

con il patrocinio di



# *Percorsi in diabetologia: dai target ai benefici per la persona con diabete*

Percorsi terapeutici della U.O.C. Medicina Interna  
ad indirizzo Diabetologico DACP - AUSL Modena



**24 Settembre 2022**  
**Modena**

RMH DES ARTS Hotel  
Via Luigi Settembrini, 10

*Percorsi in diabetologia:  
dai target ai benefici  
per la persona con diabete*

Percorsi terapeutici della U.O.C. Medicina Interna  
ad indirizzo Diabetologico DACP - AUSL Modena



# Inquadramento del rischio cardiovascolare nella persona con diabete tipo 2

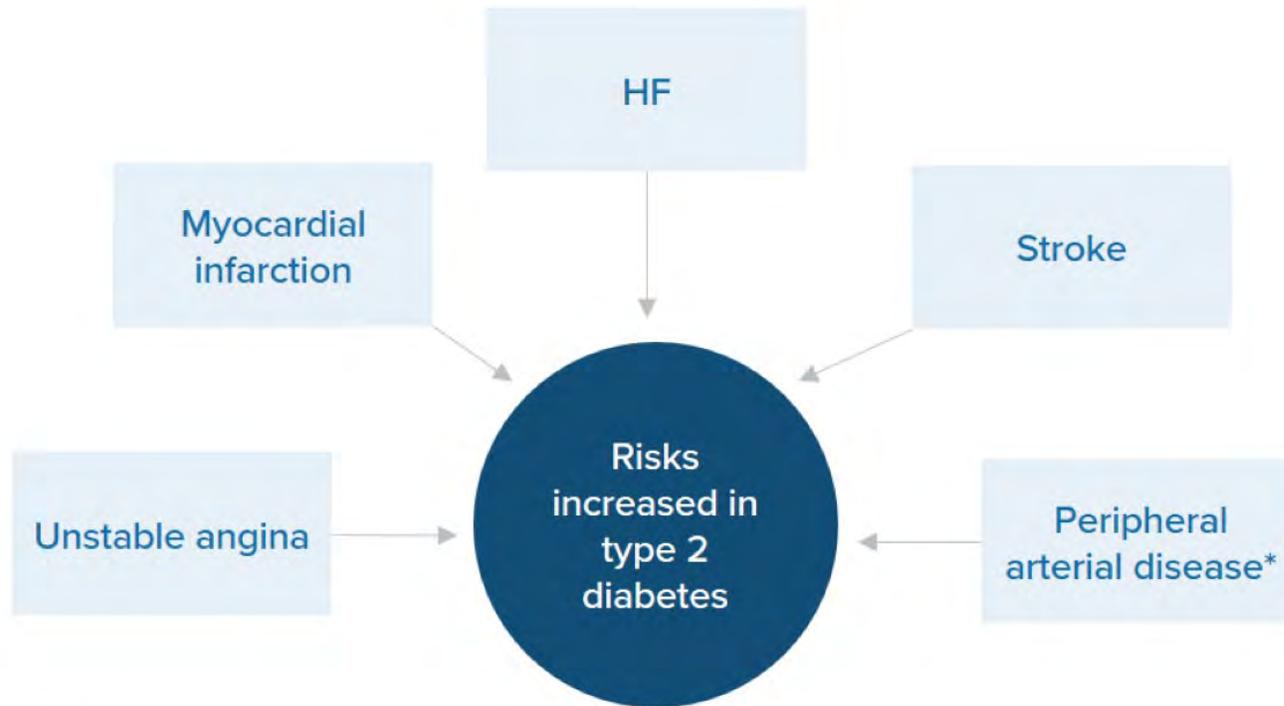
**Marcello Monesi**

**UOC Diabetologia Territoriale**

**AUSL Ferrara**

# Patologia cardiovascolare e diabete

## Increased Risk of CV Complications in Type 2 Diabetes



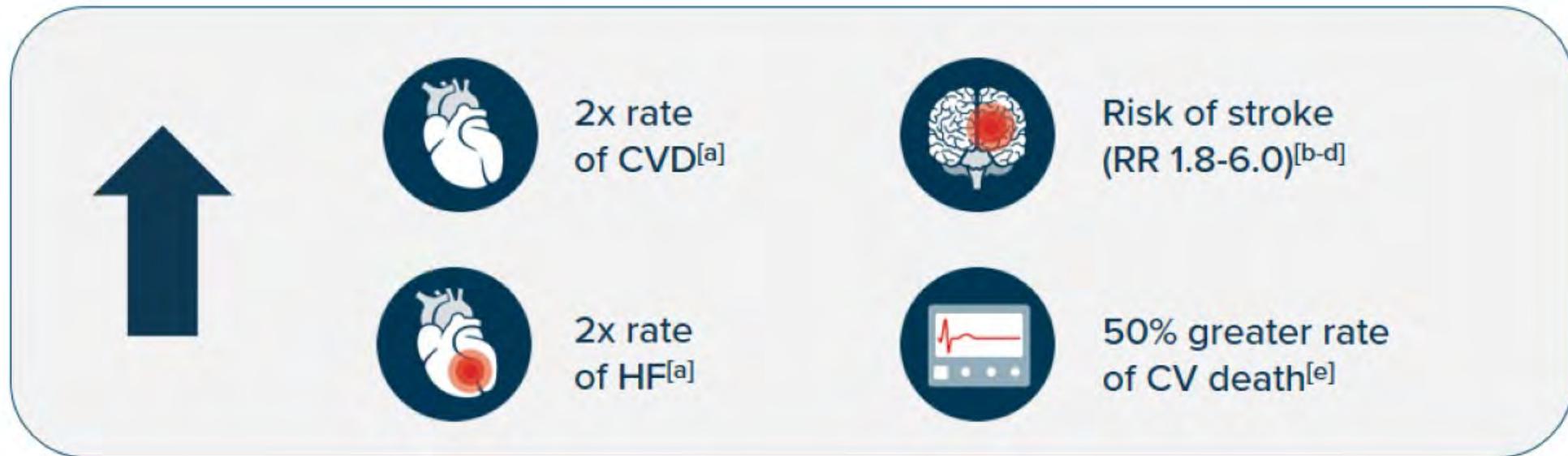
\*Corresponding to a 1% increase in HbA1c.

CV, cardiovascular; HbA1c, glycated hemoglobin; HF, heart failure.

Shah AD, et al. Lancet Diabetes Endocrinol. 2015;3:105-113; Thiruvoipati T, et al. World J Diabetes 2015;6:961-969.



# CVD Is the Leading Cause of Death in Adults With T2D

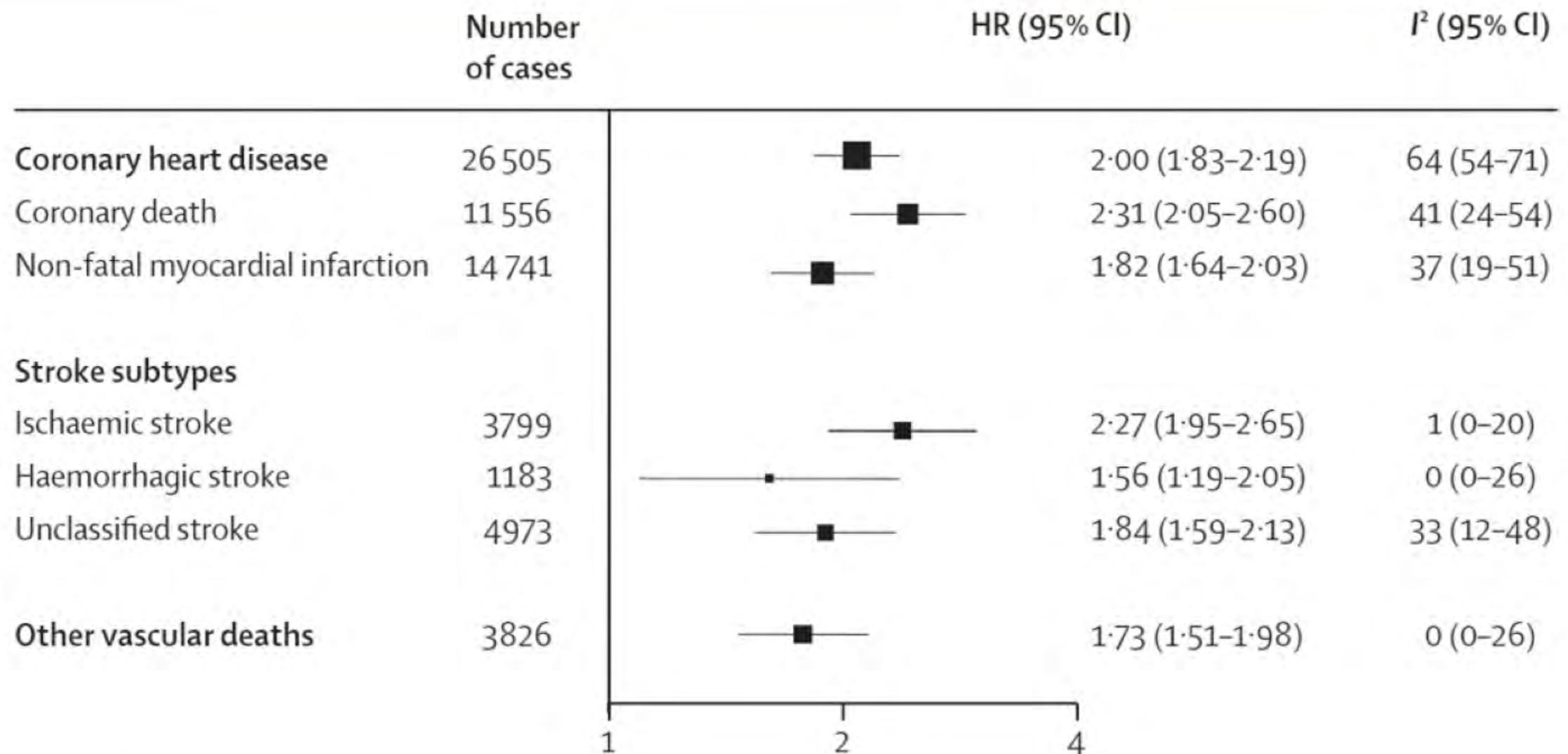


CV, cardiovascular; CVD, cardiovascular disease; RR, relative risk.

a. Go AS, et al. *Circulation*. 2014;129:e28-e292. b. Folsom AR, et al. *Diabetes Care*. 1999;22:1077-1083; c. Pyörälä M, et al. *Stroke*. 1998;29:1860-1866; d. Kuusisto J, et al. *Stroke*. 1994;25:1157-1164; e. Franco OH, et al. *Arch Intern Med*. 2007;167:1145-1151.

These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.

# Hazard Ratios for Vascular Outcomes in People With vs Without Diabetes



# Diabetes and CVD

## *Identify Risk and Treat to Prevent CV Outcomes*

**Presence of diabetes associated with increased risk of death from any cause, death from CV cause, death from CHD, and hospitalization for CVD<sup>[a]</sup>**

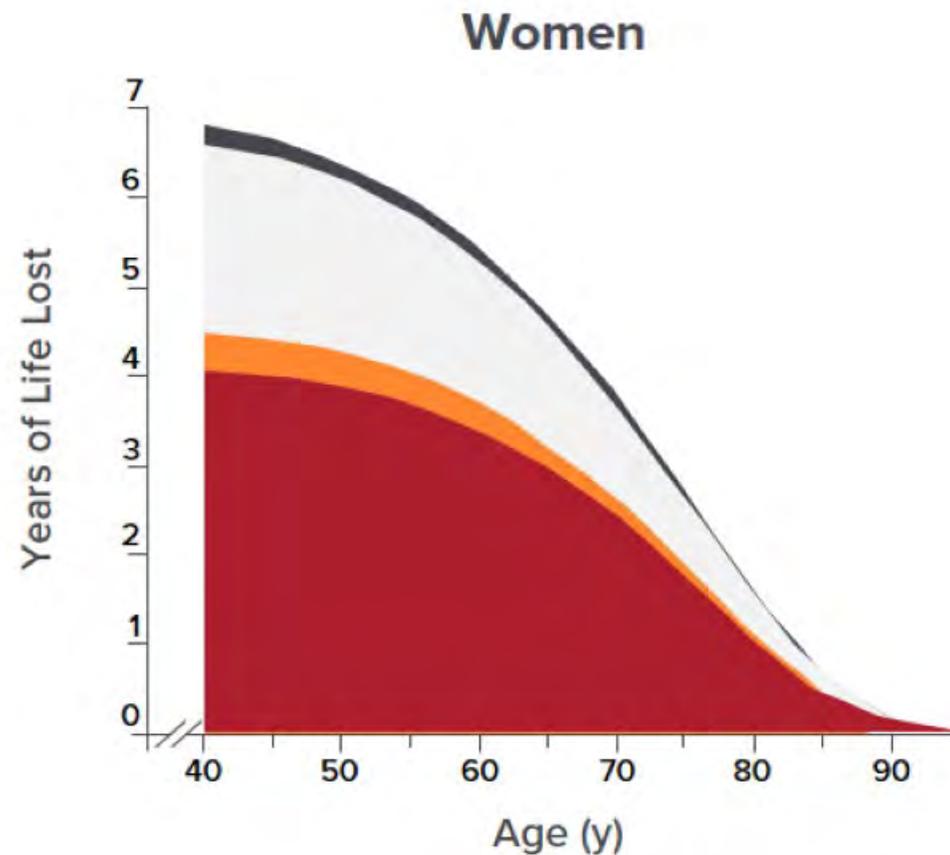
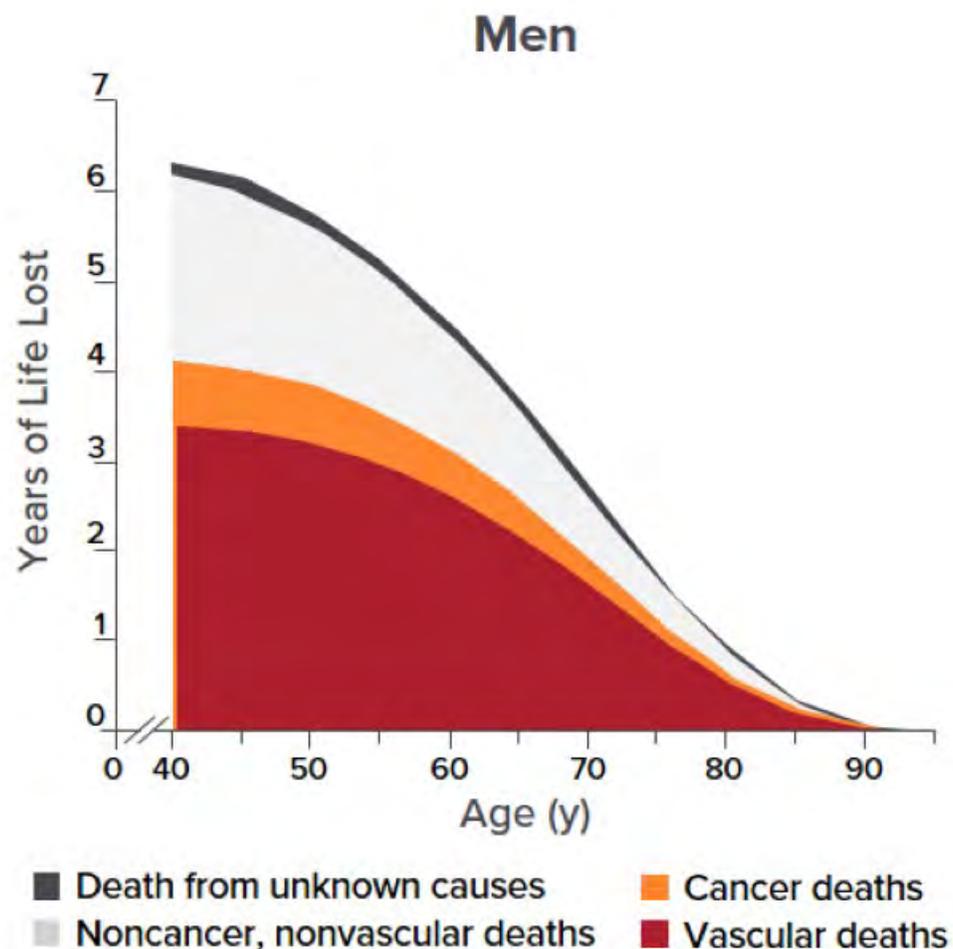
**112%  
more  
risk of  
HF<sup>[b]</sup>**

**58%  
more  
risk of  
stroke<sup>[b]</sup>**

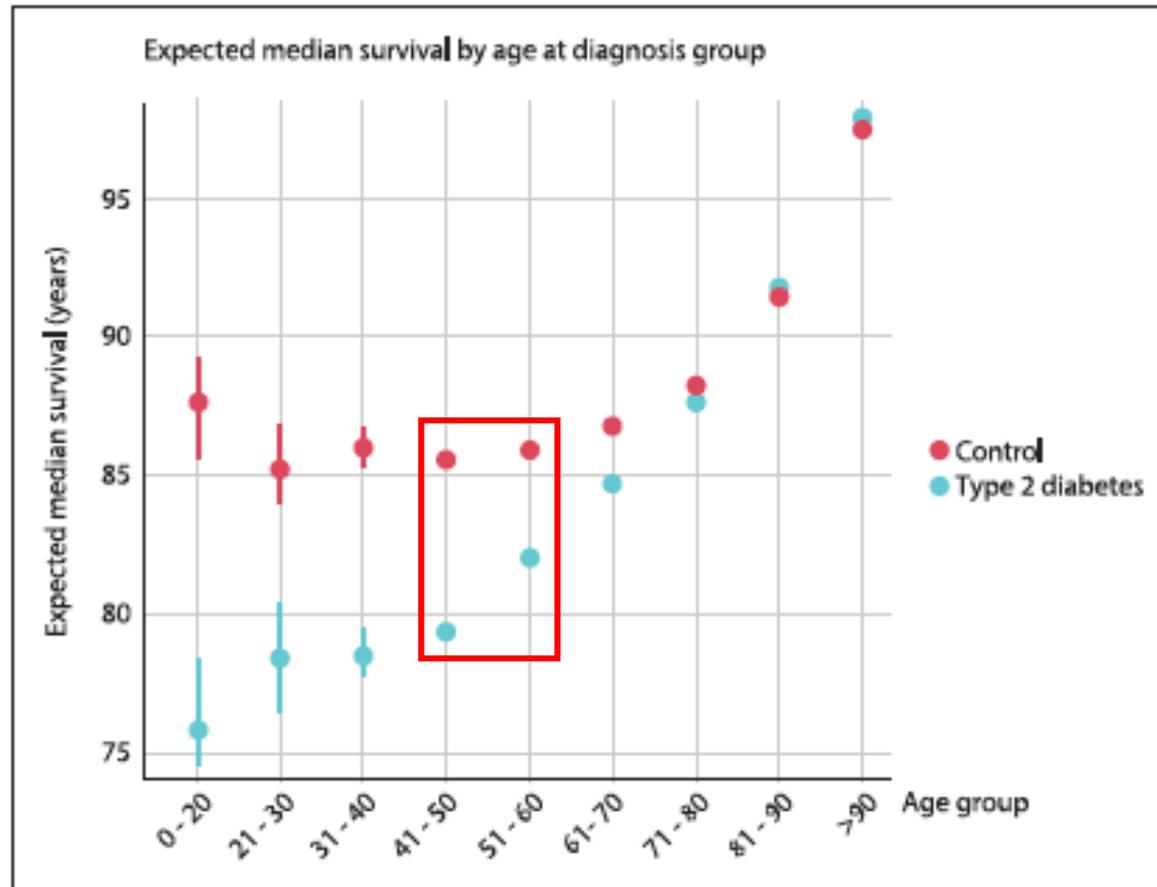
**10%  
more  
risk of  
CAD<sup>[b]</sup>**

**53%  
more  
risk of  
MI<sup>[b]</sup>**

# T2D Associated With Premature Death From CV and Non-CV Causes



# Età alla diagnosi di T2DM e perdita di anni di vita in persone senza precedenti malattie cardiovascolari

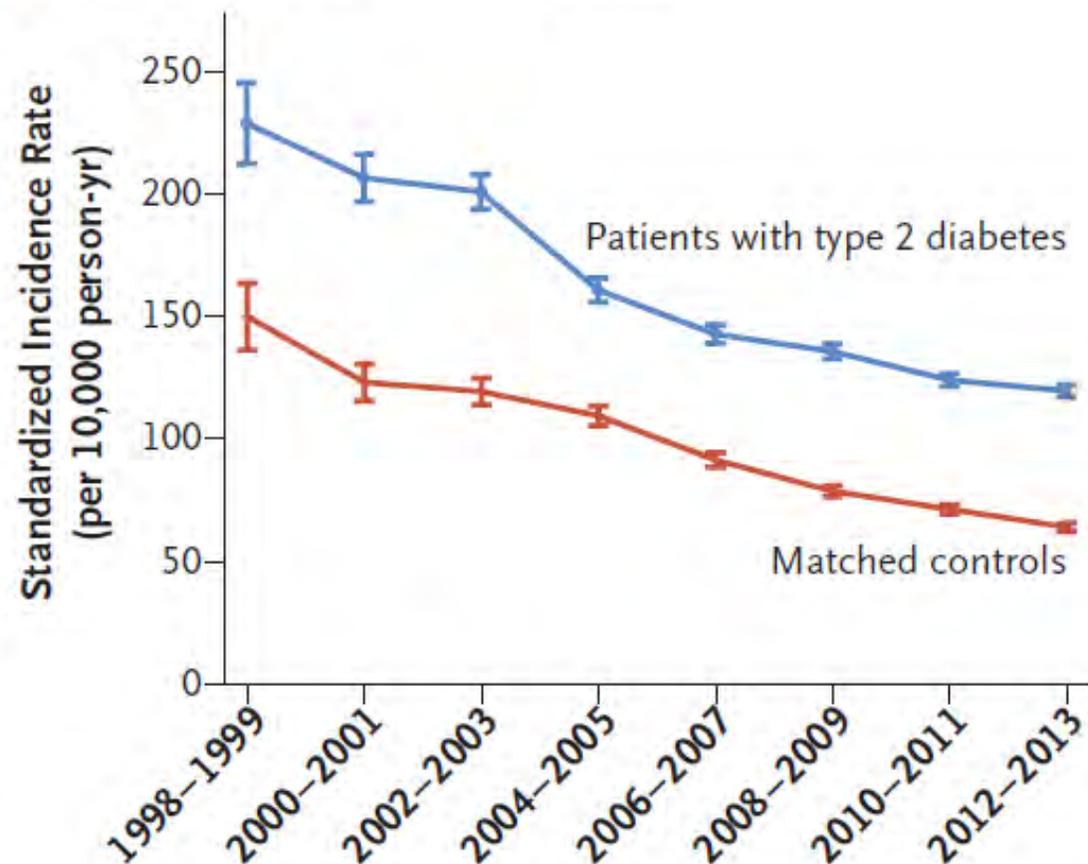


**L'età più giovane alla diagnosi si associa ad un rischio nettamente superiore di morte CV rispetto al soggetto non diabetico**

# L'aumentata incidenza di morte cardiovascolare in pazienti con diabete di tipo 2

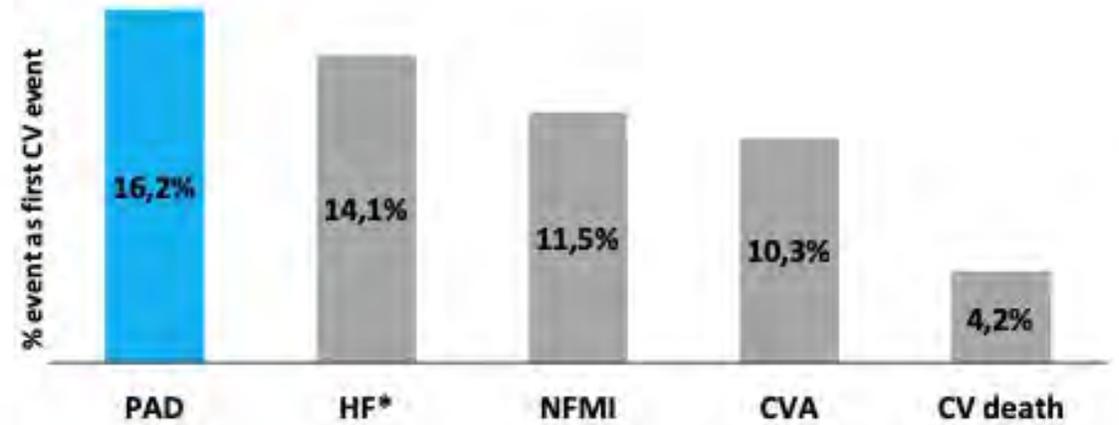
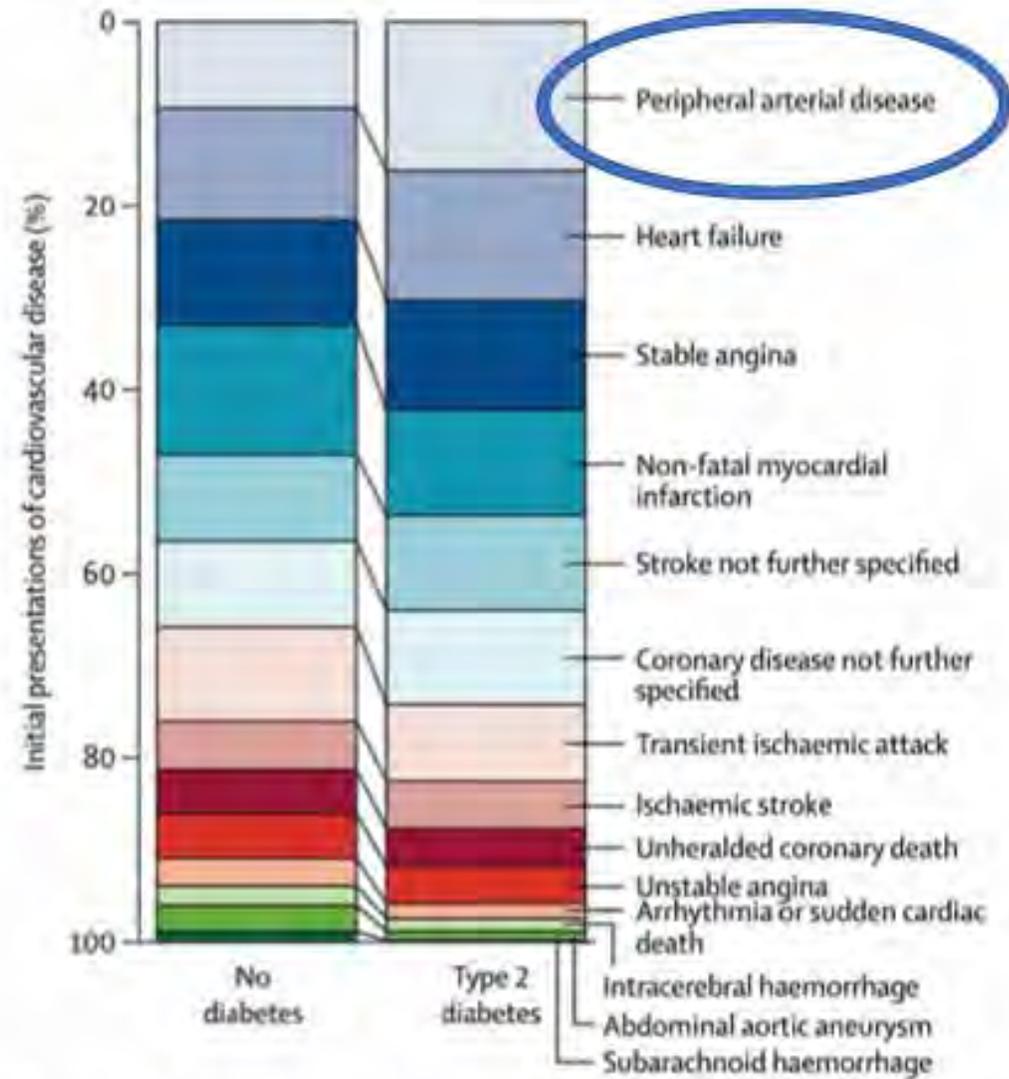
Registro nazionale svedese del diabete 1998-2012

## B Death from Cardiovascular Disease



↑ 2 x CV-mortality as compared to their non-DM counterparts

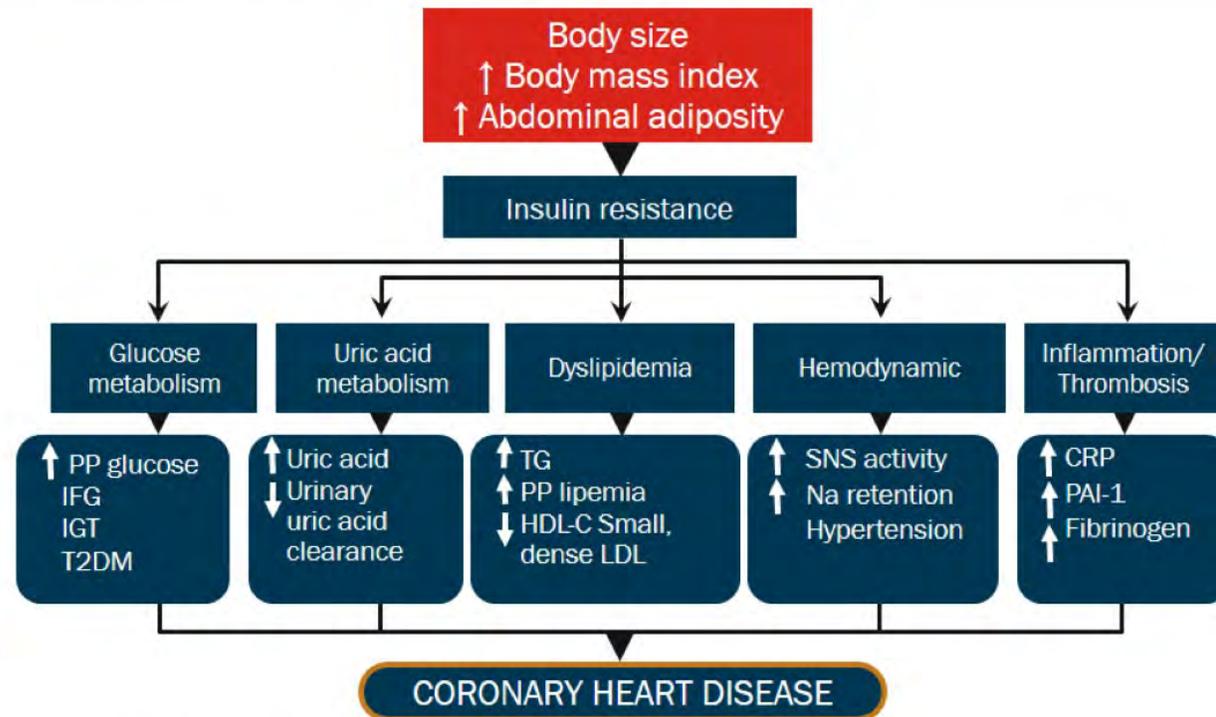
Nonostante la riduzione degli eventi di morte CV nel corso degli anni, il soggetto diabetico presenta sempre un rischio maggiore



**Figure 1: Distribution of initial presentations of cardiovascular diseases**  
 Distribution of initial presentations of cardiovascular disease in participants with and without type 2 diabetes and no history of cardiovascular disease.

# Meccanismi fisiopatologici

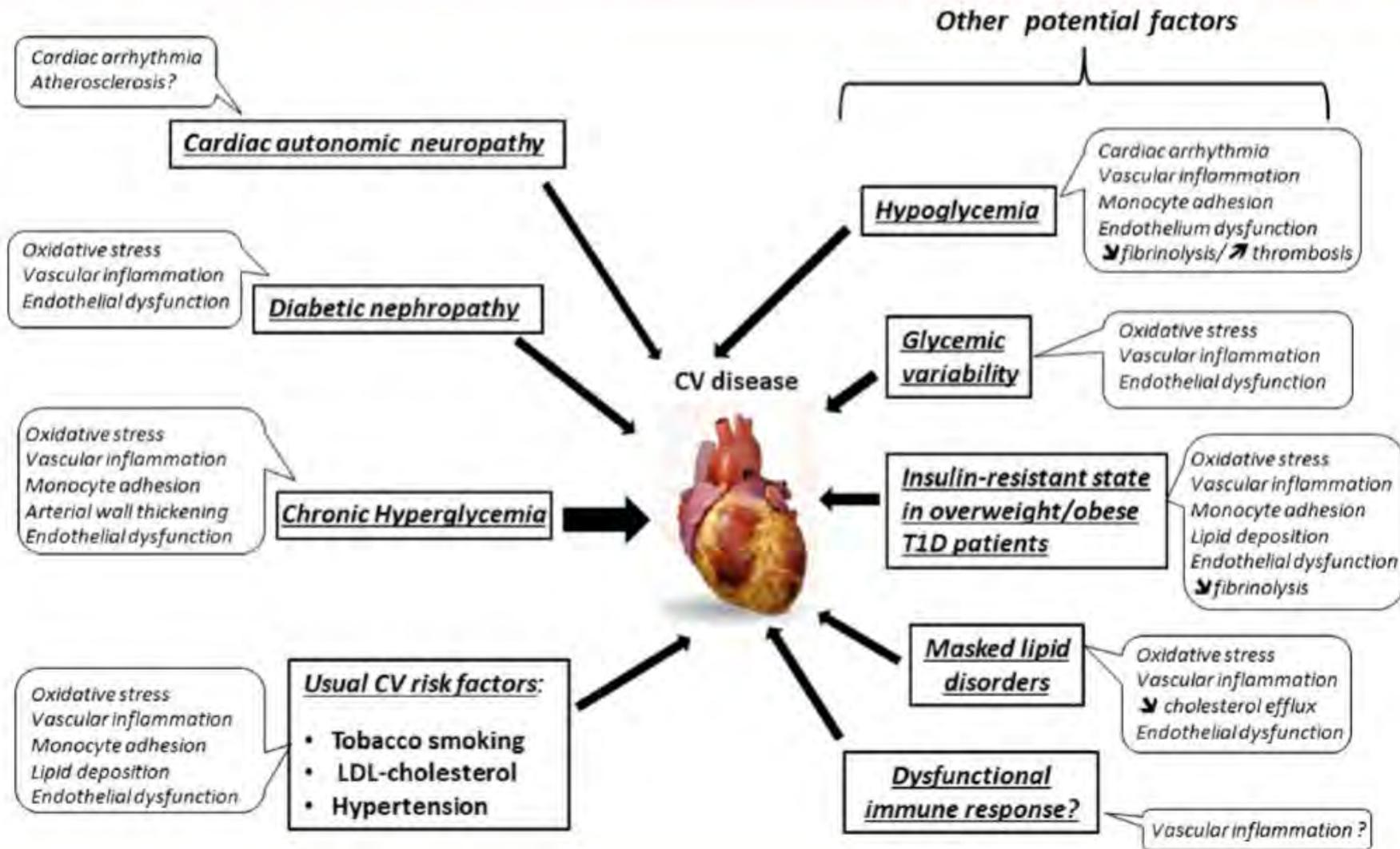
## Leading Drivers of Cardiometabolic Risk



Reaven GM. *Diabetes*. 1988;37:1595-1607; Reaven GM. *Drugs*. 1999;58(suppl):19-20.

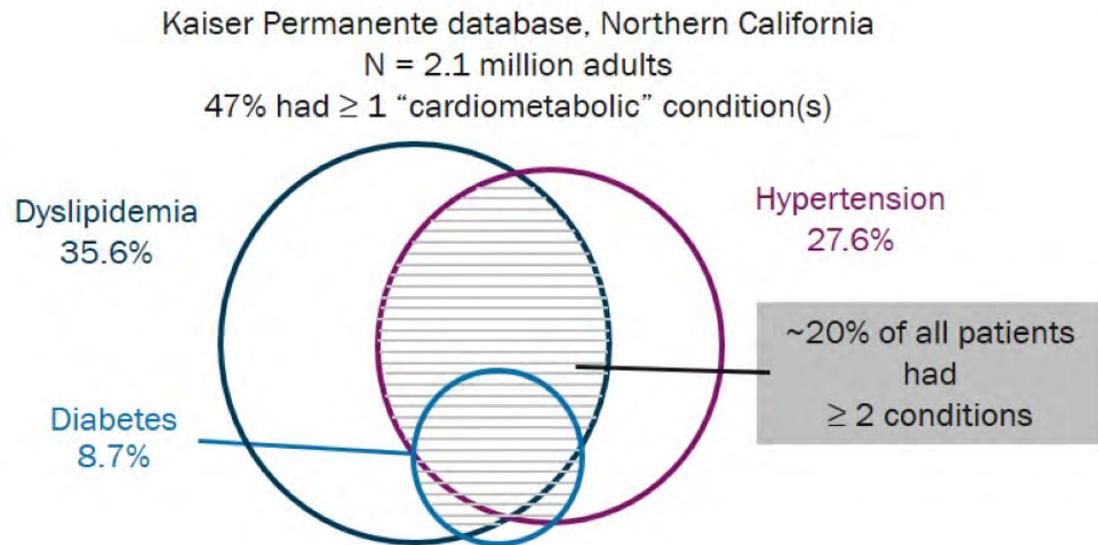
These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.

# Cardiovascular disease in diabetes



# Determinanti del rischio cardiovascolare

## “Cardiometabolic” Elements Are Common and Overlapping



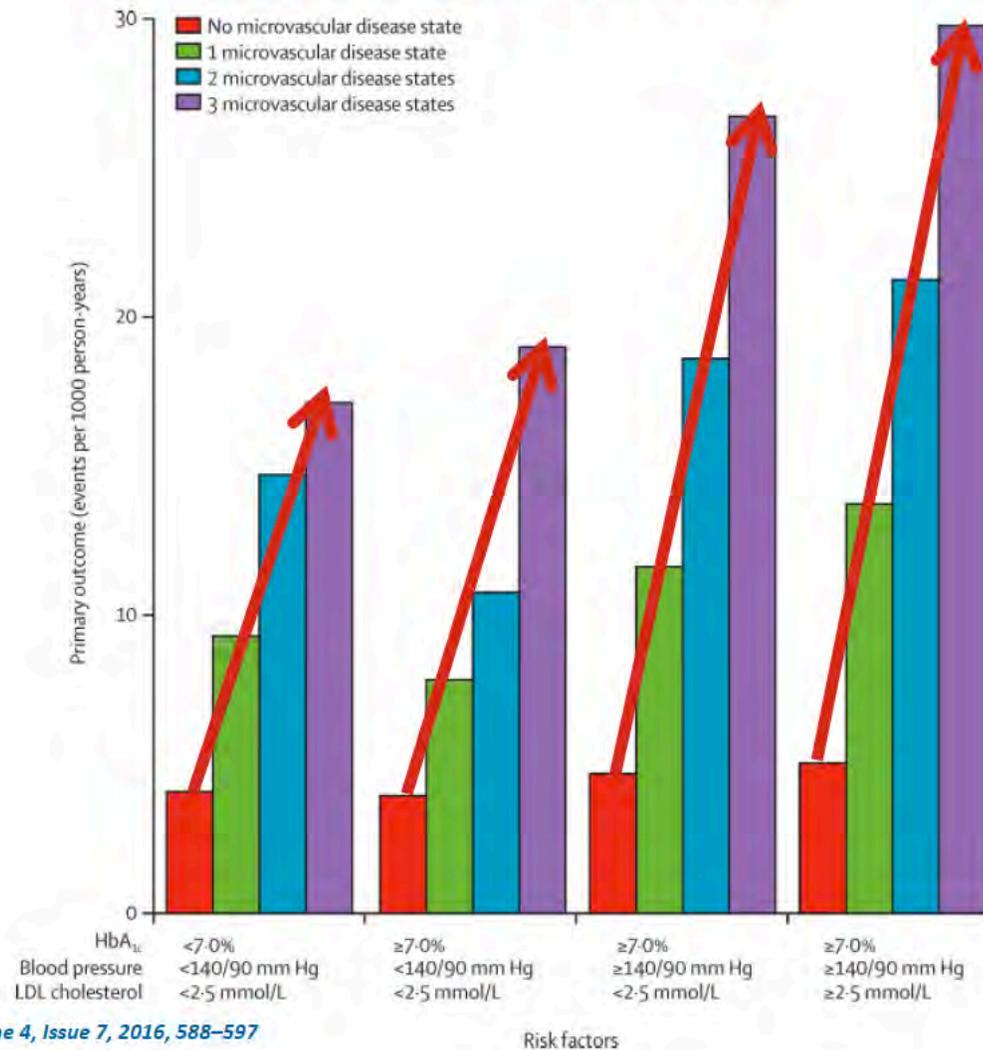
\*“Cardiometabolic” condition = dyslipidemia, hypertension, or diabetes.

Prevalence based on application of age- and sex-specific prevalence estimates for each condition from the Third National Health and Nutrition Examination Survey (NHANES III) data to the Kaiser Permanente membership to simulate full ascertainment.

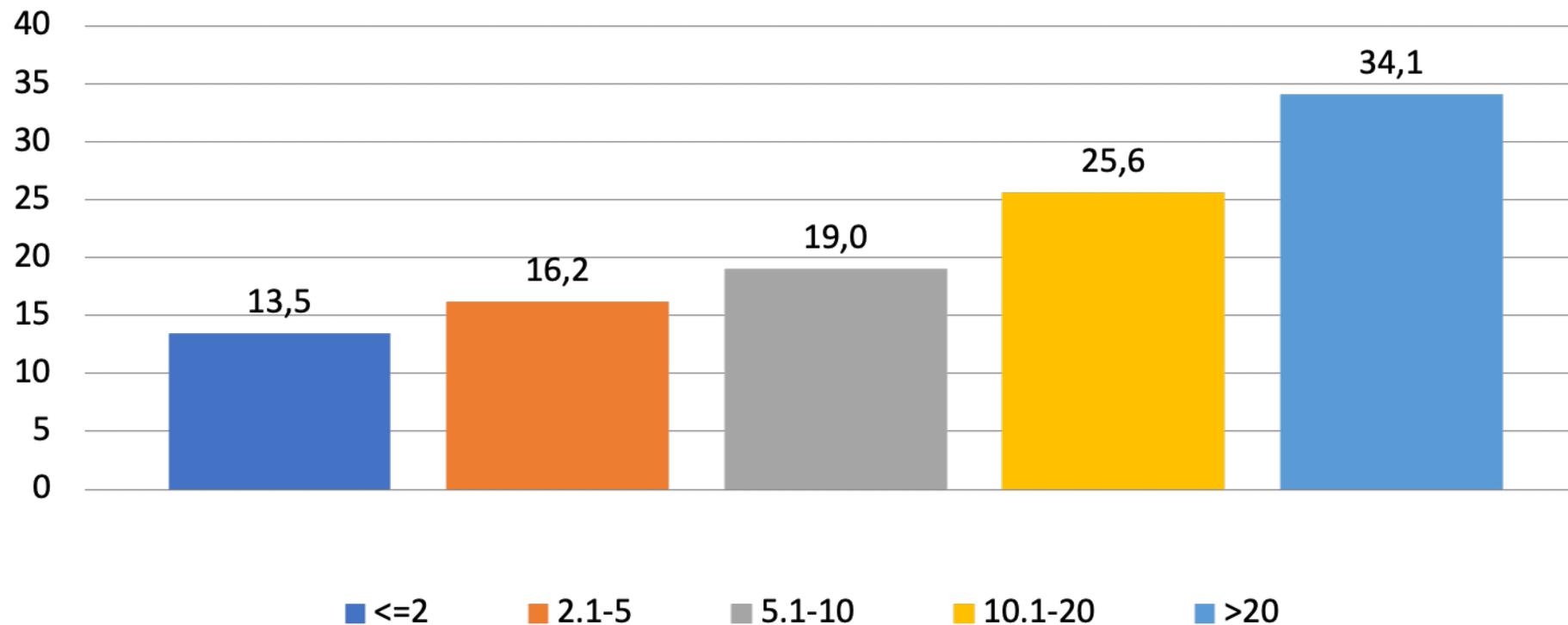
Selby JV et al. *Am J Manag Care*. 2004;10:163-170.

These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.

## La presenza di microangiopatia moltiplica il rischio di eventi cardiovascolari



## Prevalenza di complicanze cardiovascolari dipendenti dalla durata di diabete

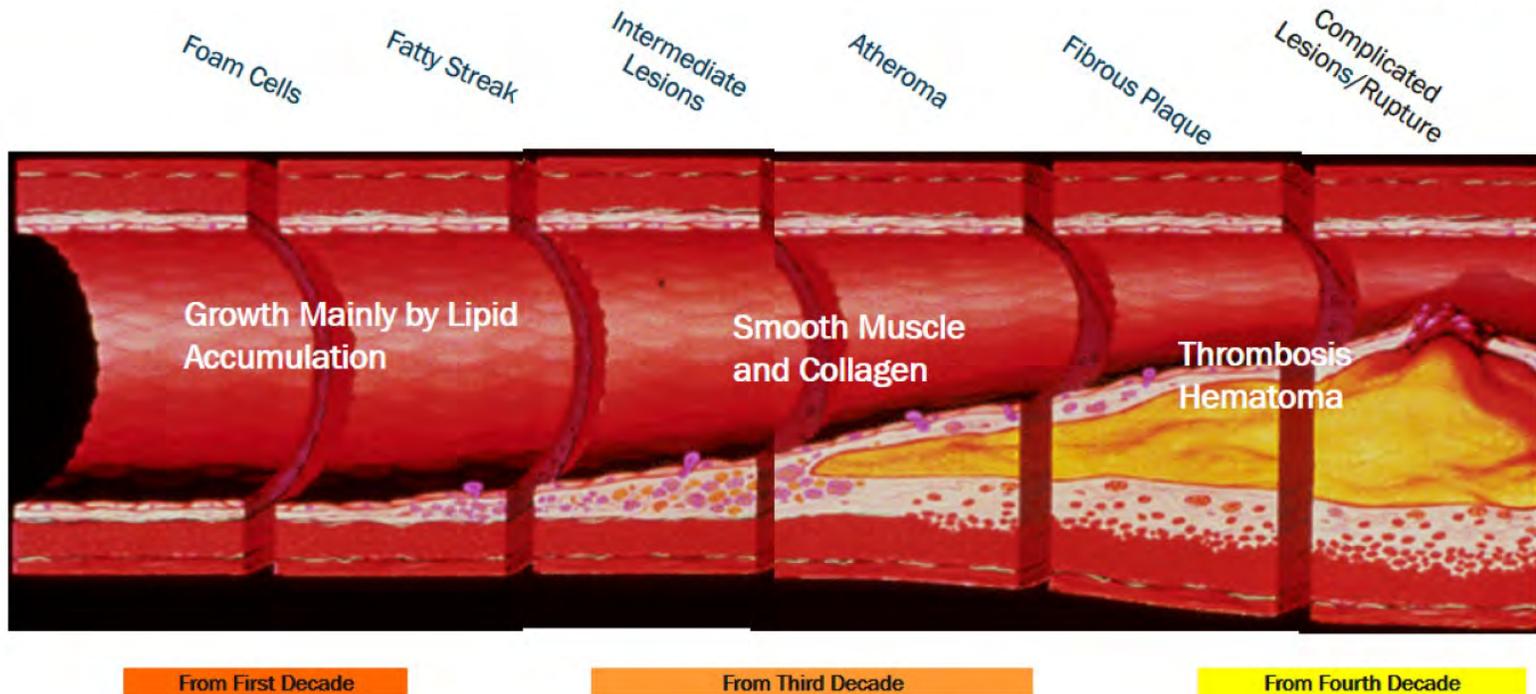


Complicazione cardiovascolari: MI, ictus, rivascolarizzazione coronarica, carotidea e periferica

**Il tempo di esposizione all'iperglicemia aumenta il rischio CV**

# Quando inizia il danno macrovascolare?

## Dyslipidemia Plaque Development and Rupture



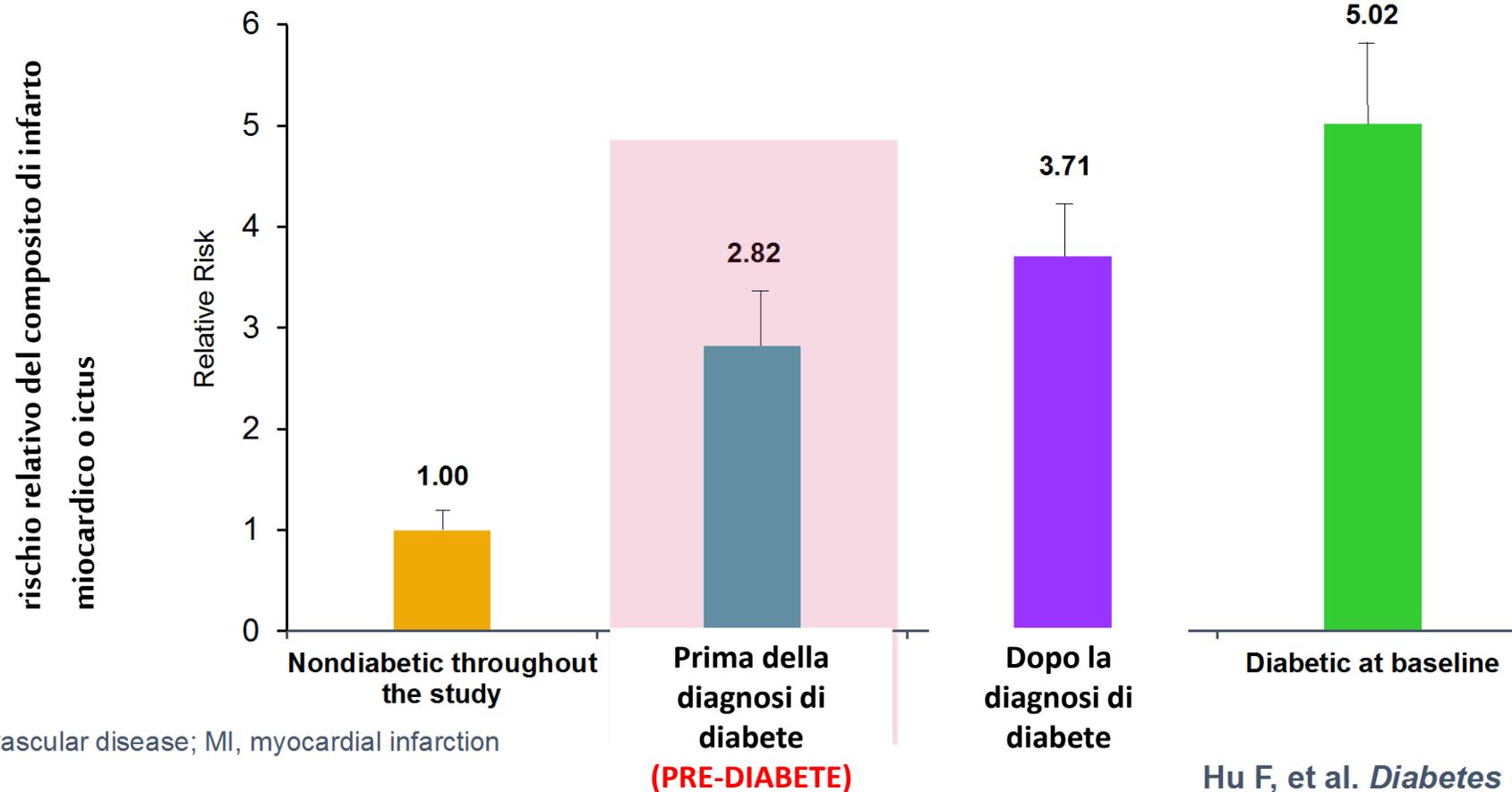
Pepine CJ. *Am J Cardiol.* 1998;82(Suppl. 10A):23S-27S.

These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.



# Esiste un rischio sostanzialmente elevato di CVD anche prima della diagnosi clinica del diabete di tipo 2

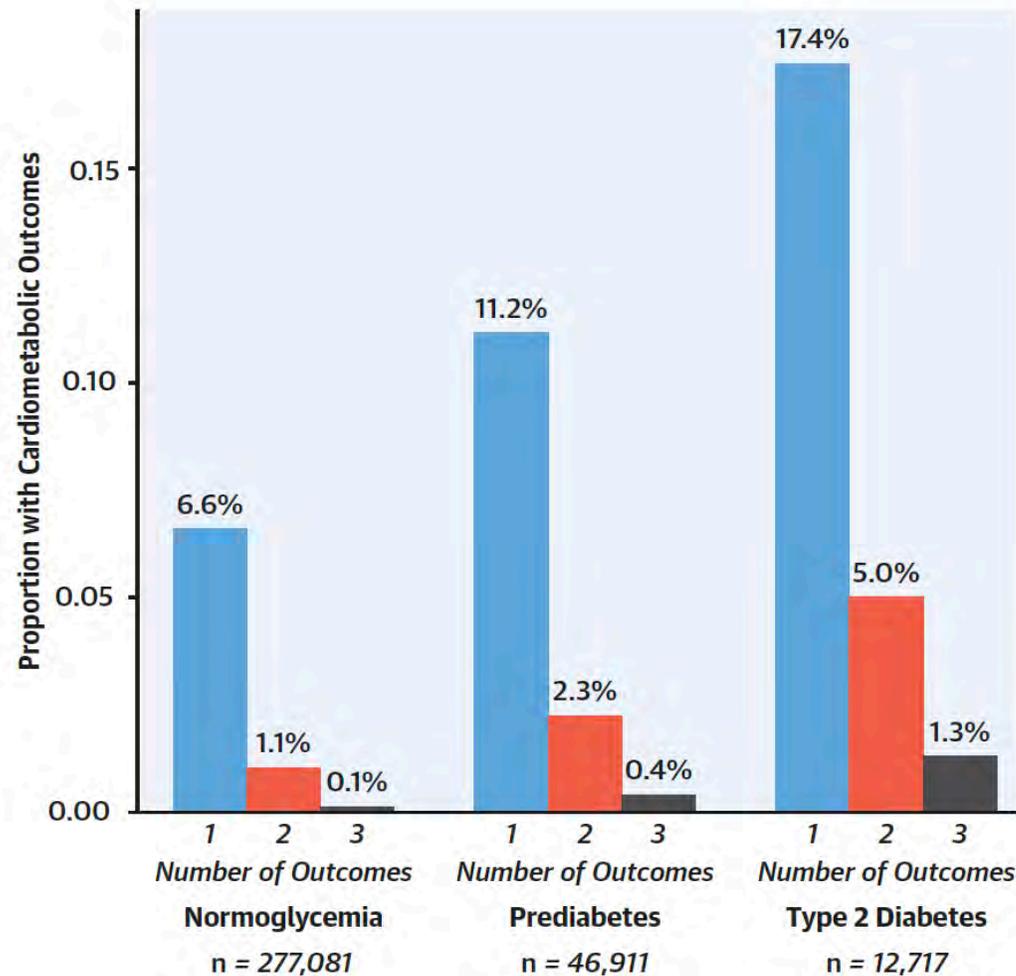
17.629 infermiere senza diagnosi di CVD al basale sono state seguite per 20 anni.



CVD, cardiovascular disease; MI, myocardial infarction

Hu F, et al. *Diabetes Care* 2002; 25:1129–1134

# Pre-Diabete e rischio di malattia cardiovascolare

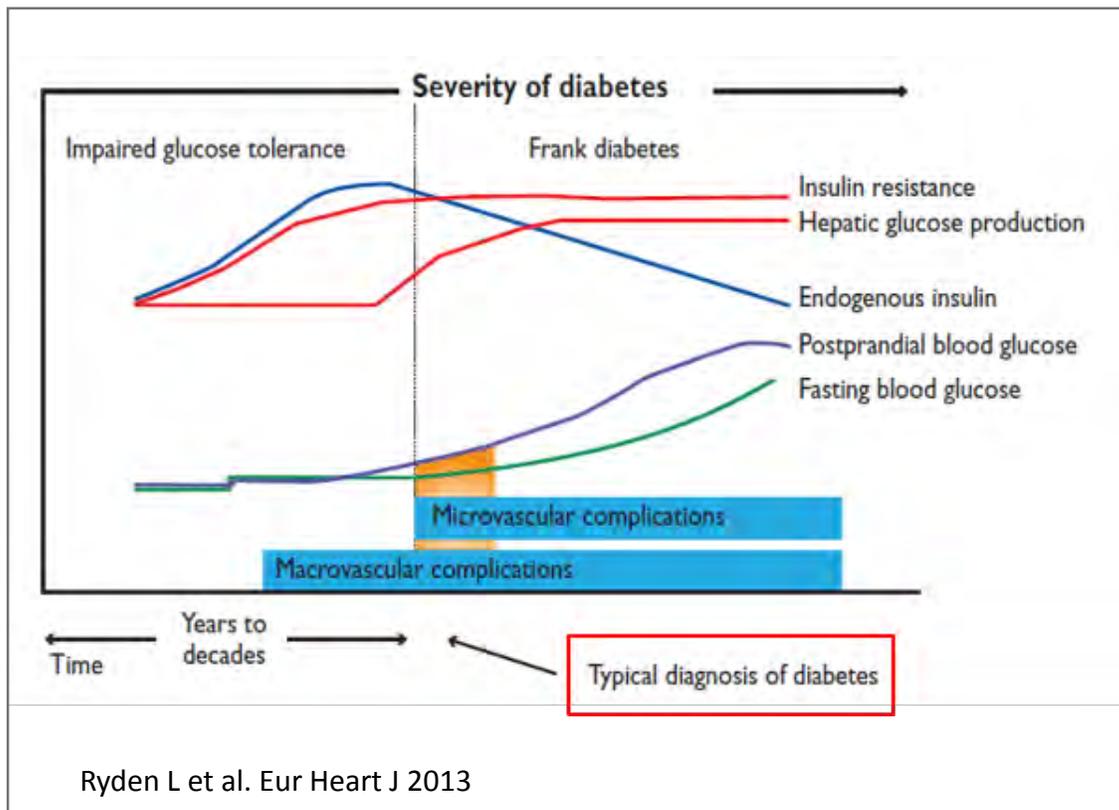


Metanalisi di 16 studi clinici

**11%** di persone con **pre-diabete** sperimenta eventi aterosclerotici (ASCVD)

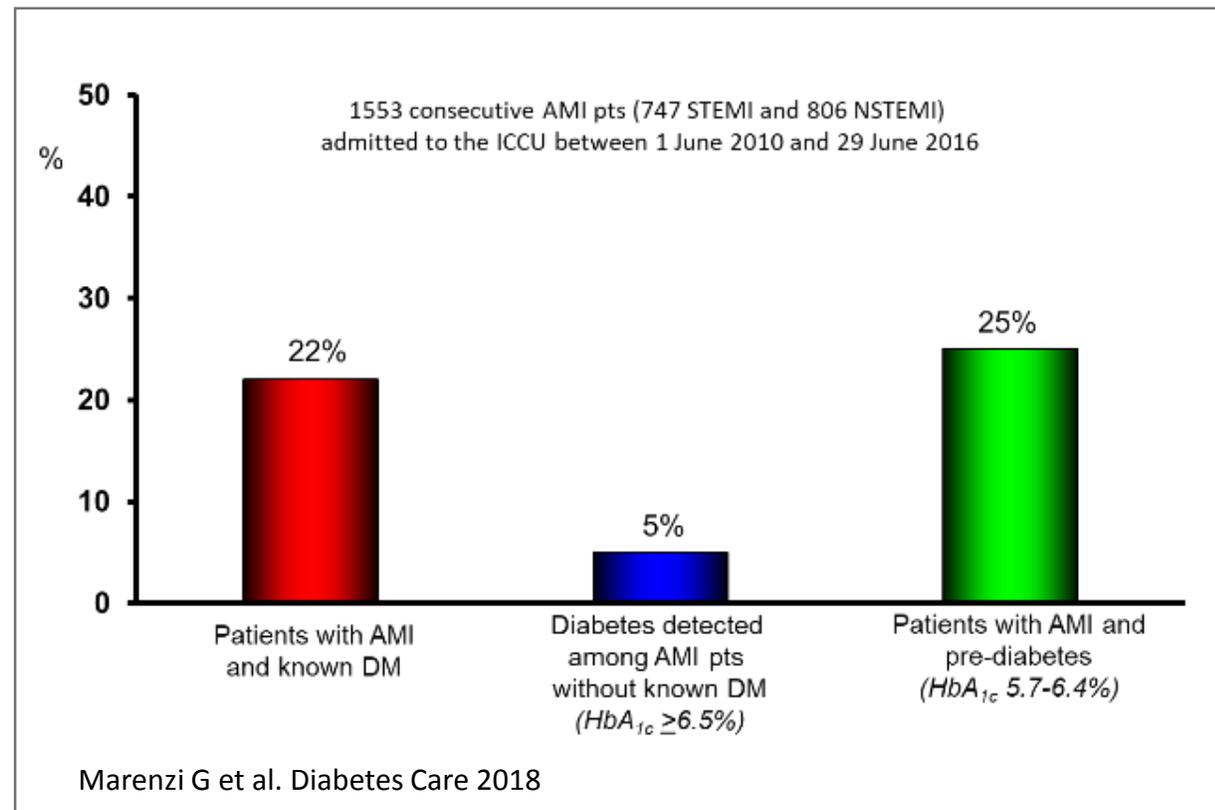
# La malattia coronarica può essere la prima manifestazione clinica del diabete di tipo 2

Comparsa della malattia CV nella storia naturale del diabete



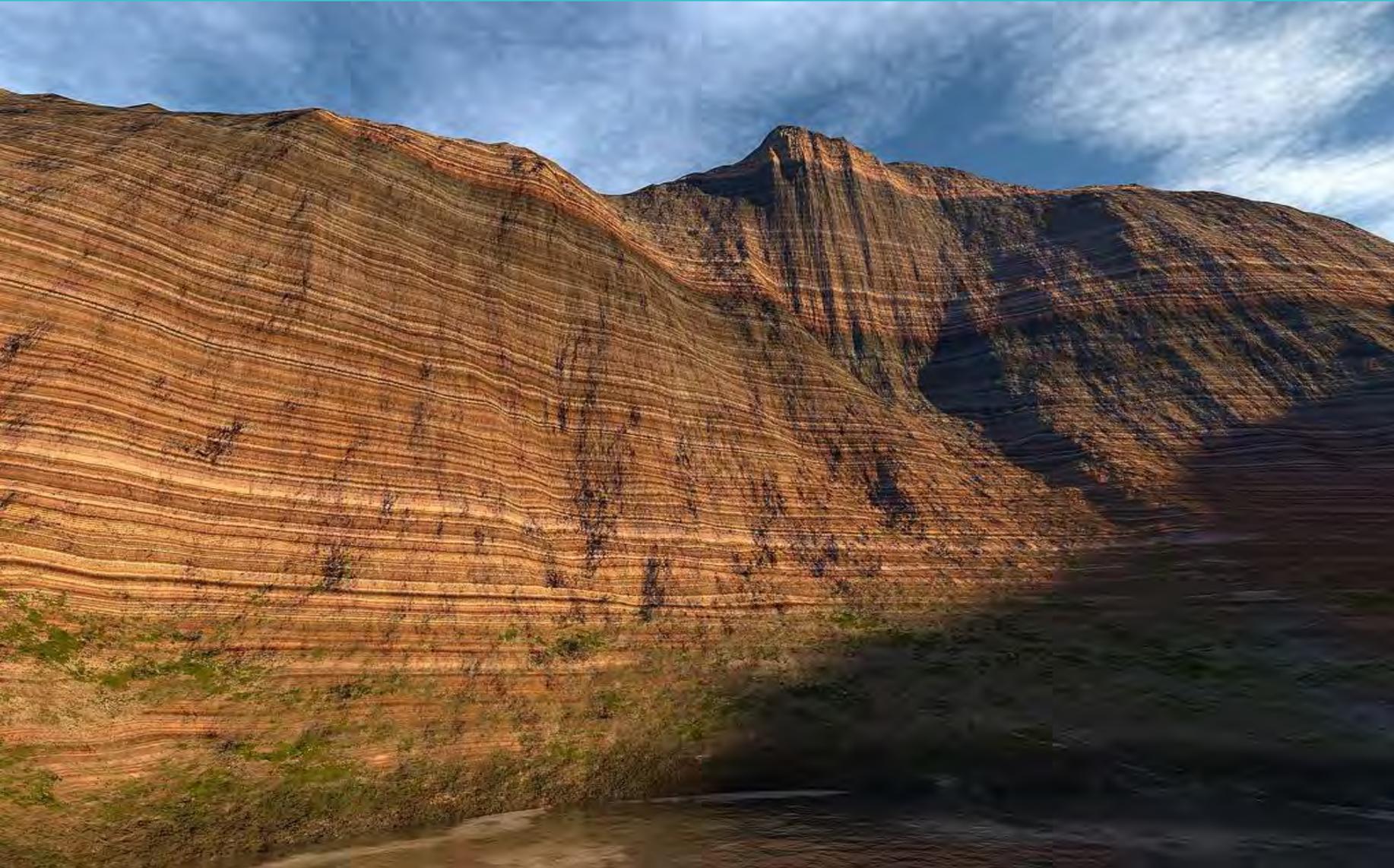
Le complicanze macrovascolari possono anticipare la diagnosi di diabete

Prima diagnosi di diabete o prediabete in occasione di accesso in UTIC per IMA



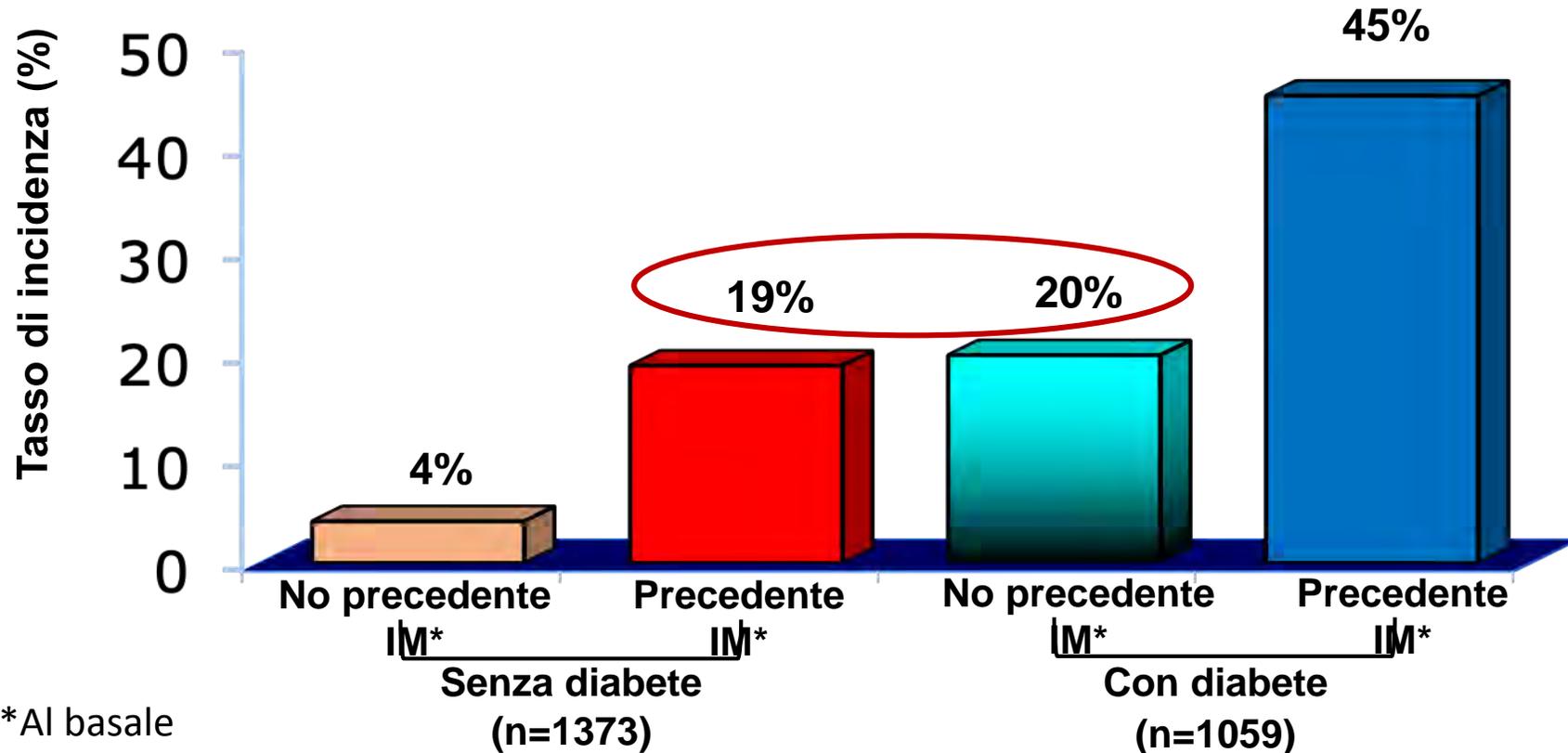
Il 25% dei dei soggetti ricoverati per infarto sono nella fase di **pre-diabete**

# Ha ancora senso la stratificazione del rischio?



# Tutti i pazienti con diabete sono ad alto rischio cardiovascolare?

Incidenza di infarto miocardico fatale e non fatale (7 anni follow-up)  
in base alla storia di precedente infarto miocardico e/o diabete al basale



\*Al basale

IM=Infarto del miocardio

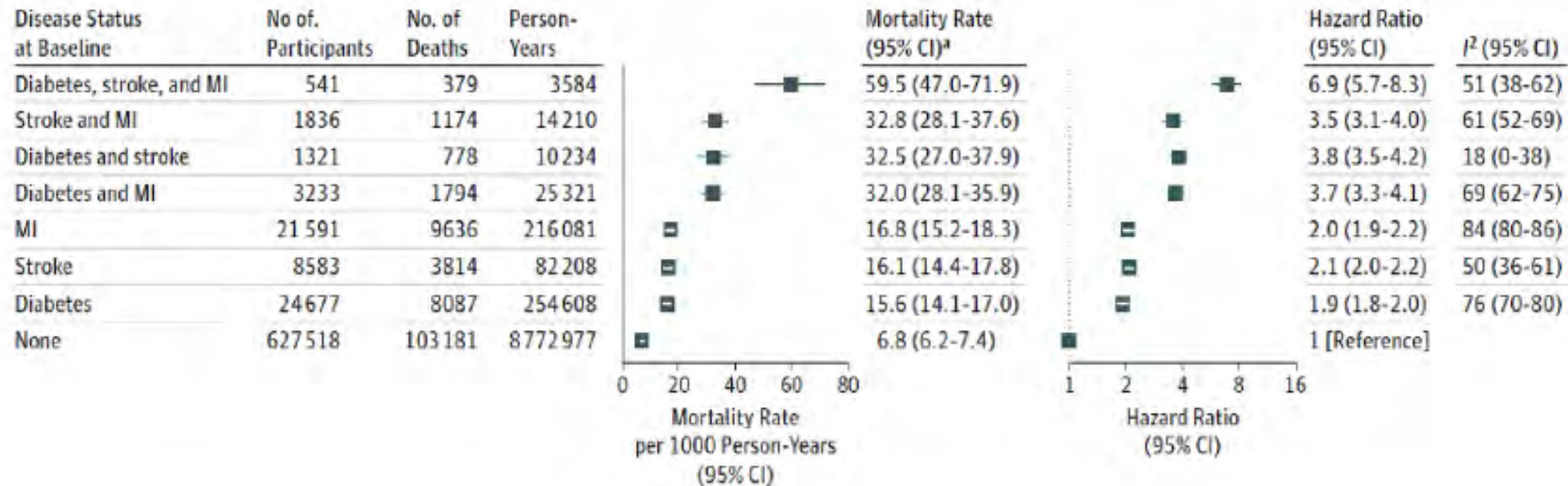
P <0.001 per precedente IM vs. no precedente IM e per con diabete vs. senza diabete

Original Investigation

# Association of Cardiometabolic Multimorbidity With Mortality

The Emerging Risk Factors Collaboration

Figure 1. All-Cause Mortality for the Emerging Risk Factors Collaboration by Disease Status of Participants at Baseline



# La stratificazione del rischio cardiovascolare nel paziente con diabete mellito come parte essenziale della gestione della malattia



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

Secondo le linee guida ESC, **non esiste un paziente con diabete a basso rischio** (anche i pazienti con diabete di tipo 2 con età <50 anni e con una durata di diabete <10 anni sono già considerati a rischio moderato!

## Very high risk

Patients with DM **and** established CVD  
**or** other target organ damage<sup>b</sup>  
**or** three or more major risk factors<sup>c</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 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.

<sup>a</sup>Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.<sup>27</sup>

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

<sup>c</sup>Age, hypertension, dyslipidemia, smoking, obesity.]

# How to Define Patients At Risk? (cont)

## ESC 2019 Guidelines<sup>[a]</sup>

CV risk categories in patients with diabetes\*

- Patients with DM and established CVD
- or other target organ damage\*\*
- or 3 or more major risk factors\*\*\*
- or early-onset T1D of long duration (> 20 years)
- Patients with DM duration ≥ 10 years without target organ damage plus any other additional risk factor
- Young patients (T1D aged < 35 years or T2D aged < 50 years) with DM duration < 10 years, without other risk factors

## 2019 ADA/EASD CONSENSUS REPORT<sup>[b]</sup>

Metformin unless contraindicated or not tolerated

Indicators of High-Risk or Established ASCVD, CKD, or HF

ASCVD predominates†

Preferably GLP-1 RA or SGLT2 inhibitor

HF or CKD predominates‡

Preferably SGLT2 inhibitor or If SGLT2 inhibitor not tolerated or contraindicated → + GLP-1 RA

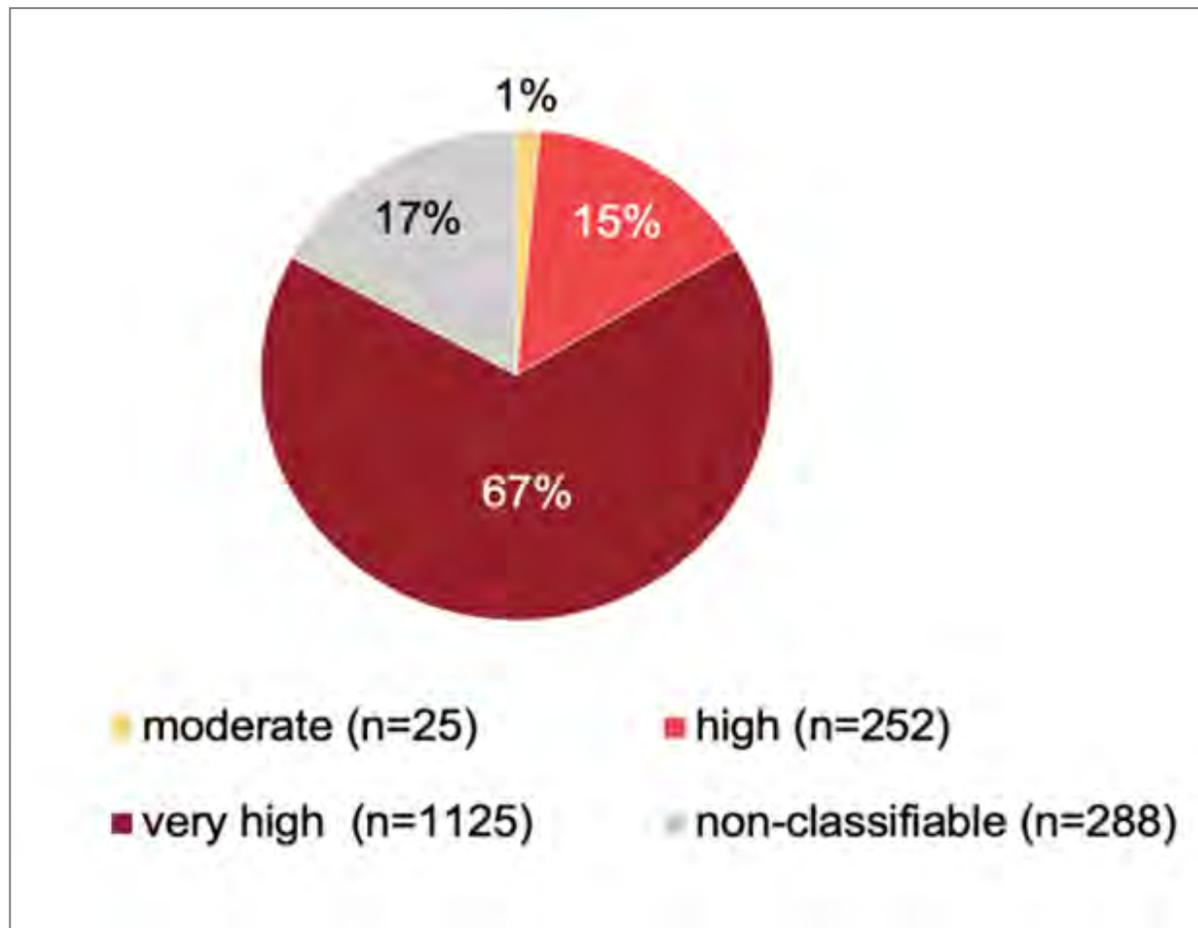
\*Modified from the 2016 European Guidelines on CVD in clinical practice, \*\*Proteinuria, renal impairment defined as eGFR < 30 mL/min/1.73 m<sup>2</sup>, LVH, or retinopathy. \*\*\*Age, hypertension, dyslipidemia, smoking, obesity.

†Established ASCVD. Indicators of high ASCVD risk (age ≥ 55 years + LVH or coronary, carotid, lower extremity artery stenosis > 50%).

‡Particularly HFrEF (LVEF < 45%). CKD: specifically eGFR 30 to 60 mL/min/1.73 m<sup>2</sup> or UACR > 30 mg/g, particularly UACR > 300 mg/g.

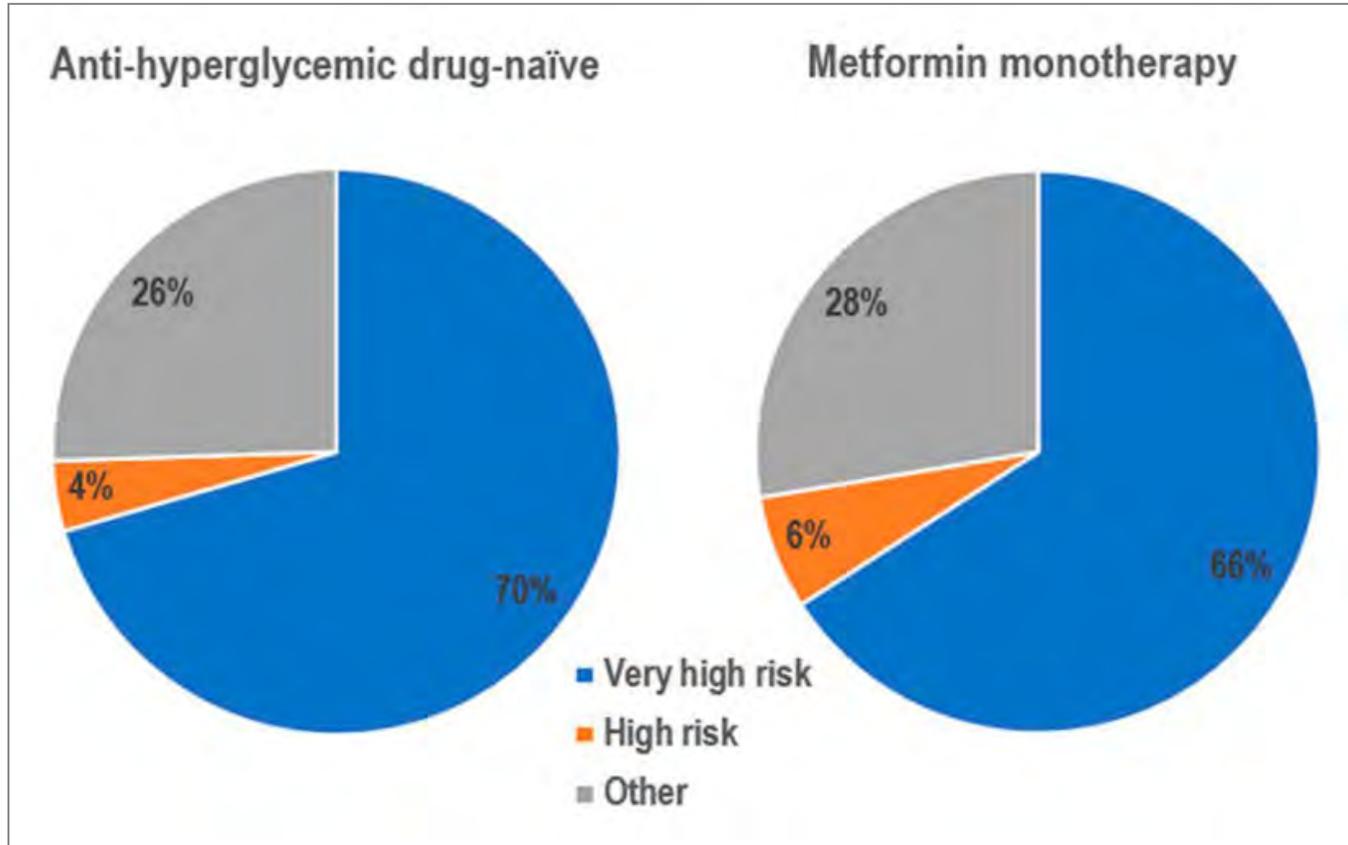
a. Cosentino F, et al. *Eur Heart J*. 2020;41:255-323; b. Buse JB, et al. *Diabetes Care*. 2020;43:487-493.

## Distribuzione della stima del rischio per un modello di rischio ESC/EASD. Austria



- Sono stati analizzati 1690 pazienti con T2DM con un follow-up di 10 anni per CVD fatale e morte per tutte le cause e un follow-up di 5 anni per CVD e ricoveri per tutte le cause.
- 288 pazienti (17,0%) non erano classificabili in base ai criteri ESC/EASD, perchè 280 pazienti avevano una durata del diabete < 10 anni con 1 o 2 (ma < 3) fattori di rischio CV accertati e 8 pazienti presentavano un diabete di durata superiore a 10 anni senza alcun fattore di rischio.

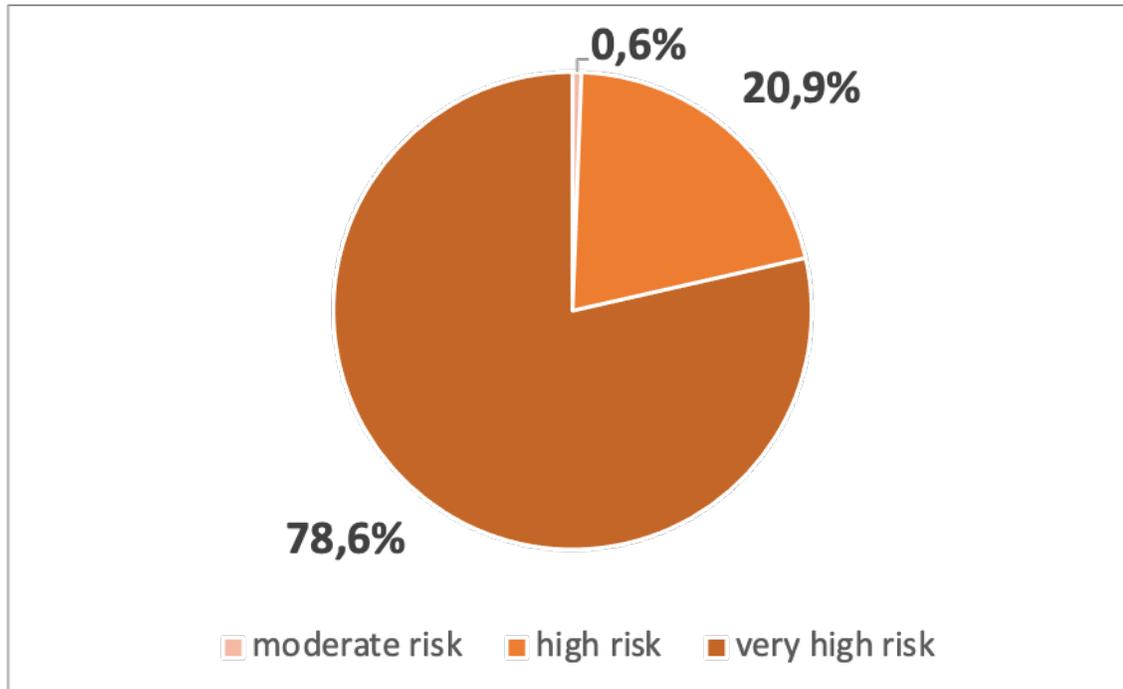
# Stratificazione del rischio delle sole popolazioni naïve ai farmaci e in monoterapia con metformina con T2D. Scozia



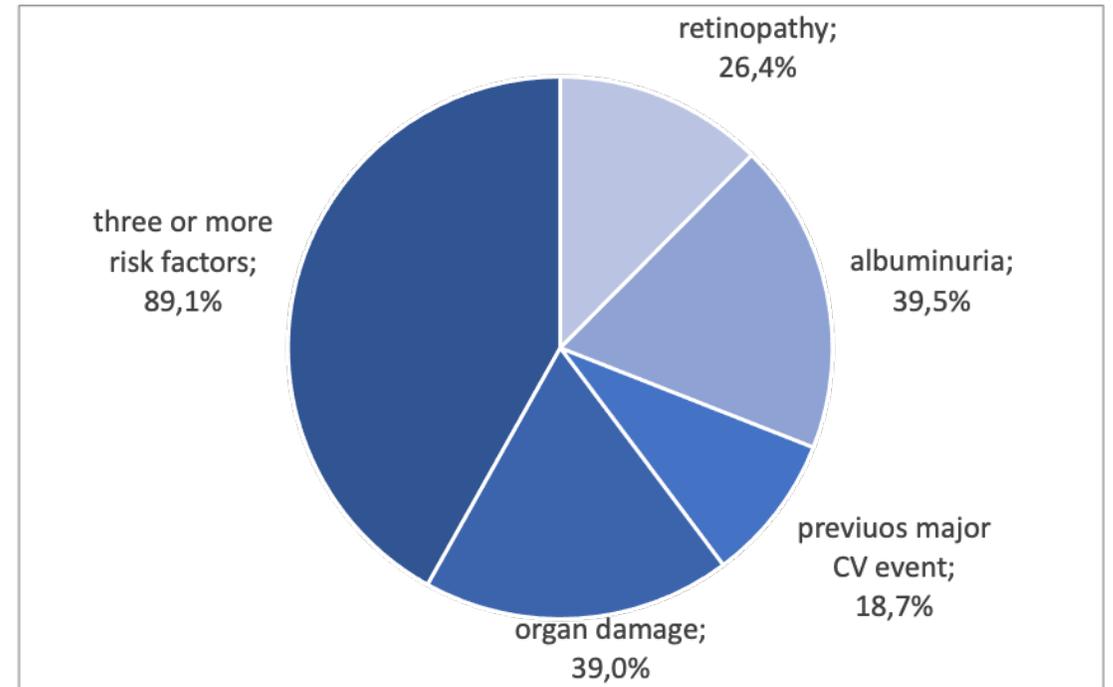
- Delle 265.774 persone con T2D in Scozia, 53.194 (20,0% del T2D) erano naïve ai farmaci e 56.906 (21,4%) erano in monoterapia con metformina.
- Di questi, rispettivamente, il **74,5%** e il **72,4%** erano considerati come ad **altissimo rischio** secondo le definizioni di rischio delle linee guida

# Caratteristiche della popolazione con diabete di tipo 2 in base al rischio cardiovascolare. Italia

473,740 T2DM

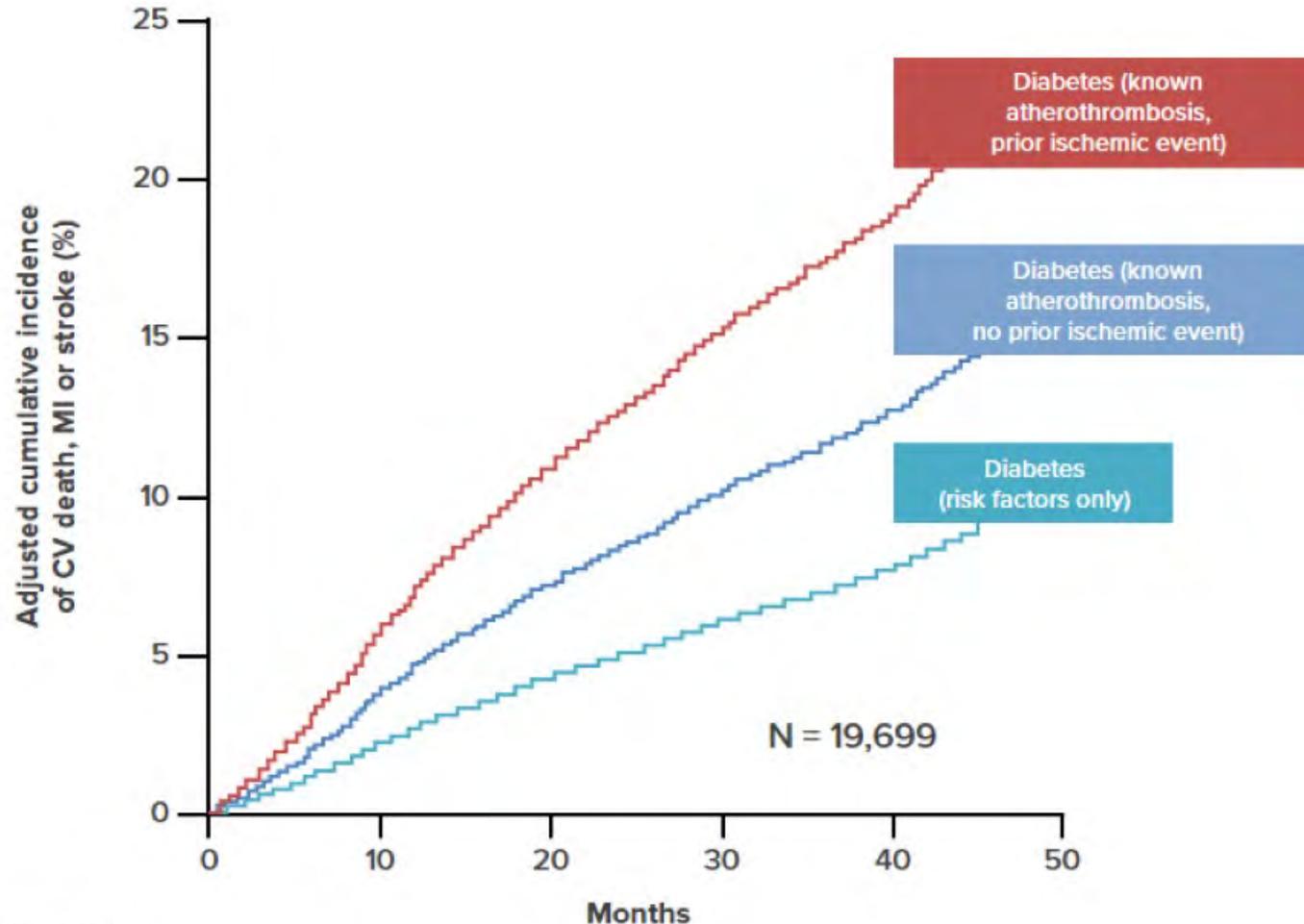


Tra le persone con T2D ad altissimo rischio:



# Known Atherothrombosis Increases CV Risk in Patients With T2D

## Adjusted Cumulative Incidence of Cardiovascular Death, MI, or Stroke



**Diabetes + known atherothrombosis with no prior MI confers greater risk than diabetes alone**

4-year hazard rates in patients with diabetes + known atherothrombosis + no prior MI:

**CV death, MI or stroke: 14.8%** (95% CI: 13.3, 16.2)

**CV death: 7.7%** (95% CI: 6.6, 8.81)

**Nonfatal MI: 4.1%** (95% CI: 3.2, 4.9)

**Nonfatal Stroke: 4.6%** (95% CI: 3.7, 5.5)

# CV Risk Categories

## 2021 ESC Guidelines

### Moderate Risk

Patients with well-controlled short-standing DM (eg, < 10 years), no evidence of TOD\* and no additional ASCVD risk factors<sup>†</sup>

### High Risk

Patients with DM without ASCVD and/or severe TOD\*, and not fulfilling the moderate risk criteria

### Very High Risk

Patients with DM with established ASCVD and/or severe TOD\*:

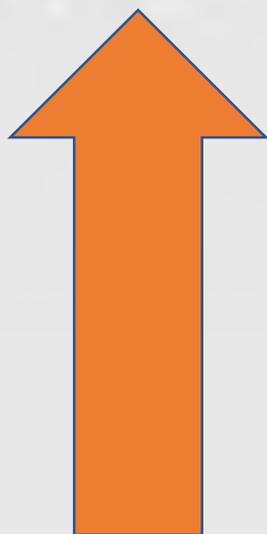
- eGFR < 45 mL/min/1.73 m<sup>2</sup>, irrespective of albuminuria
- eGFR 45 to 59 mL/min/1.73 m<sup>2</sup> and microalbuminuria (ACR 30 to 300 mg/g)
- Proteinuria (ACR > 300 mg/g)
- Microvascular disease in at least three different sites (eg, microalbuminuria, retinopathy, neuropathy)

**Use CV risk estimation tools,  
eg, ADVANCE or SMART risk scores or DIAL model**

\*Proteinuria, renal impairment defined as eGFR < 30 ml/min/1.73 m<sup>2</sup>, left ventricular hypertrophy, or retinopathy; <sup>†</sup>Age, hypertension, dyslipidemia, smoking, obesity. ACR, albumin:creatinine ratio; ADVANCE, Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DIAL, Diabetes Lifetime-perspective prediction; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; SMART, Second Manifestations of ARterial disease; TOD, target organ damage. Cosentino F, et al. Eur Heart J. 2020;41:255-323.

## Patients with type 2 diabetes mellitus

Patients with type 1 DM above 40 years of age may also be classified according to these criteria



Patients with well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors

**Moderate-risk**

N/A

Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria.

**High-risk**

Residual 10-year CVD risk estimation after general prevention goals (e.g. with the ADVANCE risk score or DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).

Patients with DM with established ASCVD and/or severe TOD:<sup>87, 93-95</sup>

- eGFR <45 mL/min/1.73 m<sup>2</sup> irrespective of albuminuria
- eGFR 45-59 mL/min/1.73 m<sup>2</sup> and microalbuminuria (ACR 30 -300 mg/g)
- Proteinuria (ACR >300 mg/g)
- Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)

**Very high-risk**

Residual 10-year CVD risk estimation after general prevention goals (e.g. with the SMART risk score for established CVD or with the ADVANCE risk score or with the DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).

# Diabetes, Cardiovascular and Renal Diseases are Closely Connected



- **63% of CKD patients** have CVD<sup>2</sup>
- 1-year mortality for stage 3-5 CKD patients with HF is **almost 25%**<sup>2</sup>

- **1 in 2 heart failure (HF) patients** die within 4 years of diagnosis<sup>2</sup>
- **35–70%** of HF patients have CKD<sup>2</sup>

\*Based on data from the US

1. *IDF Diabetes Atlas*, 8th ed. Available at: <http://www.idf.org/diabetesatlas>. Accessed May 2018. 2. Shiba N, Shimokawa H. *J Cardiol*. 2011;57:8–17.

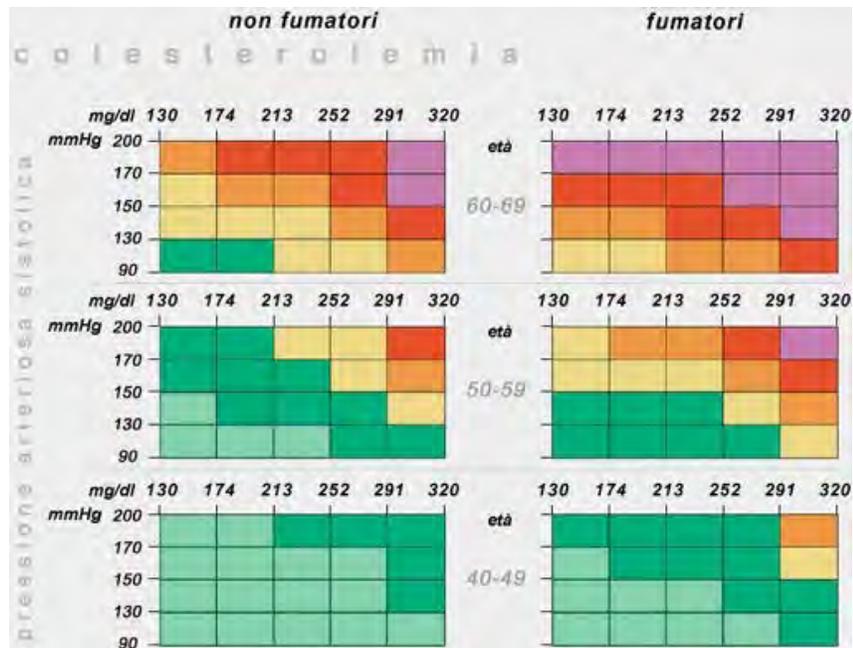
## The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

KDIGO categories	A1a	A1b	A2	A3
G1	1 (Ref.)	0.936 (0.780-1.124)	1.313 (1.079-1.599)	2.192 (1.546-3.108)
G2a	0.798 (0.667-0.956)	1.050 (0.885-1.246)	1.310 (1.089-1.575)	2.477 (1.816-3.379)
G2b	1.104 (0.833-1.120)	1.057 (0.878-1.273)	1.388 (1.148-1.678)	1.706 (1.232-2.362)
G3a	1.316 (1.071-1.617)	1.389 (1.138-1.694)	1.482 (1.218-1.804)	2.263 (1.708-3.000)
G3b	1.847 (1.400-2.438)	2.248 (1.791-2.821)	2.089 (1.686-2.590)	2.784 (2.136-3.629)
G4-5	1.613 (0.876-2.968)	2.245 (1.494-3.374)	2.785 (2.094-3.703)	4.662 (3.590-6.054)

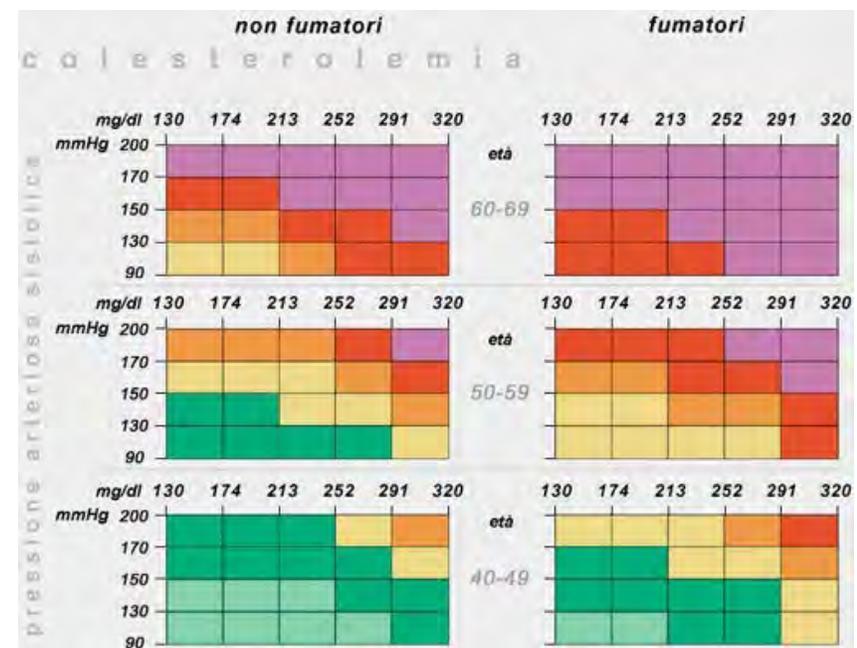
Cox proportional hazards regression, adjusted for multiple confounders

# PROGETTO CUORE ISS

Non diabetici



Diabetici



### UKPDS Risk Engine v2.0

**Input**

Age Now :  years      HbA1c :  %

Duration of Diabetes :  years      Systolic BP :  mmHg

Sex :  Male    Female      Total Cholesterol :  mmol/l

Atrial Fibrillation :  No    Yes      HDL Cholesterol :  mmol/l

Ethnicity :  ▾

Smoking :  ▾

[Options >](#)

---

**Output**

10 year risk	0	15	30	100
CHD : <input type="text" value="33.3%"/>				
Fatal CHD : <input type="text" value="24.4%"/>				
Stroke : <input type="text" value="11.6%"/>				
Fatal Stroke : <input type="text" value="1.8%"/>				

*Adjusted for regression dilution*

[Details](#)   [Copy](#)   [Print](#)  
[Help](#)   [Exit](#)

Personal Risk Profile ?

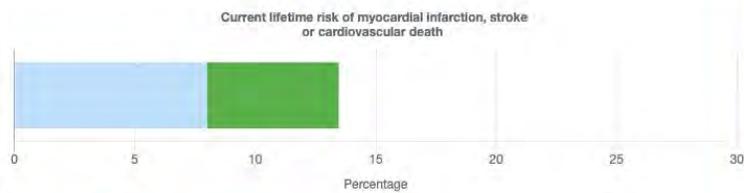
Gender	M*	History of vascular disease	-	BMI	25.1	kg/m <sup>2</sup>
Age	51	Duration of diabetes	1	years		
Geographic region	W-E*	Insulin therapy	-	Total cholesterol	240	mg/dL
Current smoking	-	Systolic blood pressure	140	mmHg	45	mg/dL
				HDL-cholesterol	160	mg/dL
				LDL-cholesterol	65	mmol
Statin	-*			HbA1c	58	mL/min
Ezetimibe	-			eGFR	-*	
PCSK9-inhibitor	-			Albuminuria		
Antithrombotic treatment	-*					

Adjust intake

CVD-free life-years

10-years risk

Lifetime risk



13.5%

Current risk ?

5.5%

Reduction with treatment ?

18

Lifetime NNT ?Future treatment ?

Statin

Rosuvastatin

Dose

10 mg

Ezetimibe



PCSK9-inhibitor



Systolic blood pressure

No treatment target

Antithrombotic treatment

No antithrombotic

HbA1c

&lt; 53 mmol/mol / &lt; 7%

Intervention start age

51

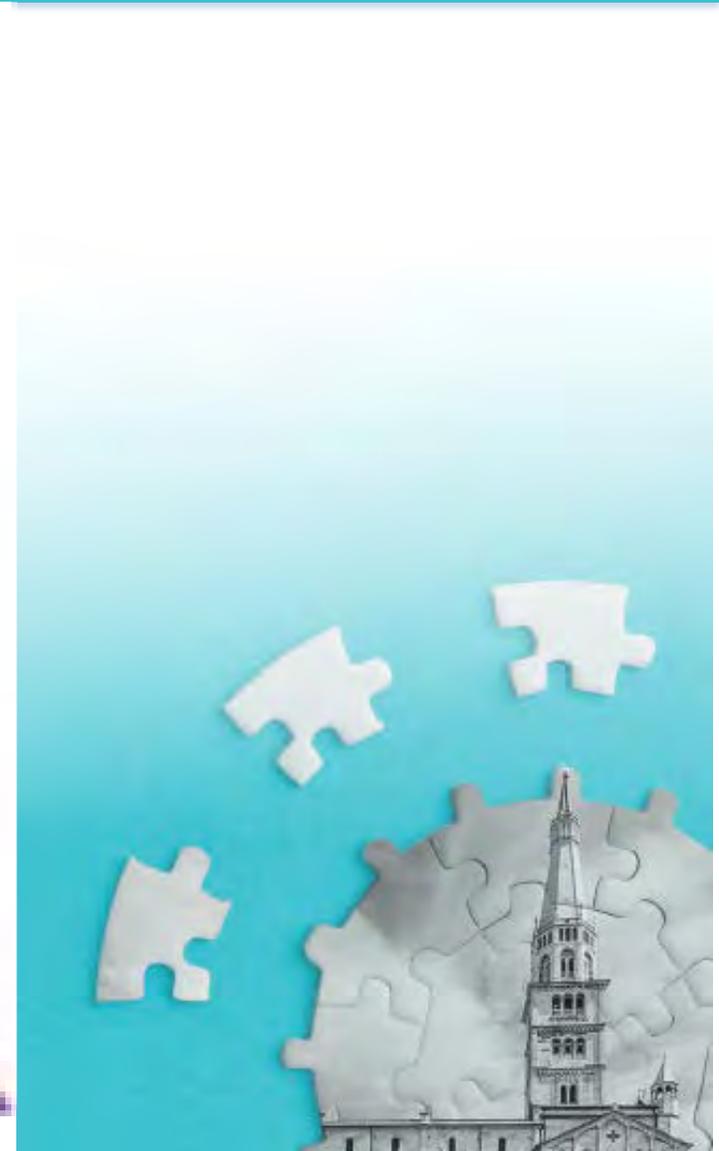
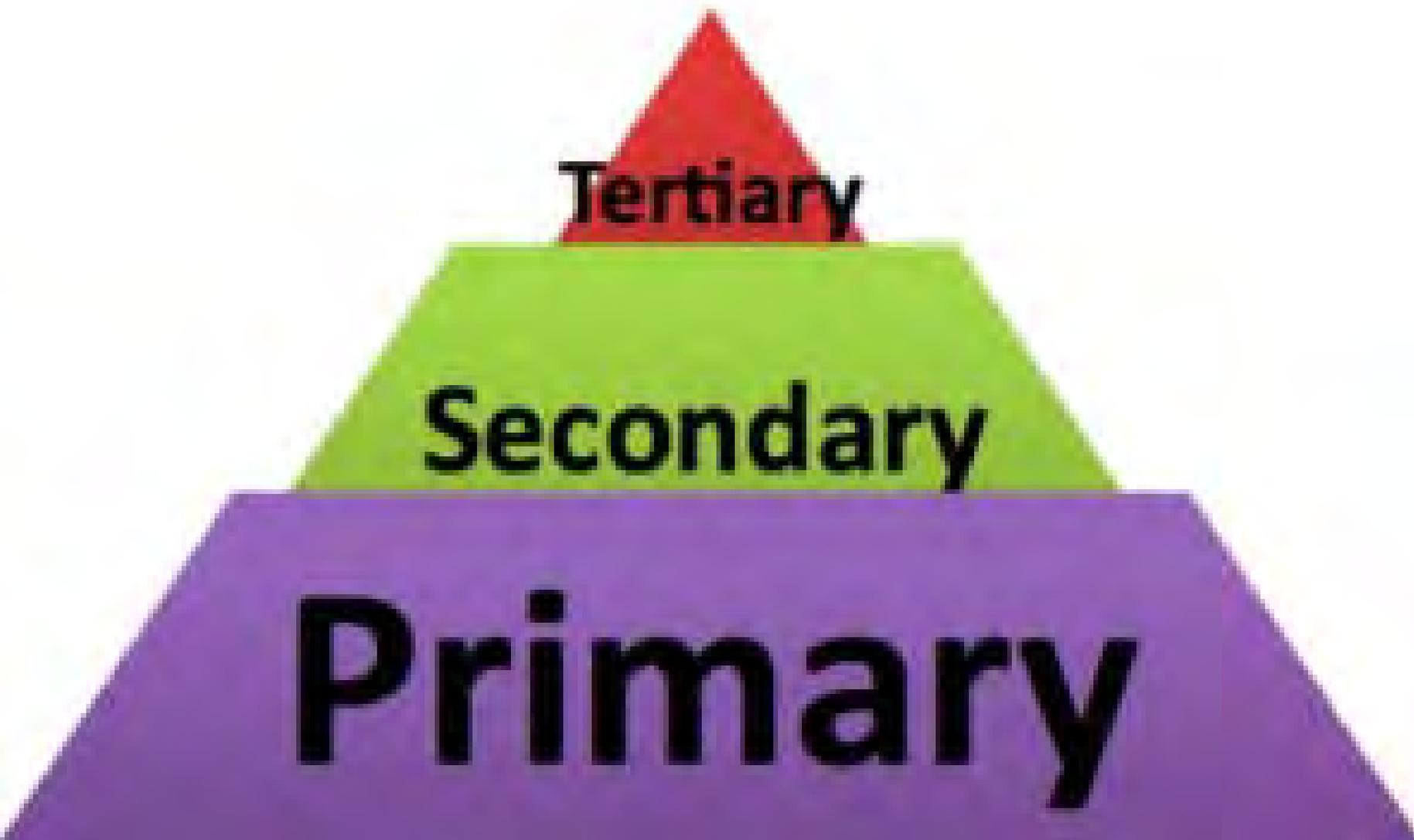
years

Reset

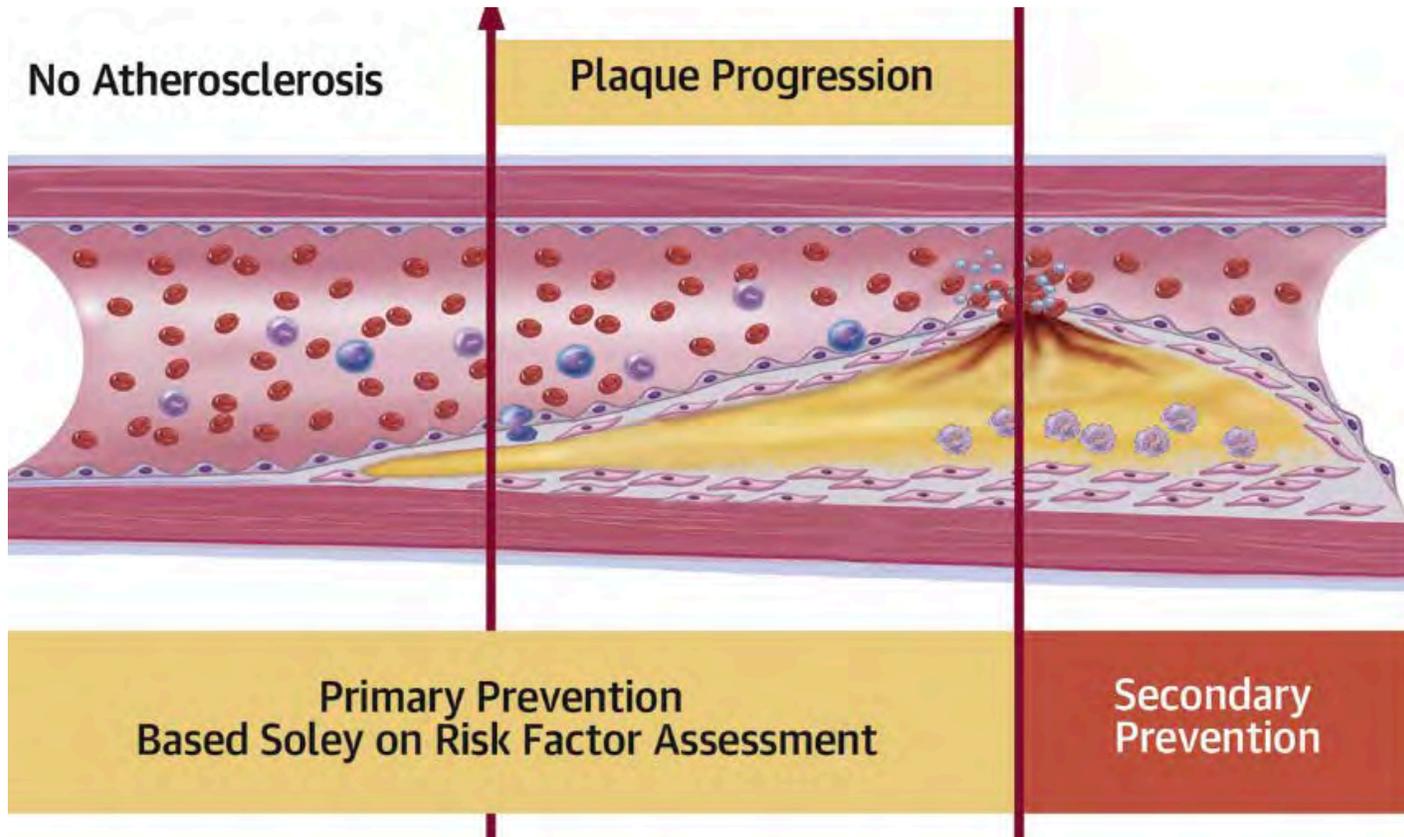
# DIAL CALCULATOR

u-prevent.com

# Prevenzione primaria o secondaria?



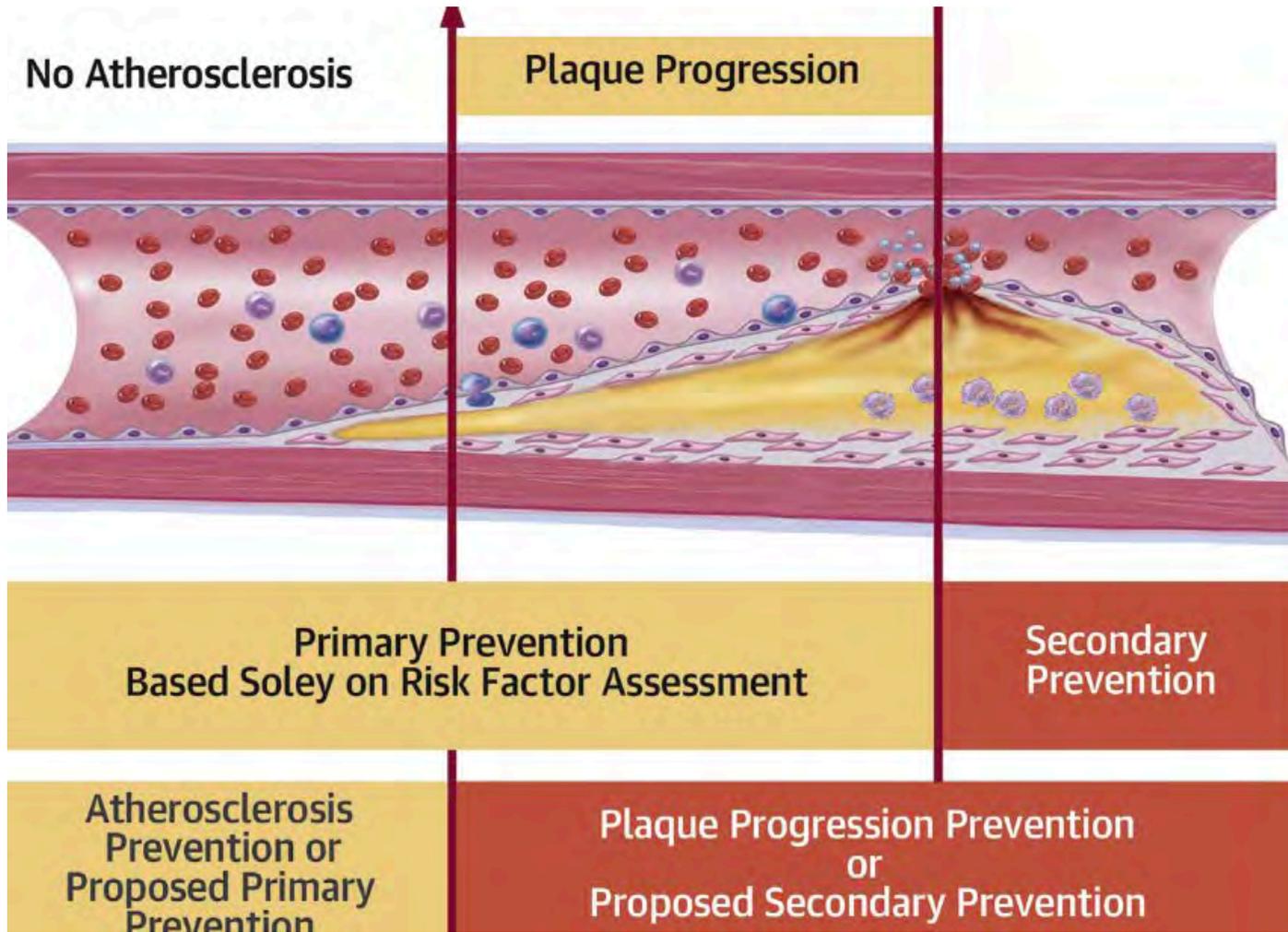
# Dalla disfunzione endoteliale all'evento clinico



Storia naturale della malattia  
aterotrombotica

**Pratica corrente:**  
Approccio legato a prevenzione  
primaria o secondaria

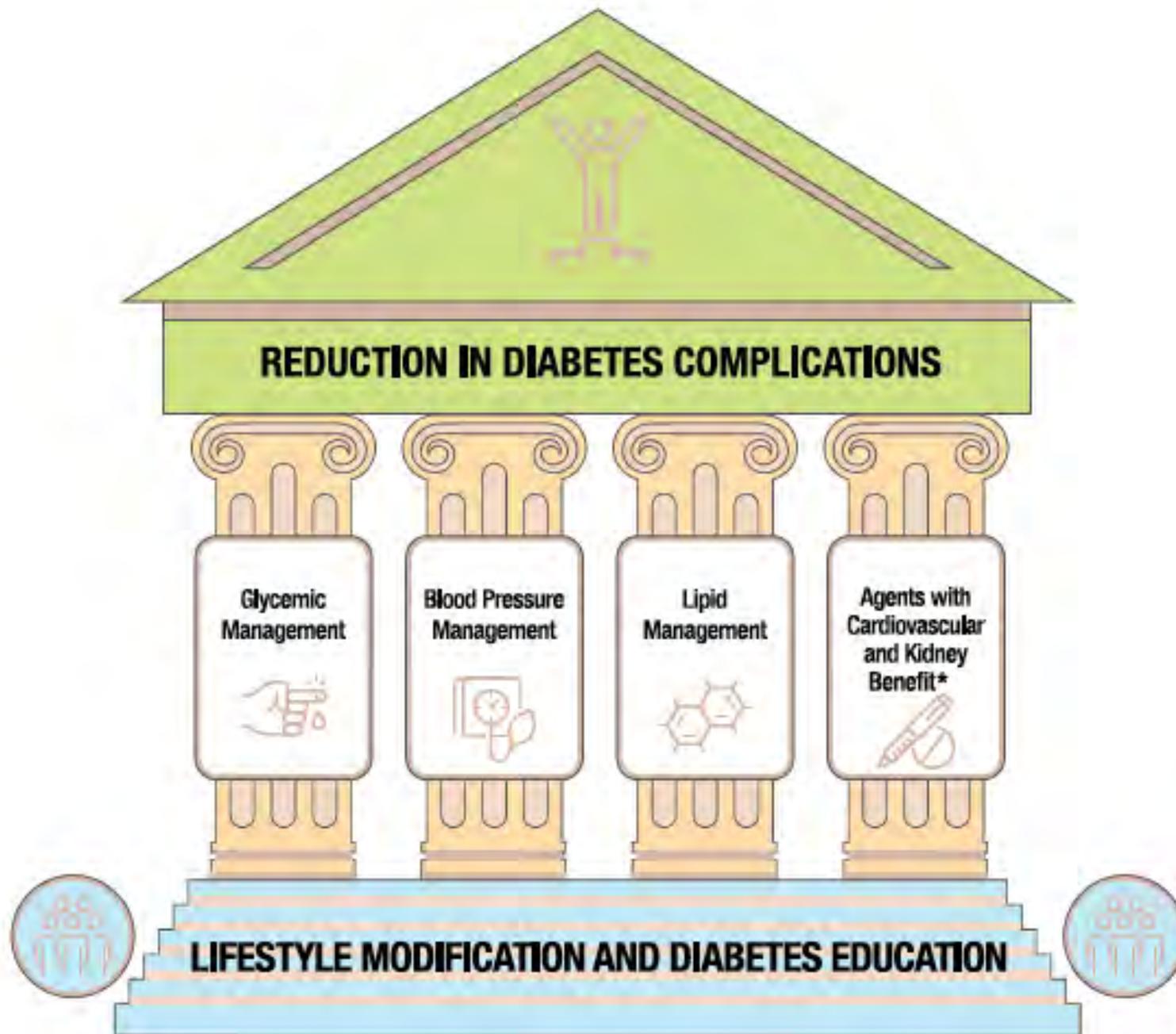
# Dalla disfunzione endoteliale all'evento clinico



**Storia naturale della malattia  
aterotrombotica**

**Pratica corrente:  
Approccio legato a prevenzione  
primaria o secondaria**

**Approccio innovativo:  
Intervenire precocemente sulla  
storia naturale dell'aterotrombosi**



ADA Standards of care 2022

# CV Risk Management



## Smoking cessation

It's recommended for all patients and guided by structured advice



## Physical activity

Moderate to vigorous aerobic and resistance exercise for > 150 min/week



## Weight

Reduced calorie intake is recommended for patients with overweight and obesity



## Diet

A Mediterranean diet rich in polyunsaturated and monounsaturated fats should be considered to reduce CV events

# CONCLUSIONI

- NON esiste un paziente con diabete T2 a basso rischio CV
- L'eccesso di rischio CV nel paziente con T2D è rimasto alto nel corso degli anni nonostante numerosi interventi sui fattori di rischio classici
- Il «prediabete» è un fattore di rischio per la patologia aterosclerotica
- Le nuove linee guida ESC hanno confermato, con la nuova classificazione, come la quasi totalità dei pazienti con diabete tipo 2 che afferiscono negli ambulatori sono a rischio cardiovascolare elevato o molto elevato
- E' necessario stratificare il rischio CV e assicurare la migliore protezione disponibile controllando ogni fattore di rischio implicato nella patogenesi

**There's no such thing as  
a sudden heart attack.  
It requires years of preparation.**





**USE THE  
RIGHT TOOL,  
FOR THE  
RIGHT JOB,  
IN THE  
RIGHT WAY.**



Grazie per l'attenzione

*m.monesi@ausl.fe.it*

