PERUGIA
22-23 NOVEMBRE 2024
Sangallo Palace Hotel

L'ipercolesterolemia nel T1 e T2 si tratta allo stesso modo?

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Disclosures

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

- ✓ Novo Nordisk;
- ✓ Guidotti;
- ✓ Ely-Lilly

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.).


YES

AGENDA

- Rischio Cardiovascolare nel T1D:
  - similmente differente rispetto al T2D?
- Dislipidemia nel T1D:
  - “un rischio mascherato” da trattare ?
- Impatto delle terapie ipolipemizzanti sugli outcomes CV:
  - Differente tra T1 vs T2?

Questionari ECM

Type 1 Diabetes:

a neglected cardiovascular disease?

"Cardiovascular disease is the most common cause of death

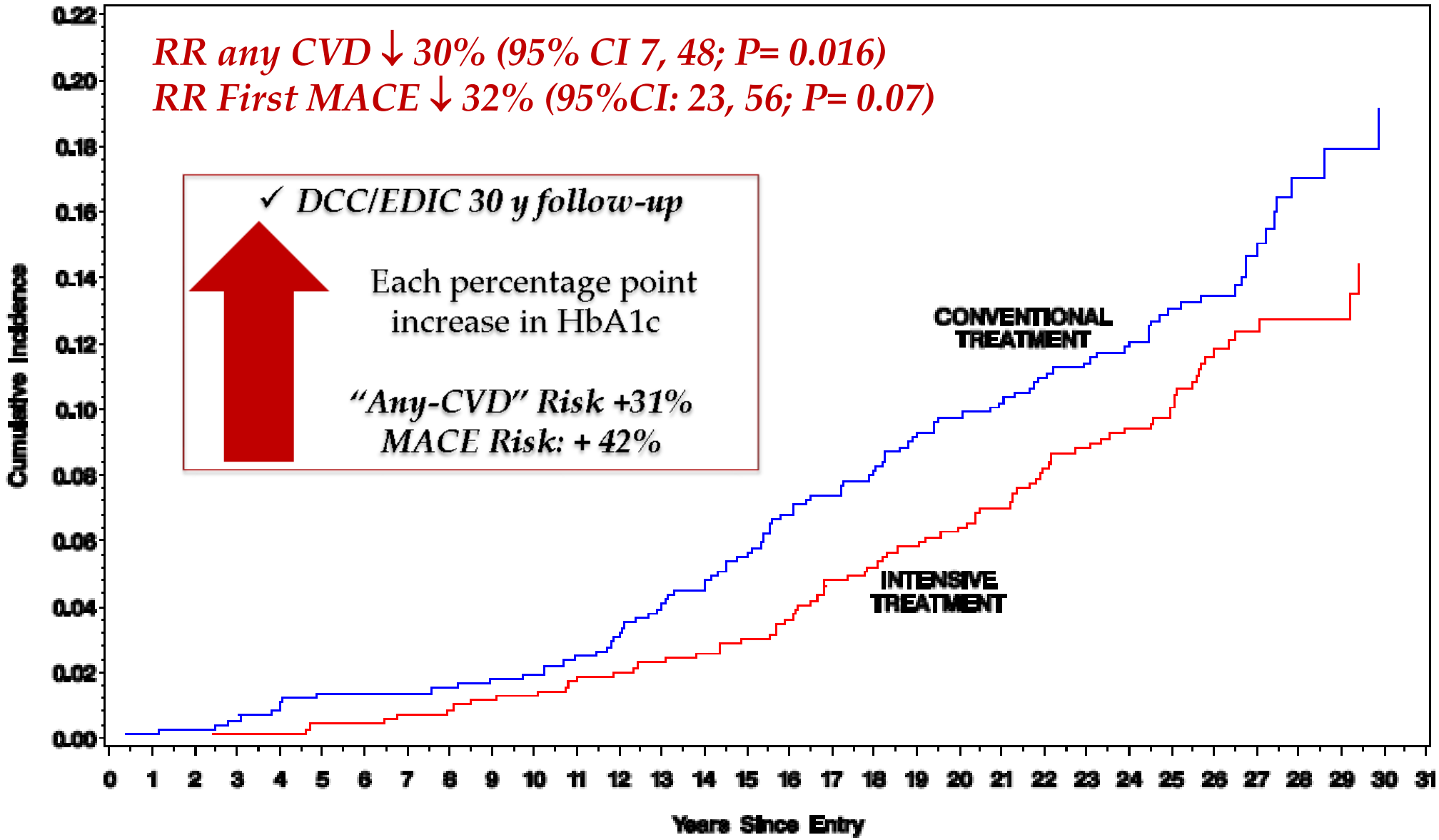
in type 1 diabetes, as it is in type 2 diabetes……

type 1 diabetes is where type 2 diabetes was 20 years ago,

in the sense that we used to be extremely ***glucose-centric….***

CV risk management receives far less attention than glucose management"

Camila Manrique-Acevedo et al N Engl J Med 2024



Diabetes Care 2016;39:686–693 | DOI: 10.2337/dc15-1990

	Treatment group adjusted for specific time-dependent covariate*	
Time-dependent covariate	HR (95% CI)	*P* value
Mean HbA_{1c} during DCCT/EDIC#		
Per 10% increase	1.00 (0.72, 1.39)	0.9843
Per 10% decrease		

Nel diabete tipo 1, l'effetto benefico della «memoria metabolica» sulla riduzione del rischio CV tende a disperdersi nel tempo

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)

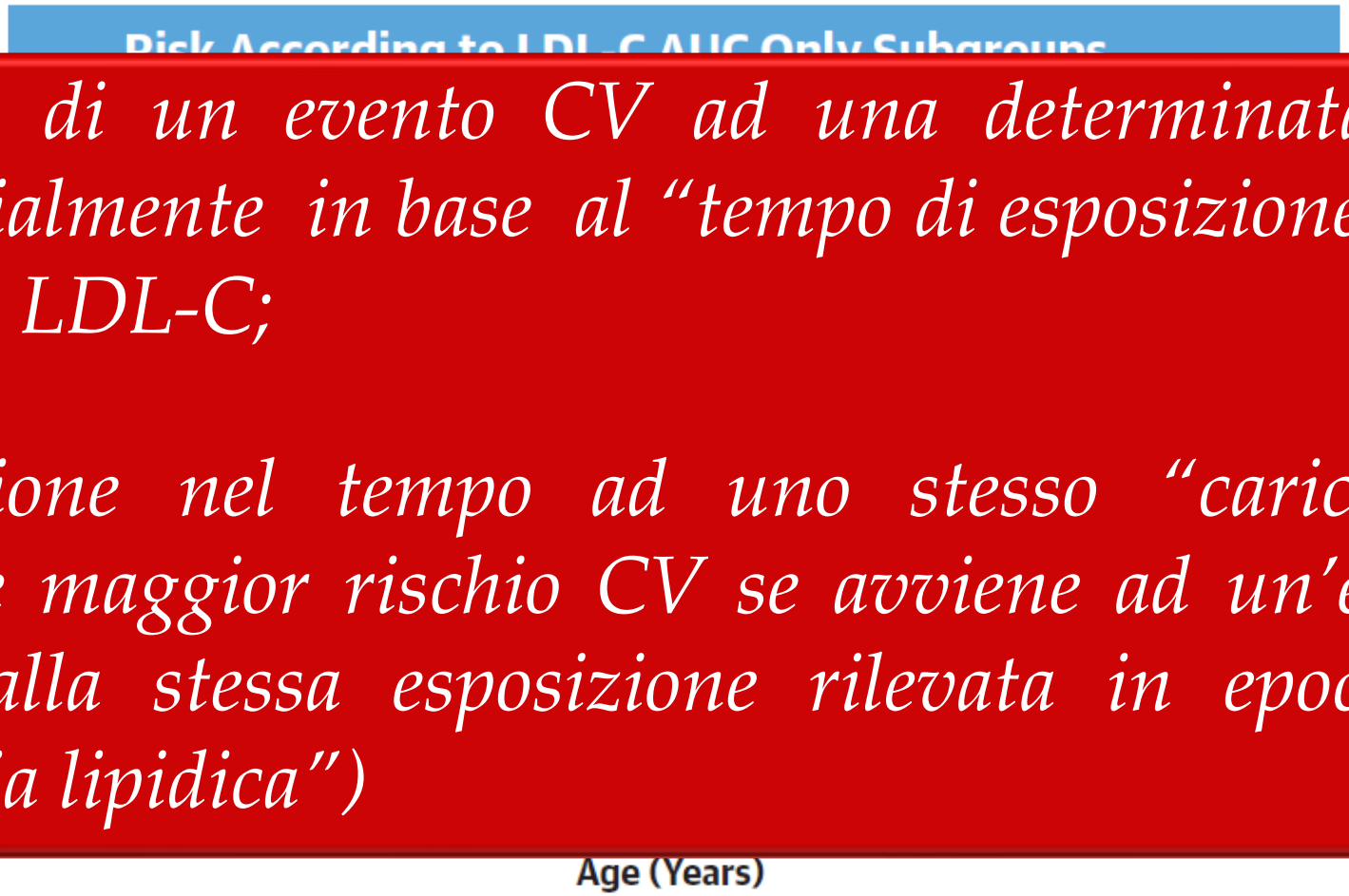
National Diabetes Register after January 1, 1998,

Il concetto di "gluco-centricità" per la predizione del rischio CV nel T1D deve esser contestualizzato nell'ambito della globalità dei fattori di rischio CV

Time Course of LDL-C Exposure and CVD Event Risk:

a «lipid memory»?

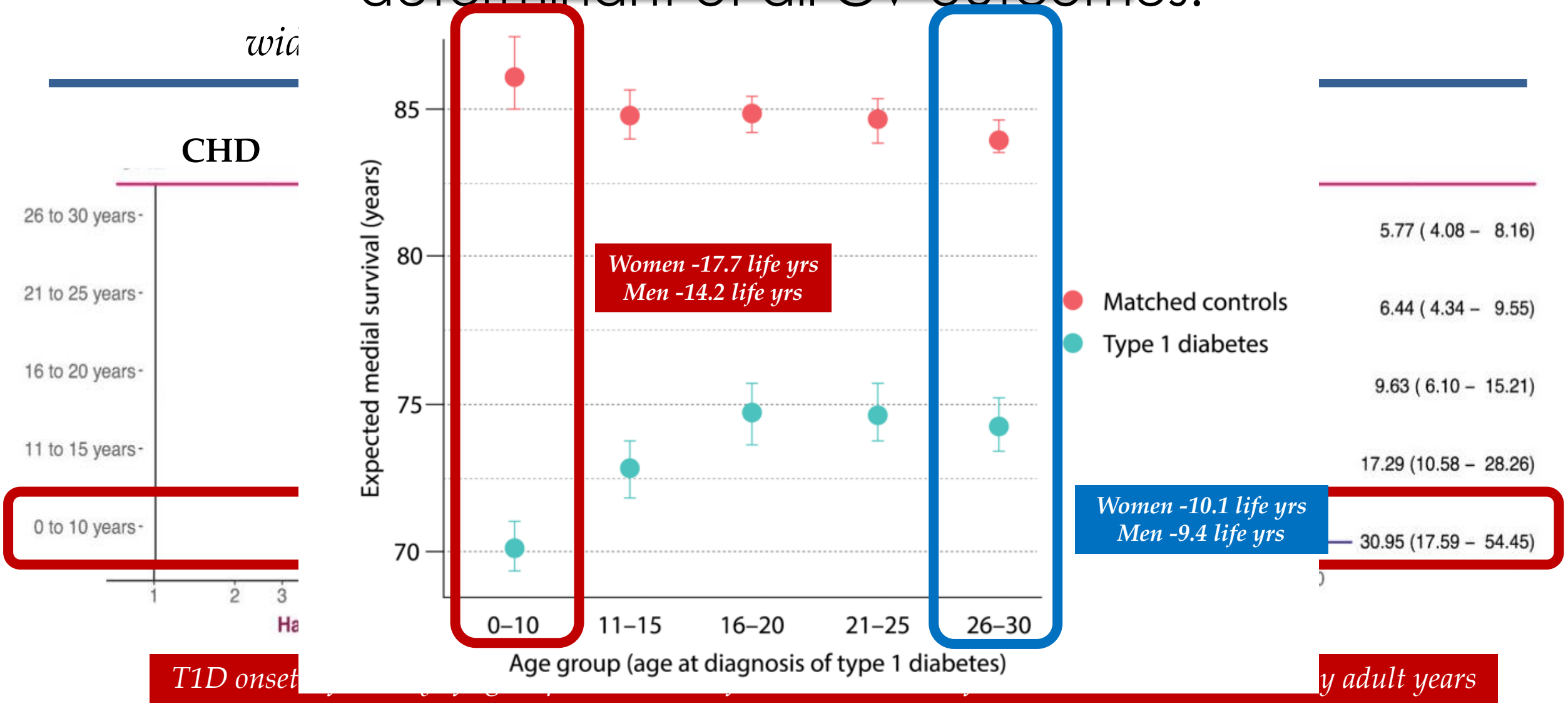
- ✓ *Il rischio di un evento CV ad una determinata età aumenta esponenzialmente in base al "tempo di esposizione" all'accumulo (AUC) di LDL-C;*
- ✓ *L'esposizione nel tempo ad uno stesso "carico" di LDL-C conferisce maggior rischio CV se avviene ad un'età più precoce rispetto alla stessa esposizione rilevata in epoca più tardiva ("memoria lipidica")*



Domanski MJ et al JACC 2020

Age at onset of type 1 diabetes is an important determinant of all CV outcomes:

Life years lost in relation to age at onset of T1D

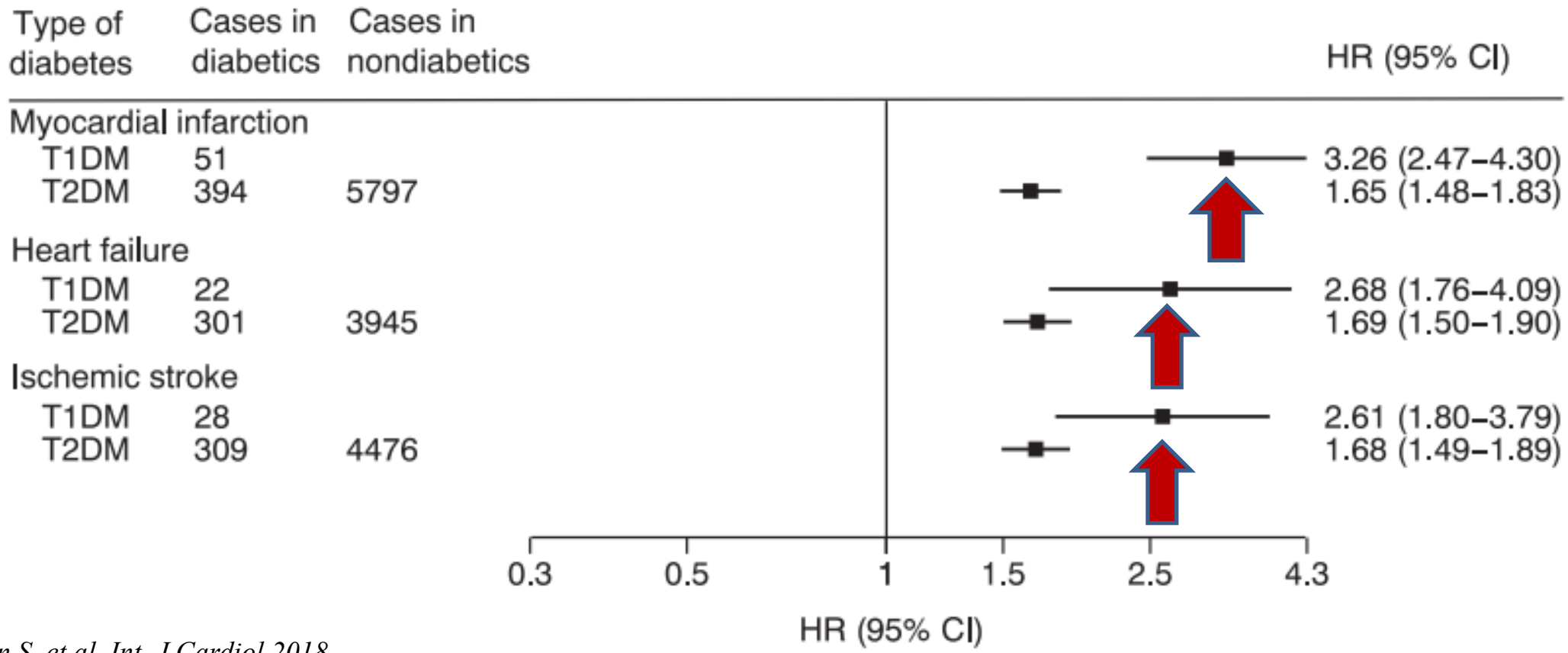


Rawshani A. et al.Lancet 2018

Type 1 and Type 2 diabetes are associated with high incidence of CV outcomes

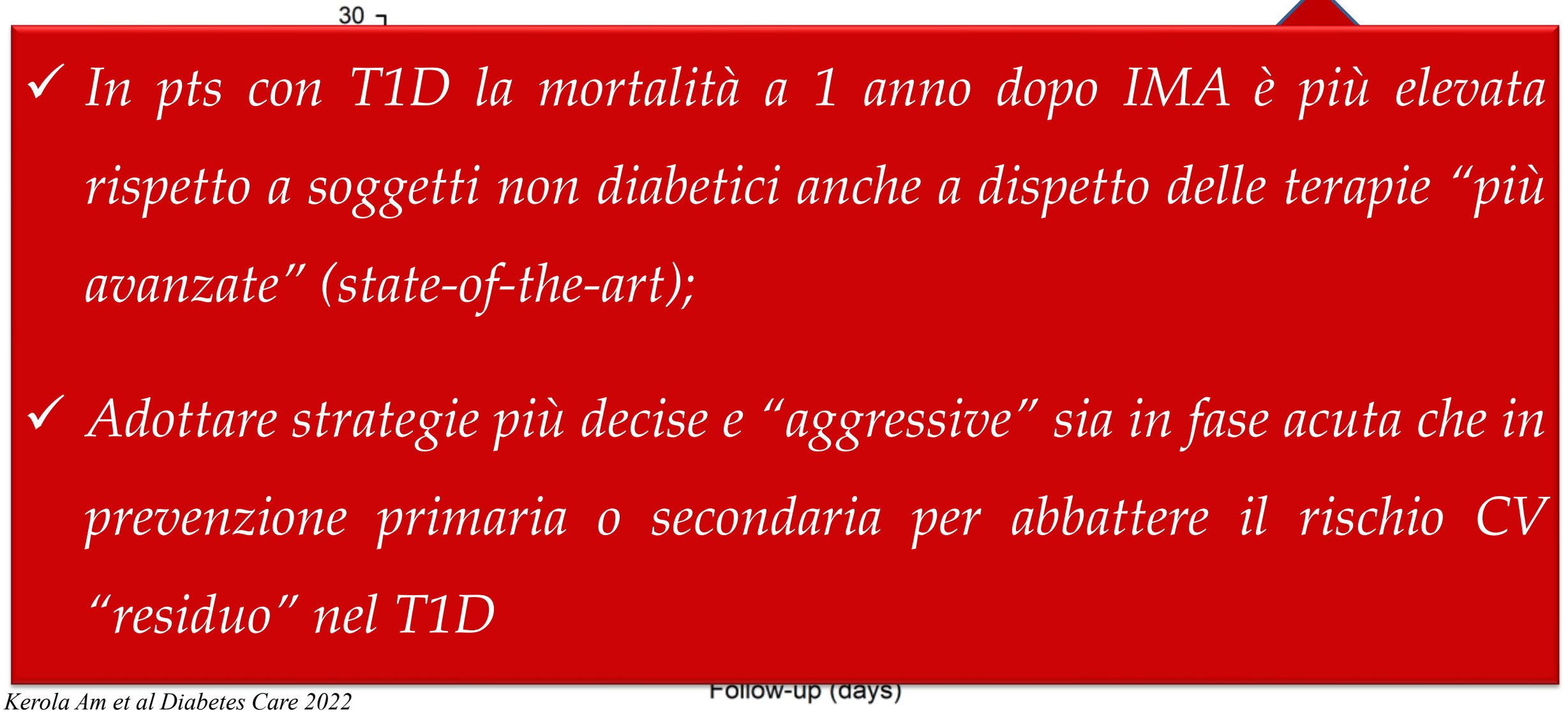
71,483 Swedish adults from two population-based prospective cohorts.

No diabetes (n=69,106) ;T1D (n =247); T2D (n=2130)



Larsson S. et al. Int J Cardiol 2018

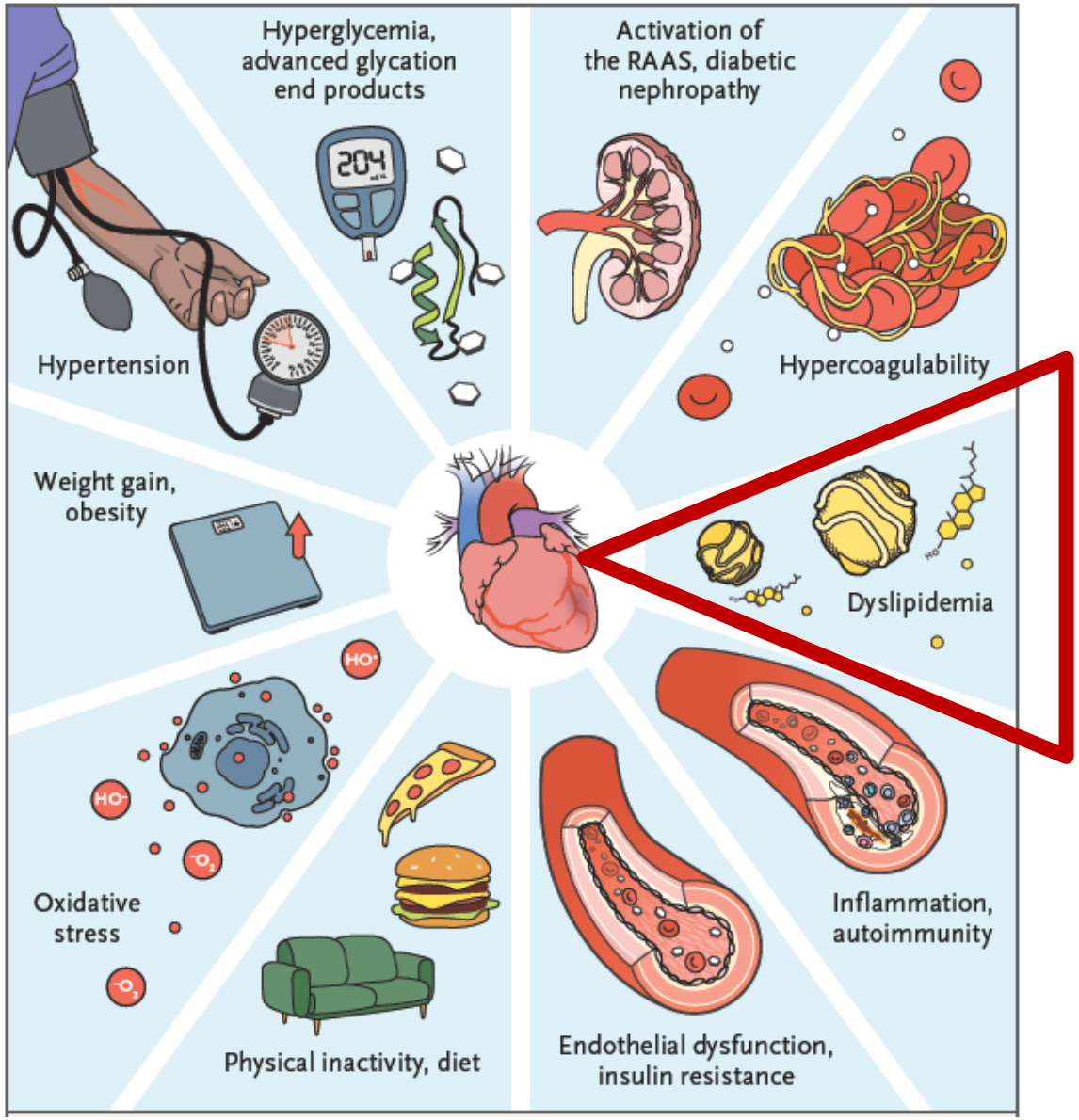
Patients with T1D are at higher risk of death after MI than patients without diabetes



- ✓ *In pts con T1D la mortalità a 1 anno dopo IMA è più elevata rispetto a soggetti non diabetici anche a dispetto delle terapie "più avanzate" (state-of-the-art);*
- ✓ *Adottare strategie più decise e "aggressive" sia in fase acuta che in prevenzione primaria o secondaria per abbattere il rischio CV "residuo" nel T1D*

Kerola Am et al Diabetes Care 2022

Similar Biology of CV Disease in Type 1 vs Type 2?



Manrique-Acevedo C et al NEJM 2024

Relative Association Between Specific CV Risk Factors and CVD Events in T1DM vs T2DM

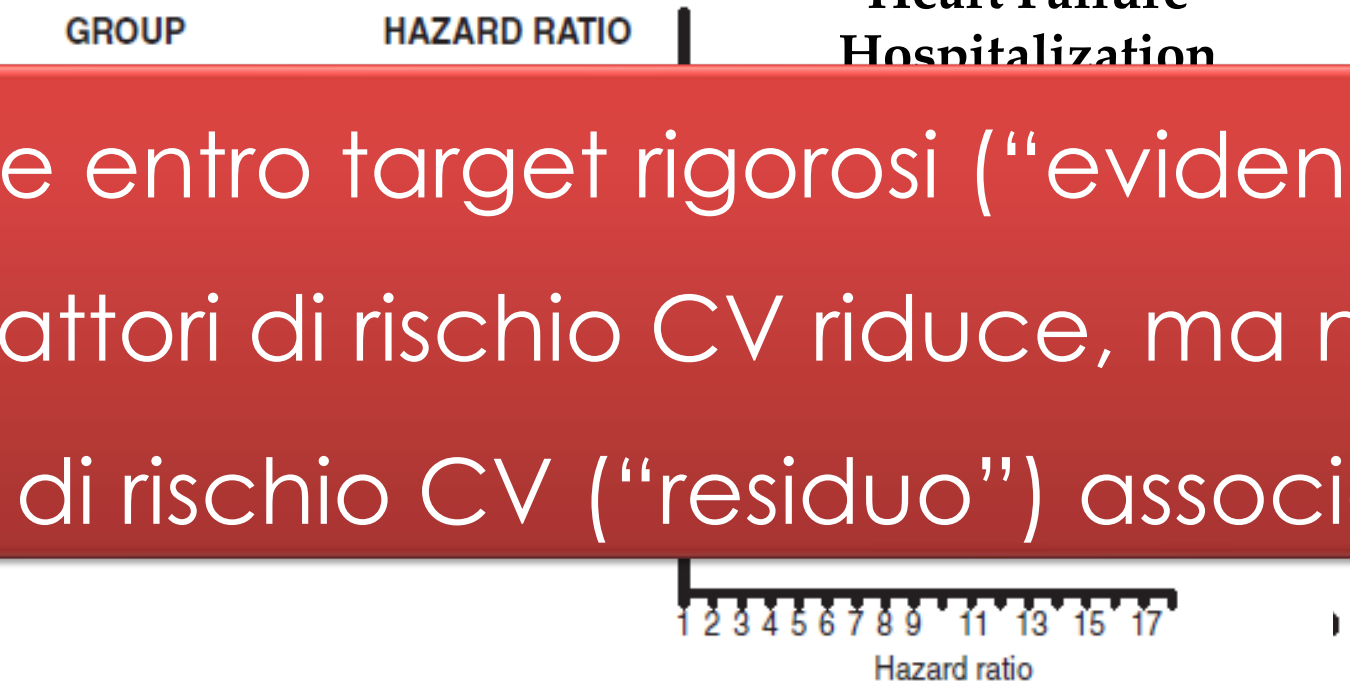
	T1DM	T2DM
Hypertension	+++	++
Cigarette smoke	++	++
Inflammation	++	++
High LDL-C	+	+++
Low HDL-C	0, +	++
Triglycerides	No data	++
Microalbuminuria	+++	+++
Insulin resistance	+	+++
Poor glycemic control	+++	+++

*CVD in T1D differs from T2D, not only in that it presents at a **younger age** but also in that **women are affected at rates equal to those in men***

Maintenance of CV risk factors "at target" and excess risk of mortality and CVD in T1D

- ✓ Swedish National Diabetes Register:
  - ✓ *33.3*
  - ✓ *Mea*

trols;

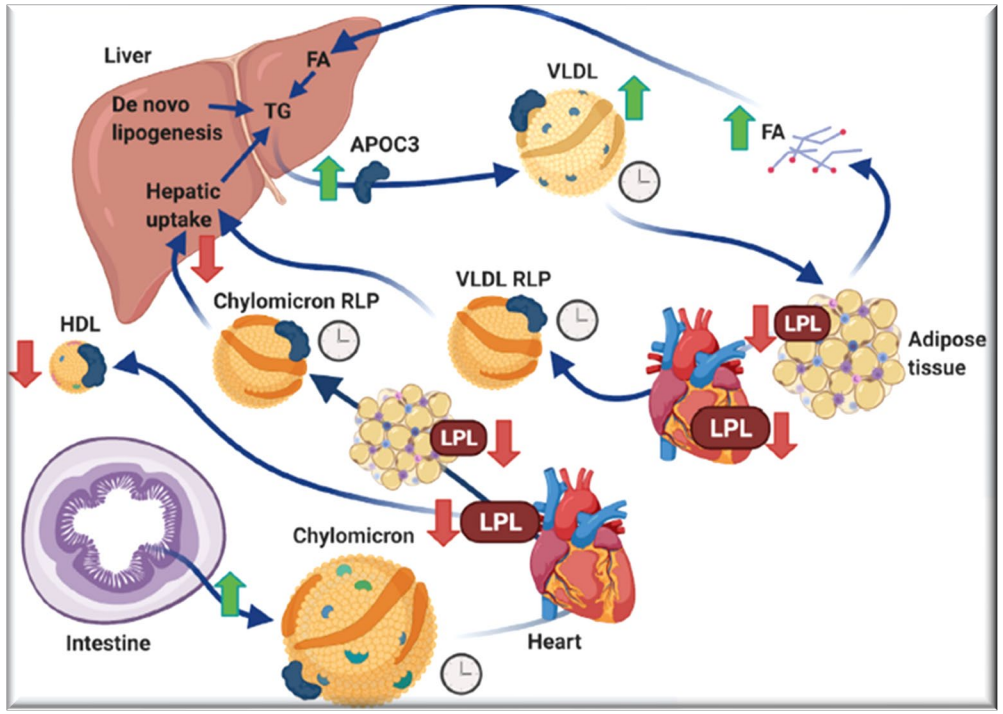


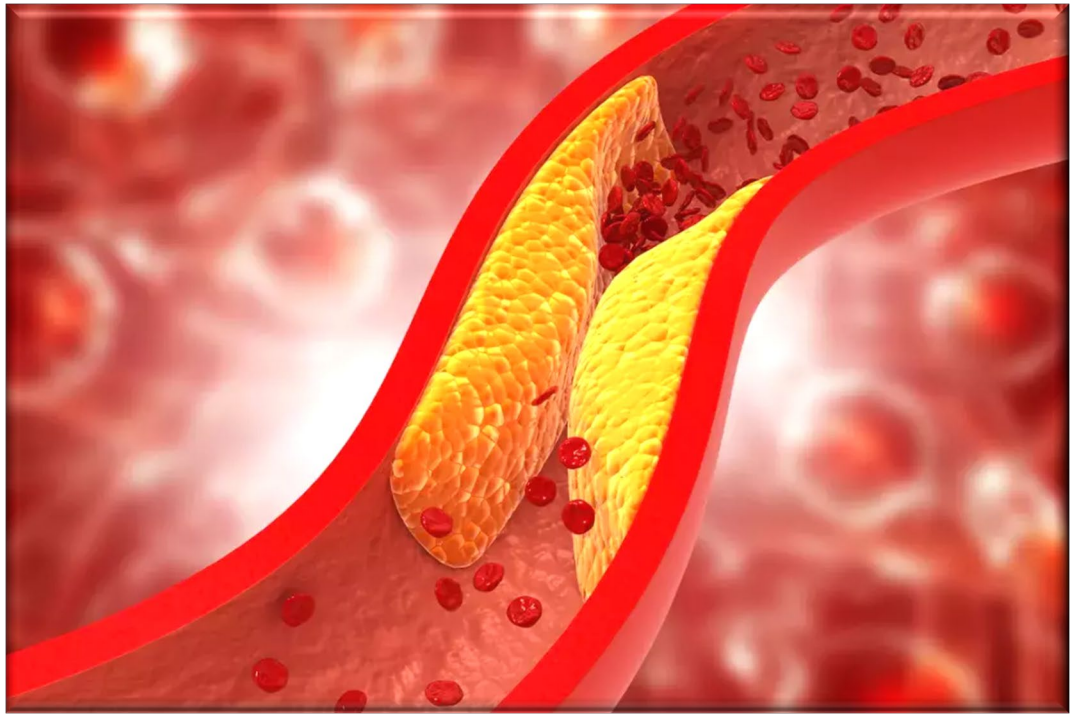
Manetenere entro target rigorosi ("evidence-based") 5 specifici fattori di rischio CV riduce, ma non elimina, l'eccesso di rischio CV ("residuo") associato al T1D

HbA_{1c}	≥53 mmol/mol (≥6.9%)

Rawshani A et al. Circualtion 2017

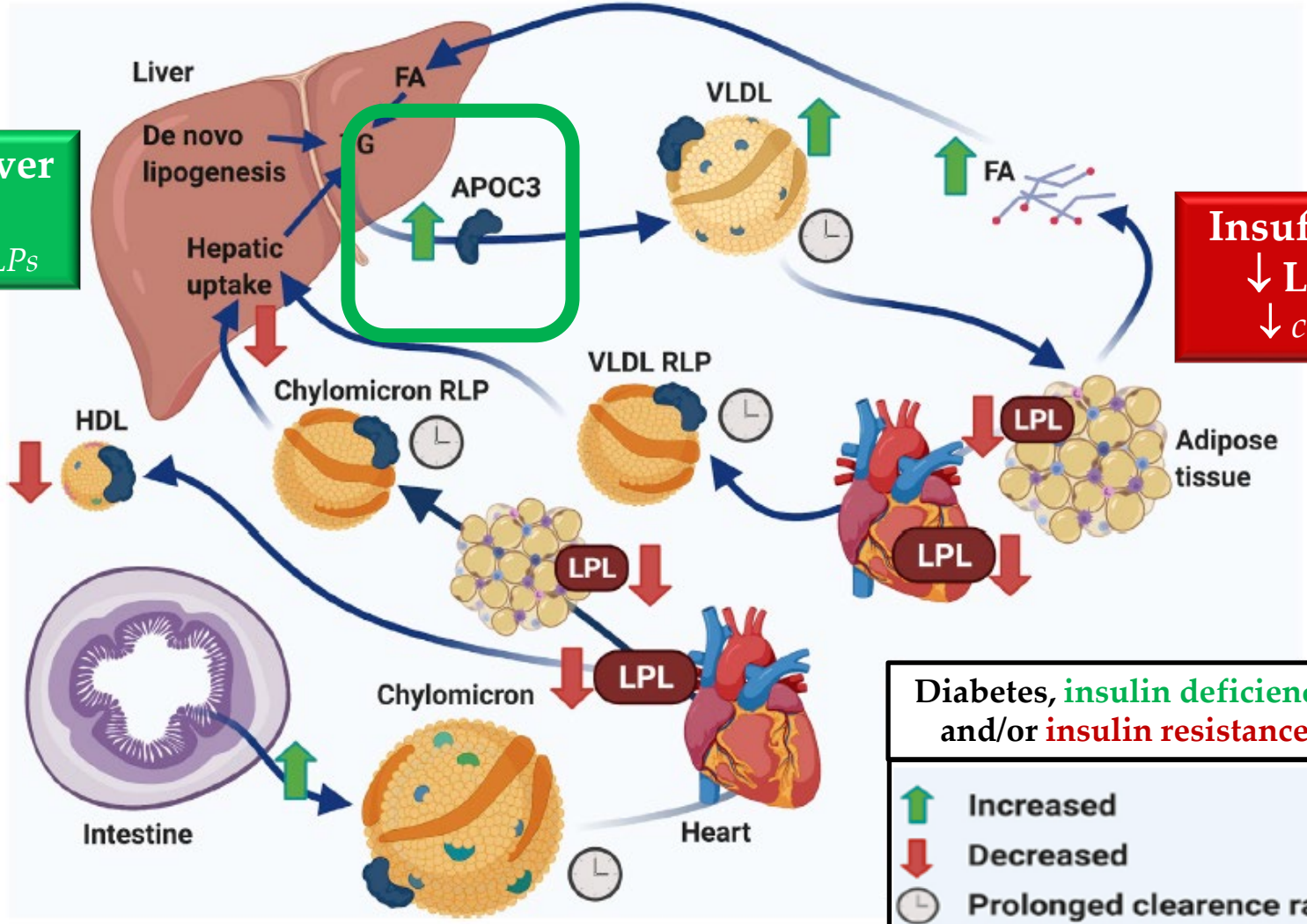
Differente «potenziale» aterogeno in base al profilo lipoproteico nel tipo 1 vs tipo 2 ?





Effects of diabetes on lipoprotein metabolism

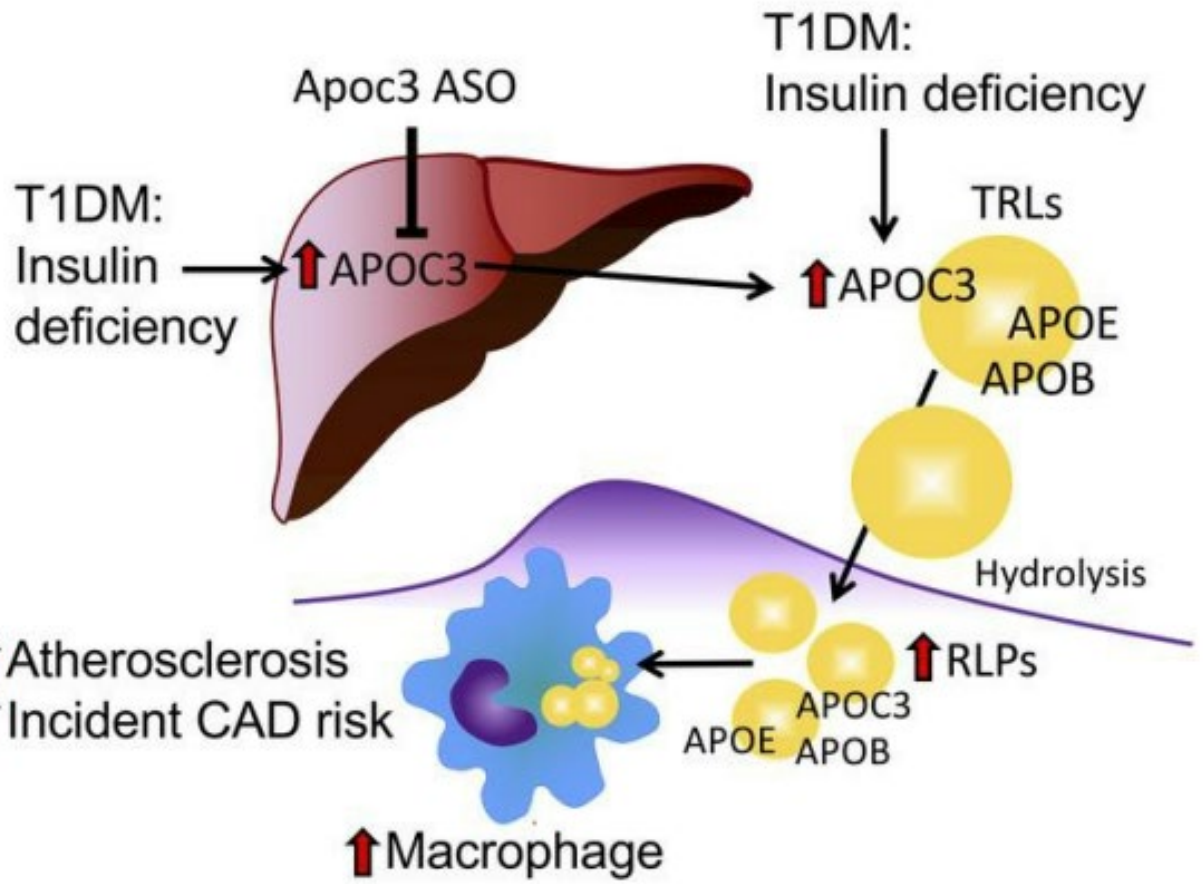
Insulin deficiency in liver
↑ APOC3:
↓ *clearance TG-rich LPs and RLPs*

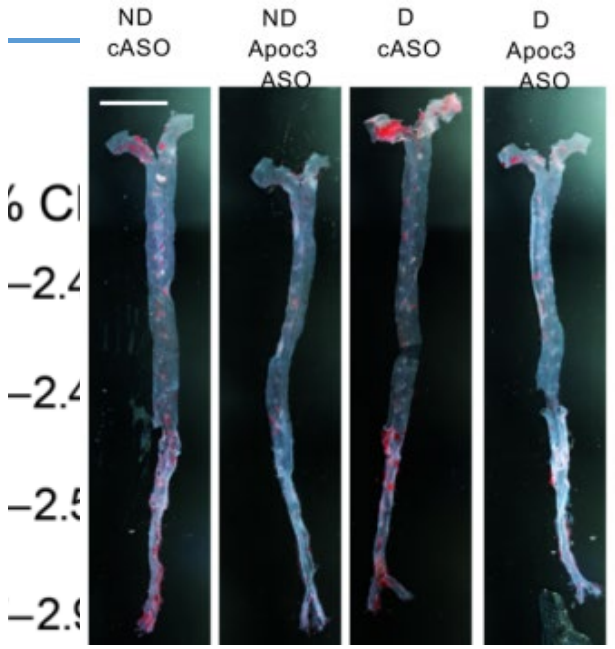


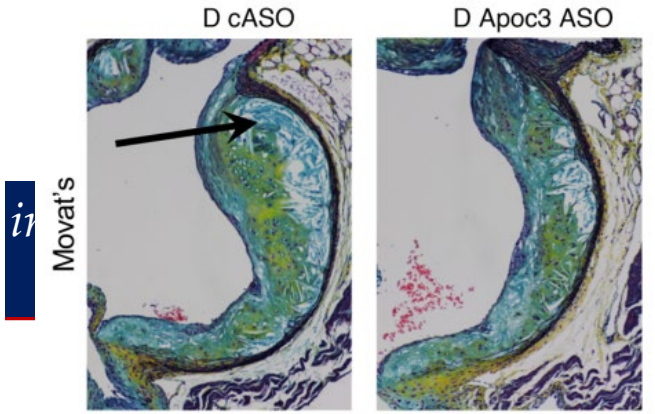
Insufficient insulin action
↓ LPL in fat and heart:
↓ *clearance of TG-rich Lps*

Eckel RH et al Cell Matab 2021

Increased apolipoprotein C3 drives CV risk in type 1 diabetes







Kanter JE et al. J Clin Invest. 2019

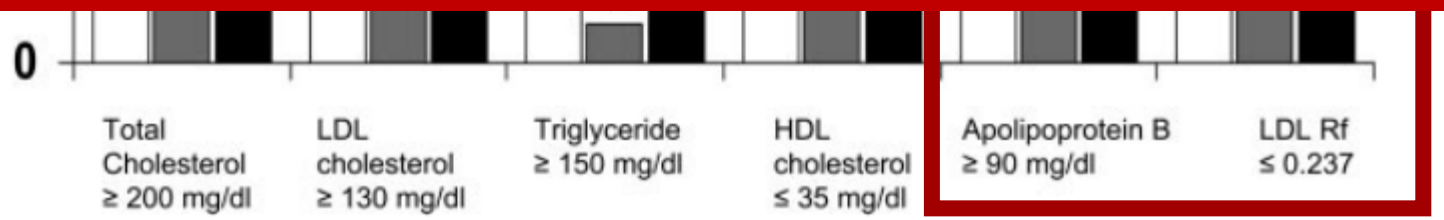
Lipid profile in youth with T1D with optimal and suboptimal glycemic control vs nondiabeitc youth:

The SEARCH Study

Cross-sectional analysis in 512 youth ***T1D (mean duration 4.2 y)*** *vs 188 healthy controls* ***aged 10-22 y*** *in Colorado and South Carolina*

most frequent lipid abnormalities in

In pts tipo 1 di giovane età, con breve durata (4.2 aa) di malattia, e con livelli "accettabili" di HbA1c, a dispetto di un profilo lipidico "super-normale" (**↑HDL-C; ↓TG***), la composizione delle lipoproteine circolanti presenta elevato potenziale aterogeno (* **↑ApoB; ↑ sdLDL***)*

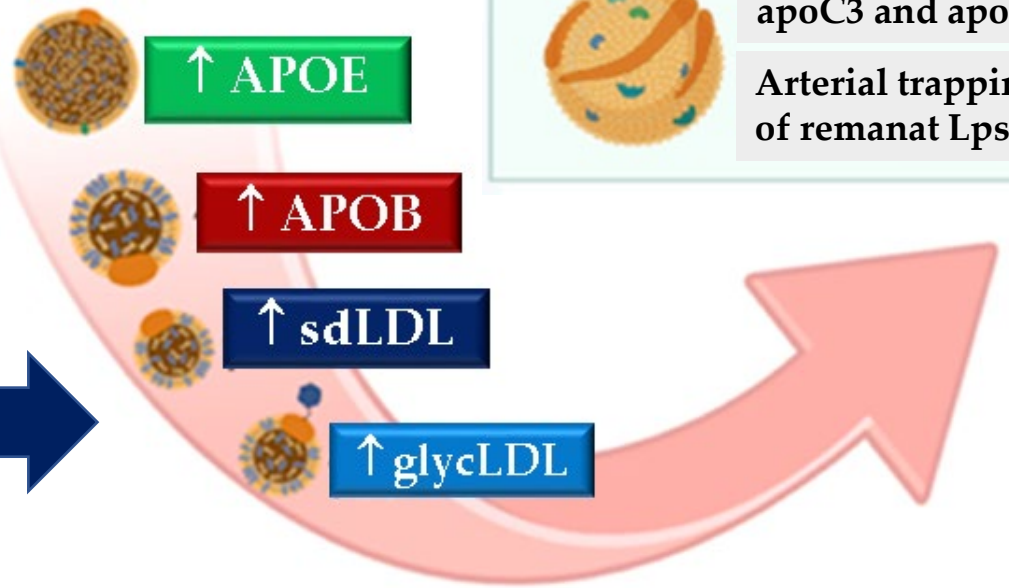


Guy J et al. Diab Care 2009

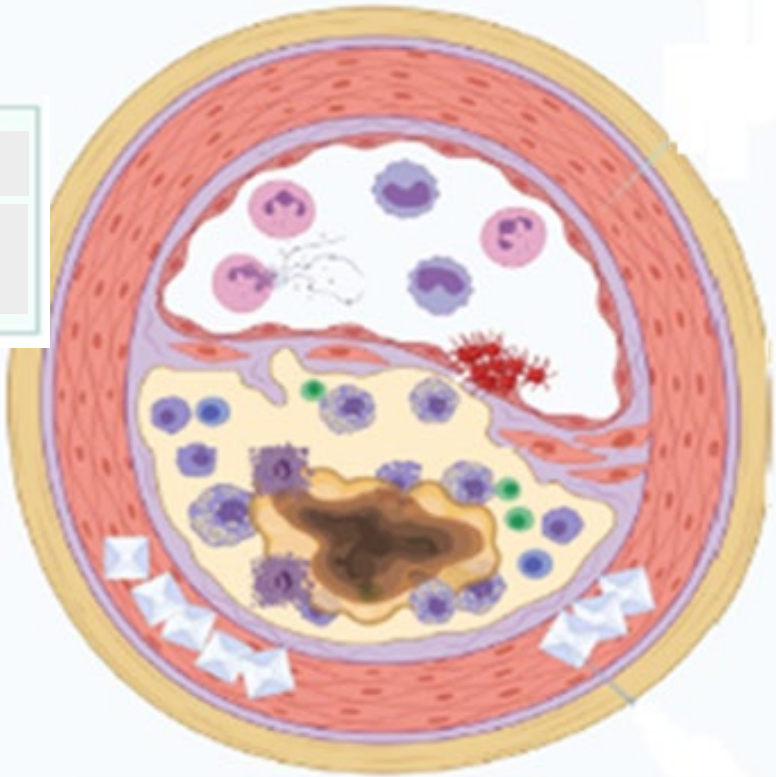
Abnormal Lipid Profile in T1D enhances atherogenesis and modifies plaque composition

Type 1 Diabetes

Abnormal Lipoproteins Profile



Atherogenesis and Plaque Composition



↑ MΦ and T cells, necrotic cores,
↑ Unstable and prone to rupturing or fissuring;
↑ Platelet activation and thrombus formation

Modified from Eckel RH et al Cell Matab 2021; Lucini L et al Atherosclrosis 2024

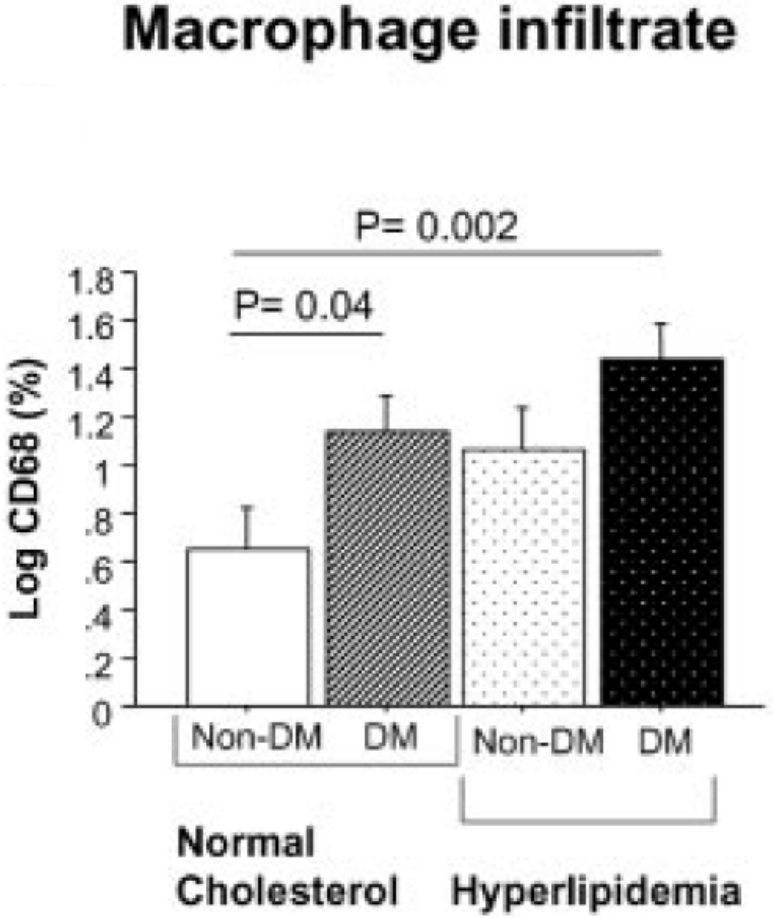
	Type I	*P* vs Nondiabetic	Type II	*P* vs Nondiabetic	Nondiabetic Subjects
Necrotic core, %				*	9.4±9.3
Macrophage plac		2			0.10±0.02†
Total plaque bur		)		1	232±128

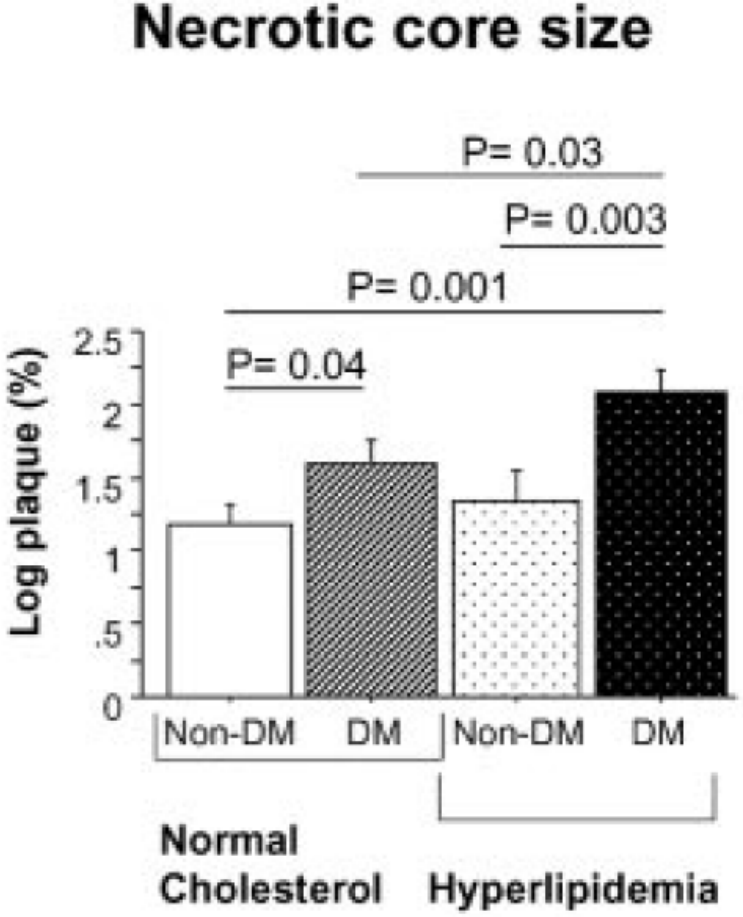
*P values calc
†P=0.006 vs

Hyperten
Body ma
TC/HDL c

-DM
-DM

5.4
30.4





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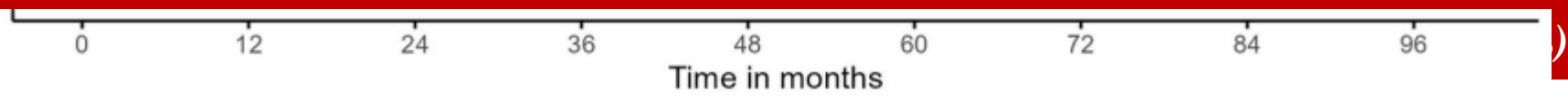
Subclinical atherosclerosis and CV risk prediction in type 1 diabetes

- ✓ *507 T1D pts (54% males) aged 48.7±13.0 y with diabetes duration 23.2±10.8 y* ***without overt CVD;***
- ✓
- ✓
- ✓

MACE

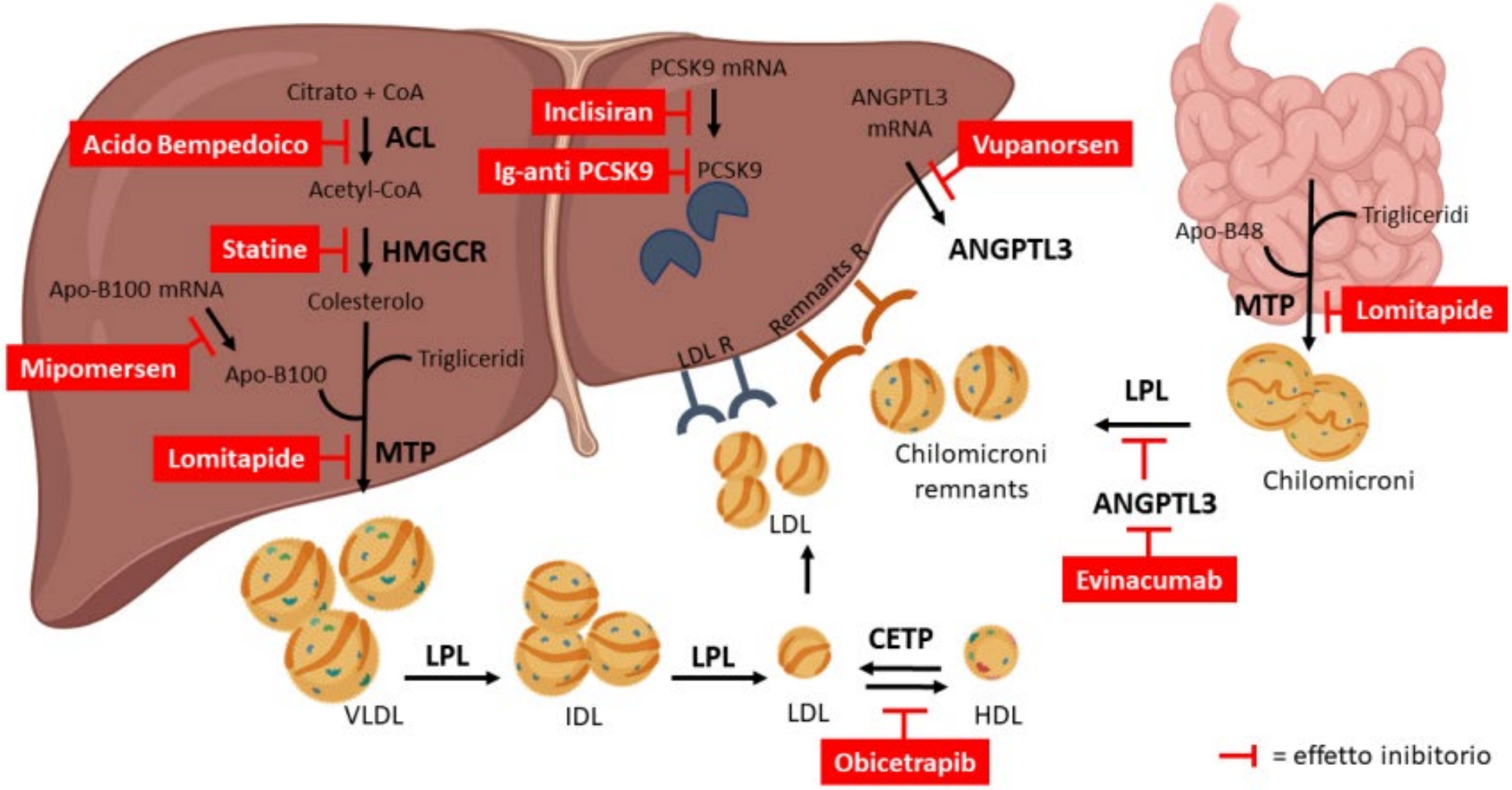
- ✓ *In pts con T1D senza precedenti CV, la presenza di aterosclerosi sub-clinica (placche carotidee o/e femorali) si associa ad aumetato rischio di MACE (inclusa mortalità), anche a dispetto di livelli di LDL-C sub-ottimali (<100 mg/dL) e del trattamento con statine;*
- ✓ *Utilità dello screening con eco-Color-Doppler carotideo e femorale per la corretta "ri-stratificazione" del rischio CV e la pianificazione di opportune strategie terapeutiche*



Sojo-Vega et al. Cardiovascular Diabetology (2024) 23:366

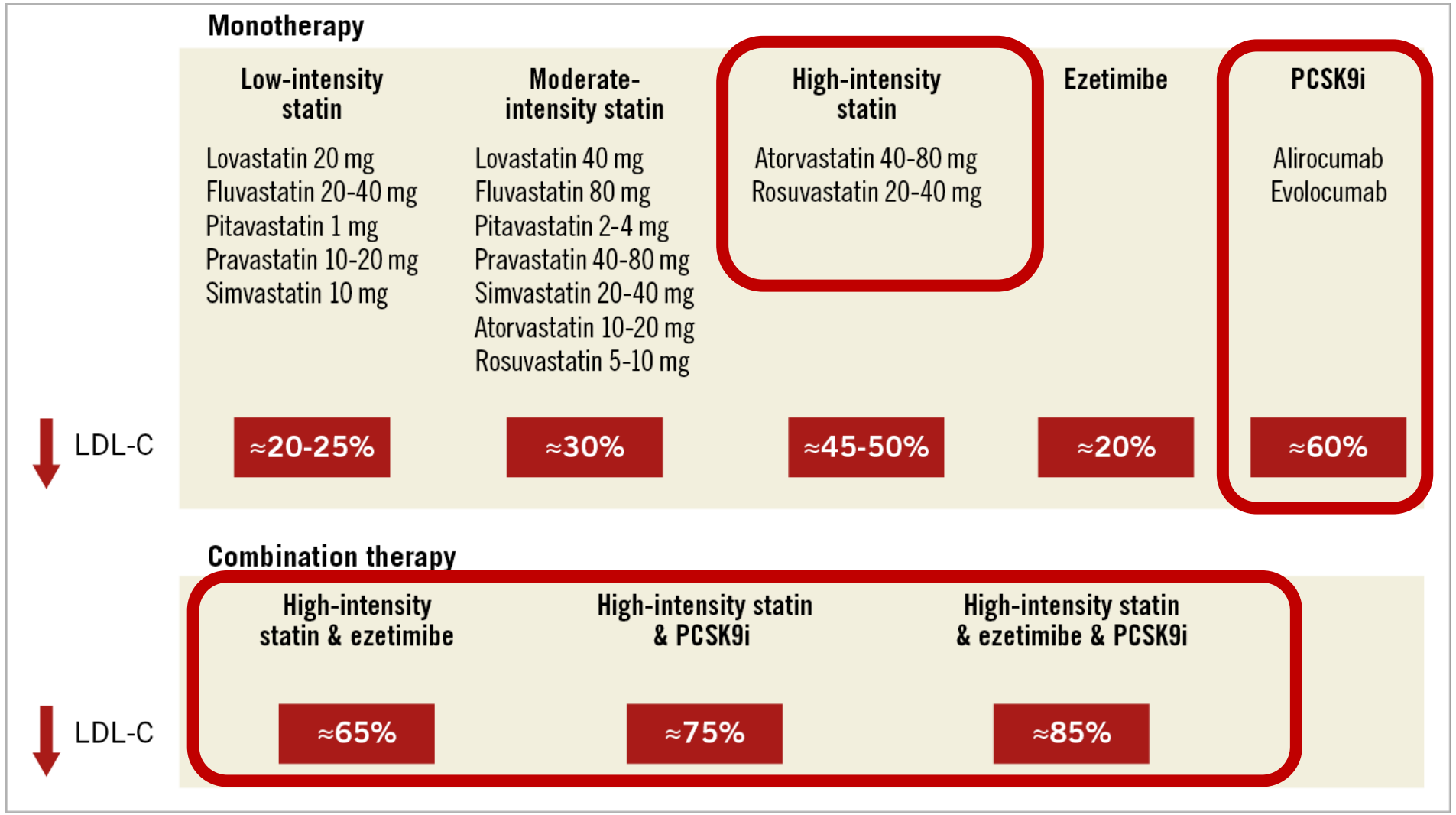
Le raccomandazioni terapeutiche per il trattamento dell'ipercolesterolemia nel T1D sono principalmente basate su analisi di "sottogruppo" o rappresentanto estrapolazioni di effetti dimostrati su popolazioni con differenti caratteristiche cliniche

Bersaglio molecolare e meccanismo d'azione dei principali farmaci ipocolesterolemizzanti

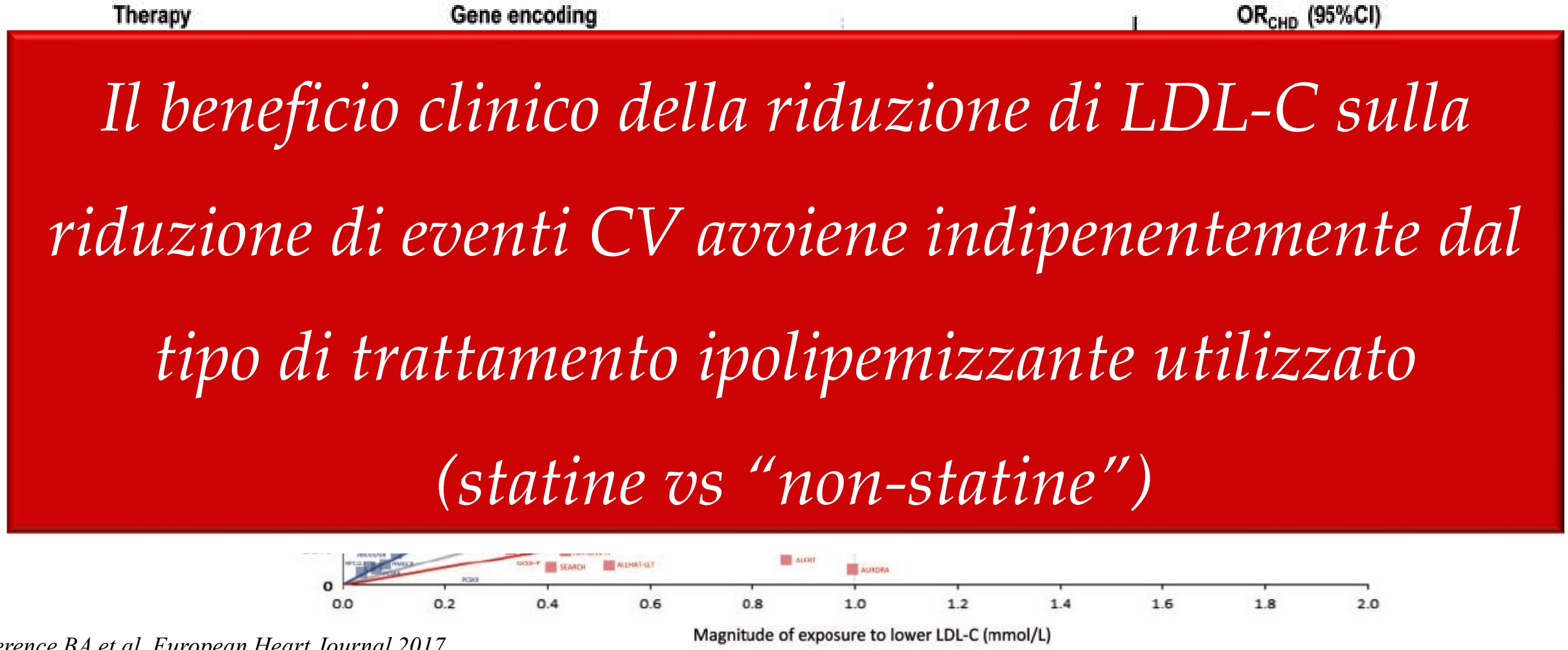


Della Pepa G. Il Diabete 2024

Expected clinical benefits of LDL-C lowering therapies



Benefit of lowering LDL-C appears to be independent of the mechanism by which LDL-C is lowered



Ference BA et al. European Heart Journal 2017

Statine e Prevenzione Primaria nel T1D

2008; 371: 117–25

Efficacy of

	Diabetes mellitus			No diabetes
	Type 1	Type 2*	Any type	
4S[15]	24 (0·5%)	178 (4·0%)	202 (4·5%)	4242 (95·5%)
WOSCOPS[16]	8 (0·1%)	68 (1·0%)	76 (1·2%)	6519 (98·8%)
CARE[17]	193 (4·6%)	393 (9·4%)	586 (14·1%)	3573 (85·9%)
CARDS[18]	3 (0·1%)	2835 (99·9%)	2838 (100%)	0
Total	1466 (1·6%)	17 220 (19·1%)	18 686 (20·7%)	71 370 (79·3%)

Data are number (%). *Includes 13 participants with diabetes of unknown type.

Global test for heterog

RR (99% CI)

RR (95% CI)

- ✓ *Lo studio CTT ha arrruolato **1,466 pts con T1D**, età media di **55 aa**, **e che nel 56% dei casi avevano già una storia di stroke, MI, o LE-PAD;***
- ✓ *Questo sottogruppo non è rappresentantivo della popolazione di pts con T1D idealmente candidabili ad una "prevenzione primaria" ;*
- ✓ *Il trial è datato di circa 20 anni: i farmaci per la cura del diabete sono stati implementati da molecole "innovative" " con comprovata efficacia CV*

21% reduction in MACE per mmol/L reduction in LDL-C similar in T1D vs T2D

Primary prevention with Lipid Lowering Therapy in T1D

e 39, June 2016

Total death

Overall cohort

- ✓ *In pts con T1D senza storia di CVD, la terapia ipolipemizzante (statine) si associa a* ***riduzione del 22-44% del rischio di CVD e di mortalità CV;***
- ✓ *Efficacia della terapia ipolipemizzante in prevenzione "primaria" nel T1D*

Survival days

Ezetimibe, bempedoic acid, and PCSK9-i also lower LDL-C but do not have sufficiently proven efficacy in type 1 diabetes

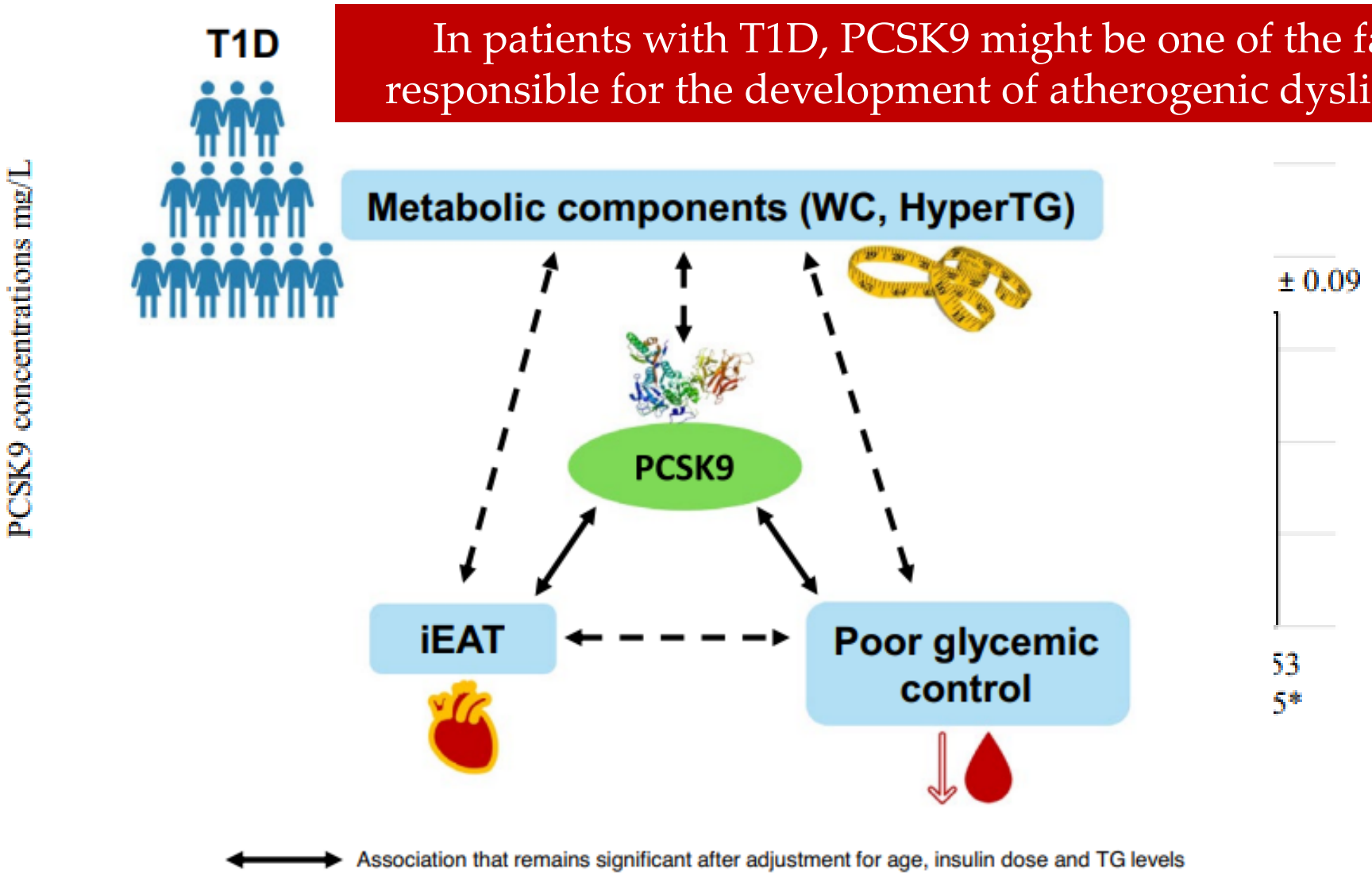
scientific reports

OPEN

PCSK9 plasma concentration is associated with epicardial adipose tissue volume and metabolic control in patients with type 1 diabetes

Helena Sardà[1,2], Cristina Colom[1], Sonia Benitez[3,4], Gemma Carreras[5,6], Judit Amigó[7], Inka Miñambres[1,2,4], David Viladés[8,9], Francisco Blanco-Vaca[10,11,4], Jose Luís Sanchez-Quesada[3,4]✉ & Antonio Pérez[1,2,4]✉

Comparative PCSK9 plasma concentration according to clinical and biochemical variables and correlation with EAT



CV Safety and Efficacy of Evolocumab in Diabetes:

A Prespecified Analysis from the FOURIER Trial

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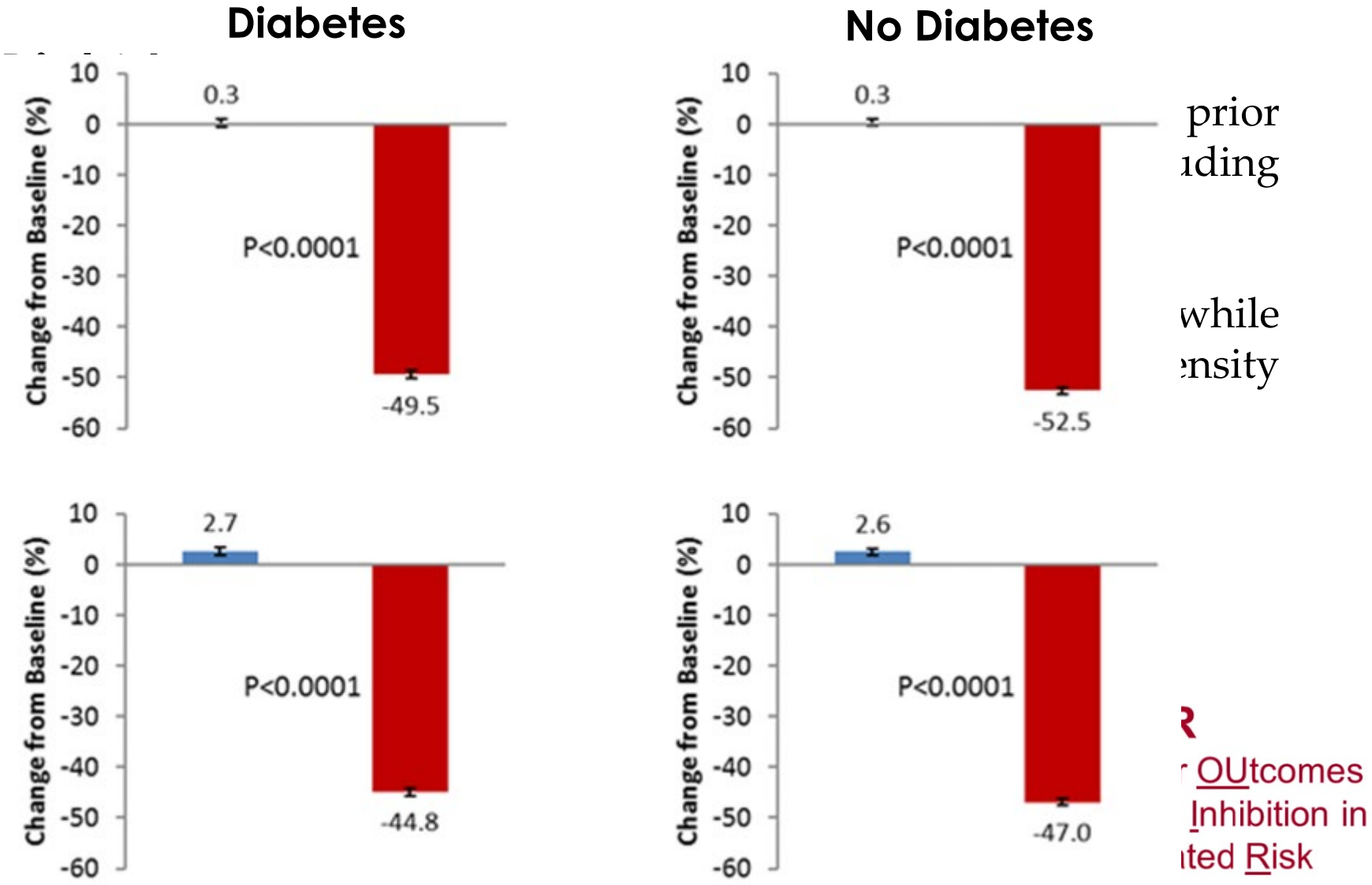

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Inhibition in
ted Risk

Sabatine M et al Lancet Diab Endocrinol 2017

Received: 28 July 2017 | Revised: 25 August 2017 | Accepted: 1 September 2017

DOI: 10.1111/dom.13114

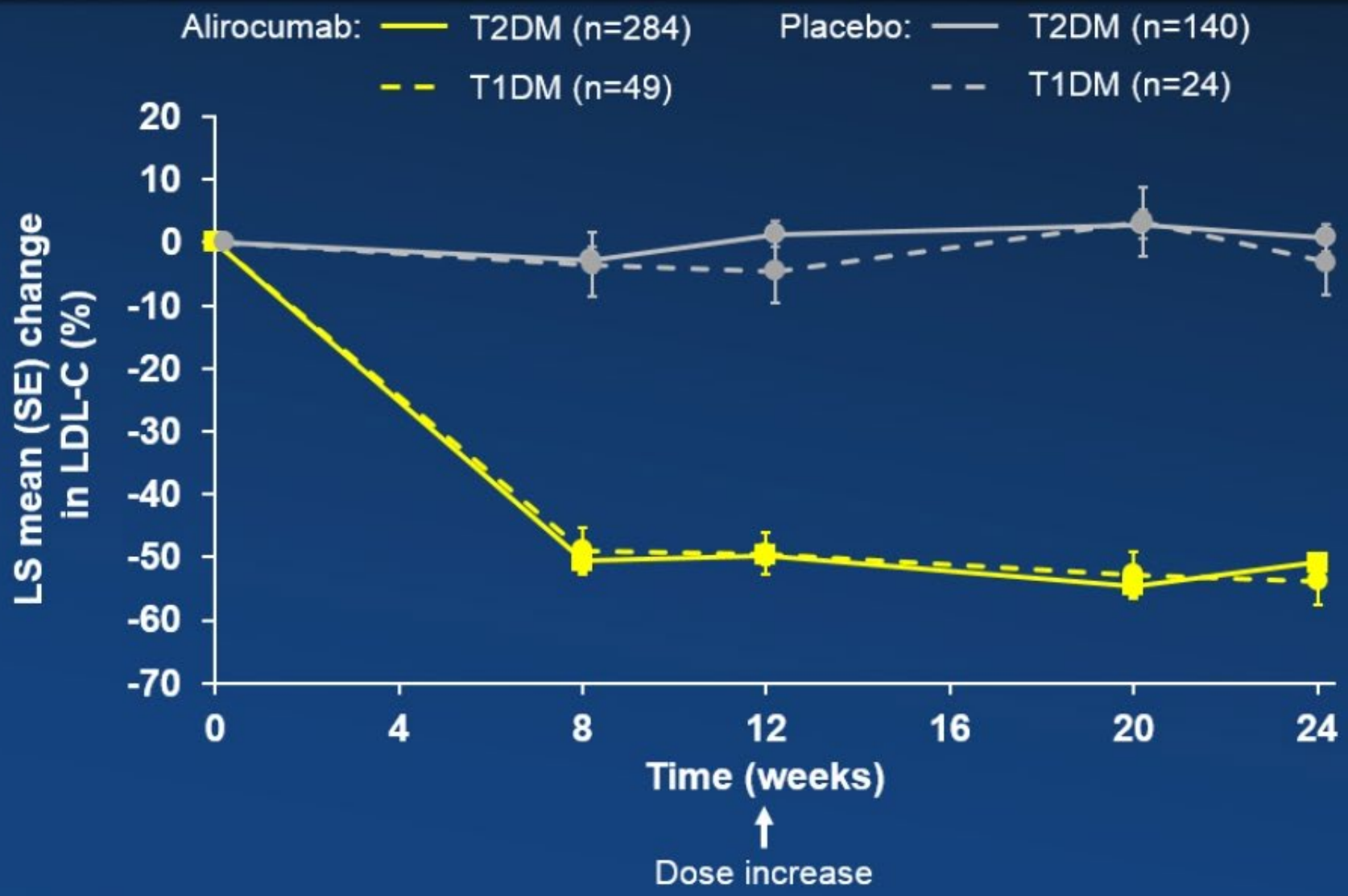
WILEY

ORIGINAL ARTICLE

Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: The ODYSSEY DM-INSULIN randomized trial

- ✓ *Participants at high CV risk with T2D (n = 441) or* ***T1D (n = 76)*** *and LDL-C levels ≥1.8 mmol/L (****≥70 mg/dL****) despite maximally tolerated statin therapy, were randomized 2:1 to alirocumab:placebo administered sc every 2 weeks, for 24 weeks' double-blind treatment;*
- ✓ *Primary endpoints: percentage change in calculated LDL-C from baseline to week 24, and safety assessments.*

LDL-C percent change from baseline over time (on-treatment)†: T2DM and T1DM



†Mixed-effect model with repeated measures analysis.

Received: 31 January 2024
DOI: 10.1111/dom.15650

ORIGINAL ARTIC

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WILEY

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Wolfgang Koenig
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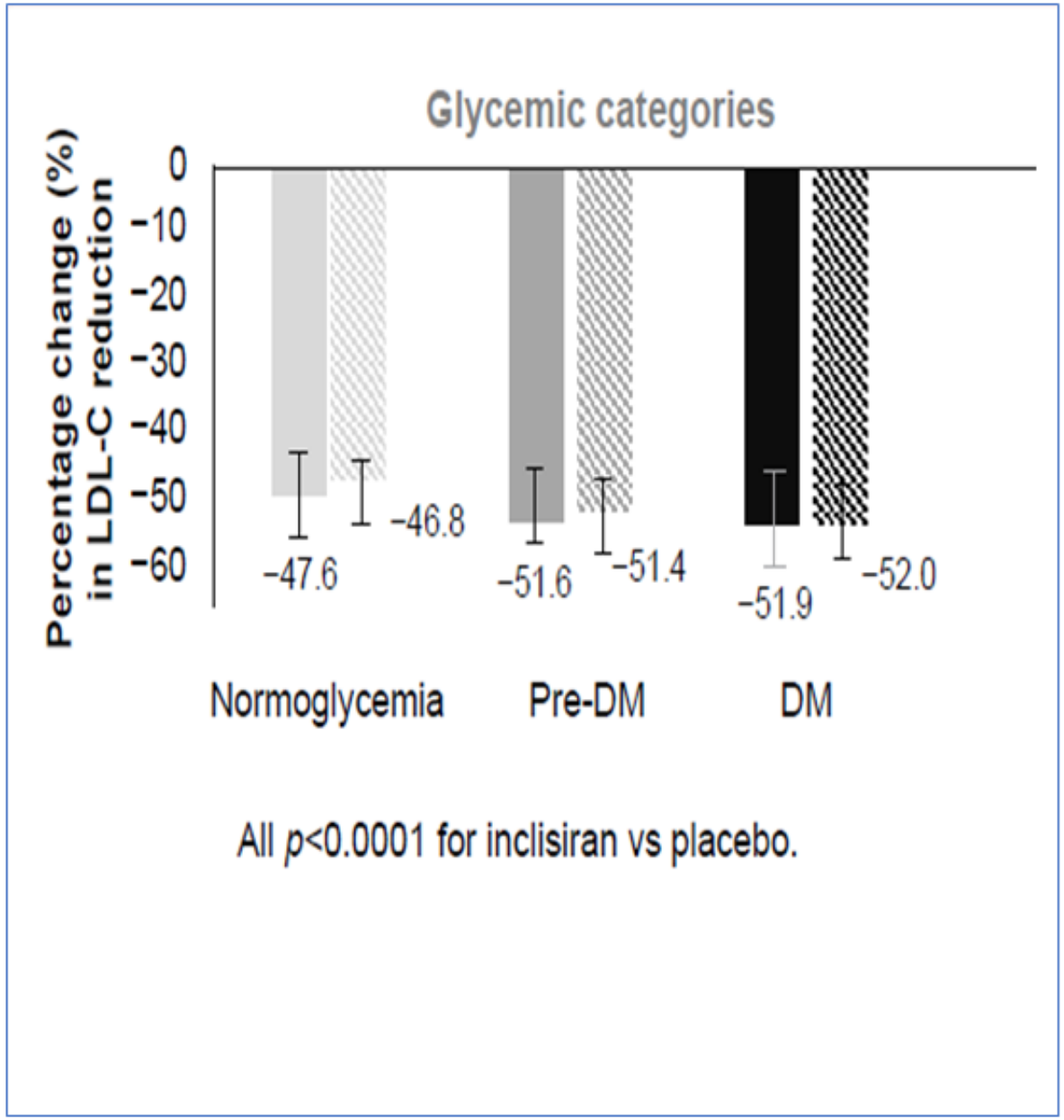

- ✓ Pooled analysis of ***3***
  - ✓ 784 (21.4%)
  - ✓ 1503 (41.1%)
  - ✓ ***1371 (37.5%)***
    - ✓ ***32 [2.3%] had type 1 DM***
    - ✓ ***16 individuals in each treatment arm***

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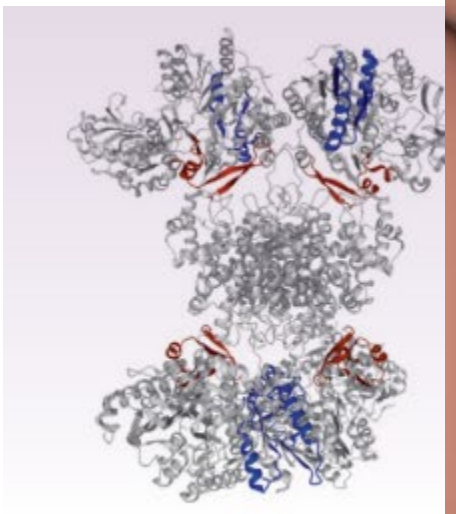

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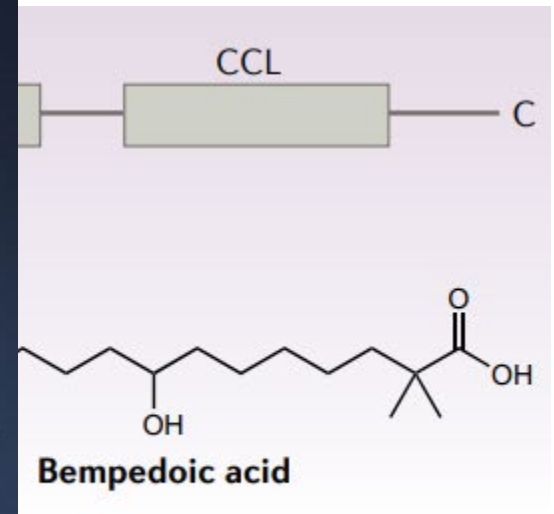
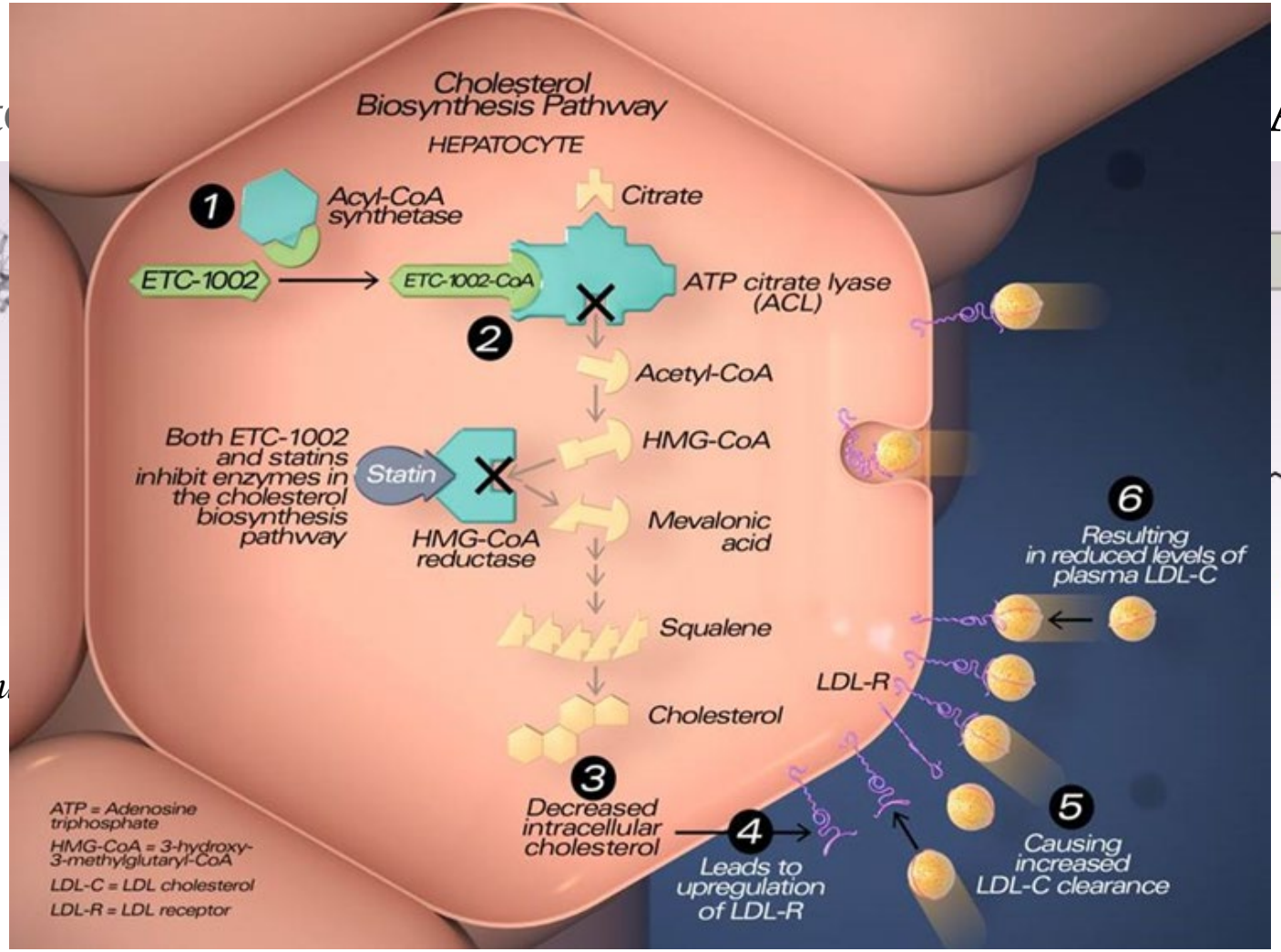
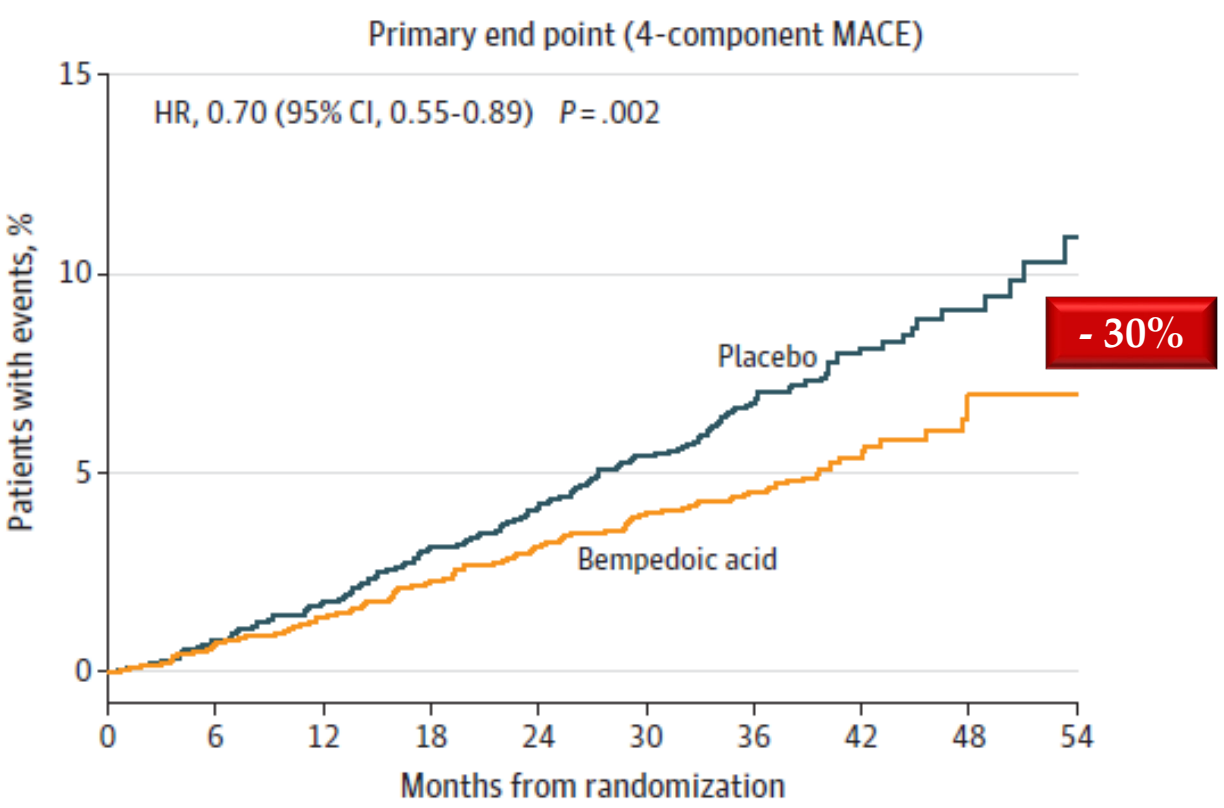
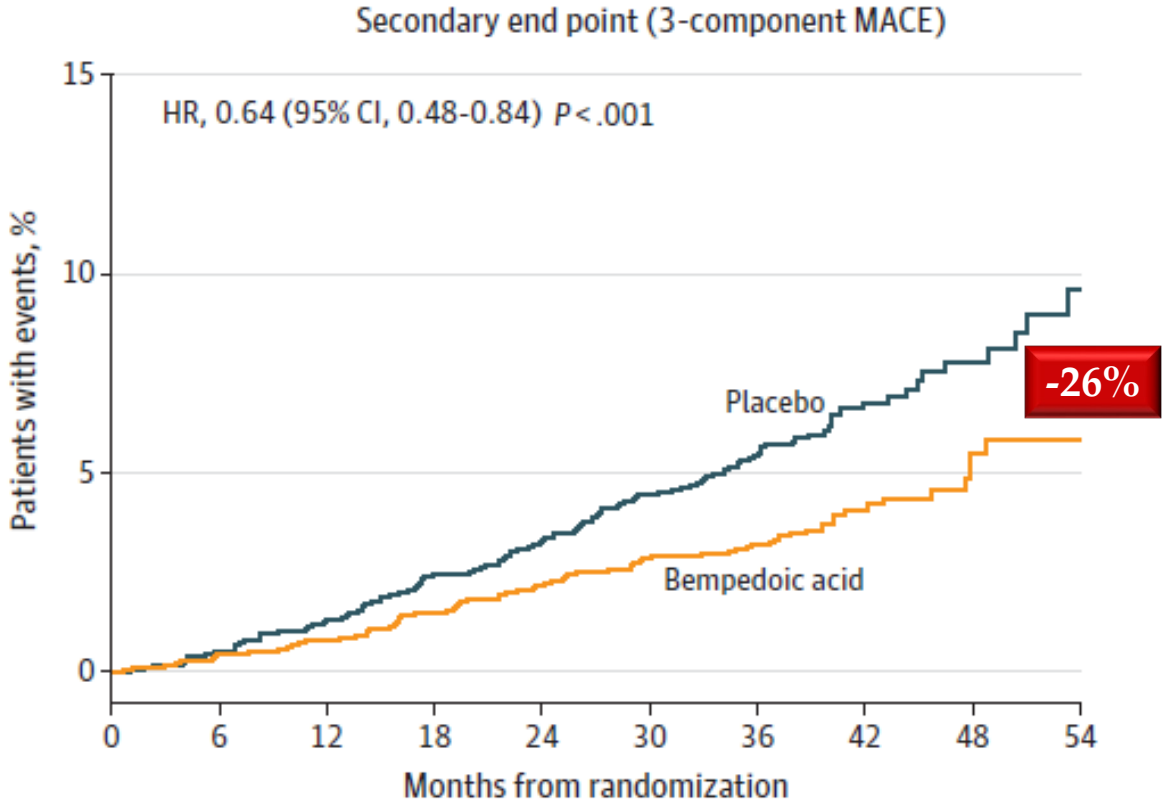
A binding site





Non statin agent which acts upstream from HMG-CoA reductase





The number needed to treat (NNT) to prevent 1 primary composite outcome was 43 patients

Characteristic	Bempedoic acid (n = 2100)	Placebo (n = 2106)
Inadequately controlled diabetes[a]	569 (27.1)	593 (28.2)
Criteria for increased risk, No. (%)		
Patients with self-reported type 1 or 2 diabetes, aged >65 (women) or >60 y (men), No. (%)	1150 (54.8)	1187 (56.4)


American
Diabetes
Association.


ESC
European Society
of Cardiology

Guidelines

10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2024;47(Suppl. 1):S179–S218 | https://doi.org/10.2337/dc24-S010

Primary Prevention

American Diabetes Association

10.22 In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin

abetes aged
ardiovascular
one or more

Anche se mancano dati definitivi, ADA suggerisce l'uso di ipolipemizzanti di tipo statine e/o di agenti "non statinici" in modo del tutto simile per il tipo 1 ed il tipo 2, particolarmente in presenza di altri fattori di rischio CV

lesterol ≥70 mg/dL (≥1.8 mmol/L), it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **B**

Secondary Prevention

10.26 For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.27 For people with diabetes and ASCVD, 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 (<1.4 mmol/L). 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**

10.28a For individuals who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used. **E**

10.28b For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, **A** bempedoic acid therapy, **A** or PCSK9 inhibitor therapy with inclisiran siRNA **E** should be considered as an alternative cholesterol-lowering therapy.

LINES

Very-high-risk	People with any of the following: DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years).
High-risk	Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ESC European Society of Cardiology

Treatment goal for LDL-C

SCORE <1%

- 3.0 mmol/L (116 mg/dL)
- 2.6 mmol/L (100 mg/dL)
- 1.8 mmol/L (70 mg/dL)
- 1.4 mmol/L (55 mg/dL)

& ≥50% reduction from baseline

Low

- ✓ SCORE ≥1% and <5%
- ✓ **Young T1DM <35 years;**
- ✓ *T2DM <50 y with DM <10 y without other risk factors*

Moderate

- ✓ SCORE ≥5% and <10%
- ✓ ***Markedly elevated single risk factors (TC>310 mg/dL; or LDL-C >190 mg/dL; or BP ≥180/110 mmHg***
- ✓ FH without other major risk factors
- ✓ Moderate CKD (eGFR 30–59 mL/min)
- ✓ **DM w/o target organ damage, with duration ≥10 y or other additional risk factor**

High

Very High

- ✓ ASCVD (clinical/imaging)
- ✓ SCORE ≥10%
- ✓ FH with ASCVD or with another major RF
- ✓ Severe CKD (eGFR <30 mL/min)
- ✓ **DM & target organ damage: ≥3 major risk factors; or early onset T1DM of long duration (>20 y)**

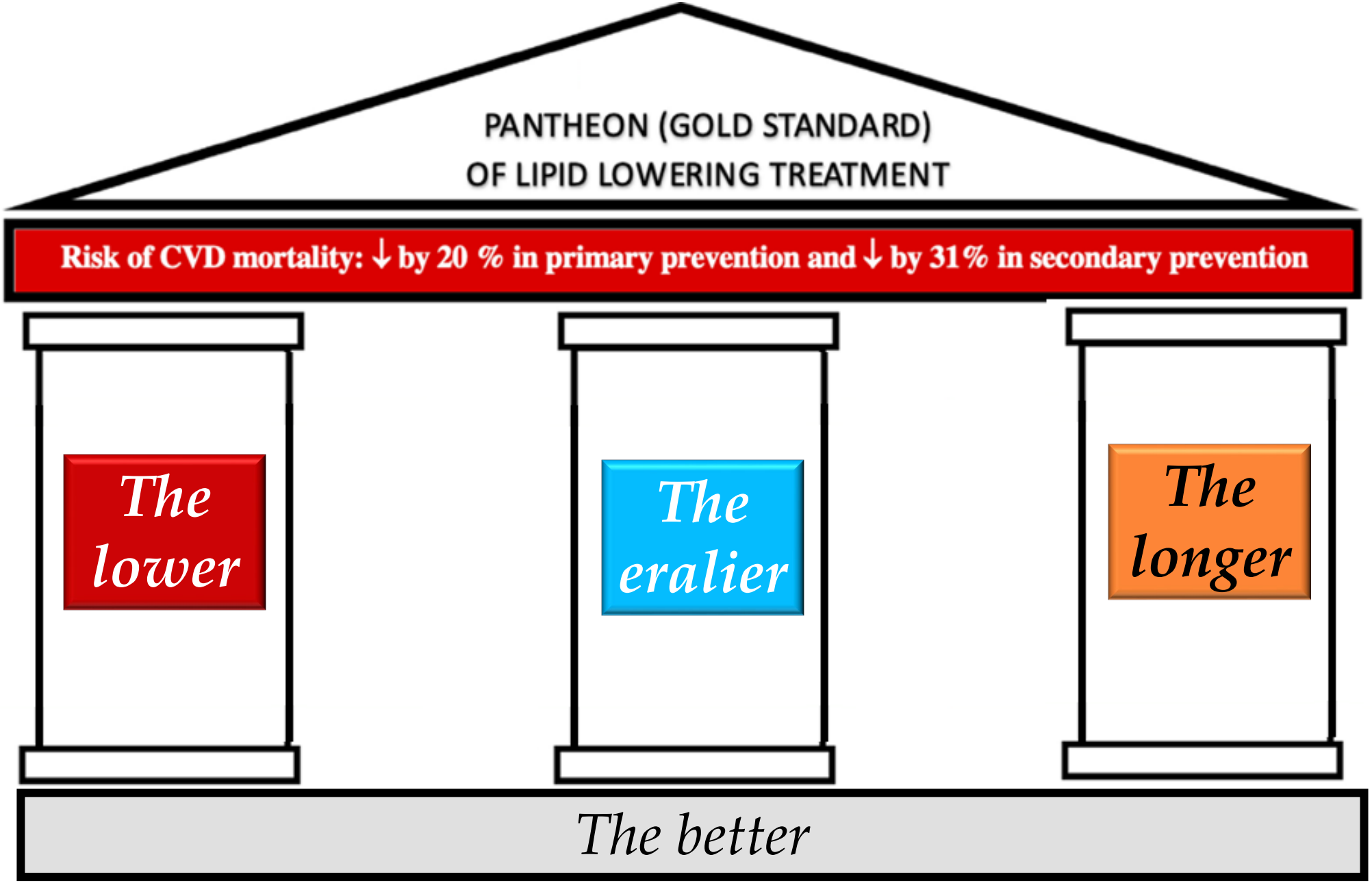
Low Moderate High Very high **CV Risk**

Statins are recommended in patients with T1DM who are at high or very-high risk.[c] [427]	I	A
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with ezetimibe should be considered.[33,299]	IIa	B
Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or an LDL-C level **>97 mg/dL**, as long as pregnancy is not being planned.	IIb	C

Il miglioramento degli indicatori di appropriatezza terapeutica risulta ancora NON soddisfacente rispetto alle indicazioni delle Linee Guida, considerando che i pazienti con T1D presentano un rischio CV (ESC/EASD) elevato o molto elevato in oltre il 90% dei casi (inerzia terapuetica)

Nel Tipo 1……

quando iniziare…. ?
quale target…. ?
per quanto tempo….. ?


PANTHEON (GOLD STANDARD)
OF LIPID LOWERING TREATMENT
Risk of CVD mortality: ↓ by 20 % in primary prevention and ↓ by 31% in secondary prevention
The lower
The eralier
The longer
The better

Effect of LDL-C Lowering on the Risk of Major Vascular Events

The lower

- ✓ In presenza di LDL-C <70 mg/dL, la riduzione indotta dall'uso di statine o ipolipemizzanti "non-statine" ("PCSK9i", "Ezetimibe", "CEPTi Anacetrapib") si associa ad ulteriore decremento dei MACE (21% per 38.7 mg/dL di LDL-C);
- ✓ Tale relazione viene mantenuta linearmente fino a livelli "mediani" di LDL-C pari a **21 mg/dL** (0.5 mM), in assenza di "*offsetting*" da eventi avversi;
- ✓ *The lower the better*: ridurre LDL-C al di sotto dei "limiti "suggeriti dalle attuali linee guida sembra conferire ulteriore "protezione" CV (anche nel tipo 1?)

Relazione mantenuta fino a livelli "mediani" di LDL-C pari a **21 mg/dl** (0.5 mmol/L), in assenza di "offsetting" da eventi avversi

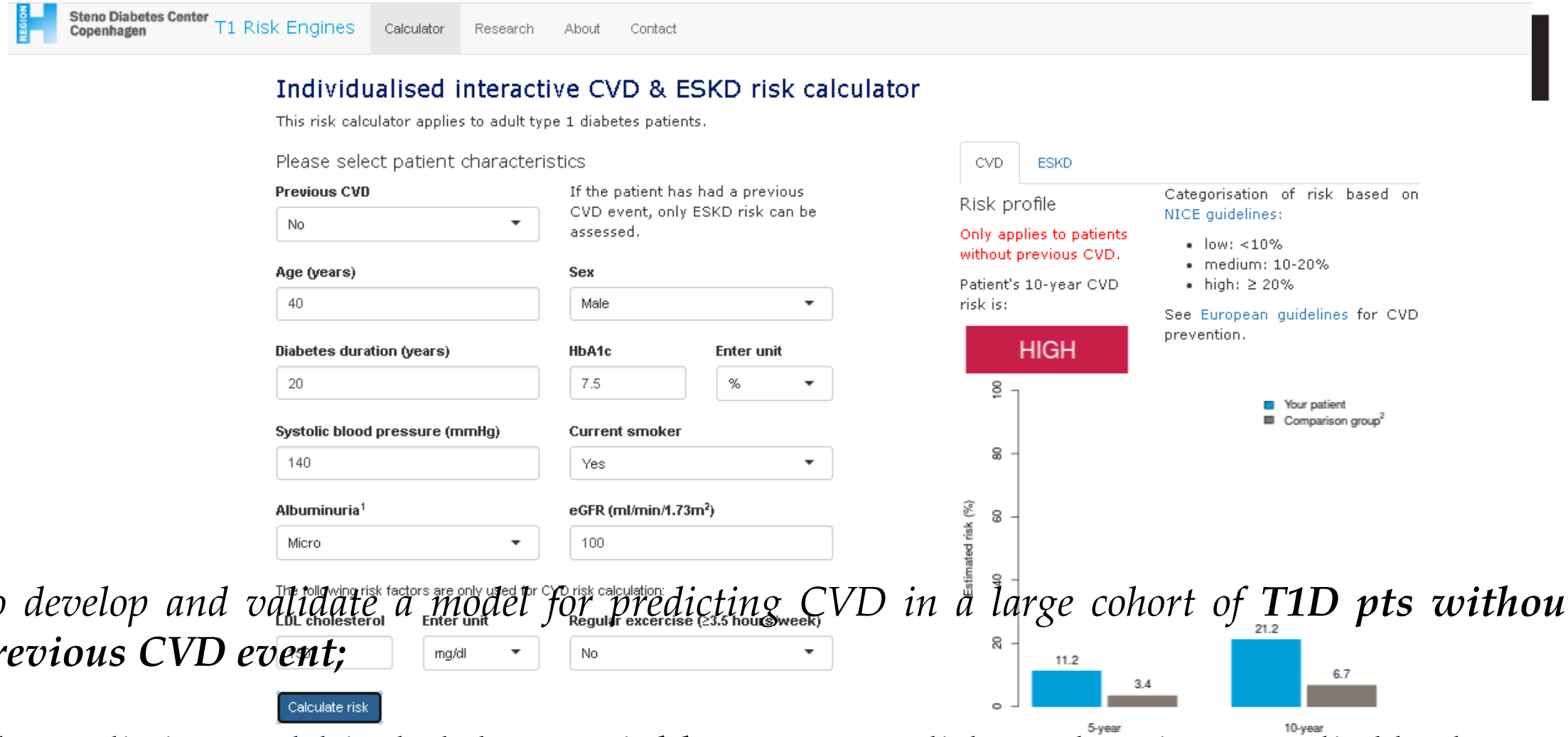
Sabatine M et al JAMA Cardiol. 2018

Conclusioni

- ✓ Il diabete tipo 1 (T1D) rappresenta una malattia cardiovascolare con memoria «glico-lipidica» similmente differente al tipo 2;
- ✓ Il profilo lipoproteico «tradizionale» può mascherare il potenziale aterogeno e confondere la stratificazione del rischio CV del T1D (apoB, apoE sdLDL-C);
- ✓ La terapia ipolipemizzante, sebbene incorporata nelle linee guida ed elargita in regime di rimborsabilità (AIFA), risulta estrapolata da studi sul T2D ed ancora sotto-utilizzata («inerzia») nel T1D;
- ✓ Il raggiungimento di target più «stringenti», ottenuti precocemente e mantenuti nel tempo, appare auspicabile per abbattere il «rischio CV residuo» nel paziente con T1D

1.0

www.steno.dk/T1RiskEngine



- ✓ *To develop and validate a model for predicting CVD in a large cohort of* ***T1D pts without a previous CVD event;***
- ✓ *The prediction model included* ***10 variables: age, sex, diabetes duration, systolic blood pressure, LDL-C, HbA1c, e-GFR, albuminuria, smoking and exercise.***

0.826 (95%CI, 0.807-0.845) *in the derivation data and a C-statistic of* ***0.803 (95%CI, 0.767-0.839)*** *in the validation data*

Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels

The lower

✓ ***Cholesterol Treatment Trialists Collaboration (CTTC) 26 statins trials***

Basal LDL-C = 131.5 mg/dL

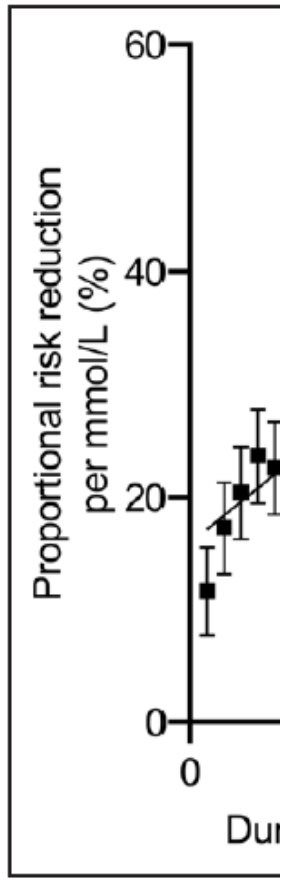
1-mmol/L (38.7 mg/dL) LDL-C;

22% reduction in major vascular events

✓ *The magnitude of clinical benefit of further LDL-C lowering in patients already with very low LDL-C levels remains debated*

Greater Relative Risk reduction in MACE with increasing duration of treatment

The longer



Baseline LDL-C (mmol/L)	Absolute reduction LDL-C (mmol/L)	Duration of treatment exposure [expected proportional risk reduction (%)]				
		5 years	10 years	20 years	30 years	40 years
7	3.5	58	68	81	89	93
7	3.0	53	62	76	85	90
7	2.5	46	56	70	79	86
7	2.0	39	48	61	71	79
7	1.5	31	39	51	61	69
5	2.5	46	56	70	79	86
5	2.0	39	48	61	71	79
5	1.5	31	39	51	61	69
5	1.0	22	28	38	46	54
3	1.5	31	39	51	61	69
3	1.0	22	28	38	46	54
3	0.5	12	15	21	27	32
2	1.0	22	28	38	46	54
2	0.5	12	15	21	27	32

270,9 (mg/dL)

193,5 (mg/dL)

116,1 (mg/dL)

77,4 (mg/dL)

-38.7(mg/dL)

f 4.4 yrs

ction in
nent is
duction

r 1

Wang N. et al. Circ Cardiovasc Qual Outcomes 2022

Ference BA et al. European Heart Journal 2017

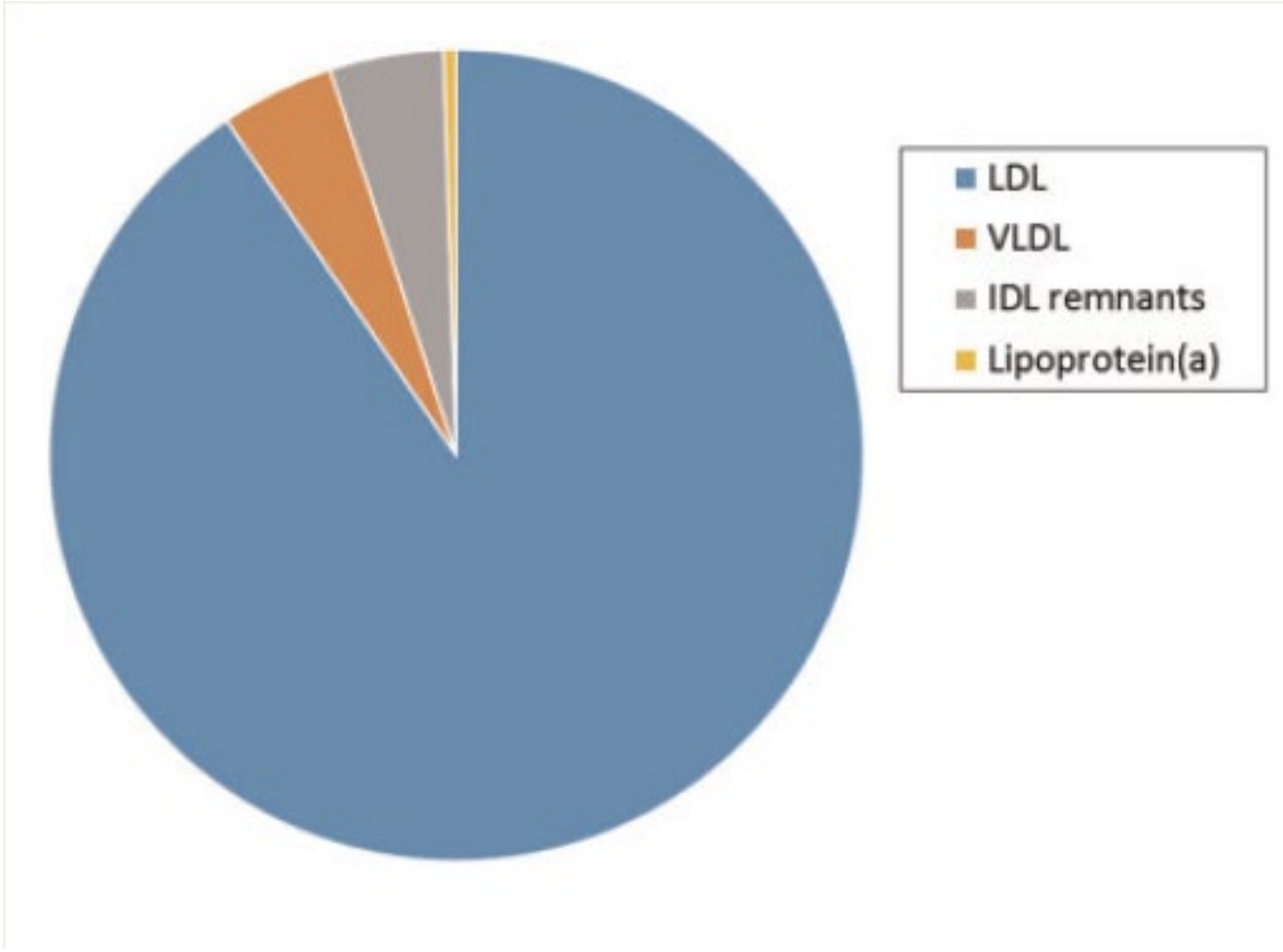
Recommendations for Lipid-Lowering Therapy as Primary Prevention for CVD in Patients with T1 Diabetes

American College of Cardiology–American Heart Association[38]	In adults 40 to 75 years of age, regardless of estimated risk of atherosclerotic cardiovascular disease, moderate-intensity statin therapy is indicated. For adults with multiple atherosclerotic cardiovascular disease risk factors,
International Society of Pediatric and Adolescent Diabetes	If the implementation of lifestyle interventions for 6 months does not lower LDL cholesterol to 130 mg/dl, statins should be considered in children >10 years of age, with an ideal LDL cholesterol target of <100 mg/dl. Simvastatin, lovastatin, and pravastatin are effective and safe in children and adolescents.
	For younger patients, statins should be considered if the patient has other cardiovascular risk factors, microvascular disease, or a 10-year cardiovascular disease risk ≥10%.

None of the recommendations specifically address the 18- to 39-year age group !

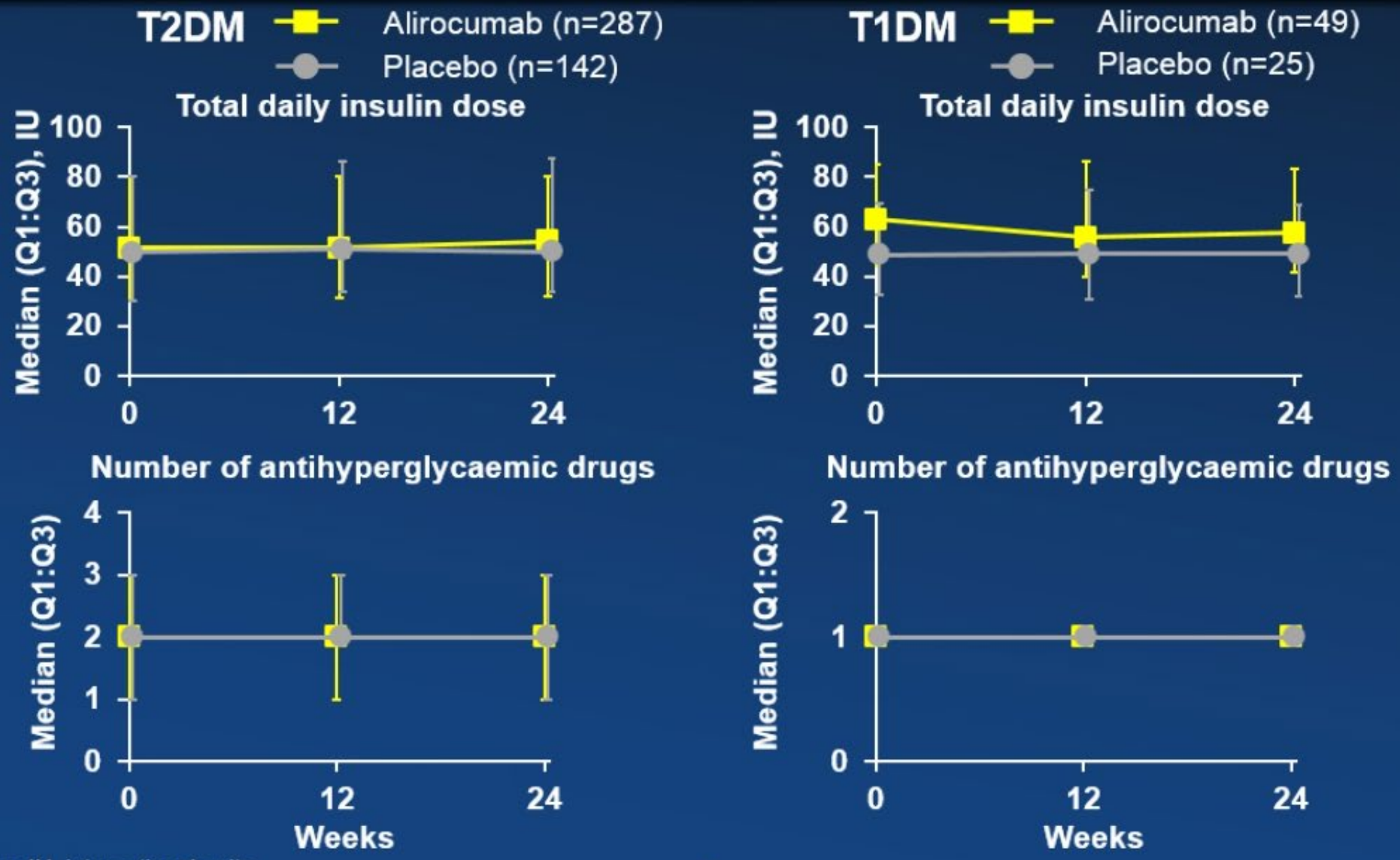
Manrique-Acevedo C et al NEJM 2024

Relative concentration of ApoB in circulating lipoproteins in normolipidaemic individuals



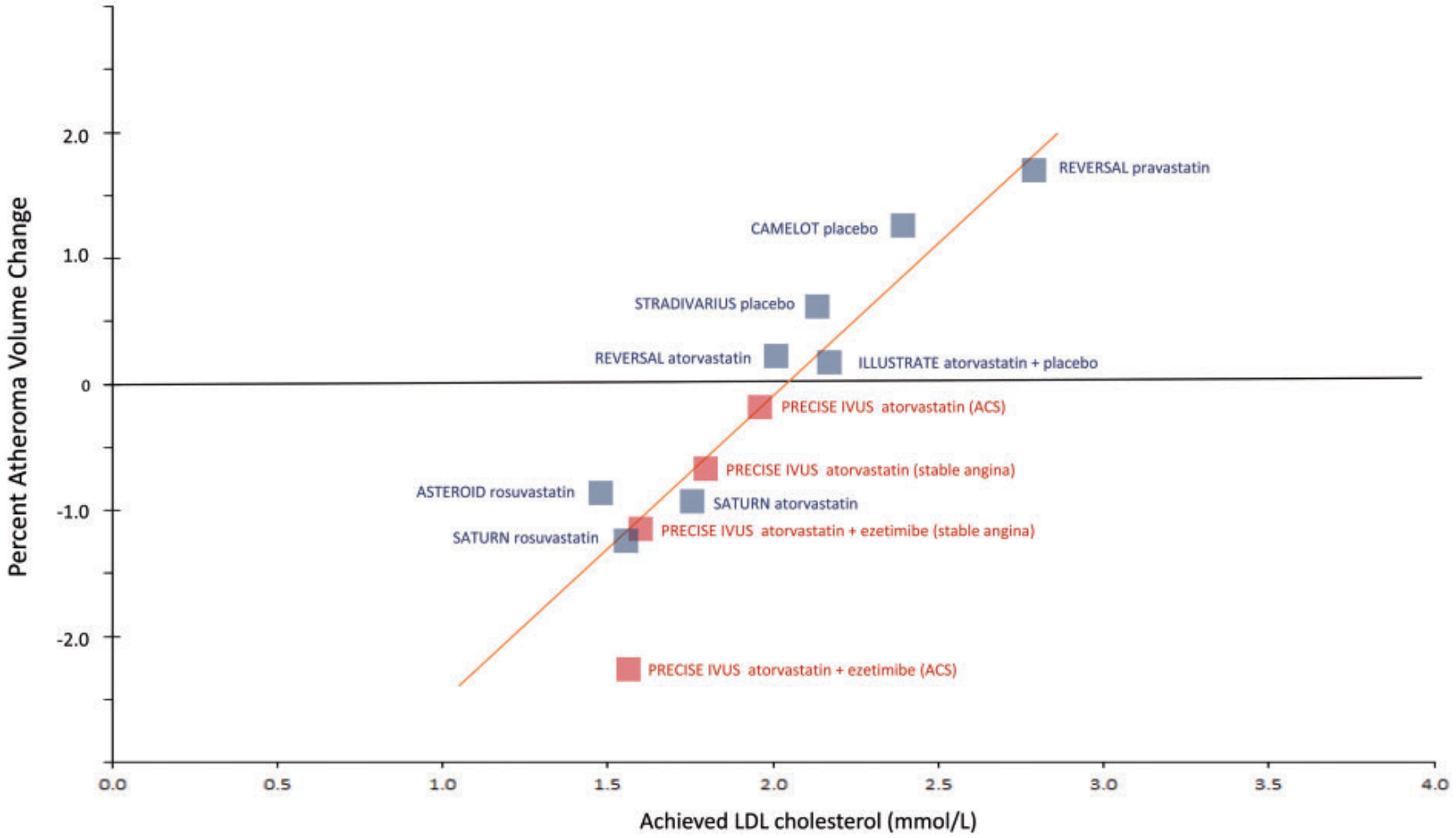
Ference BA et al. European Heart Journal 2017

Glycaemic-related parameters: Absolute values for T2DM and T1DM populations



ITT population. IU, international units.

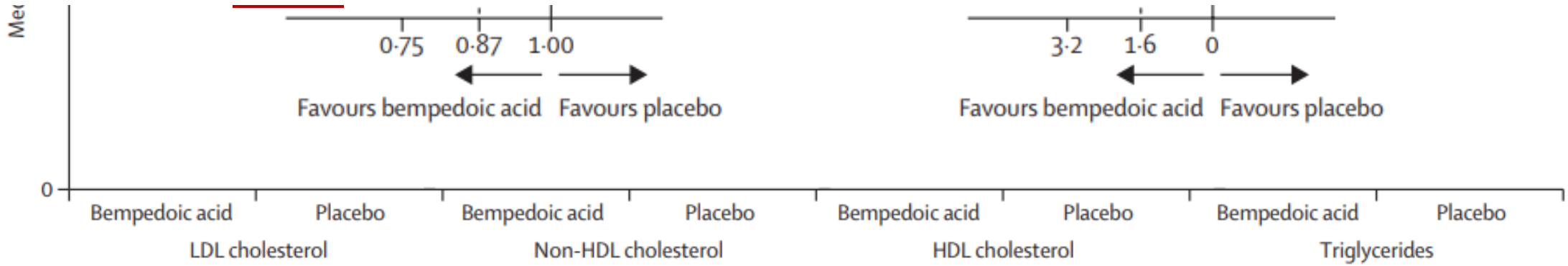
Linear association between achieved LDL-C level and progression of atherosclerosis (intravascular ultrasound)



Ference BA et al. European Heart Journal 2017

Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomised trial

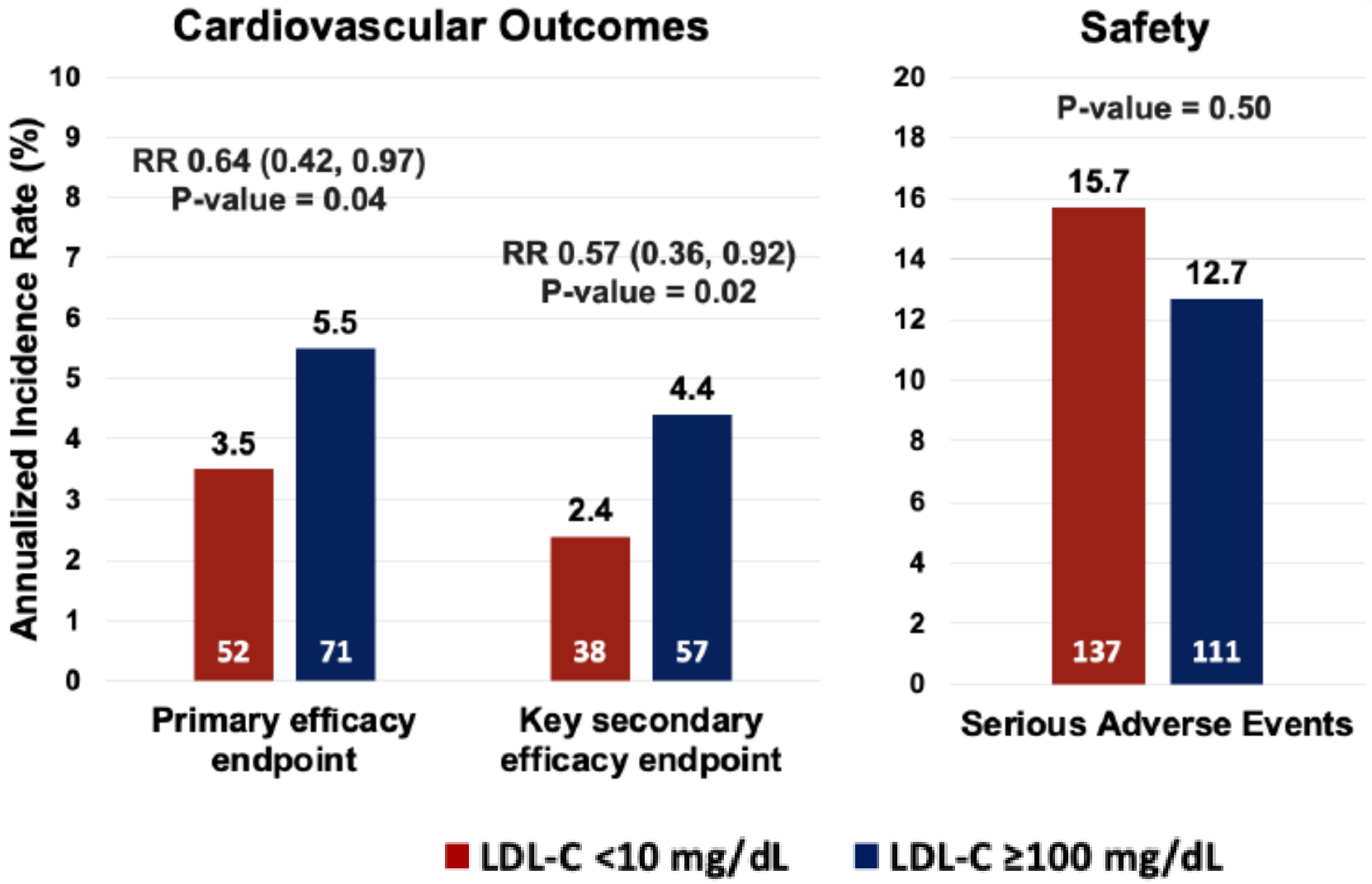
*Kausik K Ray, Stephen J Nicholls, Na Li, Michael J Louie, Danielle Brennan, A Michael Lincoff, Steven E Nissen, on behalf of the CLEAR OUTCOMES Committees and Investigators**



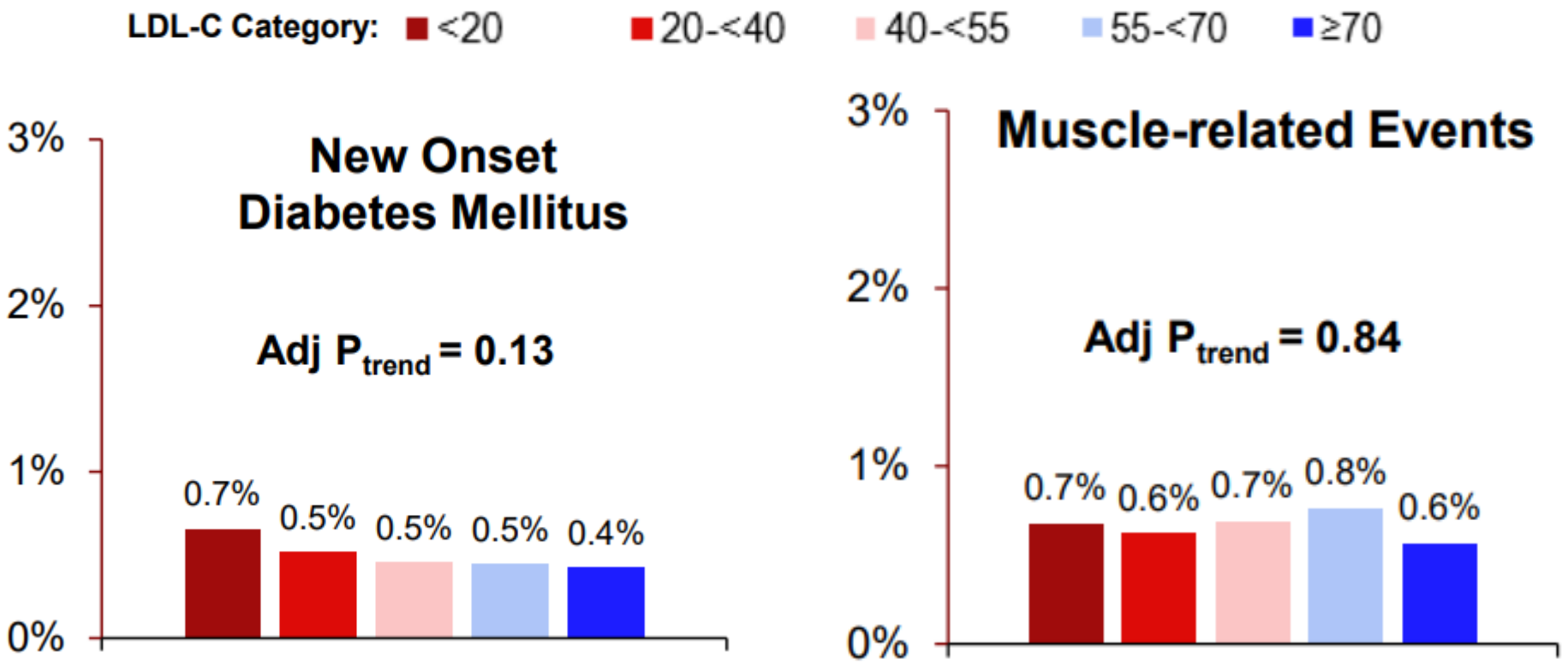
✓ *Median of 3·4 years follow up*

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.[32,34,38]	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[33]	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.[119,120]	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.[197,265,353]	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.[197,265,353]	IIb	C
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

Cardiovascular outcomes and serious adverse events in patients with achieved LDL-C C<10 vs C<100 mg/dl In FOURIEER--OLE



Safety and Achieved LDL-C



Gaba P et al.Circulation 2023