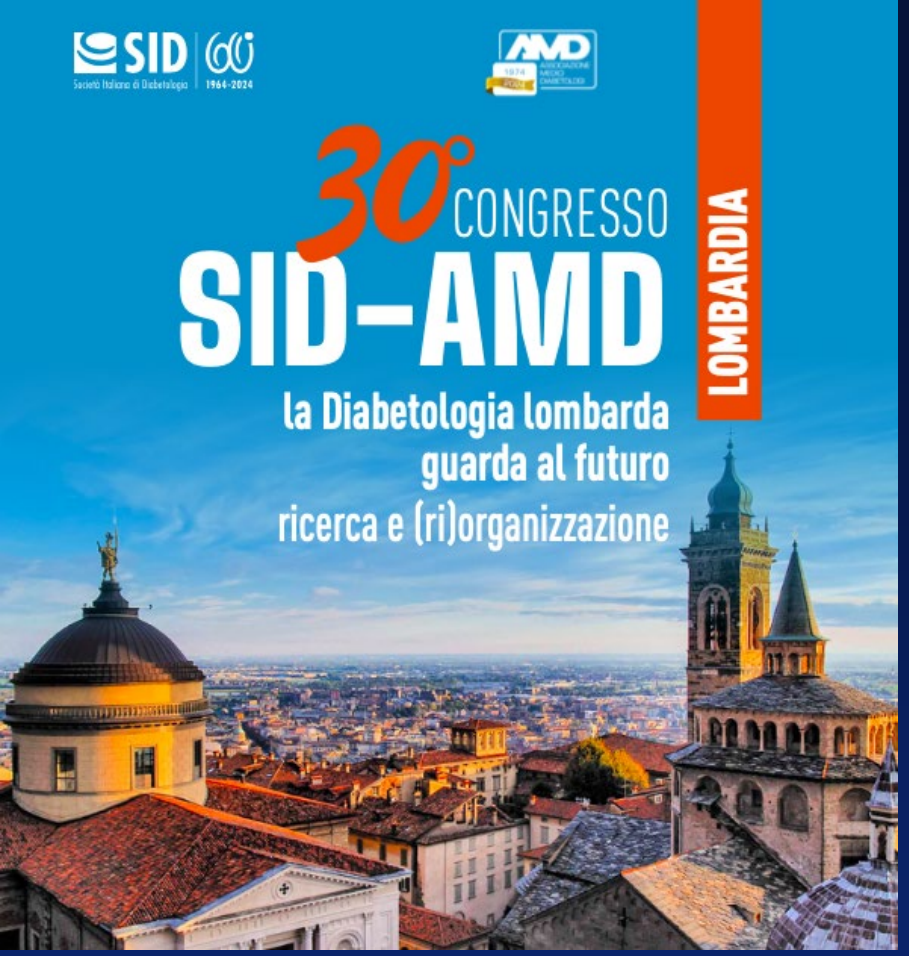


Lipidi: raccomandazioni e terapie (non così) nuove

Gianluca Perseghin

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

Department of Medicine and Rehabilitation,
Policlinico di Monza, Monza

Conflict of Interest
last 3 years

Speaker in Scientific Events
AstraZeneca
Bayer
Boheringer Ingelheim
Daiichi Sankyo
Echosens
Lilly
Menarini Diag
Merck

Scientific AB
Amgen
Bruno Farmaceutici
EG
Lilly
Merck
Novartis
Novo Nordisk
Pfizer
PikDare

Topics

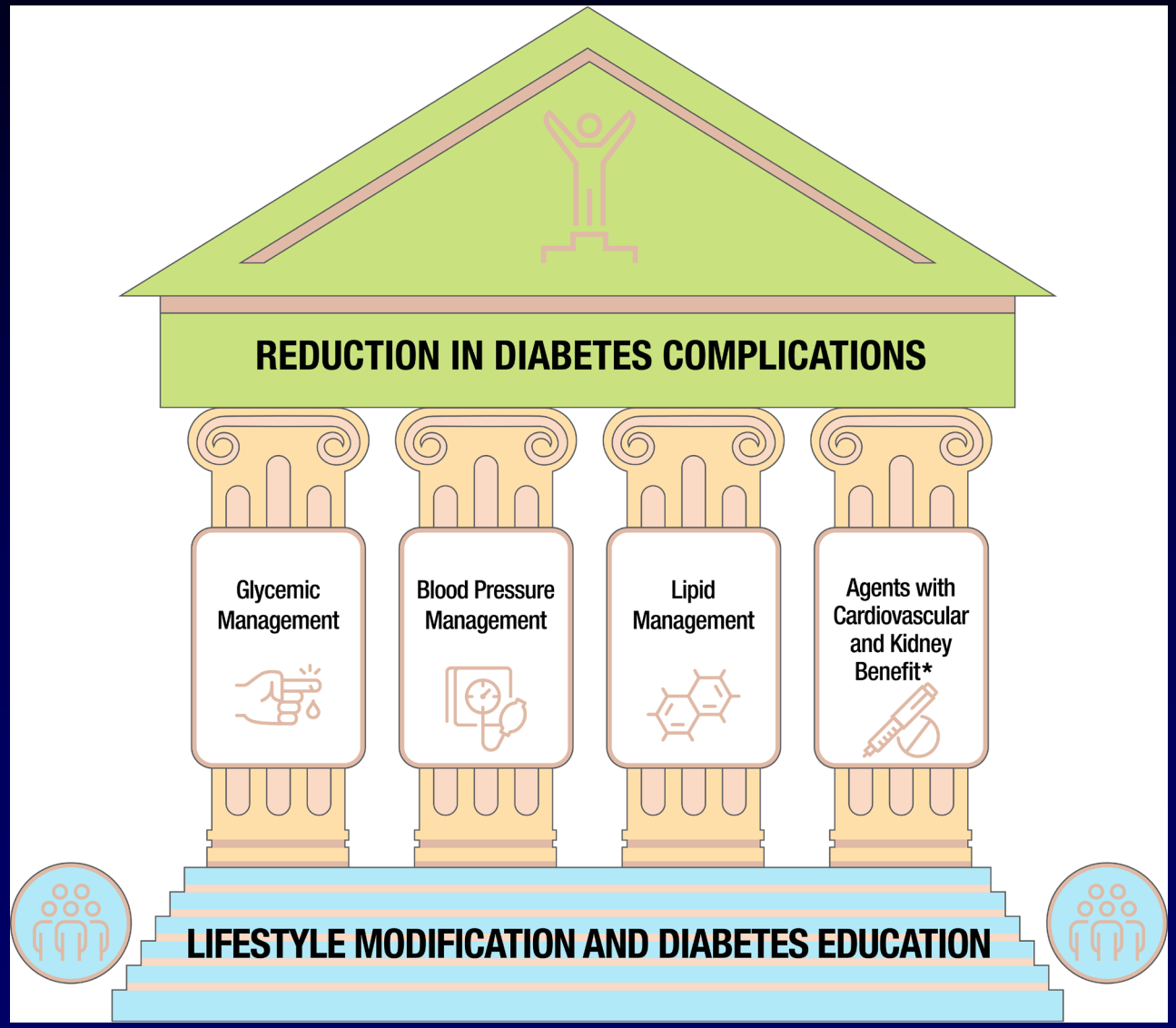
CVD risk in diabetes mellitus

CVD risk and the role of lipids

CVD risk stratification > targets > therapies

Residual CVD risk (novel targets e therapies)

CVD Risk

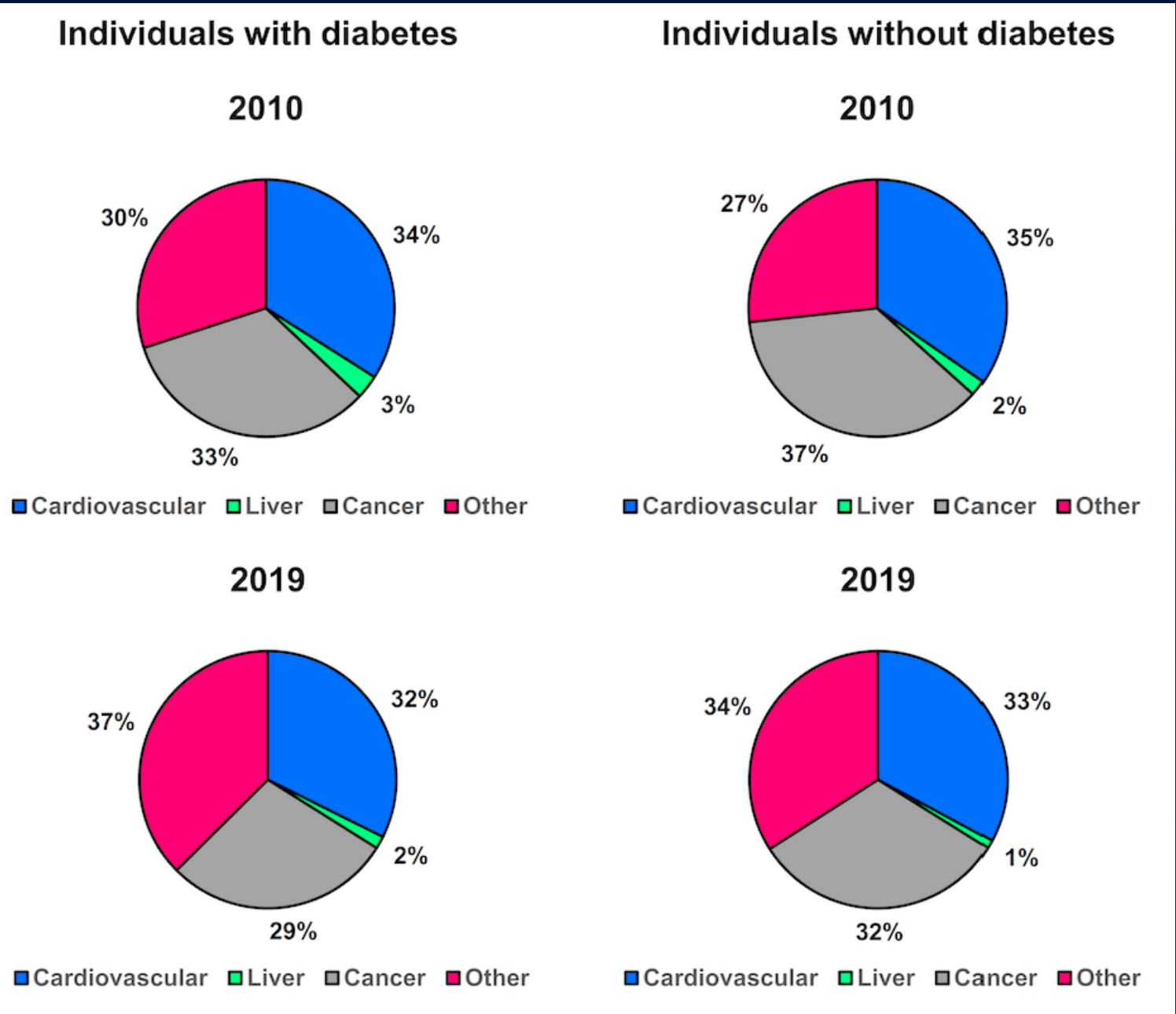


Pillars of the treatment of diabetes mellitus

The management of the diabetic patient must be multifactorial and include not only blood glucose control but also the control of other risk factors **including lipids** to prevent long-term complications and cardiovascular events

American Diabetes Association. Standard of Care, 2024
https://diabetesjournals.org/care/issue/46/Supplement_1

Mortality in Lombardy 2010-2019



Ciardullo S et al
J Clin Endocrinol Metab, 2024

In Lombardia 2010-19

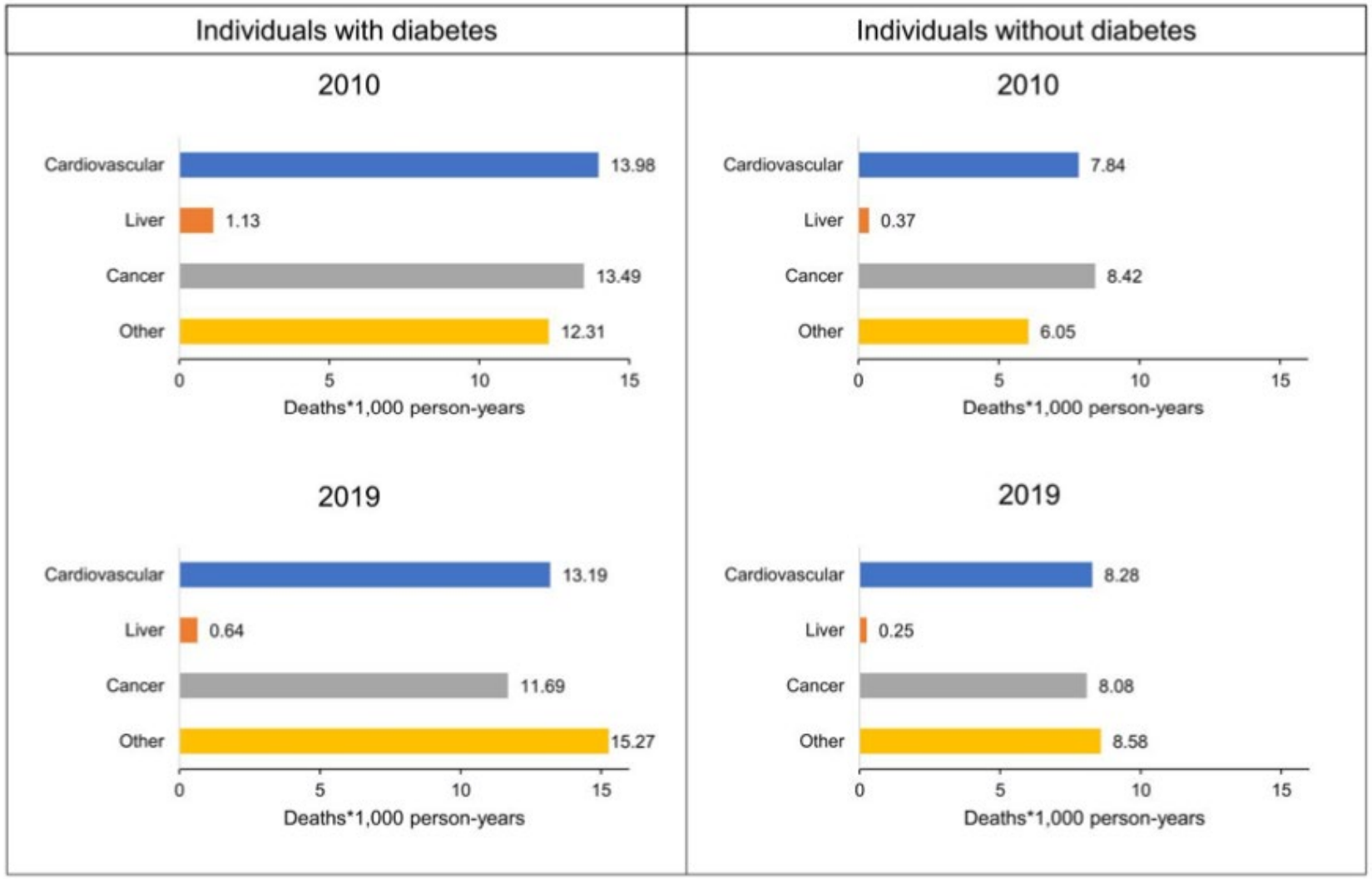


Figure 2. Absolute cause-specific mortality rates among individuals with and without diabetes at the beginning (2010) and at the end (2019) of the studied period.

CVD still matters

Ciardullo S et al
J Clin Endocrinol Metab, 2024

Lipids & CVD Risk

Why this is still an hot topic?

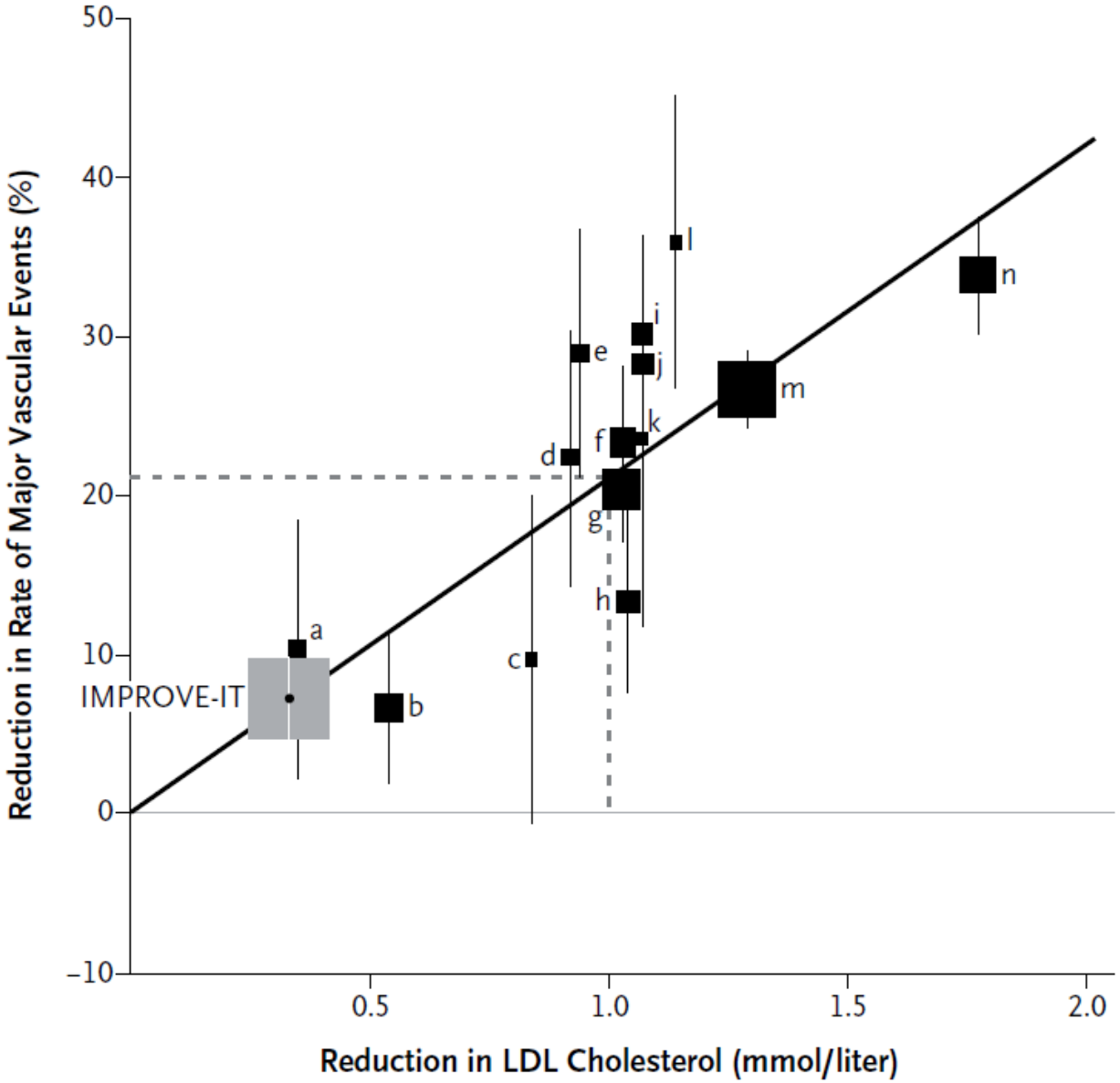
LDL-C: causa di CVD su base aterosclerotica (ASCVD)

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

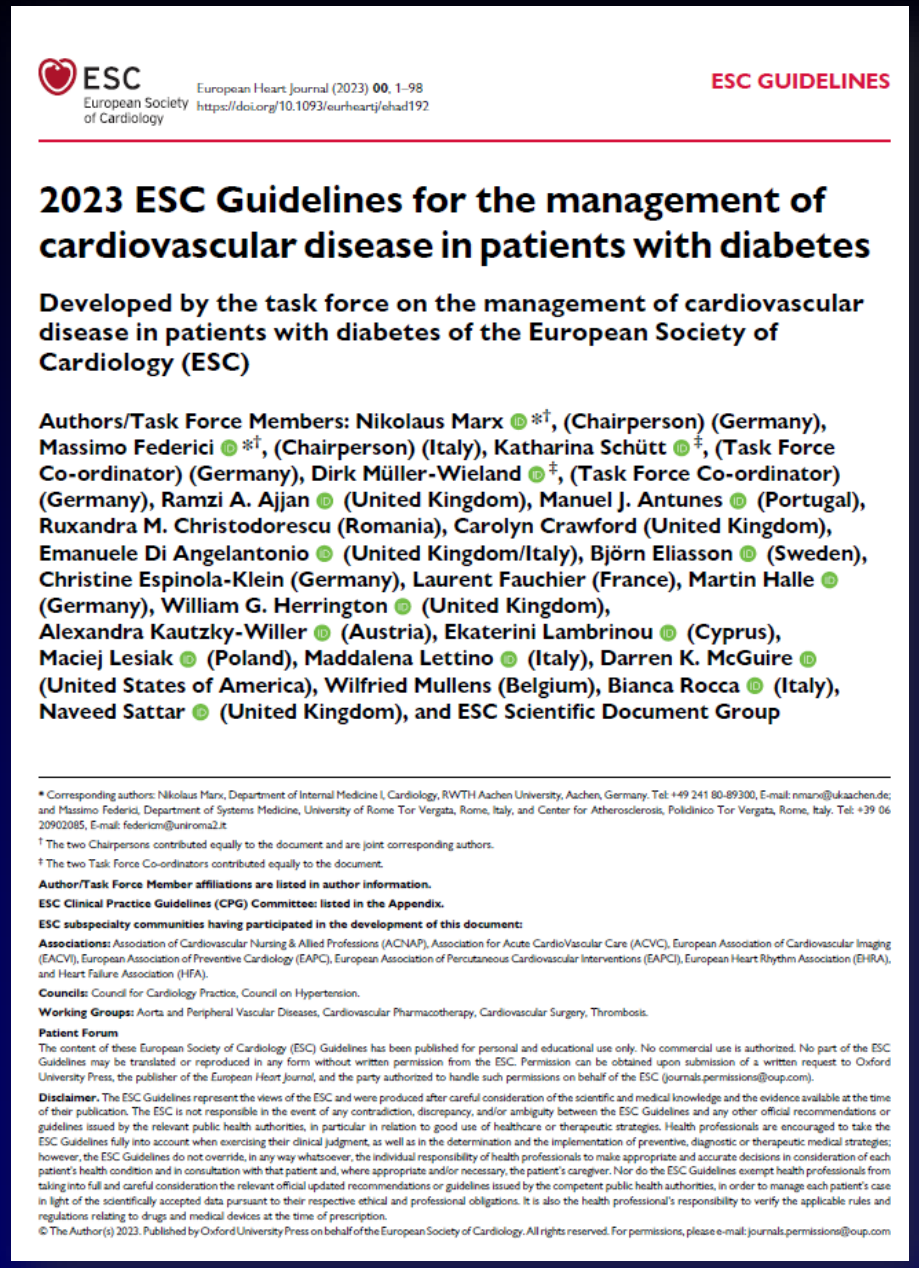
==========

riduzione del 20-25%
eventi CVD e eventi coronarici

Cholesterol Treatment Trialists Collaboration
Lancet, 2010



CVD Risk stratification



ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–98
https://doi.org/10.1093/eurheartj/ehad192

ESC GUIDELINES

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

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

Authors/Task Force Members: Nikolaus Marx *†, (Chairperson) (Germany), Massimo Federici *†, (Chairperson) (Italy), Katharina Schütt ‡, (Task Force Co-ordinator) (Germany), Dirk Müller-Wieland ‡, (Task Force Co-ordinator) (Germany), Ramzi A. Ajjan (United Kingdom), Manuel J. Antunes (Portugal), Ruxandra M. Christodorescu (Romania), Carolyn Crawford (United Kingdom), Emanuele Di Angelantonio (United Kingdom/Italy), Björn Eliasson (Sweden), Christine Espinola-Klein (Germany), Laurent Fauchier (France), Martin Halle (Germany), William G. Herrington (United Kingdom), Alexandra Kautzky-Willer (Austria), Ekaterini Lambrinou (Cyprus), Maciej Lesiak (Poland), Maddalena Lettino (Italy), Darren K. McGuire (United States of America), Wilfried Mullens (Belgium), Bianca Rocca (Italy), Naveed Sattar (United Kingdom), and ESC Scientific Document Group

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† The two Chairpersons contributed equally to the document and are joint corresponding authors.

‡ The two Task Force Co-ordinators contributed equally to the document.

Author/Task Force Member affiliations are listed in author information.

ESC Clinical Practice Guidelines (CPG) Committee: listed in the Appendix.

ESC subspecialty communities having participated in the development of this document:

Associations: Association of Cardiovascular Nursing & Allied Professions (ACNAP), Association for Acute CardioVascular Care (ACVC), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), and Heart Failure Association (HFA).

Councils: Council for Cardiology Practice, Council on Hypertension.

Working Groups: Aorta and Peripheral Vascular Diseases, Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Thrombosis.

Back to the past!

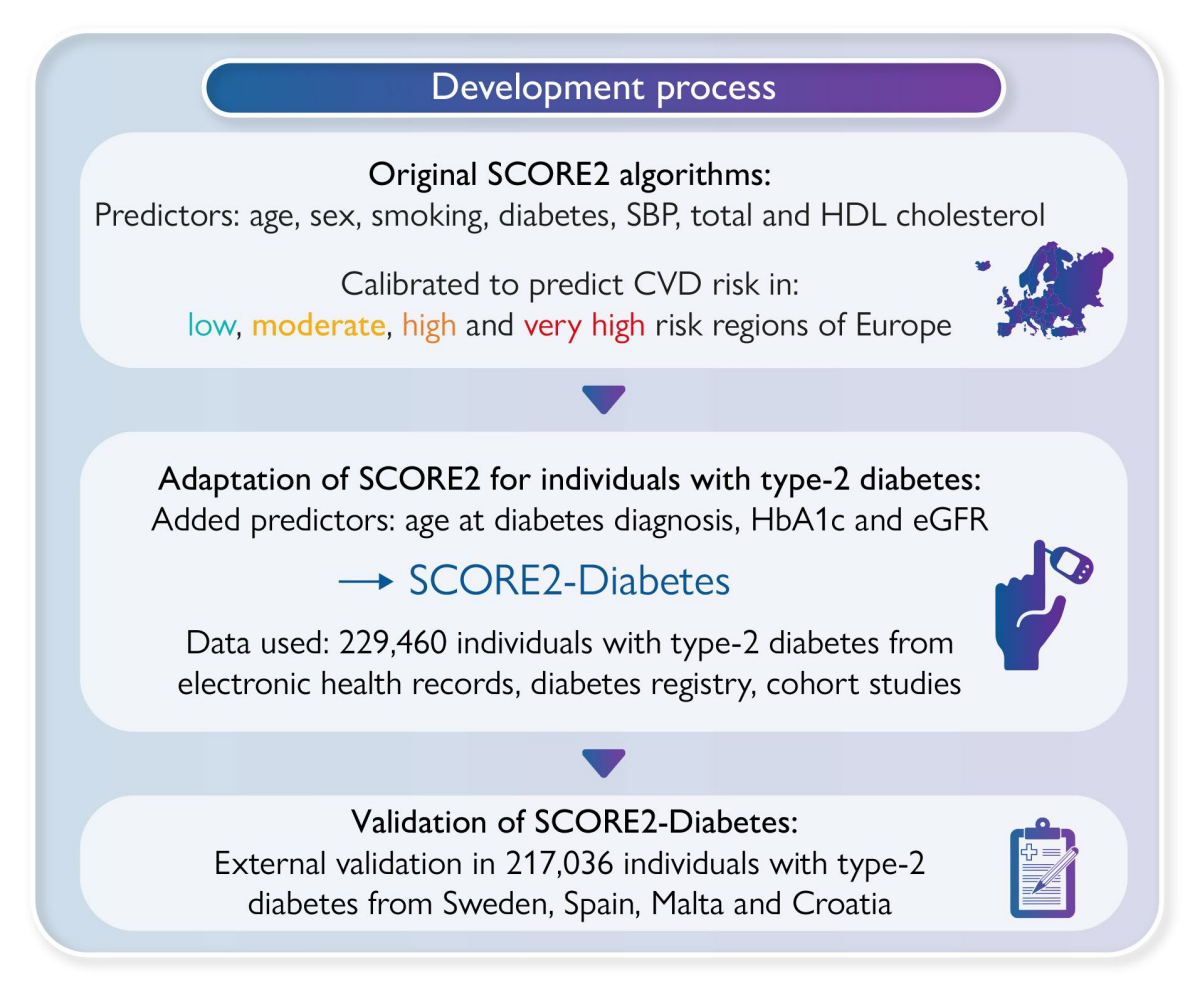
Risk stratification using calculators

Not fully NEW!!!

Marx N, et al. 2023 ESC Guidelines Eur Heart J. 2023

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

Marx N, et al. 2023 ESC Guidelines Eur Heart J, 2023

Very high risk without a previous event or equivalent of event; who is she/he?

TOD

eGFR < 45 mL/min (regardless albuminuria)
eGFR 45-60 mL/min + microalbuminuria/proteinuria
Microvascular disease: microalbuminuria + DR + neuropathy

Marx N, et al. 2023 ESC Guidelines Eur Heart J, 2023

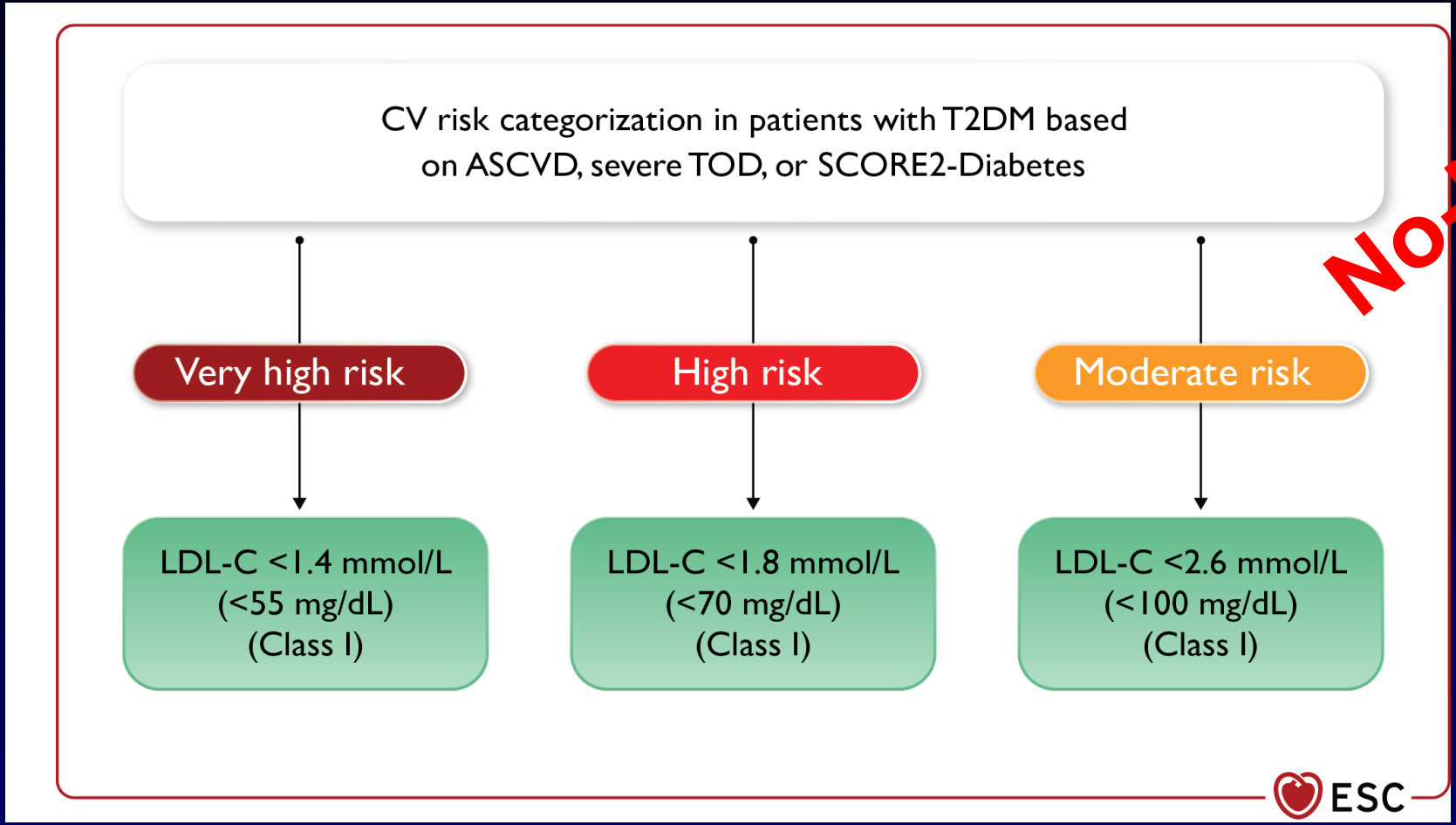
Score2 Diabetes ≥20%

F; 69 years old; diabetes since 50, smok-, SBP 138 mmHg, Tot chol 184 mg/dL, HDL-chol 41 mg/dL HbA1c 7,2%, eGFR 51 ml/min

M; 65 years old; diabetes since 56, smok+, SBP 140 mmHg, Tot chol 170 mg/dL, HDL-chol 50 mg/dL HbA1c 6.7%, eGFR 65 ml/min

Targets for LDL-cholesterol

Very high risk without a previous event (or equivalent event)



NO-NEWS!!!

Marx N, et al. 2023 ESC Guidelines Eur Heart J, 2023

Treatments for LDL-cholesterol

Recommendations	Class	Level
Lipid-lowering treatment		
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

Marx N, et al. 2023 ESC Guidelines Eur Heart J, 2023

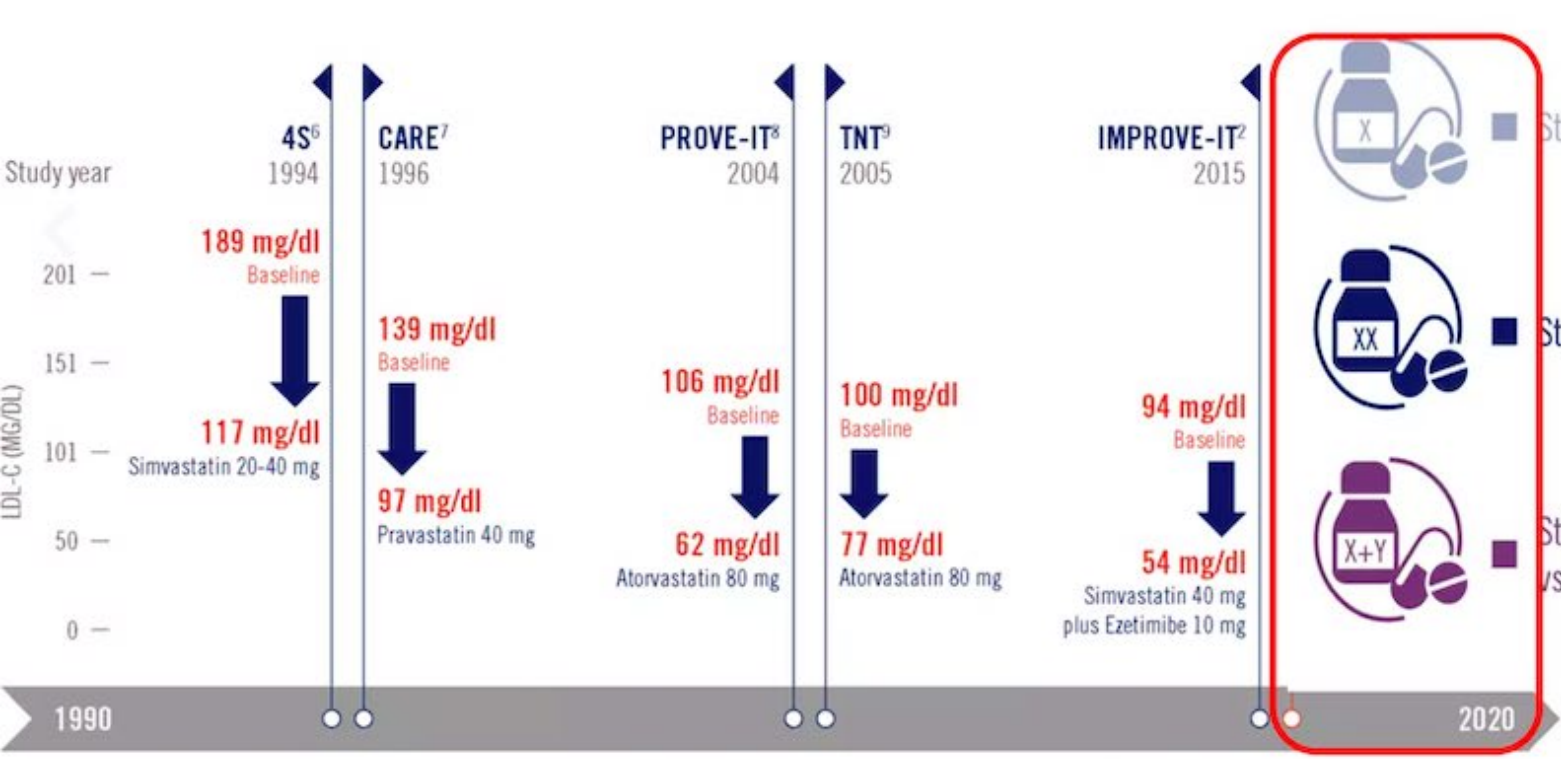
Residual Risk

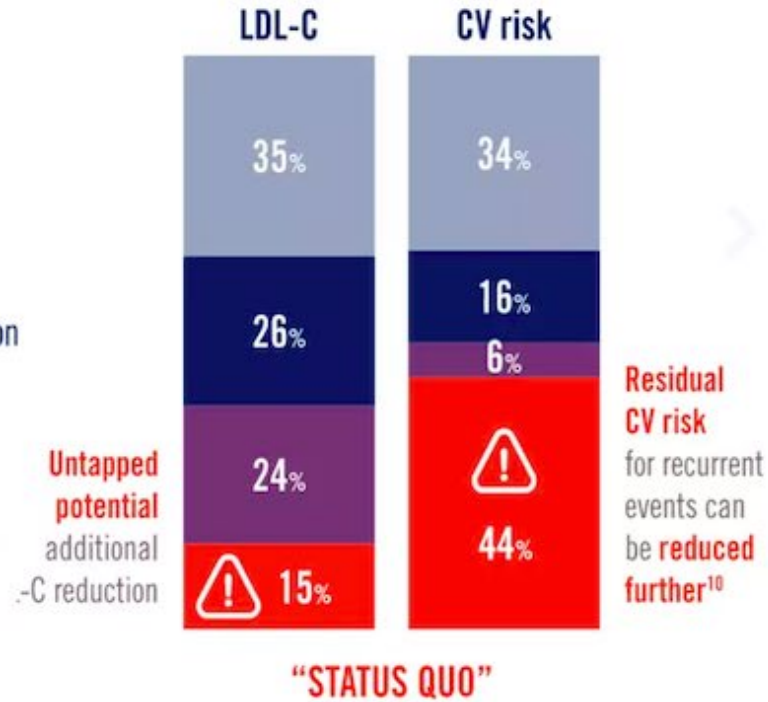
Why?

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‡





R3i; residual risk reduction initiative website

Treatments for LDL-cholesterol

Recommendations	Class	Level
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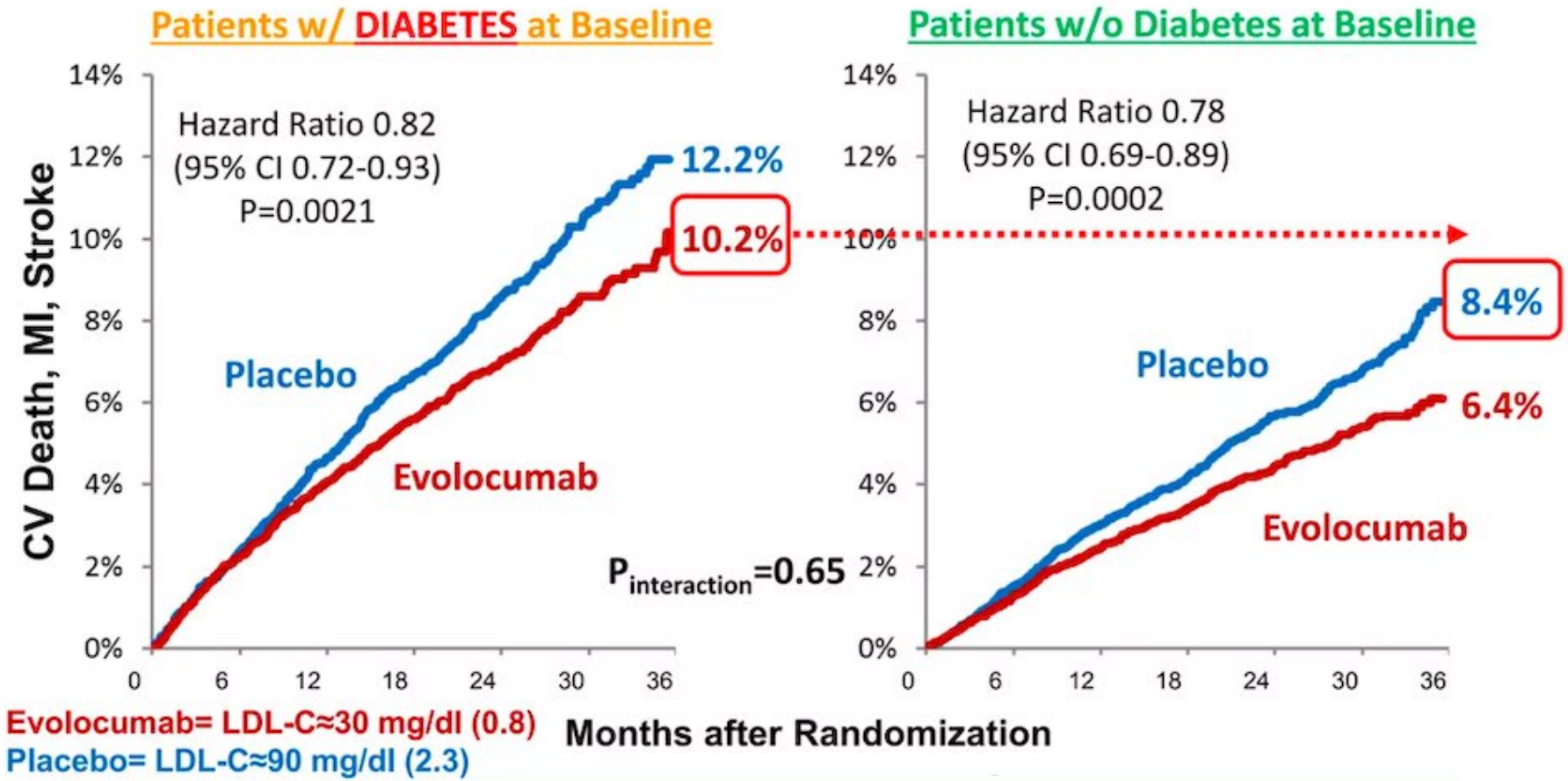
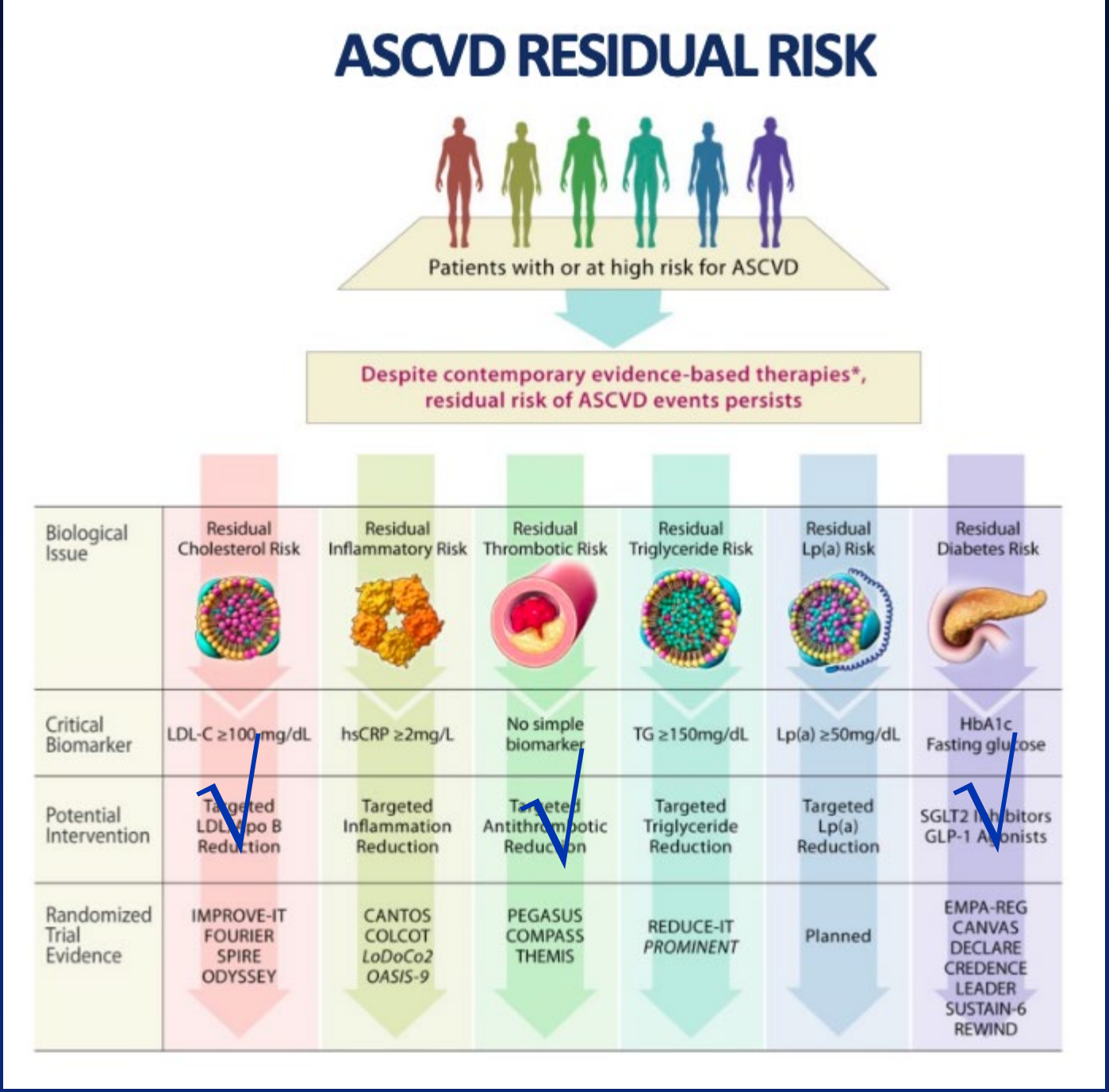
Marx N, et al. 2023 ESC Guidelines Eur Heart J, 2023

Especially - if you have T2DM!

Effect of Evolocumab on Key Secondary Endpoint



Sabatine MS et al N Engl J Med, 2017



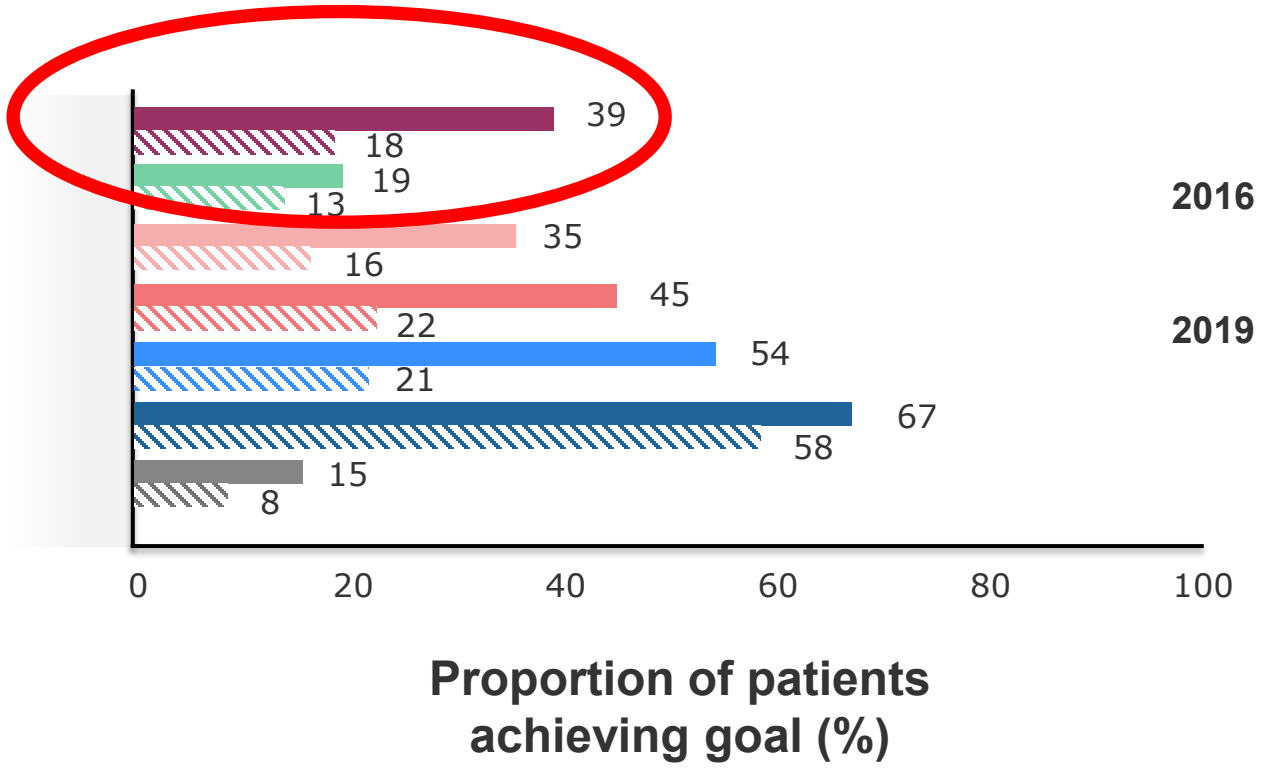
Open questions

- apoB
- non HDL cholesterol
- Inflammation
- Triglycerides
- Lp(a)

Lawler et al Eur Heart J, 2021

DA VINCI study: “Only 18% of very high-risk patients achieved LDL-C goals of <1.4 mmol/L”

(Cross-sectional study: 18 countries; N=5888)



Overall (n=2039)
Low intensity statin monotherapy (n=47)
Moderate intensity statin monotherapy (n=887)
High intensity statin monotherapy (n=764)
Ezetimibe combination (n=189)
PCSK9i combination (n=24)
Other LLT (n=128)

Ray KK, et al. Eur J Prev Cardiol 2021

PIU' DI UNA PROSPETTIVA

- Bempedoic Acid, which targets ATP citrate lyase
- an siRNA targeting PCSK9 (Inclisiran)

NEW!

Triglycerides

- a purified omega-3 fatty acid, icosapent ethyl
- an antisense oligonucleotide targeting apolipoprotein C-III (Olezarsen)

HDL-chol

- CETP inhibitors (Obicetrapib)

LDL-chol

- an anti-angiopoietinlike-3 antibody (Evinacumab)
- Oral PCSK9-i
- 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

Beliard S, et al. Diabetologia, 2024

Conclusions

- Dyslipidaemias are major CVD risk factors, especially in people with diabetes
- In patients with diabetes stratification of the risk is strongly suggested (now with calculators: 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 diabetes with low, moderate and high risk dependening on the target
- Ezetimibe is recommended, if the target is not achieved
- In patients at very high risk, PCSK9-i is recommendend if LDL-chol remains > than the target despite max tolerated Statin/Ezetimibe or drug intolerance

Acknowledgments

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R.N.
Paola Parmeggiani (Education)
Barbara Biffi
Lucia Mastria

Adm Office
Anna Maria Costa
Monica Cambiaghi

Clinical Psychology
Simonetta Sarro

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Guido Lattuada

Department of Statistics
UNIMIB
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PRIN 2022

Hypertension Unit
UNIMIB
Guido Grassi
Giuseppe Mancia

Papa Giovanni XXIII - BG
UNIMIB
Roberto Trevisan

Youngest UNIMIB

Celeste Ronchetti
Michela Vergani
Matteo Conti
Mariangela Rizzo

Risk stratification

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥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

?

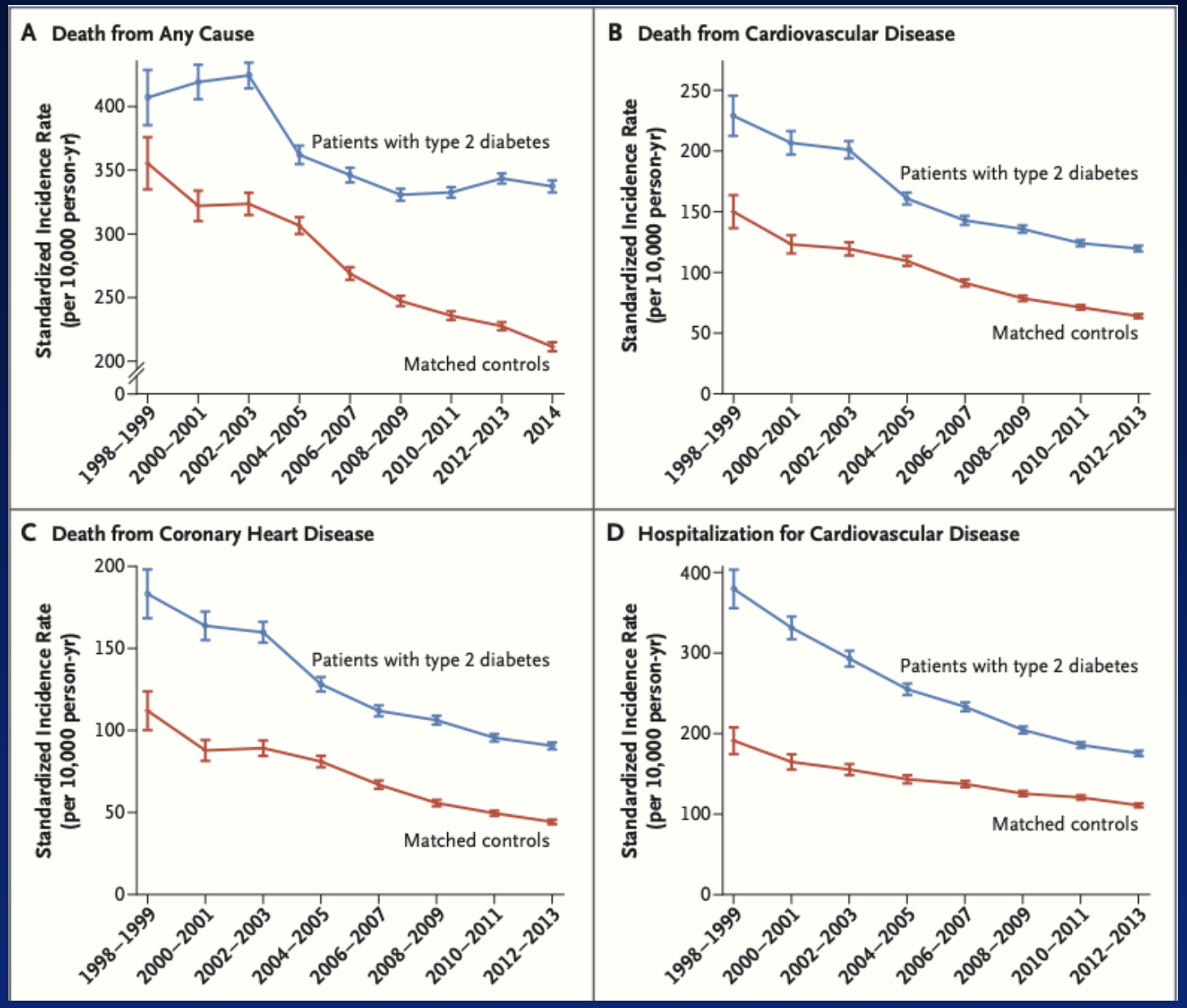
Majority

Some/many

few

Marx N, et al. 2023 ESC Guidelines Eur Heart J, 2023

CVD, CAD & T2DM (Europe)

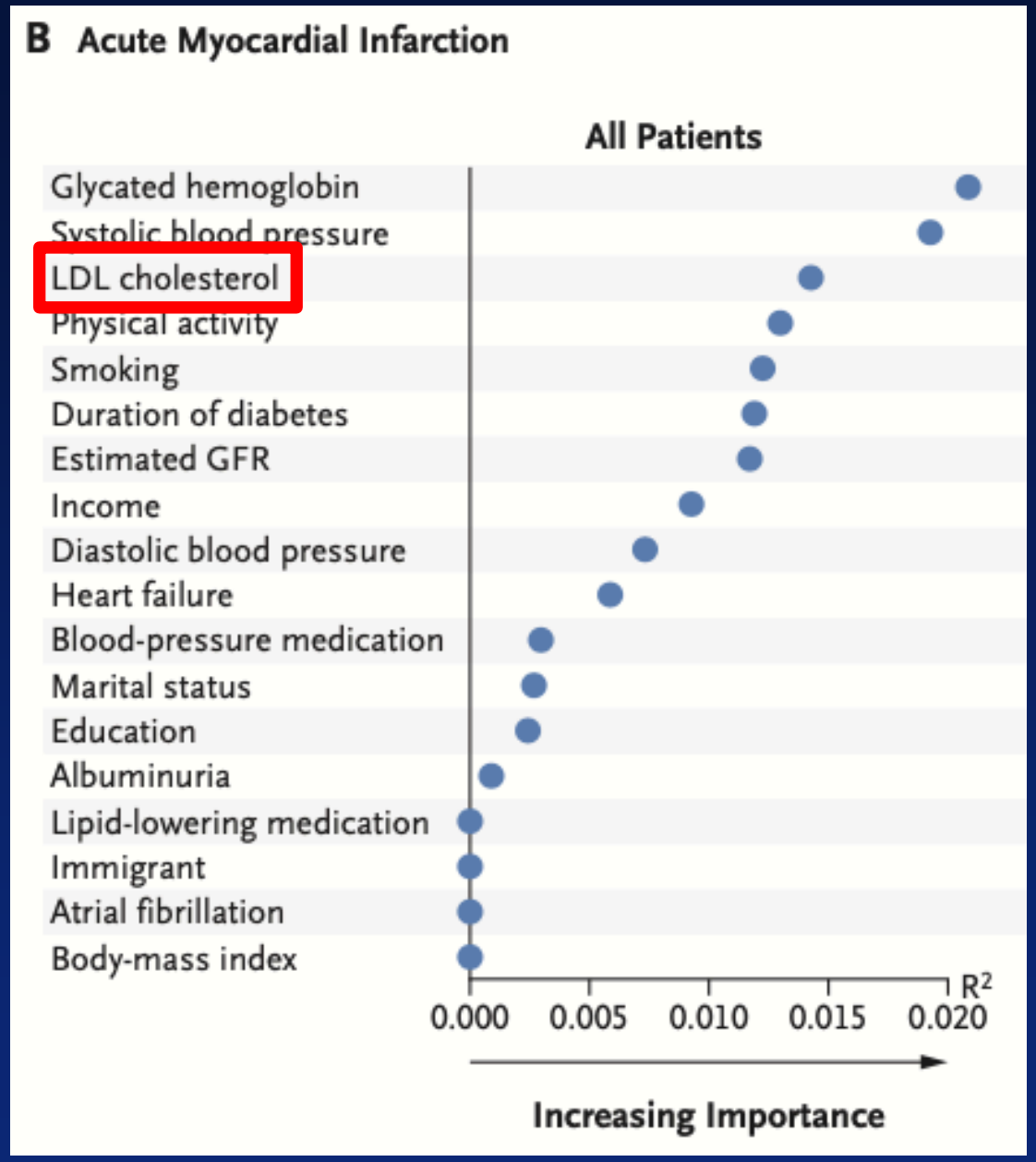


Swedish National Diabetes Register
271,174 patients with T2DM *vs.*
1,355,870 matched controls on the basis of age, sex, and county

Follow-up 5.7 years
175,345 deaths occurred

Rawshani A et al N Engl J Med, 2017

LDL counts!



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

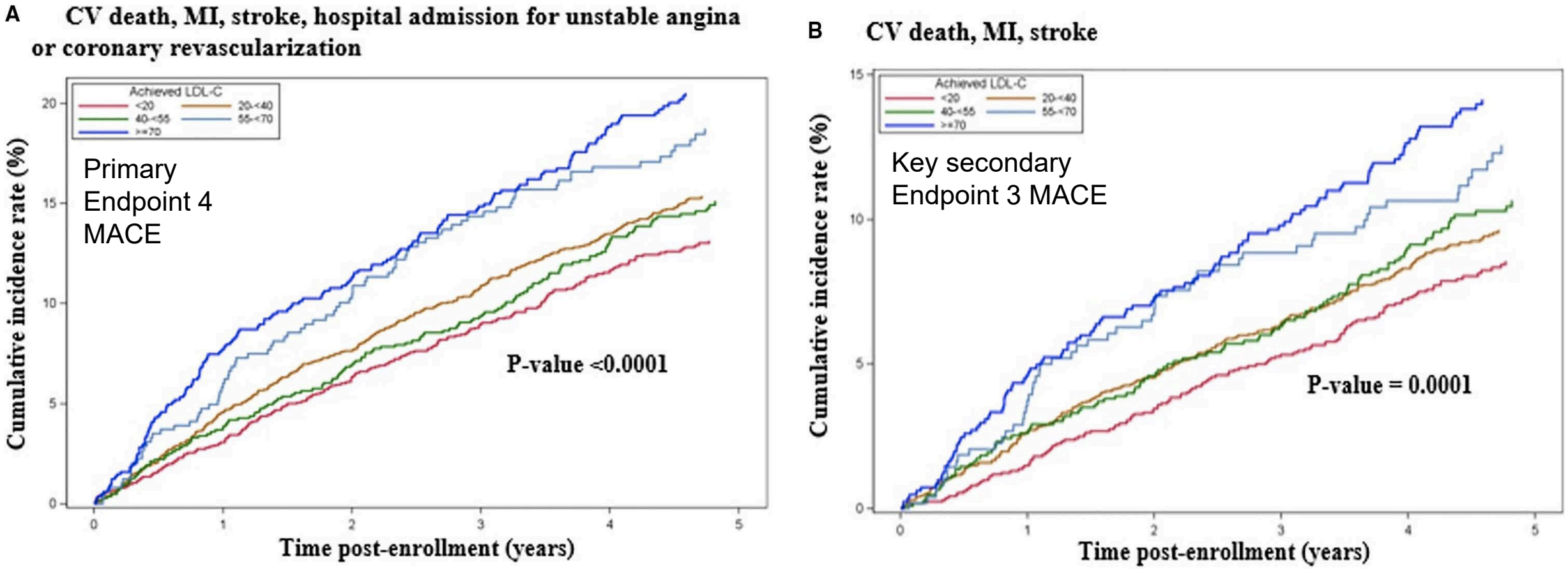
Follow-up 5.7 years
175,345 deaths occurred

Risk factors:

- elevated HbA1c
- elevated LDL-chol
- albuminuria
- smoking cigarettes
- elevated blood pressure

Rawshani A et al N Engl J Med, 2018

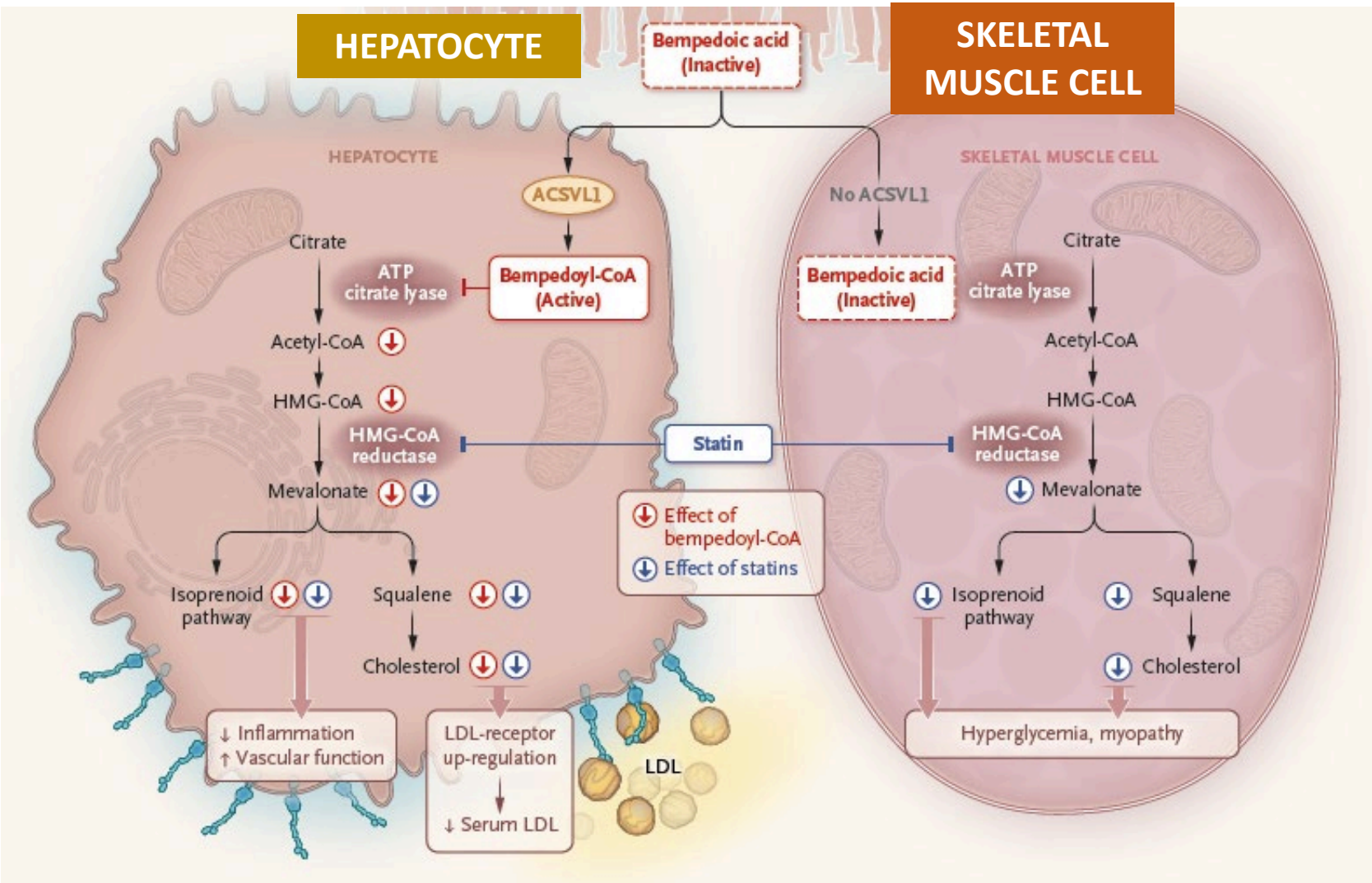
Evolocumab and Long-Term Cardiovascular and Safety Outcomes



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.

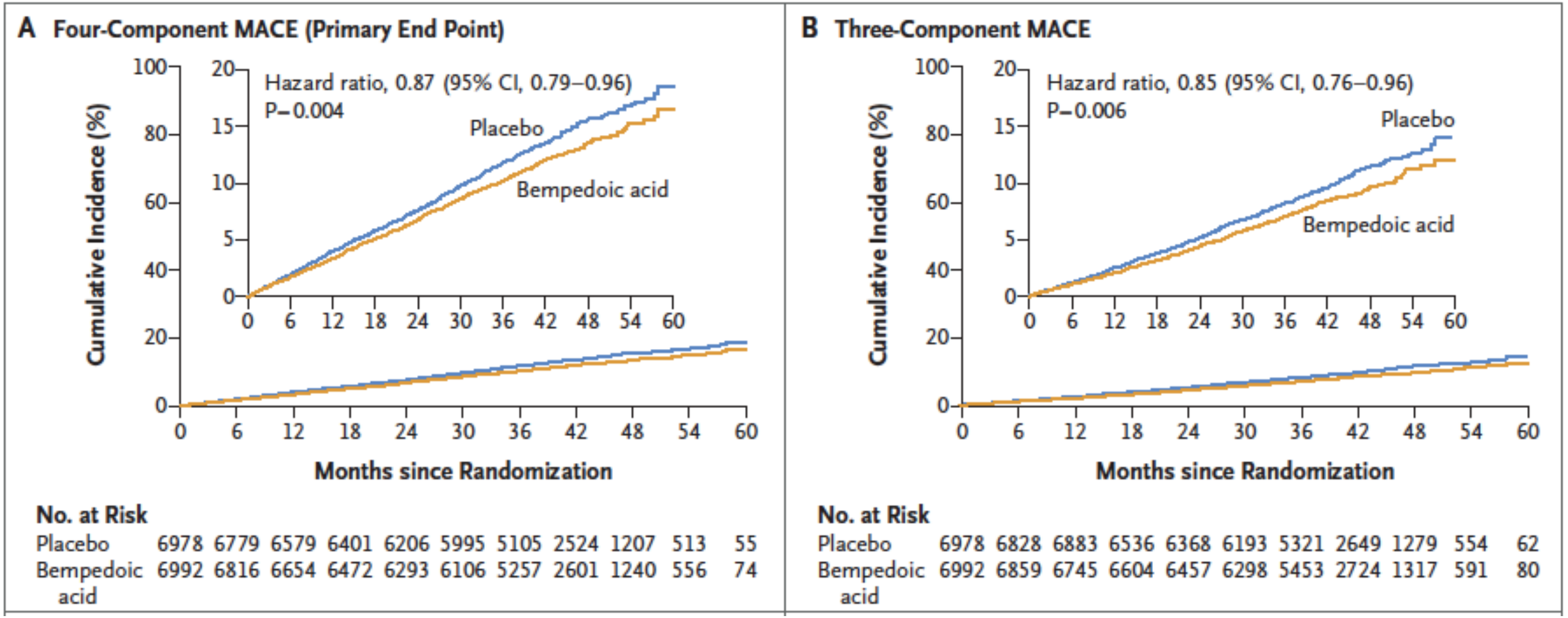
Gaba P, et al. Circulation. 2023

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



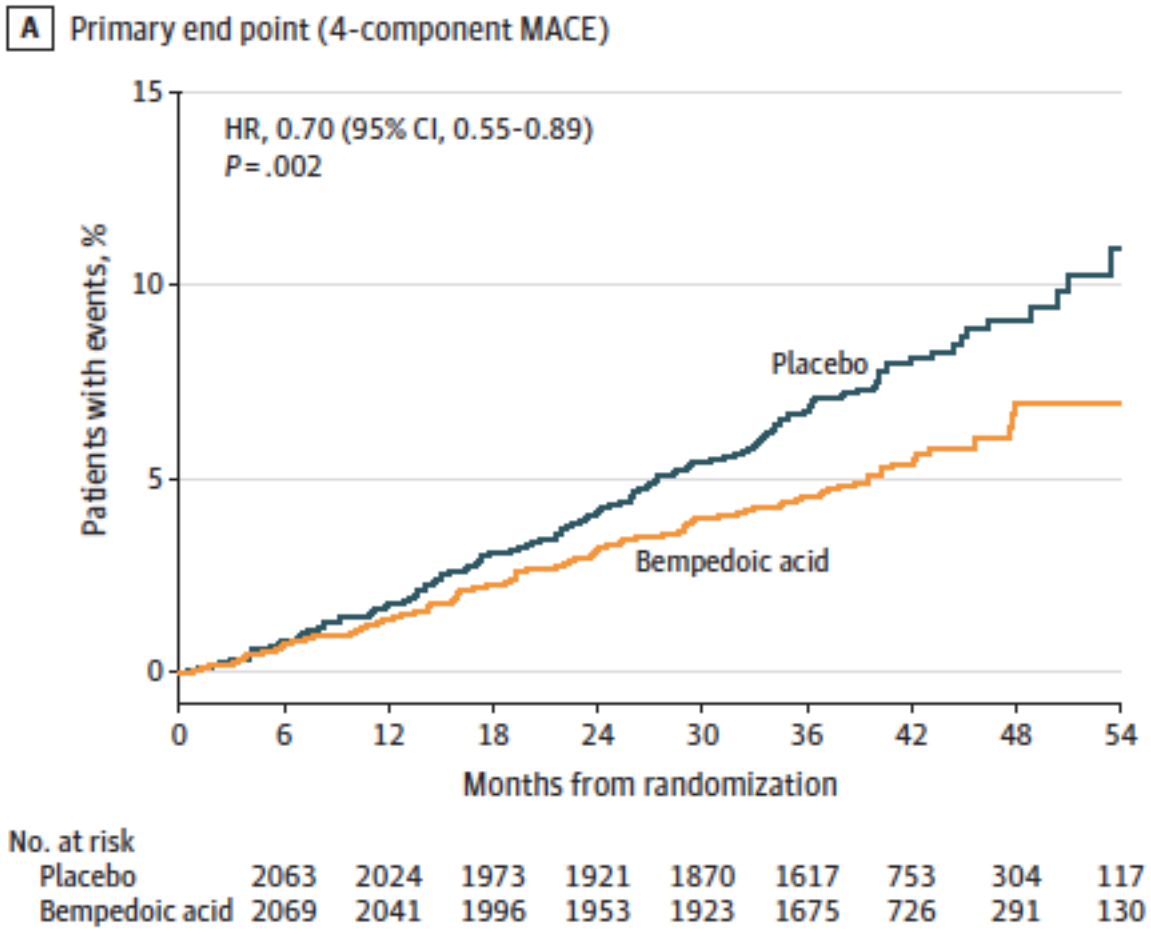
Keaney JF, N Engl J Med 2023

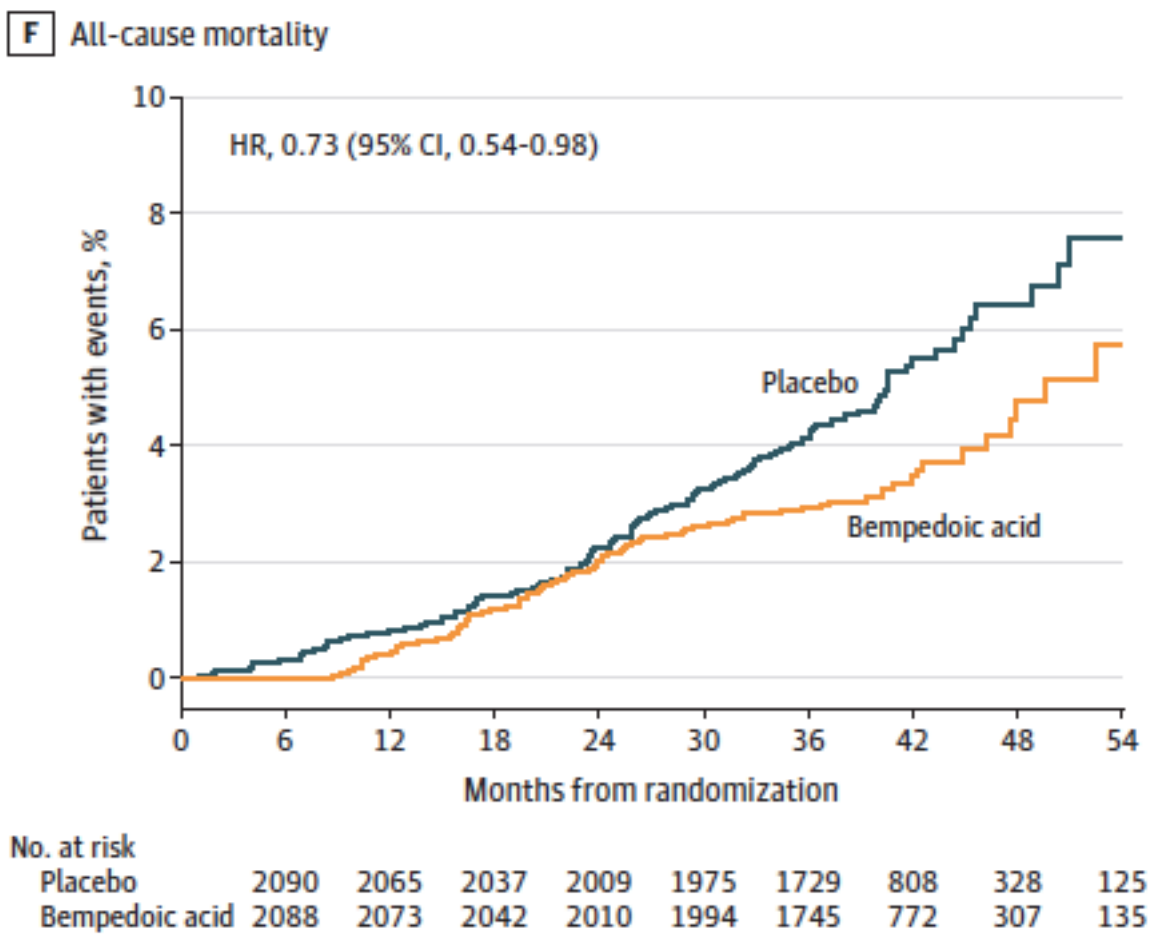
Bempedoic Acid and CVOT in Statin-Intolerant Patients
The CLEAR trial



Nissen SE et al N Engl J Med, 2023

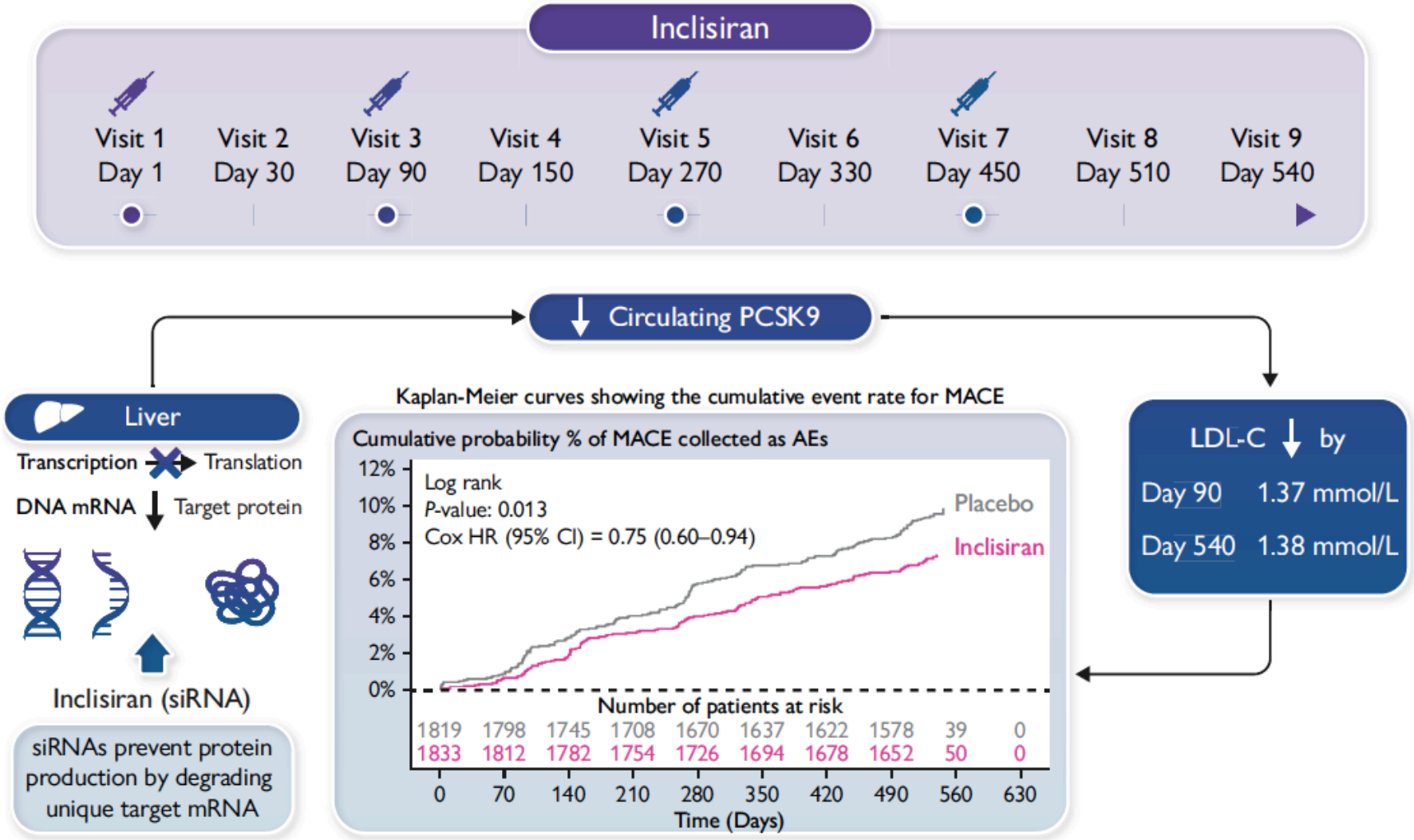
Bempedoic Acid for Primary Prevention of CVOT in Statin-Intolerant Patients





Nissen SE, et al. JAMA, 2023

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



Ray KK, et al, for the ORION Phase III Investigators. Eur Heart J, 2023