

**GLICEMIA,
DIABETE,
OBESITA:**
state of the (he)art

14 GIUGNO 2024 | ROZZANO (MI) | Centro Congressi Humanitas

La dislipidemia diabetica: novità e prospettive

Gianluca Perseghin

**Department of Medicine and Surgery
Università degli Studi di Milano Bicocca**

**Department of Medicine and Rehabilitation
Policlinico di Monza, Monza**



CONFLITTI DI INTERESSE

last 3 years

Speaker in Scientific Events

AstraZeneca

Bayer

Boheringer Ingelheim

Daiichi Sankyo

Echosens

Lilly

Menarini Diag

Merck

Novartis

Novo Nordisk

Pfizer

PikDare

Roche Diag

Sanofi

Servier

Scientific AB

Amgen

Bruno Farmaceutici

EG

Lilly

Merck

Novartis

Novo Nordisk

Pfizer

PikDare

CVD – no NEWS!

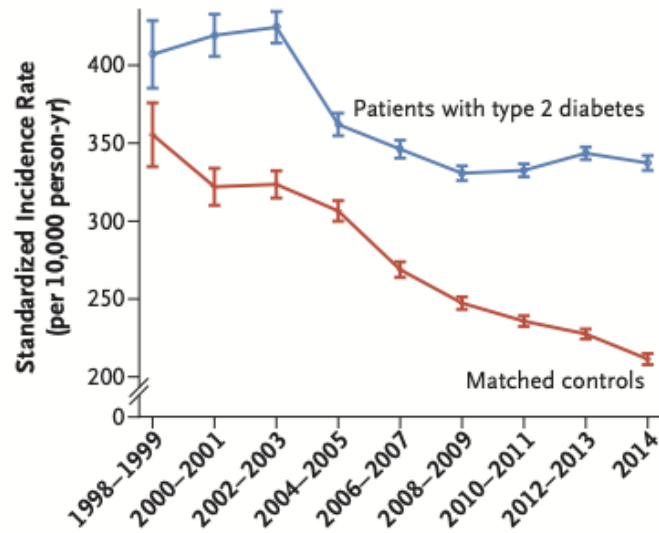
Why this is still an hot topic?

CVD, CAD & T2DM (Europe)

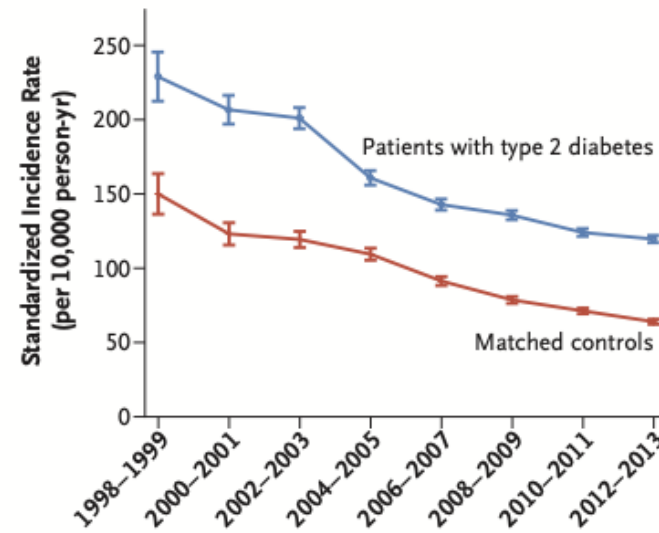
Swedish National Diabetes Register
271,174 patients with T2DM vs.
1,355,870 matched controls on the
basis of age, sex, and county

Follow-up 5.7 years
175,345 deaths occurred

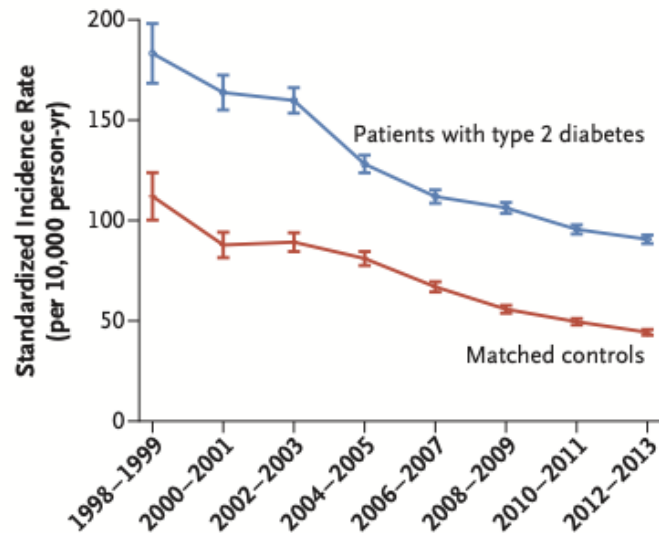
A Death from Any Cause



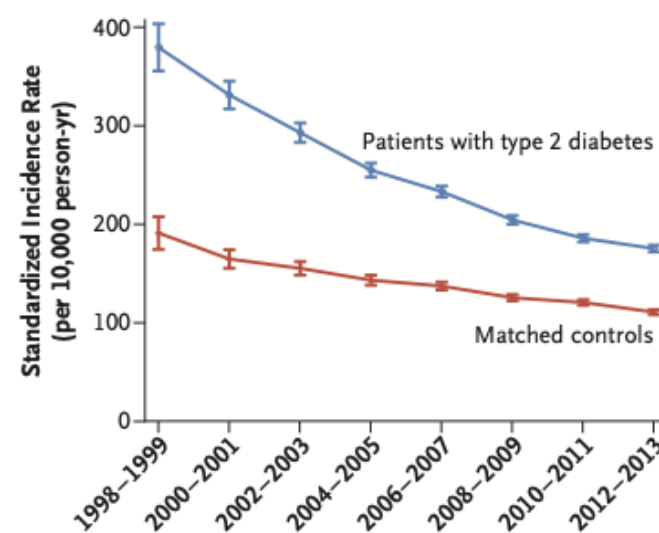
B Death from Cardiovascular Disease



C Death from Coronary Heart Disease



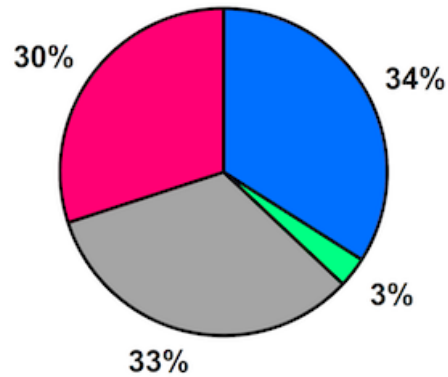
D Hospitalization for Cardiovascular Disease



Mortality in Lombardy 2010-2019

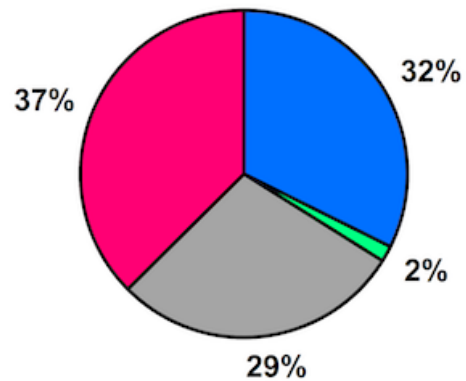
Individuals with diabetes

2010



■ Cardiovascular ■ Liver ■ Cancer ■ Other

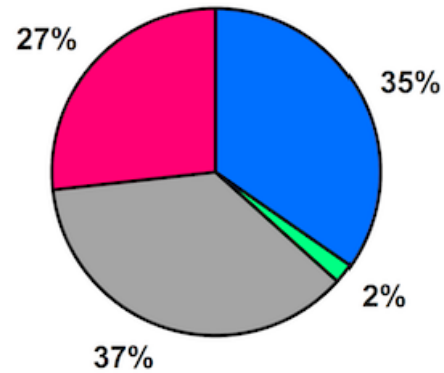
2019



■ Cardiovascular ■ Liver ■ Cancer ■ Other

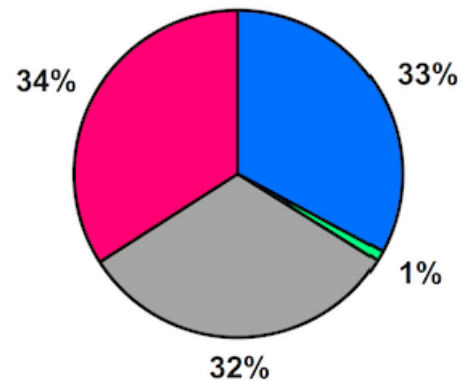
Individuals without diabetes

2010



■ Cardiovascular ■ Liver ■ Cancer ■ Other

2019

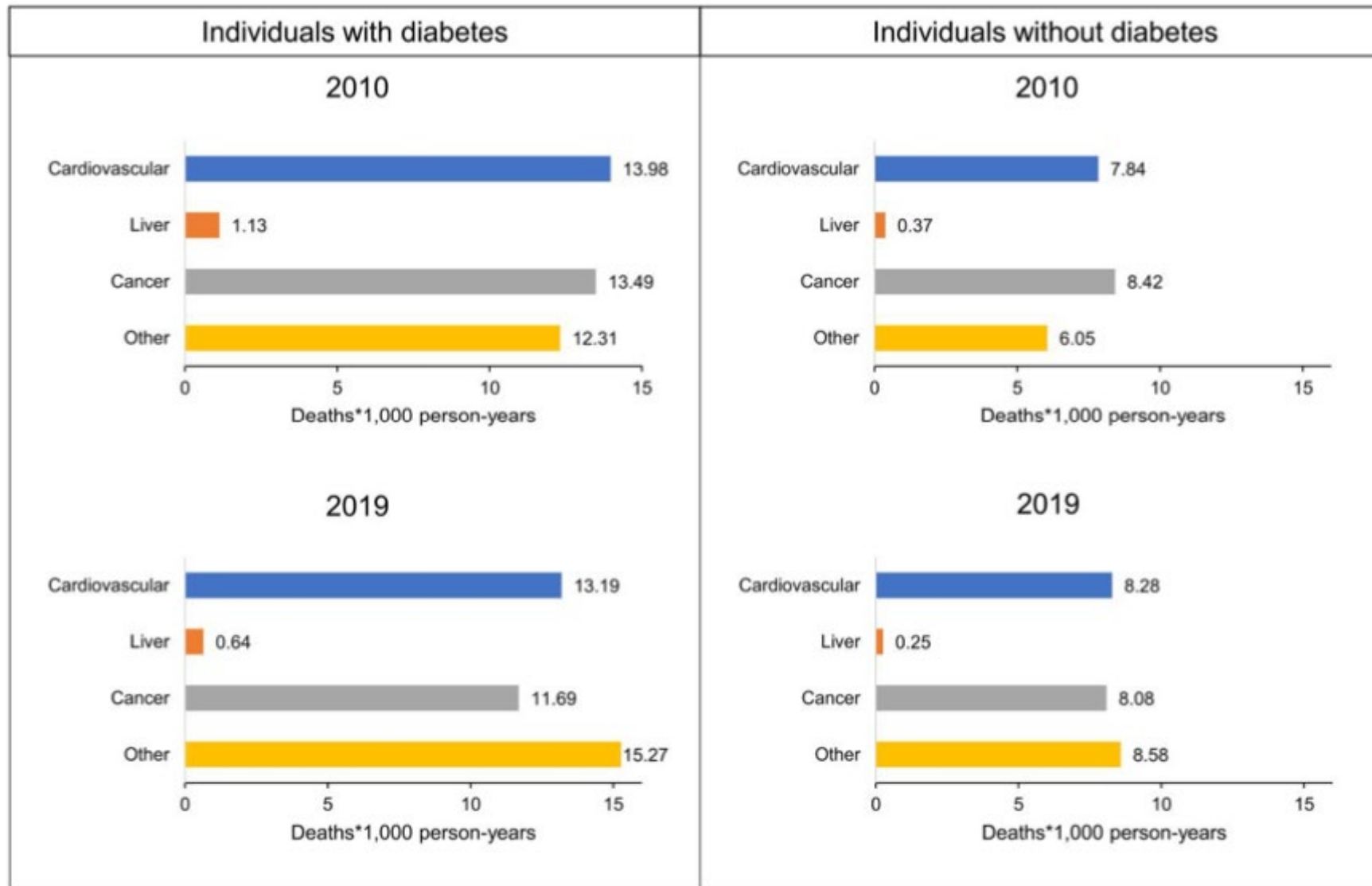


■ Cardiovascular ■ Liver ■ Cancer ■ Other

CVD still matters

Ciardullo S et al
J Clin Endocrinol Metab, 2024

In Lombardia



**CVD
still matters
!!!**

**Giardullo S et al
J Clin Endocrinol Metab, 2024**

Figure 2. Absolute cause-specific mortality rates among individuals with and without diabetes at the beginning (2010) and at the end (2019) of the studied period.

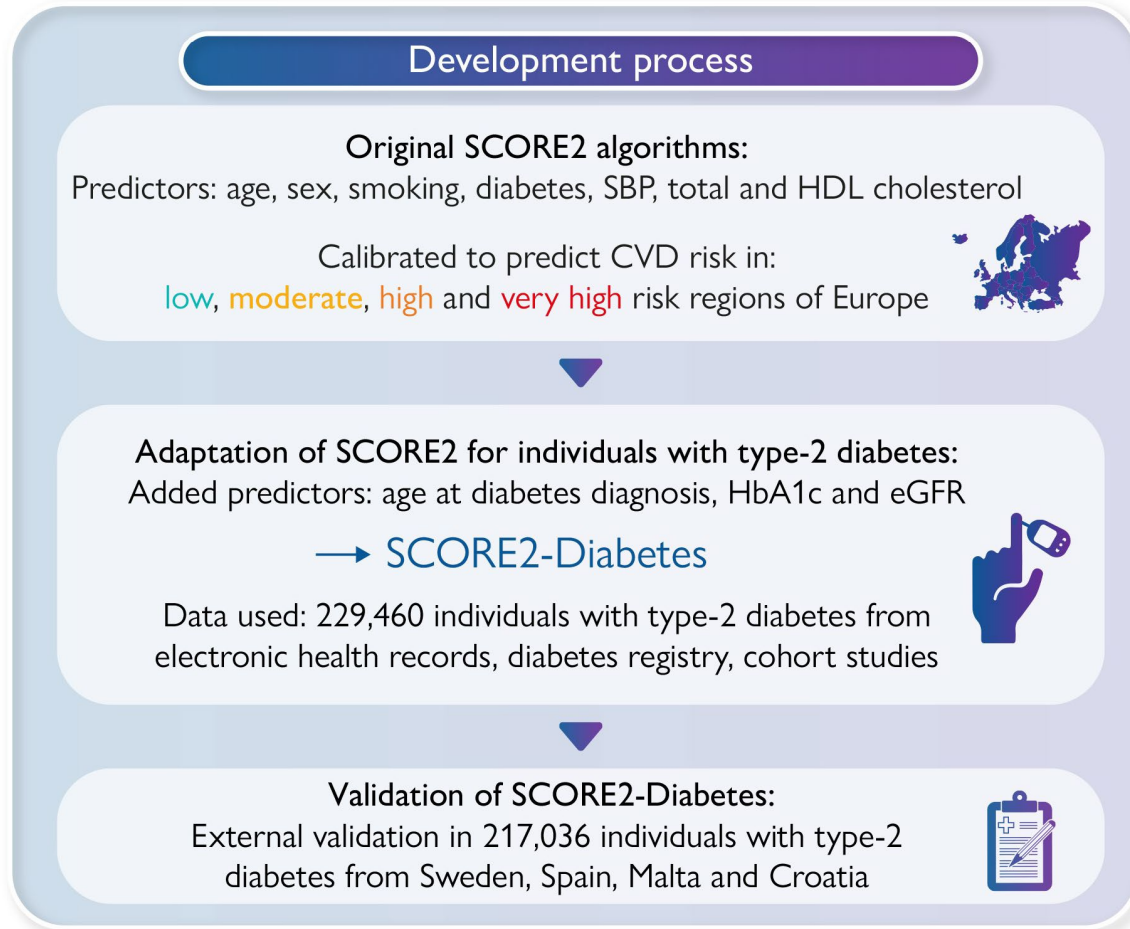
Back to the past!

Risk stratification using calculators

**Not fully
NEW!!!**

SCORE2-Diabetes: a new risk prediction tool

NEW!!!



**ITALY up-graded
to Moderate-Risk**

NEW!!!

Pennells L et al, Eur Heart J 2023

Risk stratification

SCORE2-Diabetes

Classical RFs

Age
Actual smoking
Systolic blood pressure
Total cholesterol
HDL-cholesterol



Diabetes-related RFs

Age at onset
HbA1c
eGFR

Risk stratification

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk $\geq 20\%$ using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to $<20\%$ using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to $<10\%$ using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk $<5\%$ using SCORE2-Diabetes

?

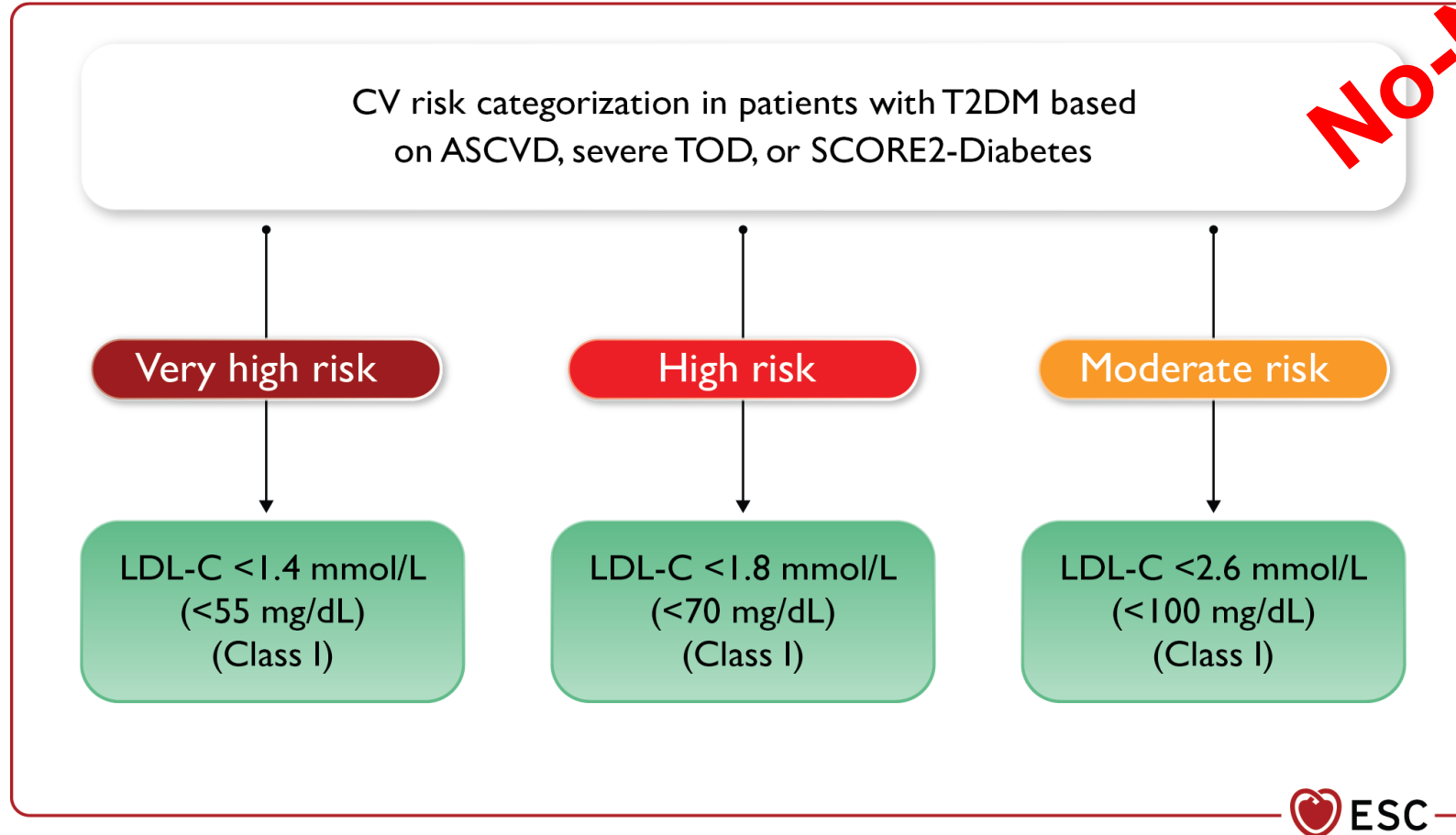
Majority

Some/many

few

Targets for LDL-cholesterol

NO-NEWS!!!



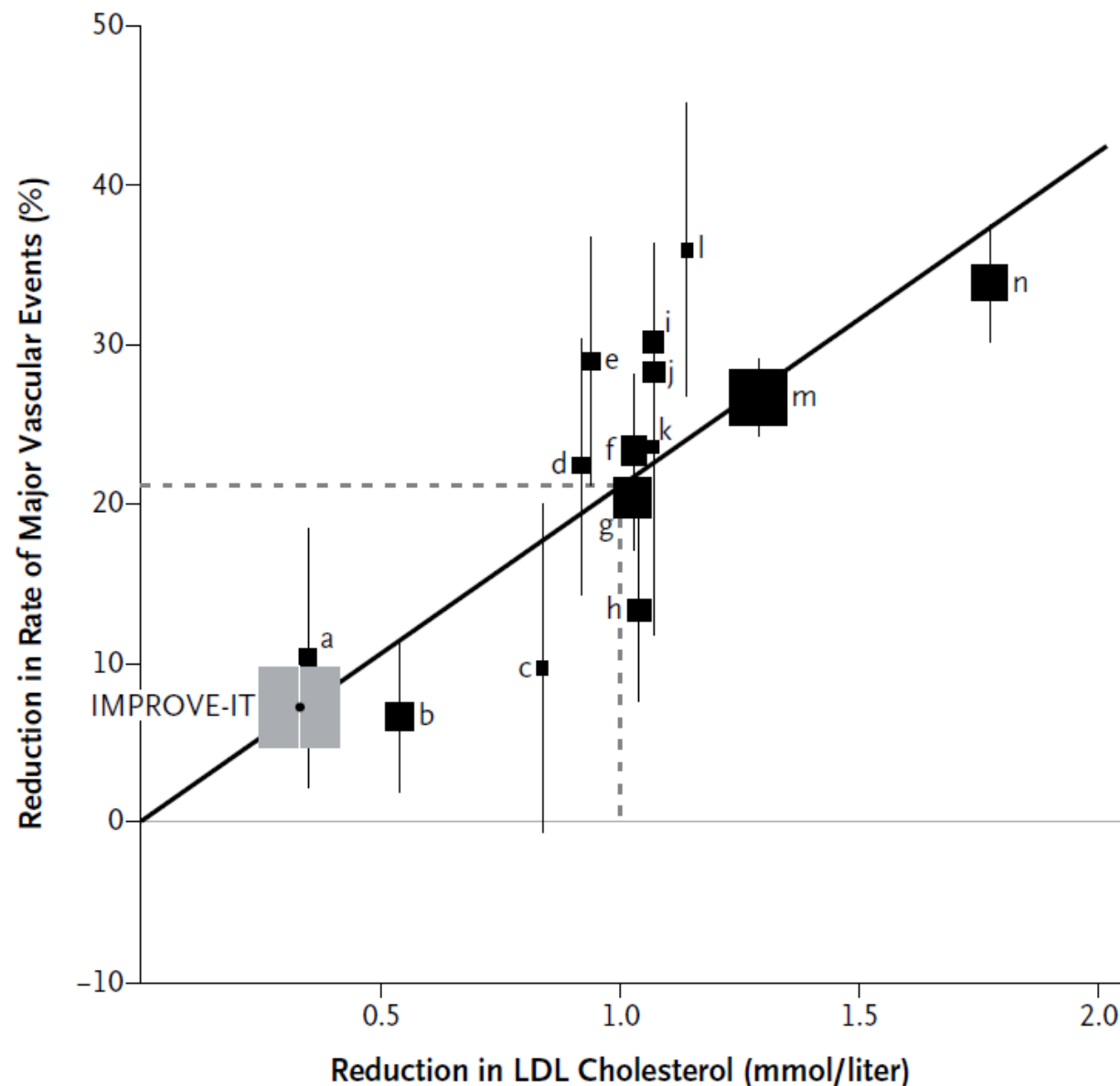
LDL-C: causa di CVD su base aterosclerotica (ASCVD)

**Riduzione LDL-Col
1.0 mmol/L
(~40 mg/dL)**

=====

**riduzione del 20-25%
eventi CVD e eventi
coronarici**

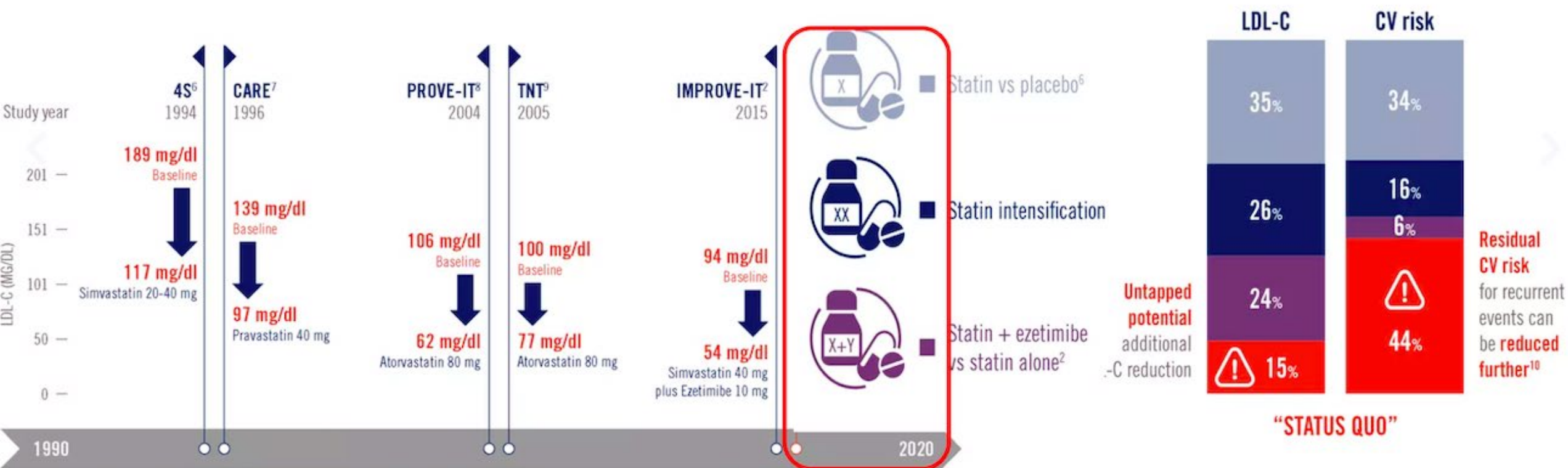
**Cholesterol Treatment Trialists Collaboration
Lancet, 2010**



STATINS ALONE LOWER LDL-C, BUT SOMETIMES NOT ENOUGH

For more than 20 years, statins have helped millions of people avoid CV events.⁴ But many very-high-risk patients don't reach LDL-C goals with a statin alone.⁵

Results of lipid-lowering trials[‡]



Treatments for LDL-cholesterol

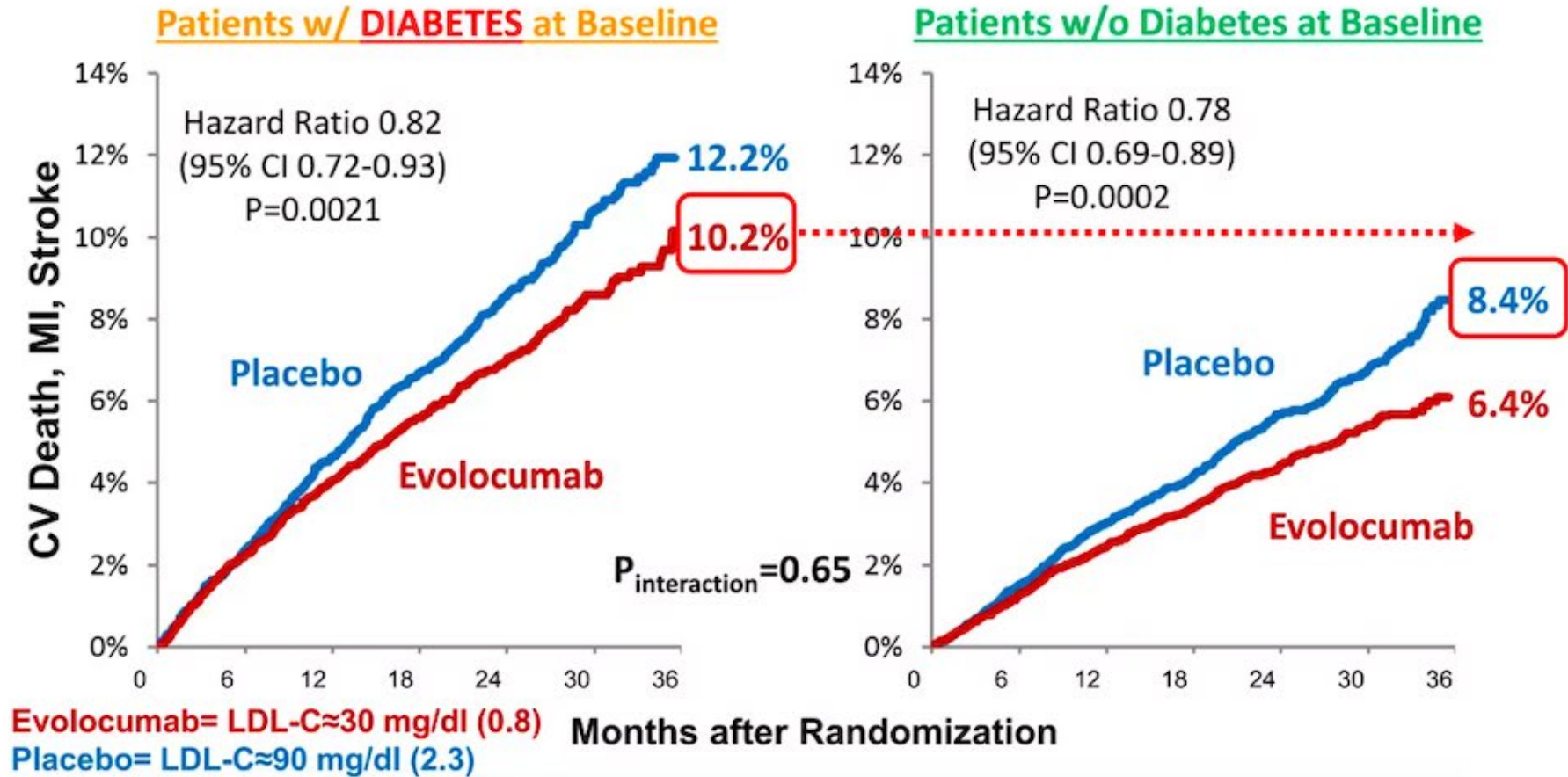
Recommendations	Class	Level
<i>Lipid-lowering treatment</i>		
Statins are recommended as the first-choice LDL-C-lowering treatment in patients with diabetes and above-target LDL-C levels. Administration of statins is defined based on the CV risk profile of the patients and the recommended LDL-C (or non-HDL-C) target levels.	I	A
A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.	I	A
If the target LDL-C is not reached with statins, combination therapy with ezetimibe is recommended.	I	B

NEW!!

Especially - if you have T2DM!



Effect of Evolocumab on Key Secondary Endpoint



PIU' DI UNA PROSPETTIVA

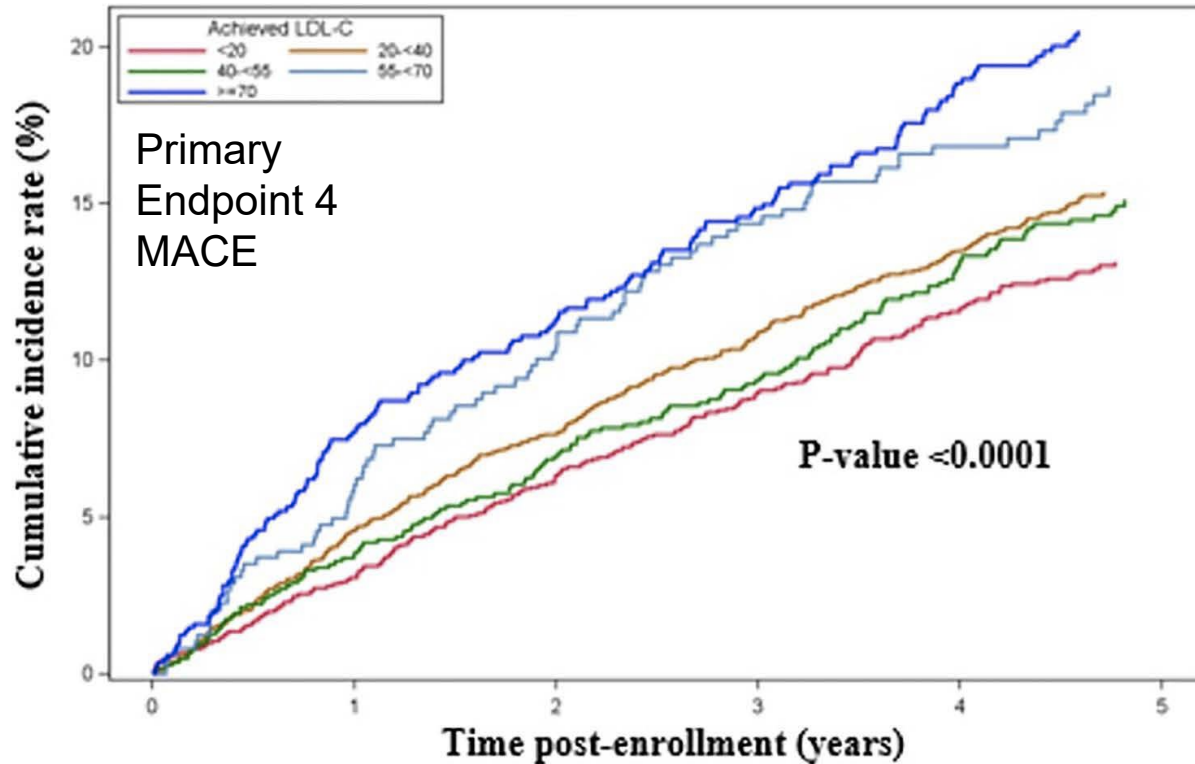
- anti-proprotein convertase subtilisin/kexin 9 (PCSK9) antibodies
- Bempedoic Acid, which targets ATP citrate lyase
- an siRNA targeting PCSK9 (Inclisiran)

NEW!

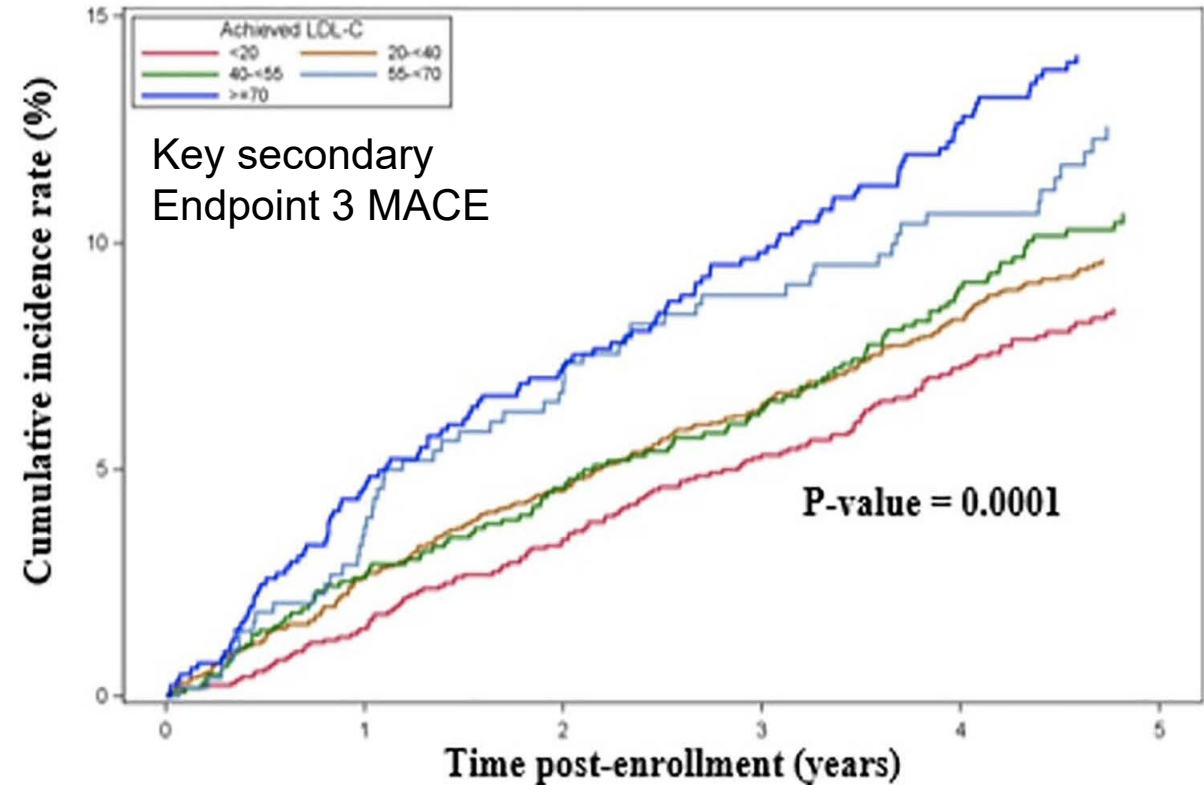
- a purified omega-3 fatty acid, icosapent ethyl
- an antisense oligonucleotide targeting apolipoprotein C-III (Olezarsen)
- CETP inhibitors (Obicetrapib)
- an anti-angiopoietinlike-3 antibody (Evinacumab)
- adnectin (recombinant fusion protein of a PCSK9-binding domain and human serum albumin), Lerodalcibep (monthly sc inj with 60–70% LDL reduction)
- a vaccine against PCSK9 and a gene editing approach (CRISPR)–Cas9 technology

Evolocumab and Long-Term Cardiovascular and Safety Outcomes

A CV death, MI, stroke, hospital admission for unstable angina or coronary revascularization



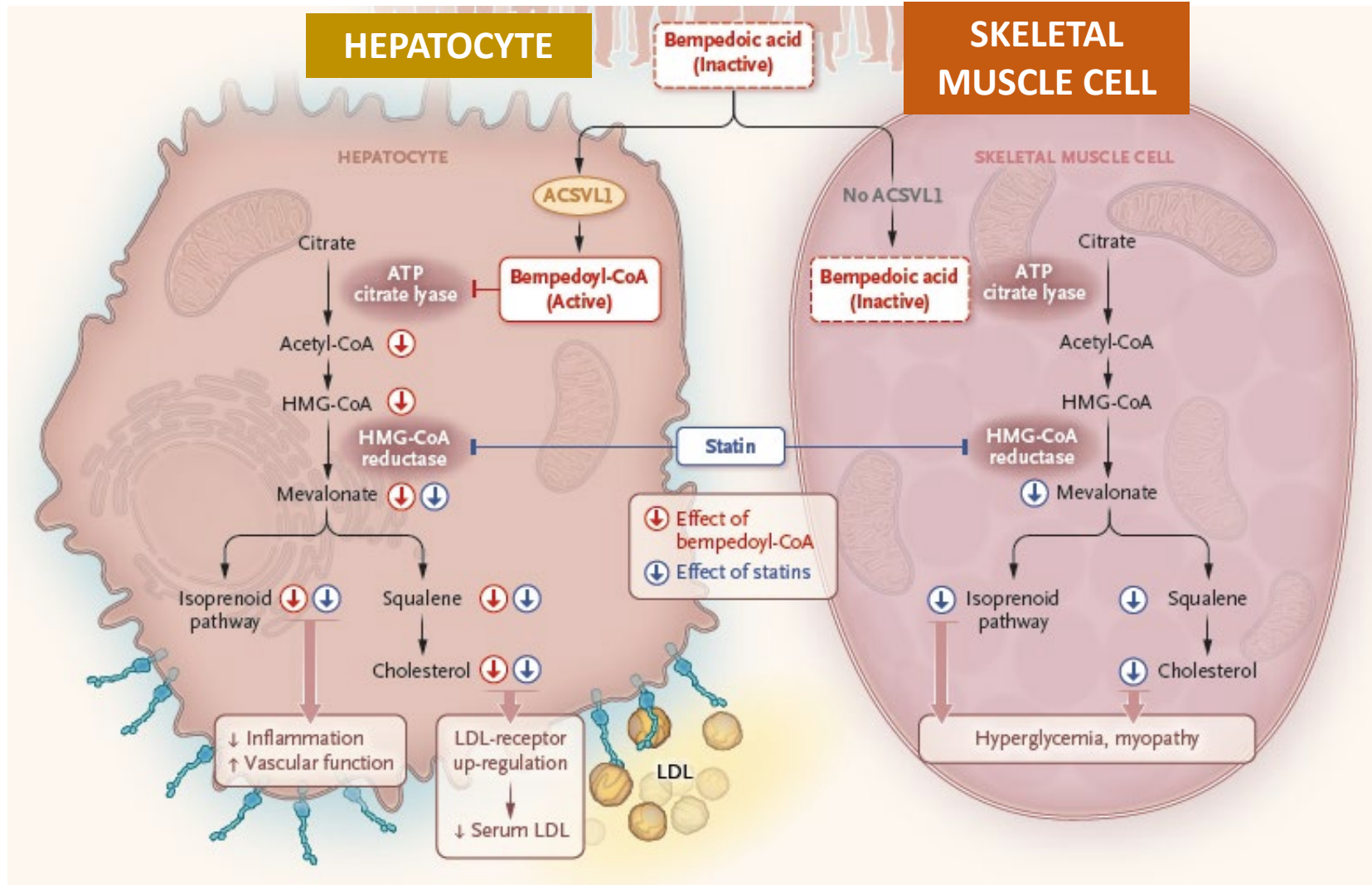
B CV death, MI, stroke



Cumulative incidence rates of cardiovascular outcomes in **FOURIER-OLE** (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk Open-Label Extension).

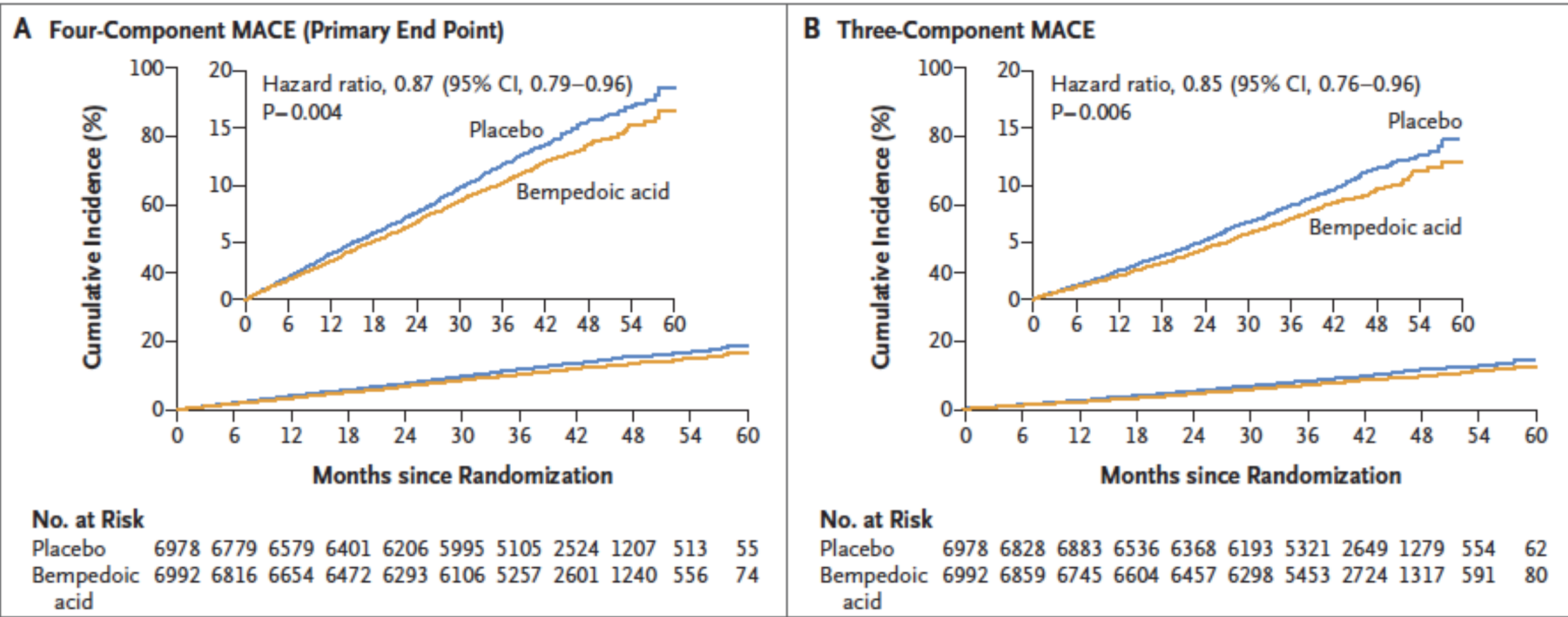
P value for trend in incidence rates across achieved low-density lipoprotein cholesterol (LDL-C) categories.

Very-long-chain acyl-CoA synthetase 1 (ASCVL1) is required to activate bempedoic acid



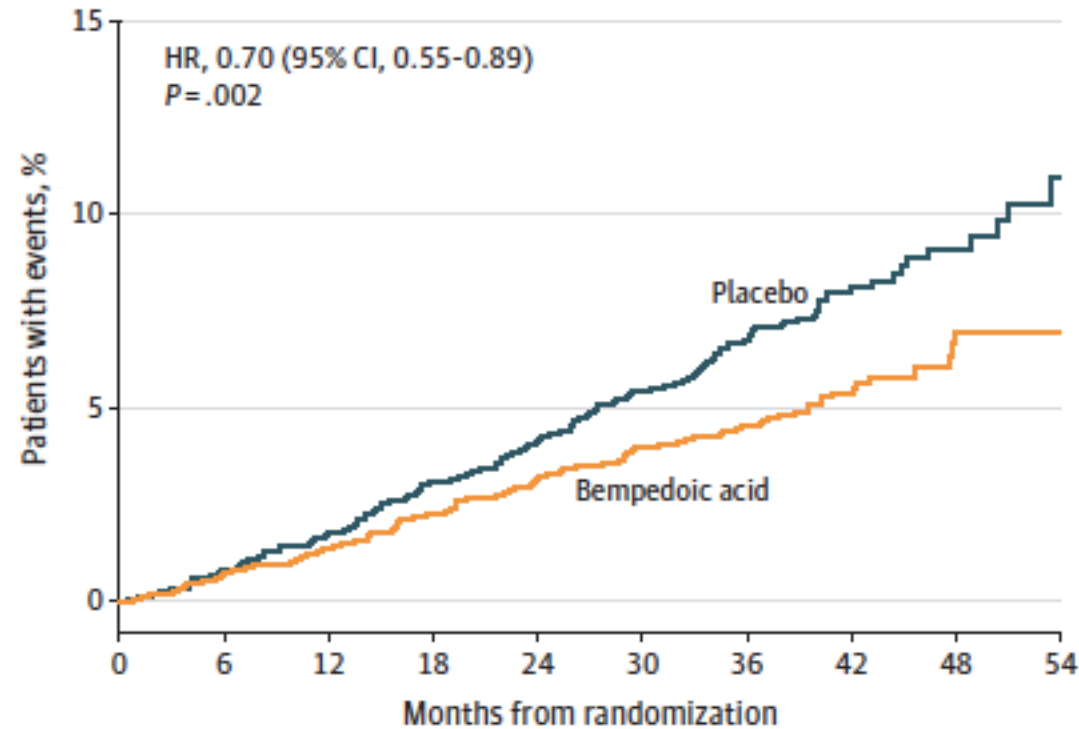
Bempedoic Acid and CVOT in Statin-Intolerant Patients

The CLEAR trial



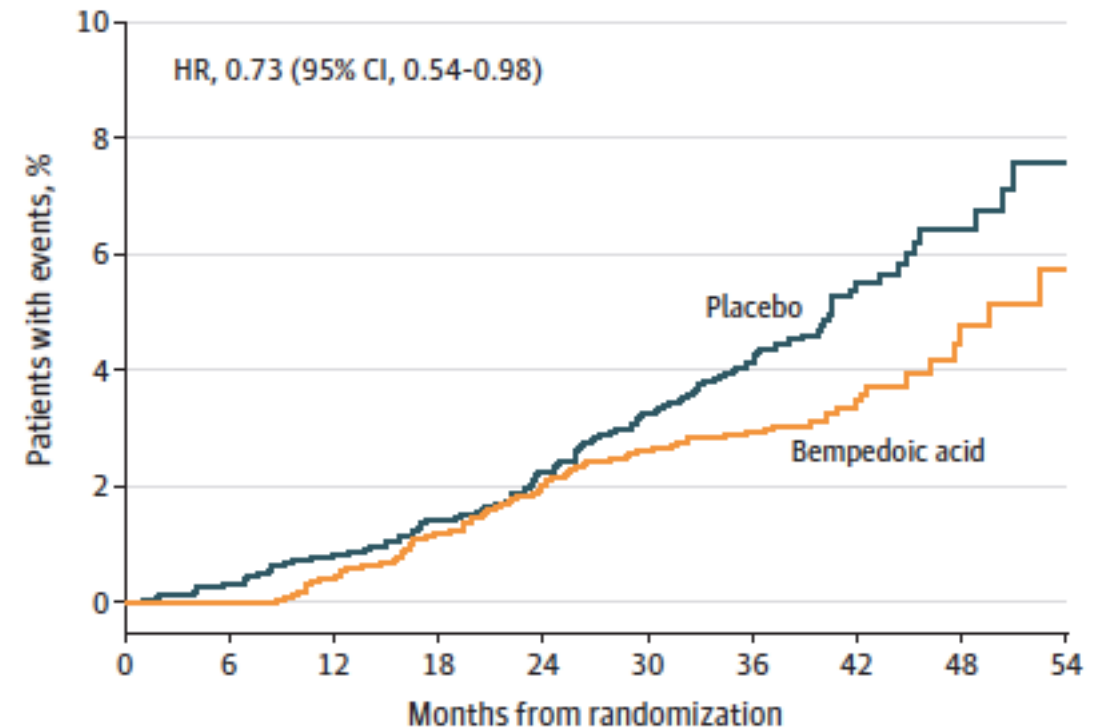
Bempedoic Acid for Primary Prevention of CVOT in Statin-Intolerant Patients

A Primary end point (4-component MACE)



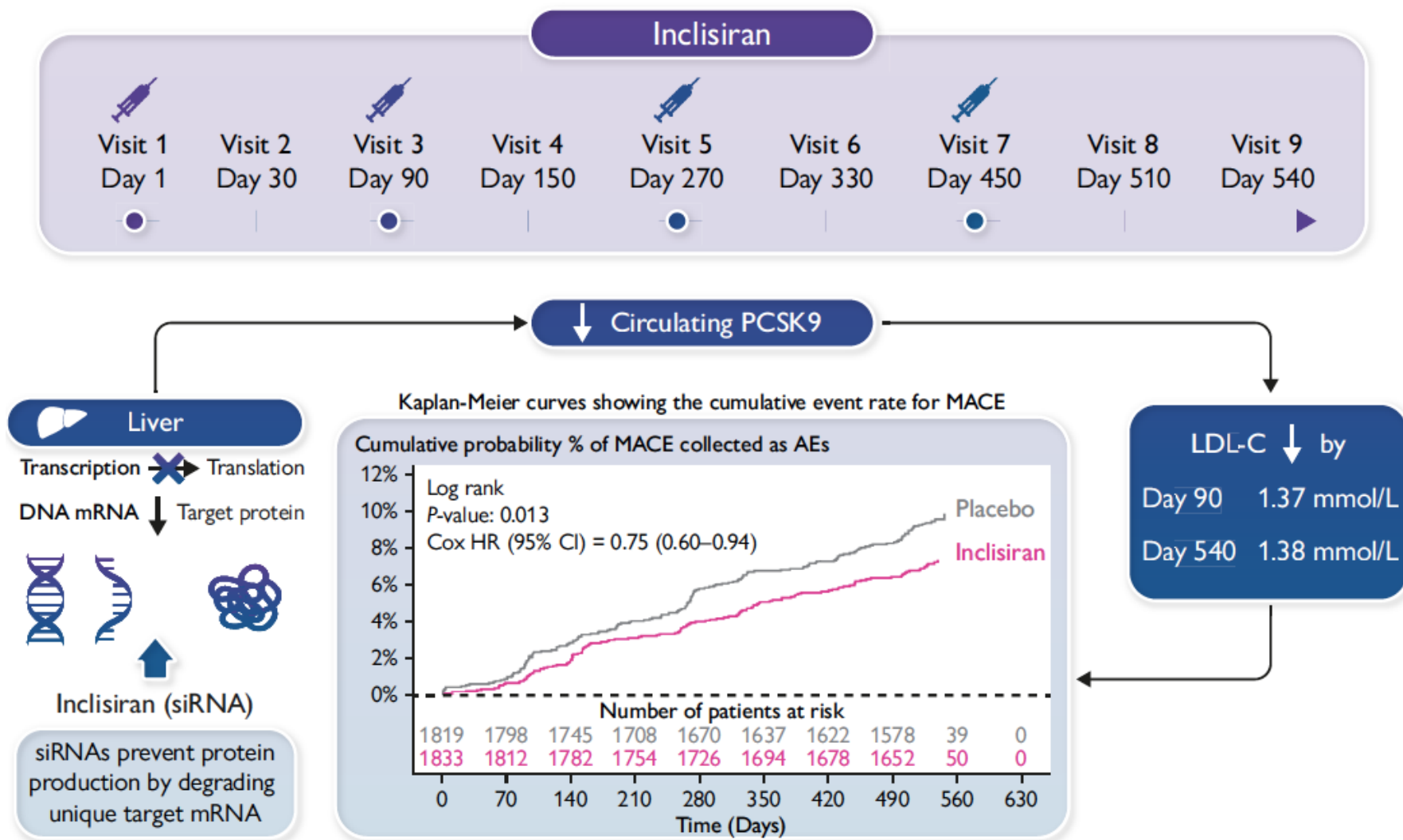
No. at risk									
Placebo	2063	2024	1973	1921	1870	1617	753	304	117
Bempedoic acid	2069	2041	1996	1953	1923	1675	726	291	130

F All-cause mortality

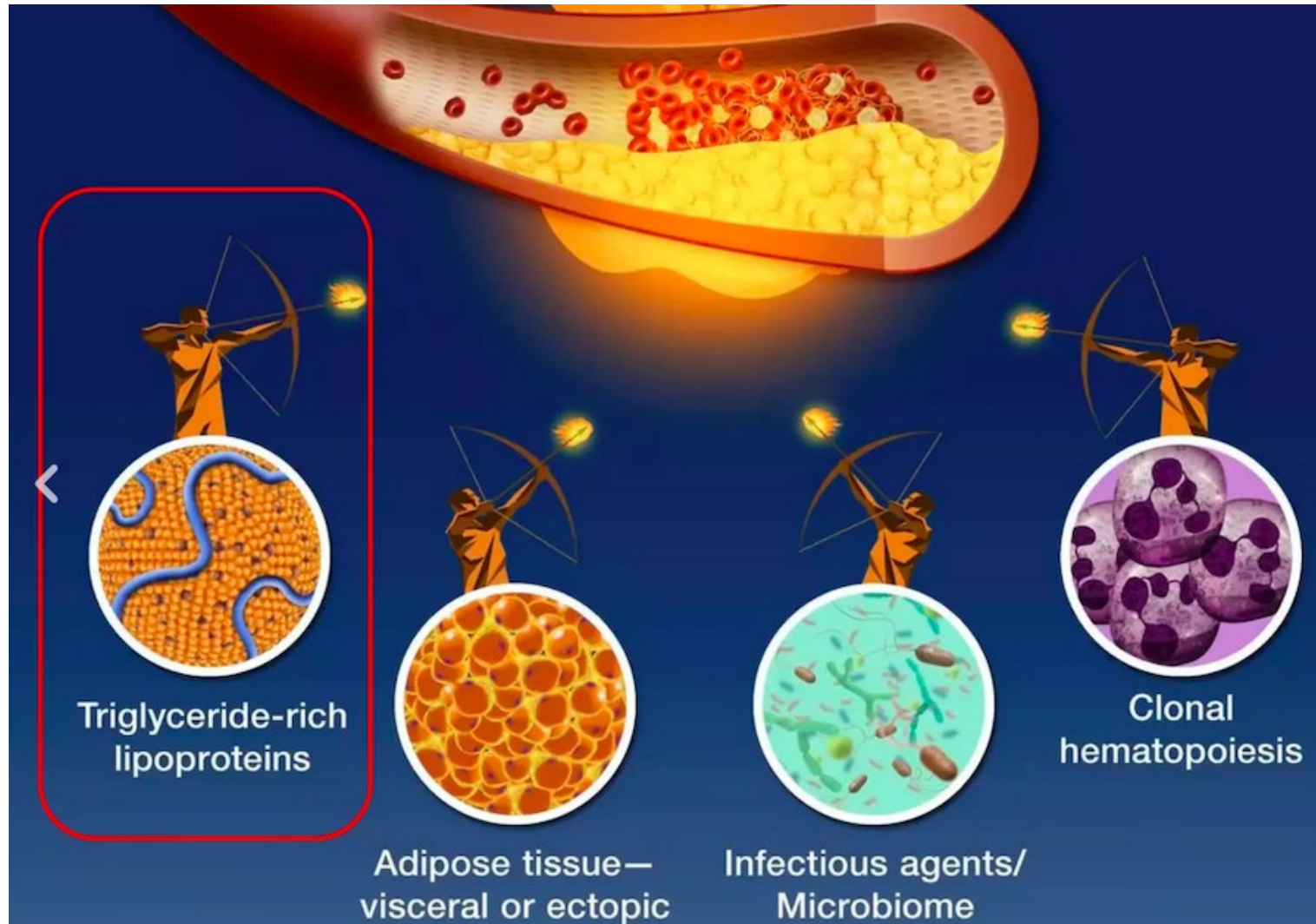


No. at risk									
Placebo	2090	2065	2037	2009	1975	1729	808	328	125
Bempedoic acid	2088	2073	2042	2010	1994	1745	772	307	135

Inclisiran and cardiovascular events: a patient-level analysis of phase III trials (ORION-9, ORION-10 and ORION-11 trials)



Emerging Risk Factors



VLDL ...

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

A. Das Pradhan, R.J. Glynn, J.-C. Fruchart, J.G. MacFadyen, E.S. Zaharris, B.M. Everett, S.E. Campbell, R. Oshima, P. Amarenco, D.J. Blom, E.A. Brinton, R.H. Eckel, M.B. Elam, J.S. Felicio, H.N. Ginsberg, A. Goudev, S. Ishibashi, J. Joseph, T. Kodama, W. Koenig, L.A. Leiter, A.J. Lorenzatti, B. Mankovsky, N. Marx, B.G. Nordestgaard, D. Páll, K.K. Ray, R.D. Santos, H. Soran, A. Susekov, M. Tendera, K. Yokote, N.P. Paynter, J.E. Buring, P. Libby, and P.M. Ridker, for the PROMINENT Investigators*

CONCLUSIONS

Among patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, and low HDL and LDL cholesterol levels, the incidence of cardiovascular events was not lower among those who received pemafibrate than among those who received placebo, although pemafibrate lowered triglyceride, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels. (Funded by the Kowa Research Institute; PROMINENT ClinicalTrials.gov number, NCT03071692.)

Das Pradham A et al N Engl J Med, 2022

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

CONCLUSIONS

Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361.)

The effect was not related to the triglycerides levels at baseline or during the trial

Bhatt DL et al N Engl J Med, 2018

Conclusions

- Dyslipidaemias are major CVD risk factors, especially in people with diabetes
- In patients with diabetes stratification of the risk is strongly suggested (ASCVD risk estimator plus, Score2-Diabetes)
- Patients with diabetes may be at low, moderate, high and very high CVD risk; the LDL-target is proportional to the estimated risk
- Moderate intensity or high intensity statin therapy is first choice treatment for patients with low, moderate, high risk depending on the target
- Ezetimibe is recommended if the target is not achieved
- In patients at very high risk, PCSK9-i is recommended if LDL-chol remains > than the target despite max tolerated Statin/Ezetimibe or drug intolerance
- Bempedoic Acid and Inclisiran are also available
- More, much more, to come



Acknowledgments



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Barbara Biffi
Lucia Mastria

Adm Office

Anna Maria Costa
Monica Cambiaghi

Clinical Psychology

Simonetta Sarro

Data Manager

Guido Lattuada

Department of Statistics

UNIMIB

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Matteo Compagnoni
Laura Savarè
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Hypertension Unit

UNIMIB

Guido Grassi
Giuseppe Mancia

Papa Giovanni XXIII - BG

UNIMIB

Roberto Trevisan

Youngest UNIMIB

Celeste Ronchetti
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