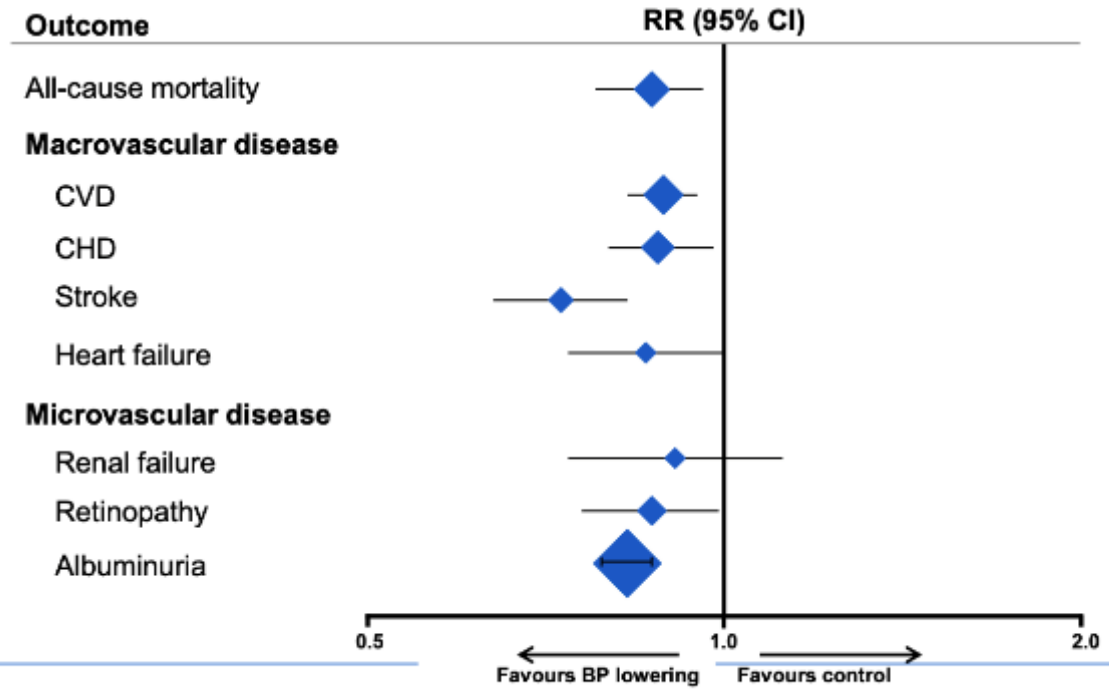
I bars indicate 95% confidence intervals.

N Engl J Med 2010;362:1575-85.

Controllo della pressione arteriosa

10 mmHg reduction in SBP reduces all-cause mortality and macrovascular and microvascular outcomes in Type 2 diabetes

- Meta-analysis of 40 large-scale, randomised, controlled trials of BP-lowering treatment including patients with diabetes (n=100,354 participants)



iP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease; RR, relative risk; SBP, systolic blood pressure
:mdin CD, et al. *JAMA* 2015;313:603–615

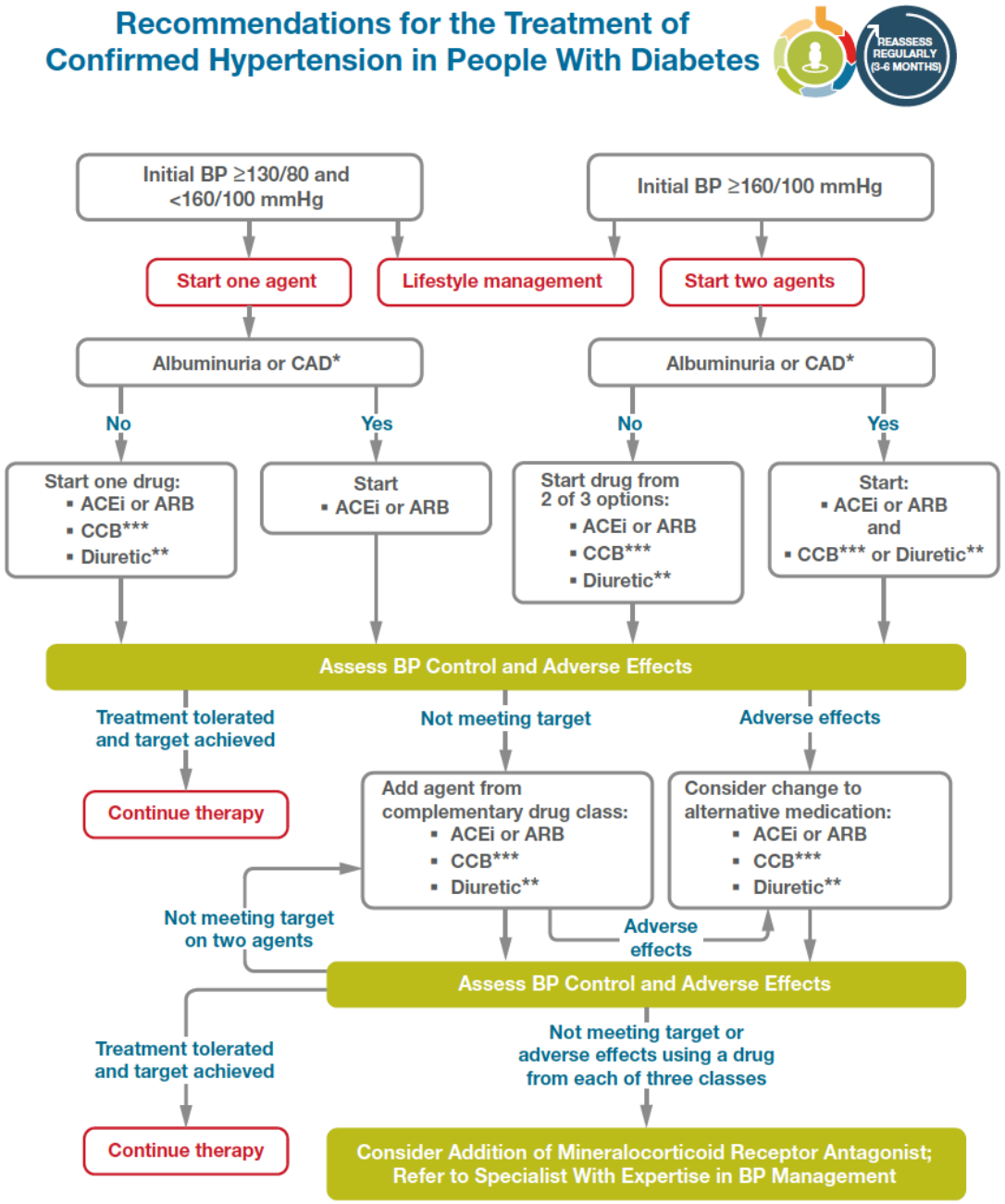
Imperial College London

ADA Standard of care 2023

Diagnosis:
PAS **≥130** mmHg
or
PAD **≥80** mmHg
(≥2 meas. on ≥2 occasions)

Target
on-treatment BP goal is
<130/80 mmHg
(if it can be safely attained)
(<120/80 mmHg unsafe)

PAS = 120-130



Use these drugs

ACEi/ARBs
CCBs
(Dihydrop.)
Diuretics
(Indap/chlort. preferred)
MRA

ßBlockers
indicated only if prior
MI
Angina
HfrEF

(have not been shown to reduce mortality in the absence of these conditions)

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

Table 23 **Office blood pressure treatment target range**

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
≤ 65aa	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	**Target to <140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	70–79
65-79 aa	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
≥80 aa	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

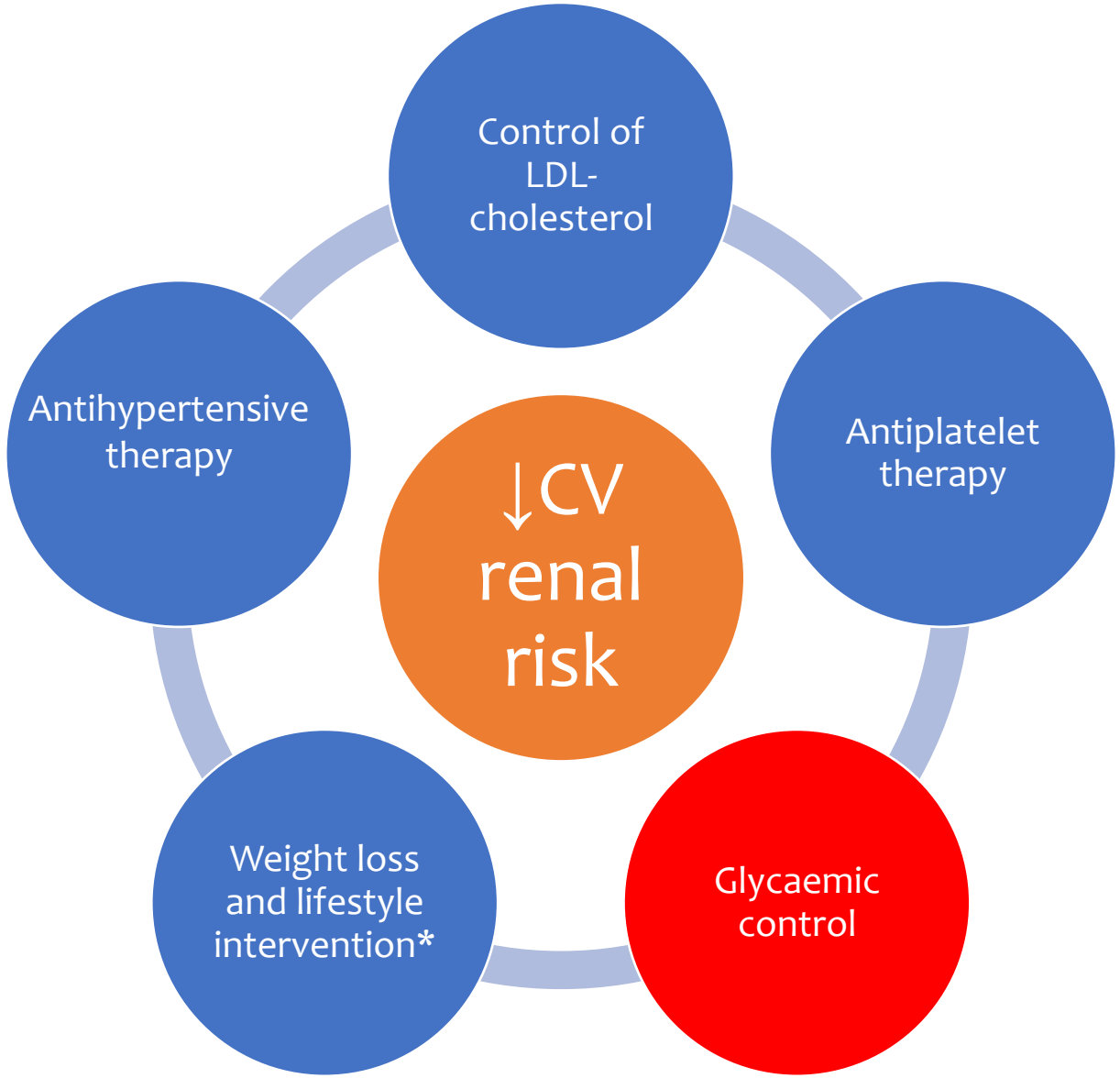
©ESC/ESH 2018

CAD = coronary artery disease; CKD = chronic kidney disease (includes diabetic and non-diabetic CKD); DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

[a]Refers to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.

[b]Treatment decisions and blood pressure targets may need to be modified in older patients who are frail and independent.

Management of CV renal risk factors



- *Includes smoking cessation.
  Rydén et al. Eur Heart J 2013;34:3035–87.

GLUCOSE CONTROL

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

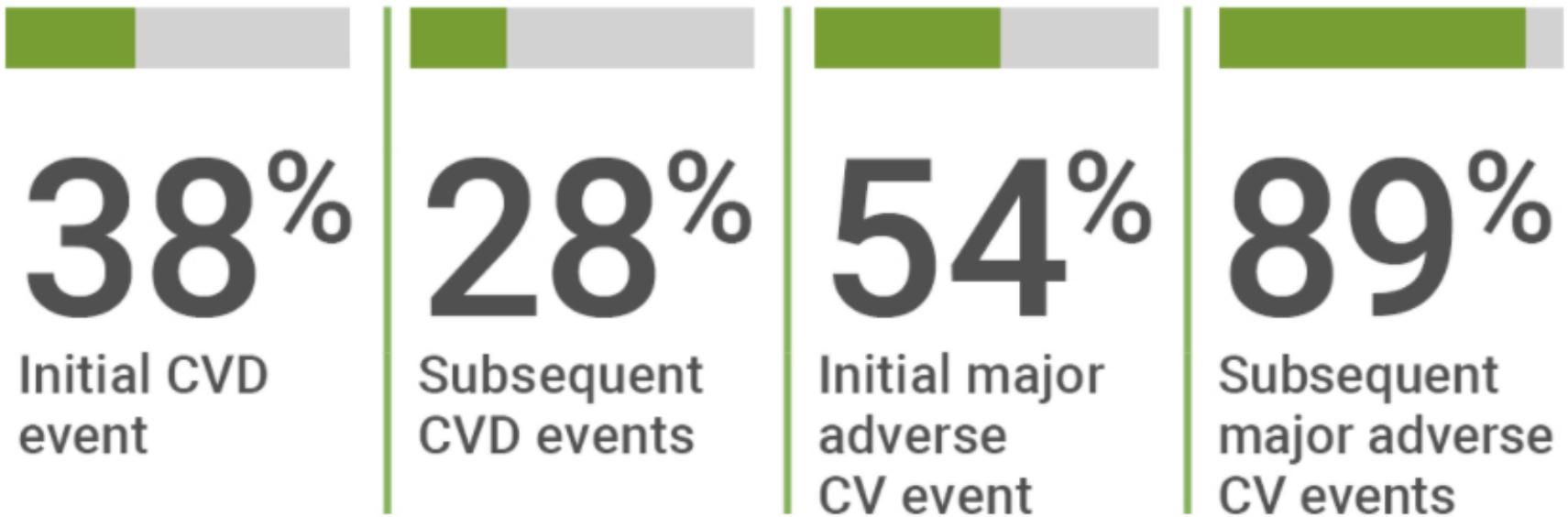
After median 8.5 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	9%
	P:	0.029	0.040
Microvascular disease	*RRR:*	25%	24%
	P:	0.0099	0.001
Myocardial infarction	*RRR:*	16%	15%
	P:	0.052	0.014
All-cause mortality	*RRR:*	6%	13%
	P:	0.44	0.007

RRR = Relative Risk Reduction, P = Log Rank

N Engl J Med 2008;359:1577-89.

Increase in cardiovascular event risks for each 1% increase in HbA1c:

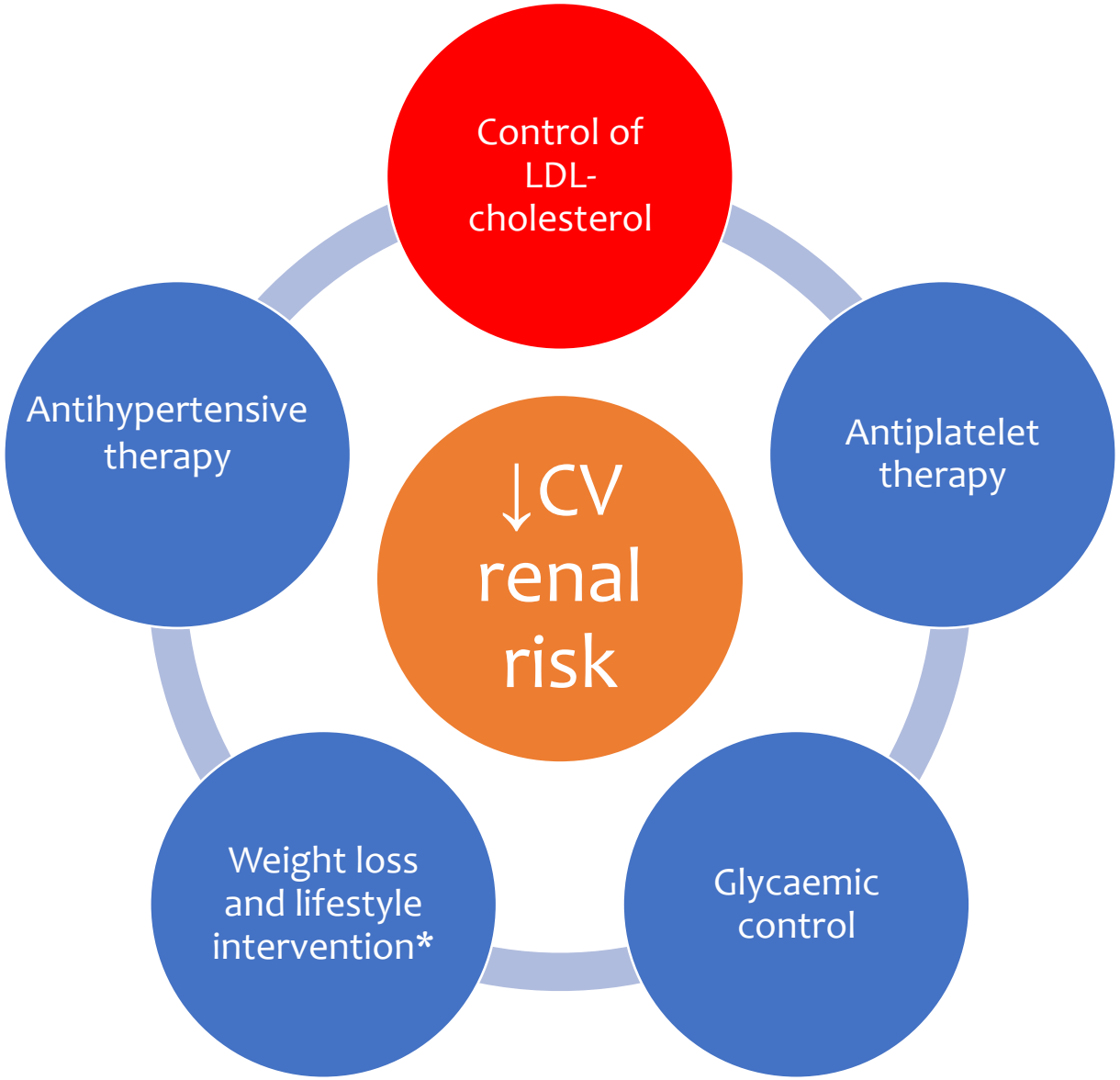


GLUCOSE CONTROL

Udell JA et al: Lancet DE 3:356, 2015

Trials included: UKPDS, PROactive, ADOPT, DREAM, ACCORD, ADVANCE, BARI2D, RECORD, VADT, ORIGIN, EXAMINE, Look-AHEAD, SAVOR-TIMI 53, AleCardio

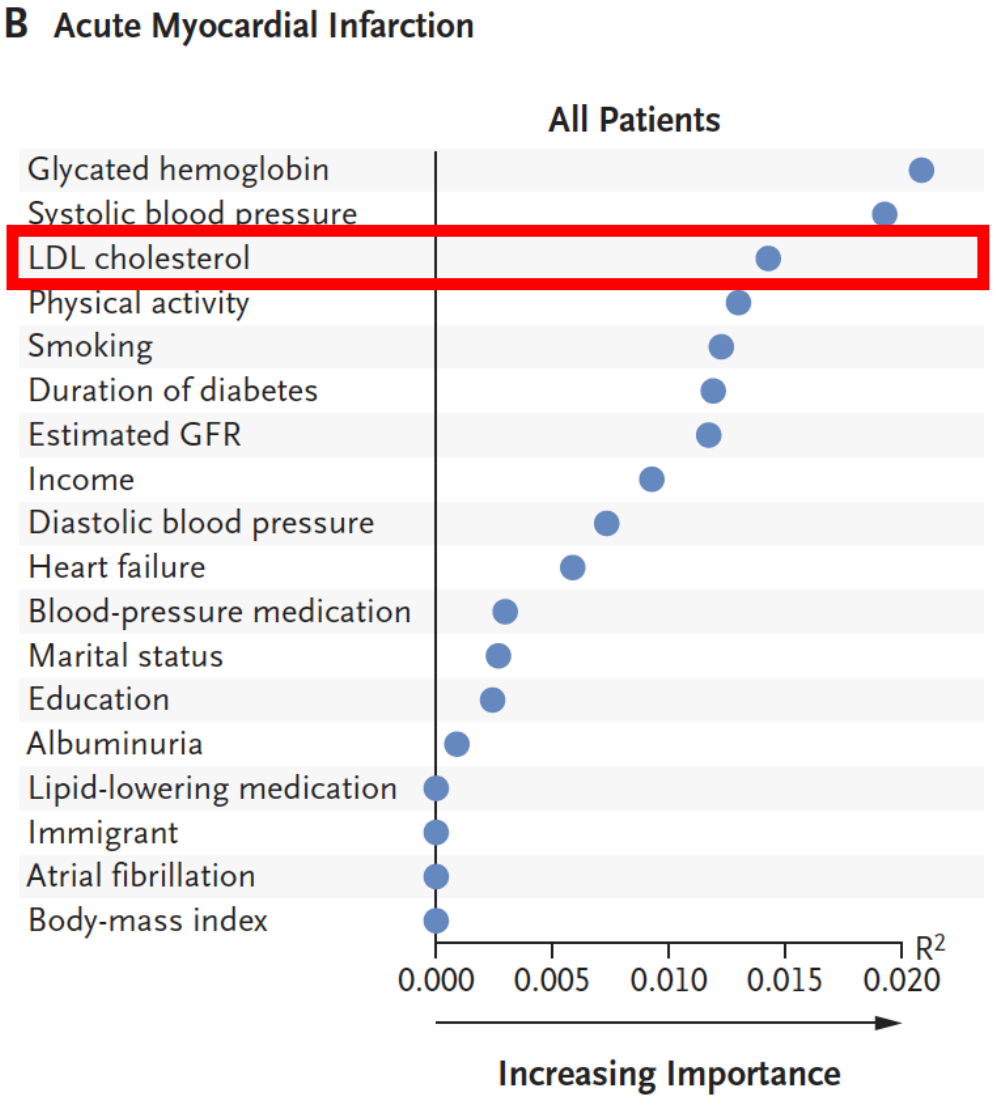
Management of CV risk factors



- *Includes smoking cessation.
  Rydén et al. Eur Heart J 2013;34:3035–87.

LDL cholesterol control

Relative Importance of Risk Factors for Predicting Death from Acute Myocardial Infarction, among Patients with Type 2 Diabetes



Rawshani et al. NEJM 2018

LDL Chol CONTROL

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

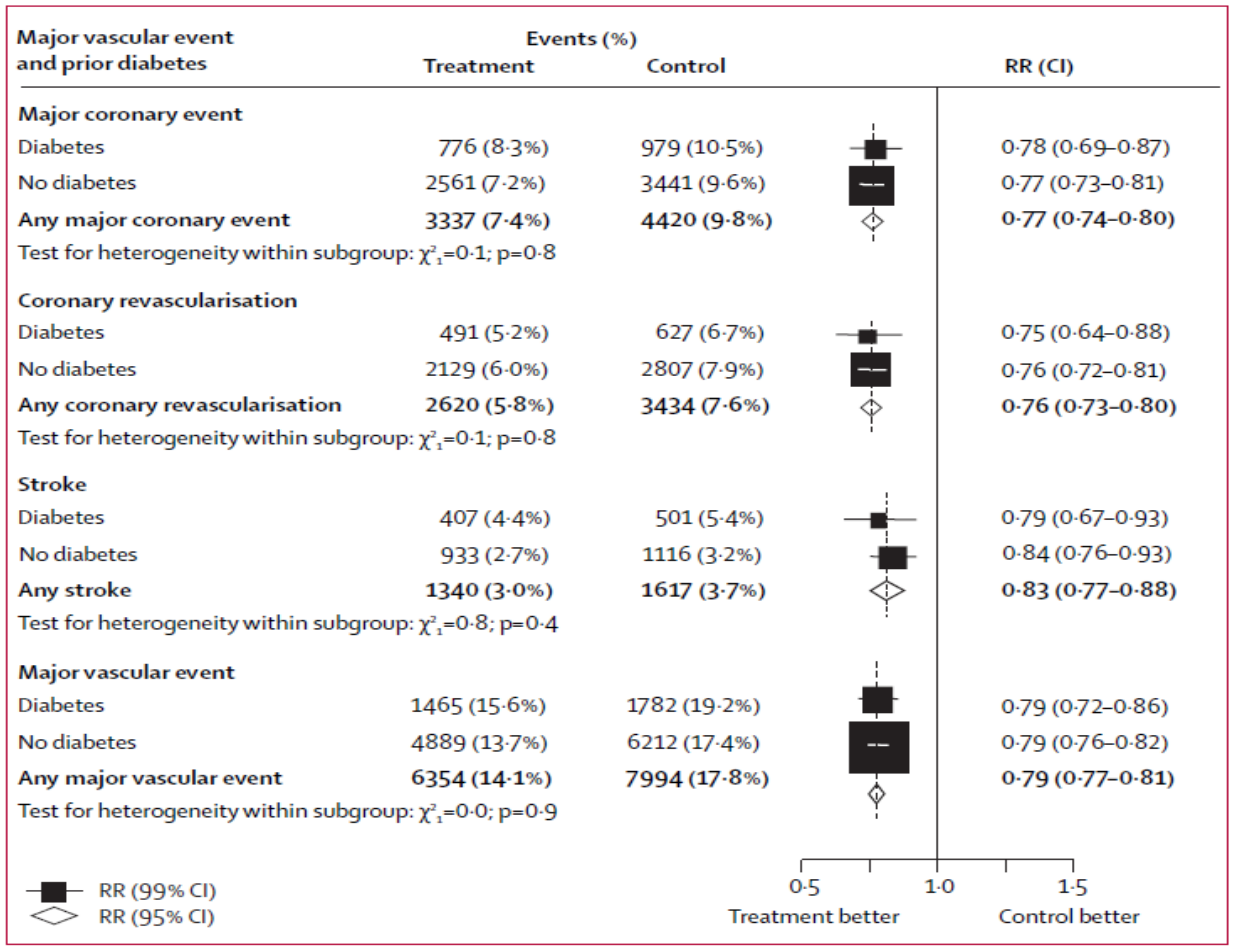
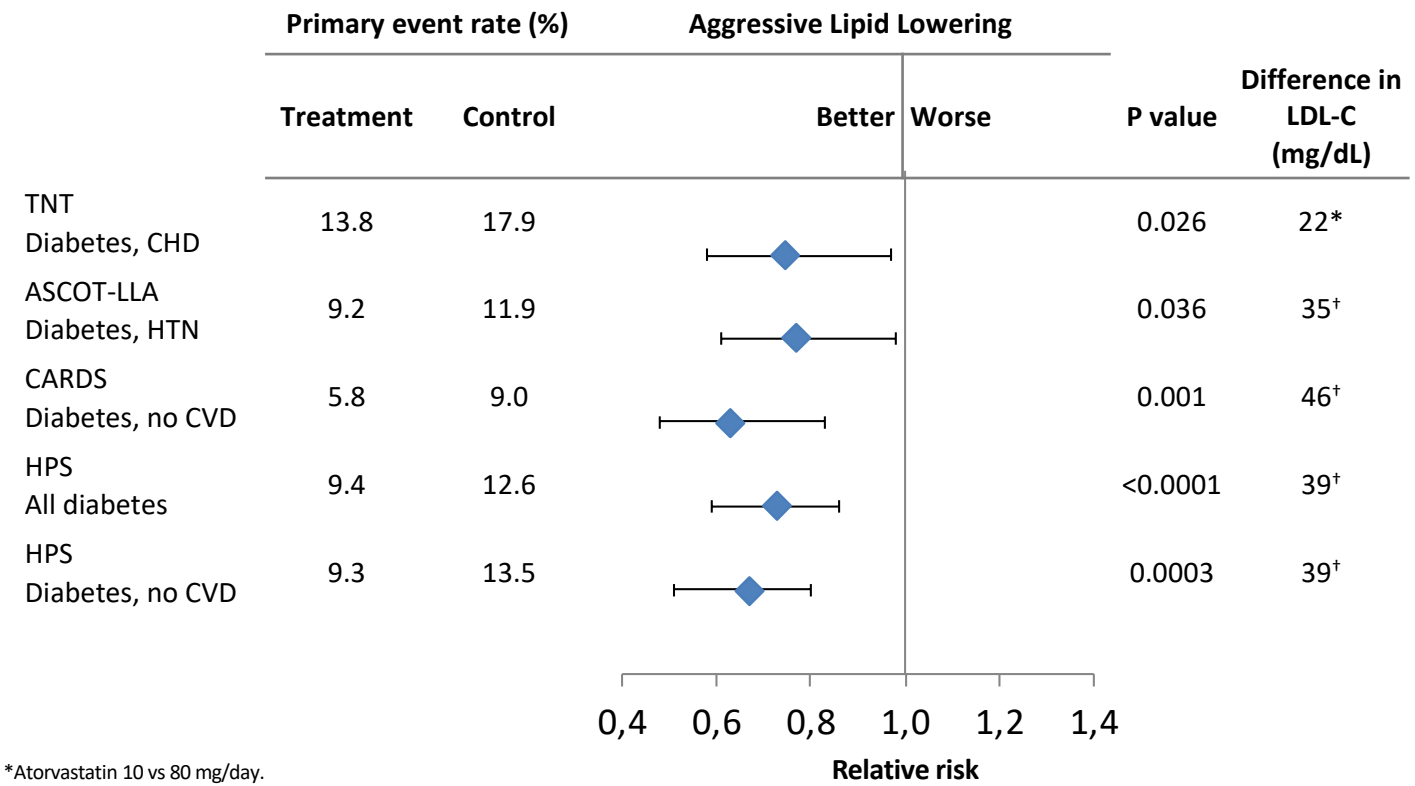


Figure 2: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes**

Lancet 2008; 371: 117–25

LDL cholesterol control

Benefits of Aggressive LDL-C Lowering in Diabetes



*Atorvastatin 10 vs 80 mg/day.
†Statin vs placebo.

Shepherd J, et al. *Diabetes Care.* 2006;29:1220-1226. Sever PS, et al. *Diabetes Care.* 2005;28:1151-1157.
Colhoun HM, et al. *Lancet.* 2004;364:685-696. HPS Collaborative Group. *Lancet.* 2003;361:2005-2016.

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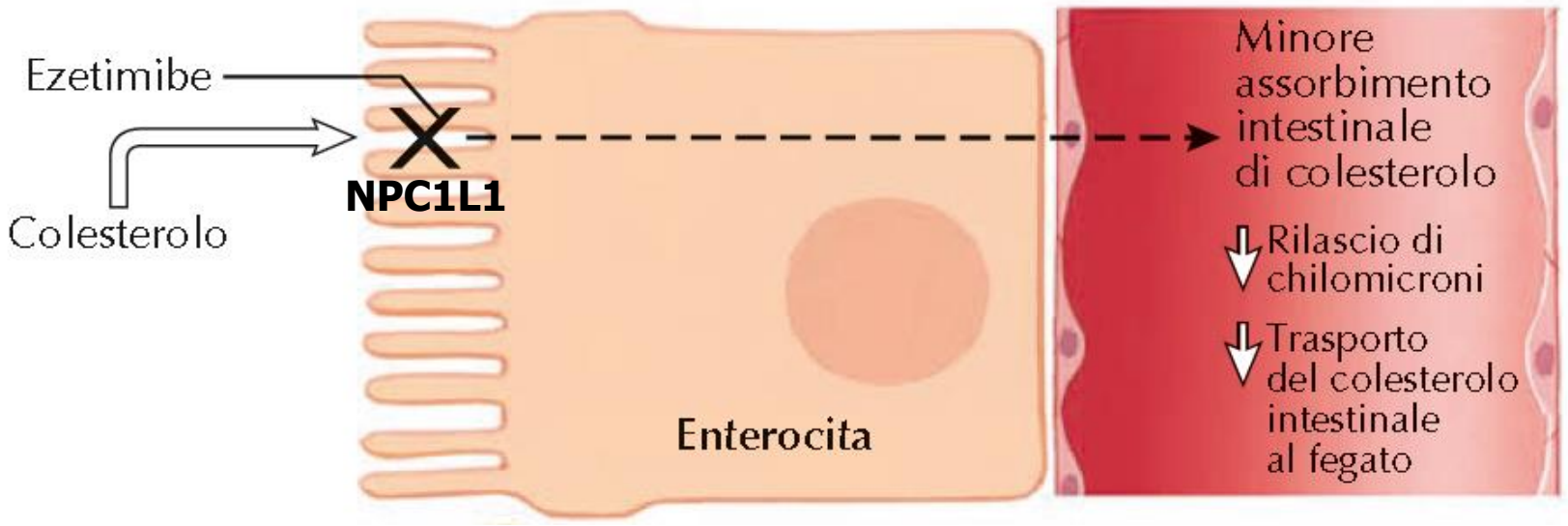
Pharmacologic therapy for Hypercholesterolemia
Cholesterol Absorption Inhibitors

- **Cholesterol within the lumen of the small intestine is derived from the diet (about one-third) and the bile (about two-thirds) and is actively absorbed by the enterocyte through a process that involves the protein Niemann-Pick C1 Like 1 Protein (NPC1L1).**
- **Ezetimibe is a cholesterol absorption inhibitor that binds directly to and inhibits NPC1L1 and blocks the intestinal absorption of cholesterol.**

Ezetimibe.
Si localizza a livello dell'orletto a spazzola dell'intestino. Blocca l'assorbimento del colesterolo intestinale



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

Cardiovascular risk categories in patients with diabetes

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.

Cosentino F. et al European Heart Journal 41(2):255-323, 2020

Cardiovascular disease and risk management: ADA Standards of Care in Diabetes—2023

Primary Prevention (People Without ASCVD)

10.20 For people with diabetes aged 40–75 at higher cardiovascular risk, including those with one or more atherosclerotic cardiovascular disease risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by ≥50% of baseline and to target an LDL cholesterol goal of <70 mg/dL. **B**

10.21 For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple atherosclerotic cardiovascular disease risk factors and an LDL cholesterol ≥70 mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **C**

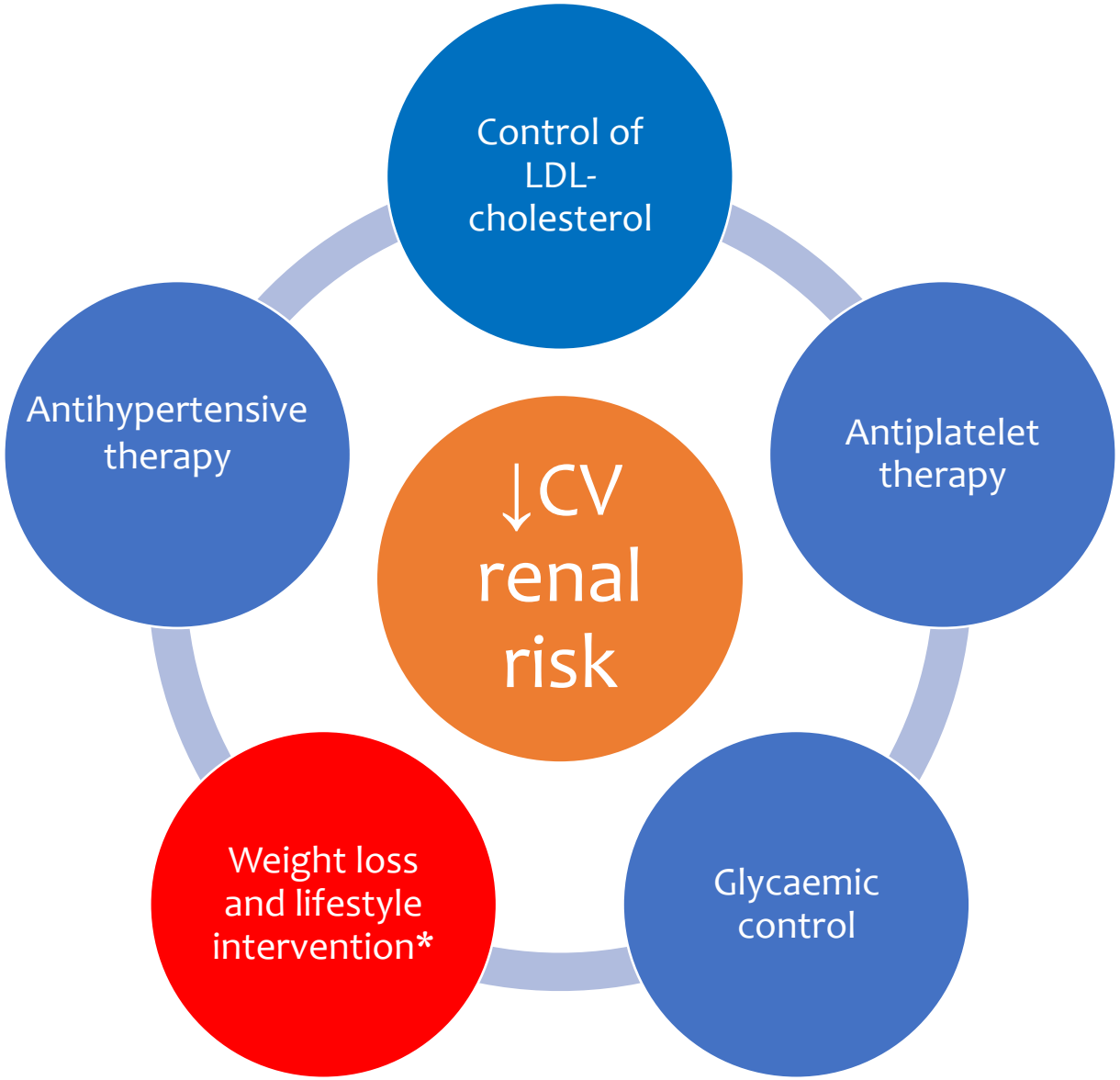
Secondary Prevention (People With ASCVD)

10.25 For people of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.26 For people with diabetes and atherosclerotic cardiovascular disease, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL. Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. **B**

Diabetes Care 46(Suppl. 1):S158–S190, 2023

Management of CV renal risk factors



- *Includes smoking cessation.
  Rydén et al. Eur Heart J 2013;34:3035–87.

Trattamento dell’obesità nel paziente con diabete mellito tipo 2

Annali AMD 50% dei pazienti con Diabete Mellito tipo 2 sono obesi !

Stile di vita Sedentario? Metabolicamente inattivo ?

Dieta chetogenica ? Mediterranea? Vegetariana? Digiuno intermittente?

10000 passi ? 30 minuti ? 1 ora ? Aerobico? Anaerobico?

Sedentario? Metabolicamente inattivo ?

Trattamento farmacologico

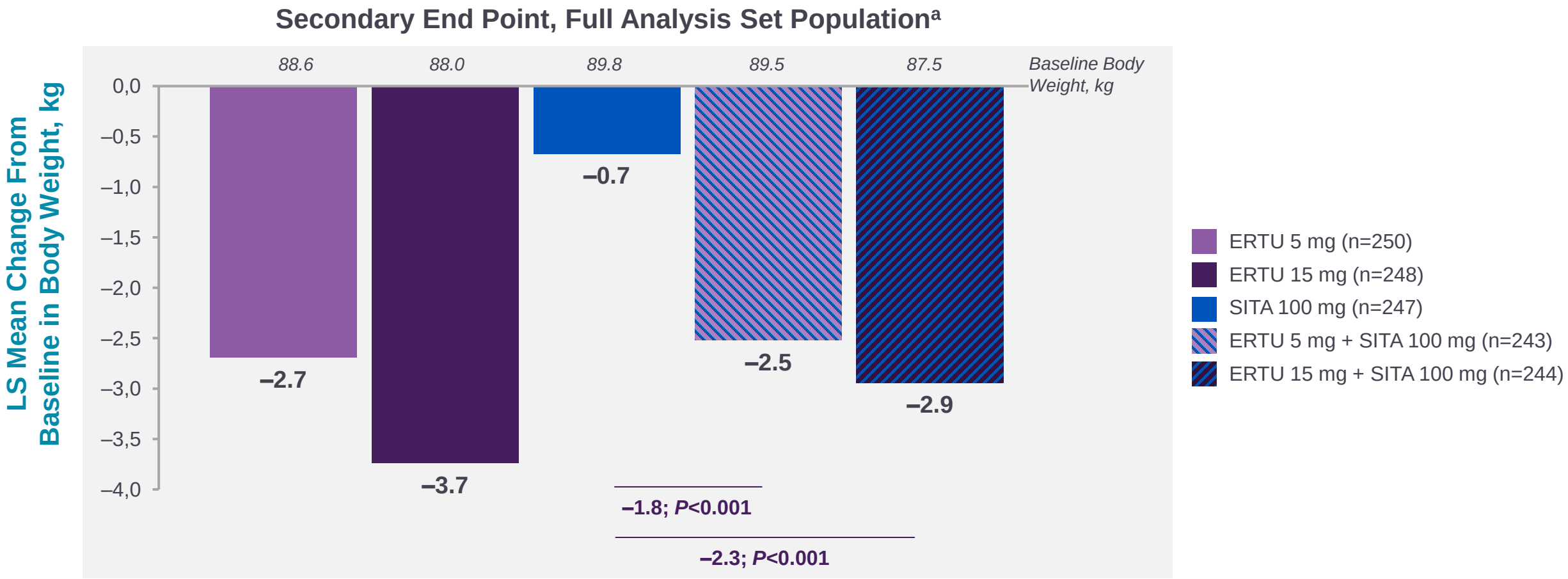
aGLP 1

iSLT2

In associazione

Chirurgia Bariatrica? Chirurgia Metabolica ?

VERTIS FACTORIAL: Reductions in Body Weight at Week 26[1]



Ertugliflozin is not indicated for body weight reduction.

[a]The population includes all randomized, treated patients who had at least 1 measurement of the outcome variable (baseline or post-baseline).

LS = least-squares; ERTU = ertugliflozin; SITA = sitagliptin.

1. Pratley RE et al. *Diabetes Obes Metab*. 2018;20:1111–1120.

Se la diagnosi di Diabete è relativamente facile

le sfide sono tante

dalla prevenzione al trattamento alla remissione

per garantire qualità e durata di vita

auspicando la cura definitiva !

Grazie !