

# 30° CONGRESSO SID-AMD

la Diabetologia lombarda  
guarda al futuro  
ricerca e (ri)organizzazione

LOMBARDIA



## Lipidi: raccomandazioni e terapie (non così) nuove

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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**

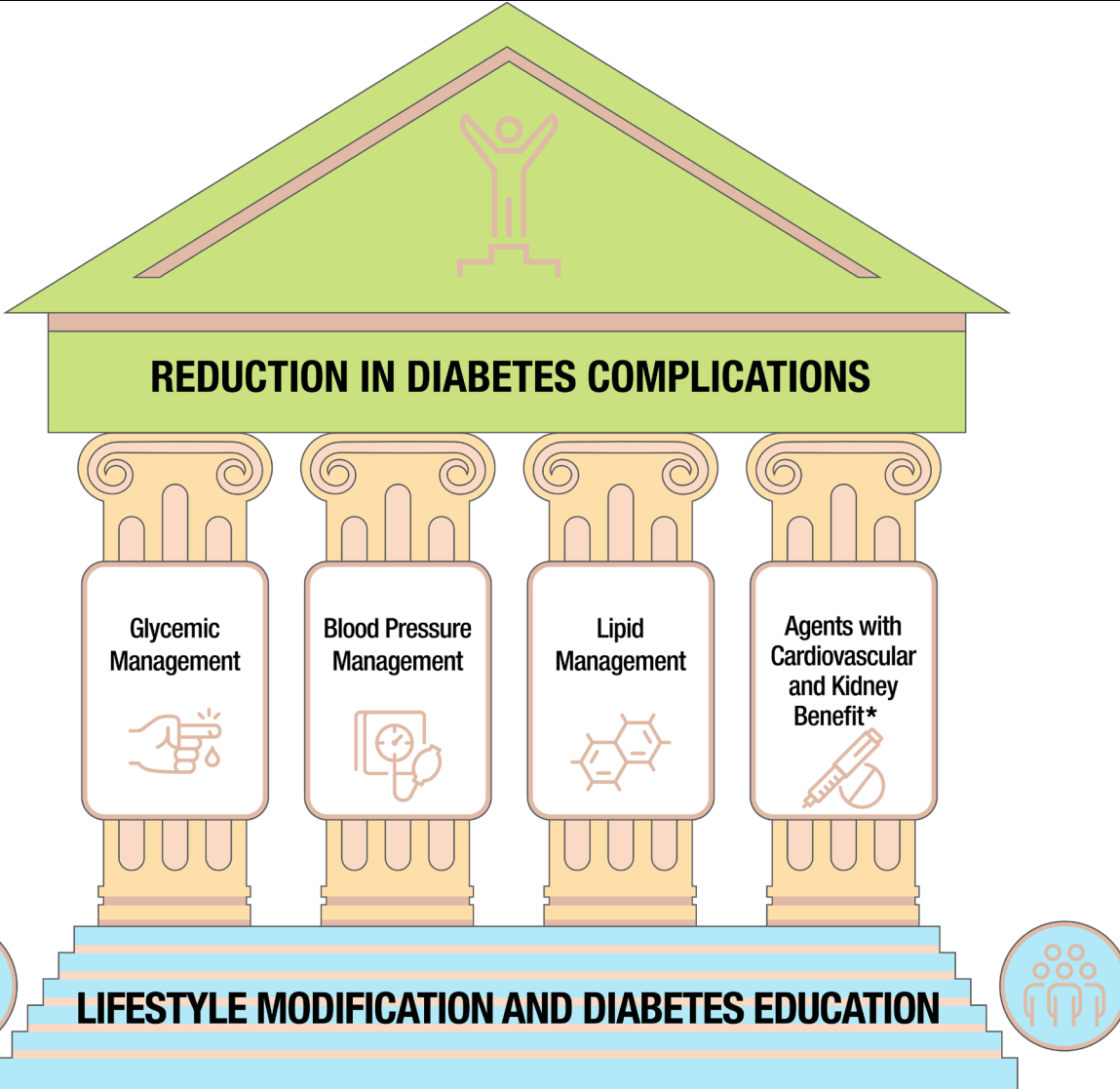
**CVD risk stratification > targets > therapies**

**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

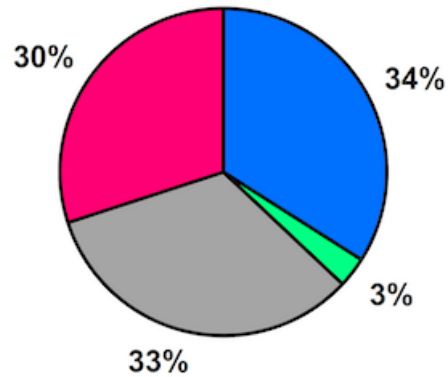


American Diabetes Association. Standard of Care, 2024  
[https://diabetesjournals.org/care/issue/46/Supplement\\_1](https://diabetesjournals.org/care/issue/46/Supplement_1)

# Mortality in Lombardy 2010-2019

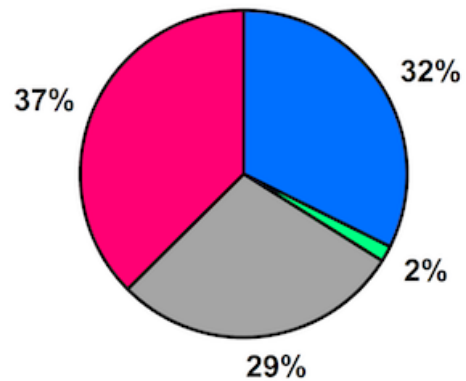
Individuals with diabetes

2010



■ Cardiovascular ■ Liver ■ Cancer ■ Other

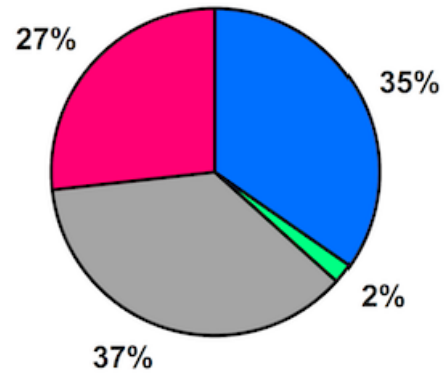
2019



■ Cardiovascular ■ Liver ■ Cancer ■ Other

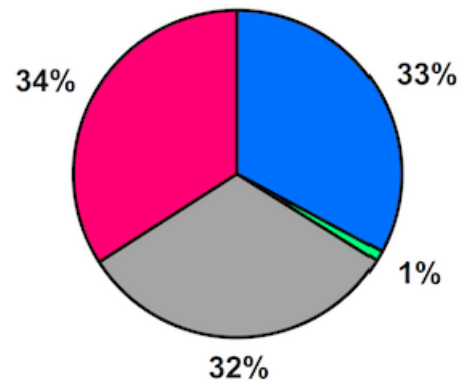
Individuals without diabetes

2010



■ Cardiovascular ■ Liver ■ Cancer ■ Other

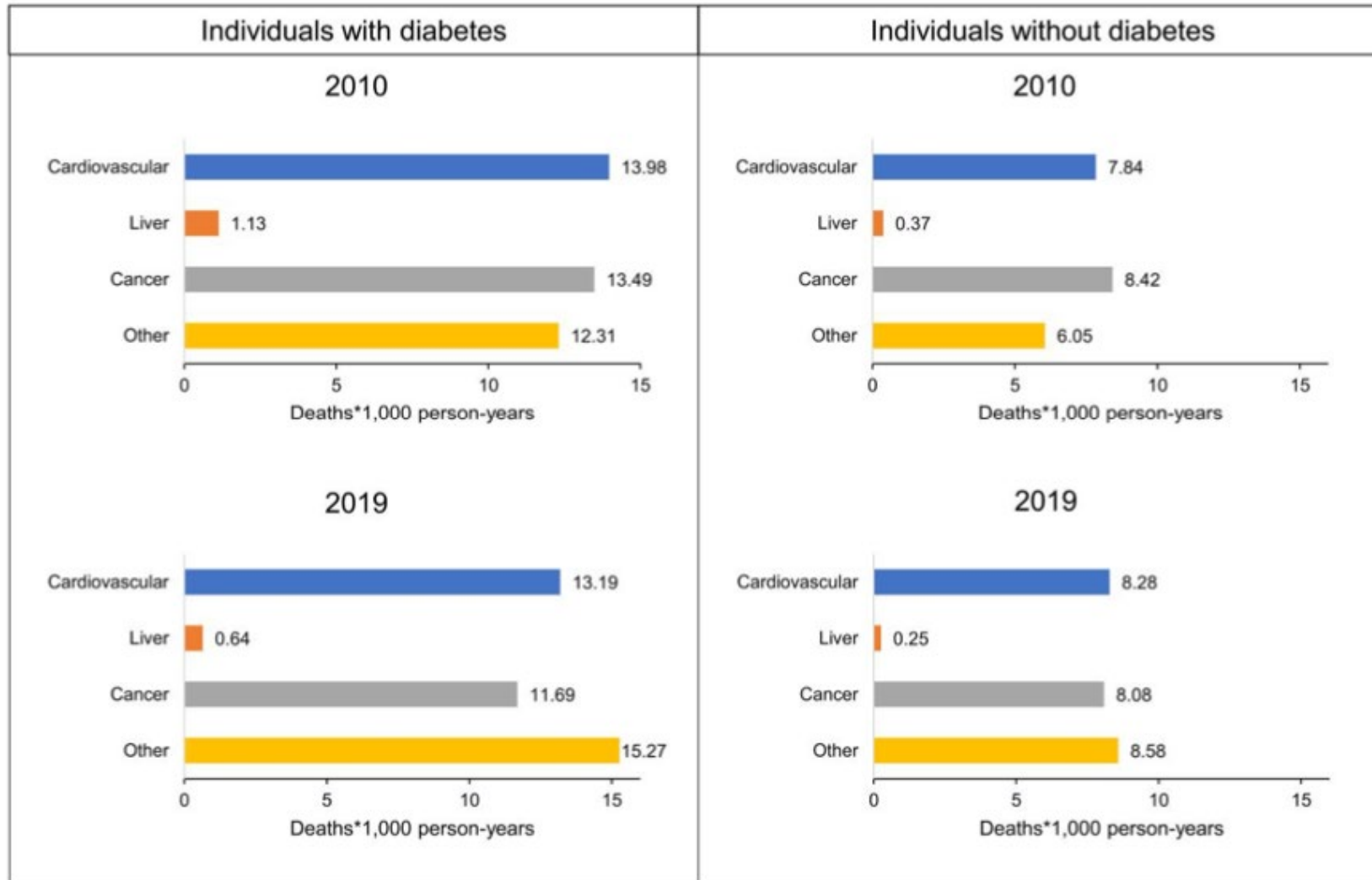
2019



■ Cardiovascular ■ Liver ■ Cancer ■ Other

# In Lombardia 2010-19

CVD still matters



**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.

# Lipids & CVD Risk

**Why this is still an hot topic?**

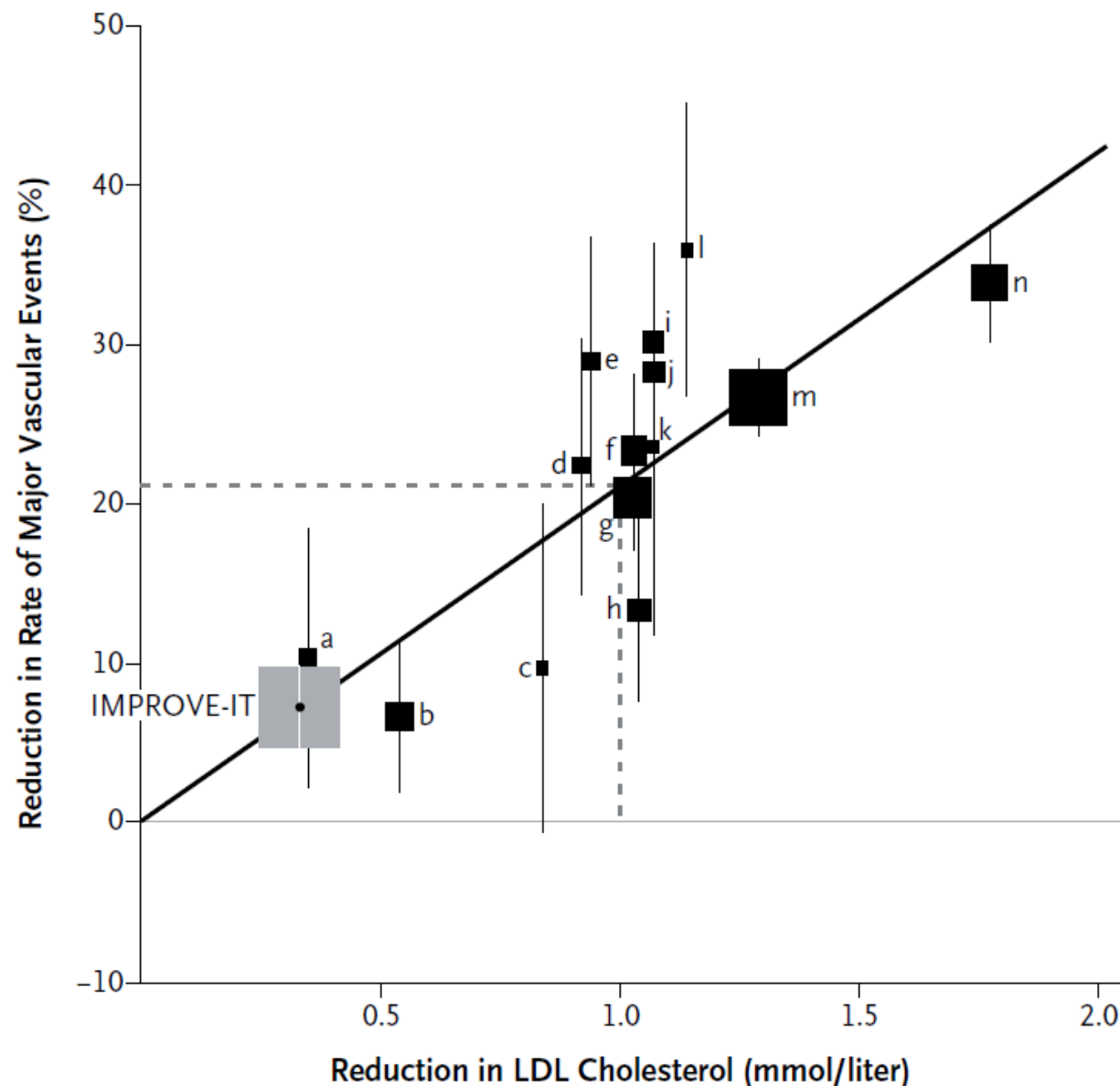
# LDL-C: causa di CVD su base aterosclerotica (ASCVD)

**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**

## 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)

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**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 (ACNAF), Association for Acute CardioVascular Care (AACV), 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.

**Patient Forum**

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# 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!!!**

## Development process

### Original SCORE2 algorithms:

Predictors: age, sex, smoking, diabetes, SBP, total and HDL cholesterol

Calibrated to predict CVD risk in:

low, moderate, high and very high risk regions of Europe



### Adaptation of SCORE2 for individuals with type-2 diabetes:

Added predictors: age at diabetes diagnosis, HbA1c and eGFR

→ SCORE2-Diabetes

Data used: 229,460 individuals with type-2 diabetes from electronic health records, diabetes registry, cohort studies



### Validation of SCORE2-Diabetes:

External validation in 217,036 individuals with type-2 diabetes from Sweden, Spain, Malta and Croatia



**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

# 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

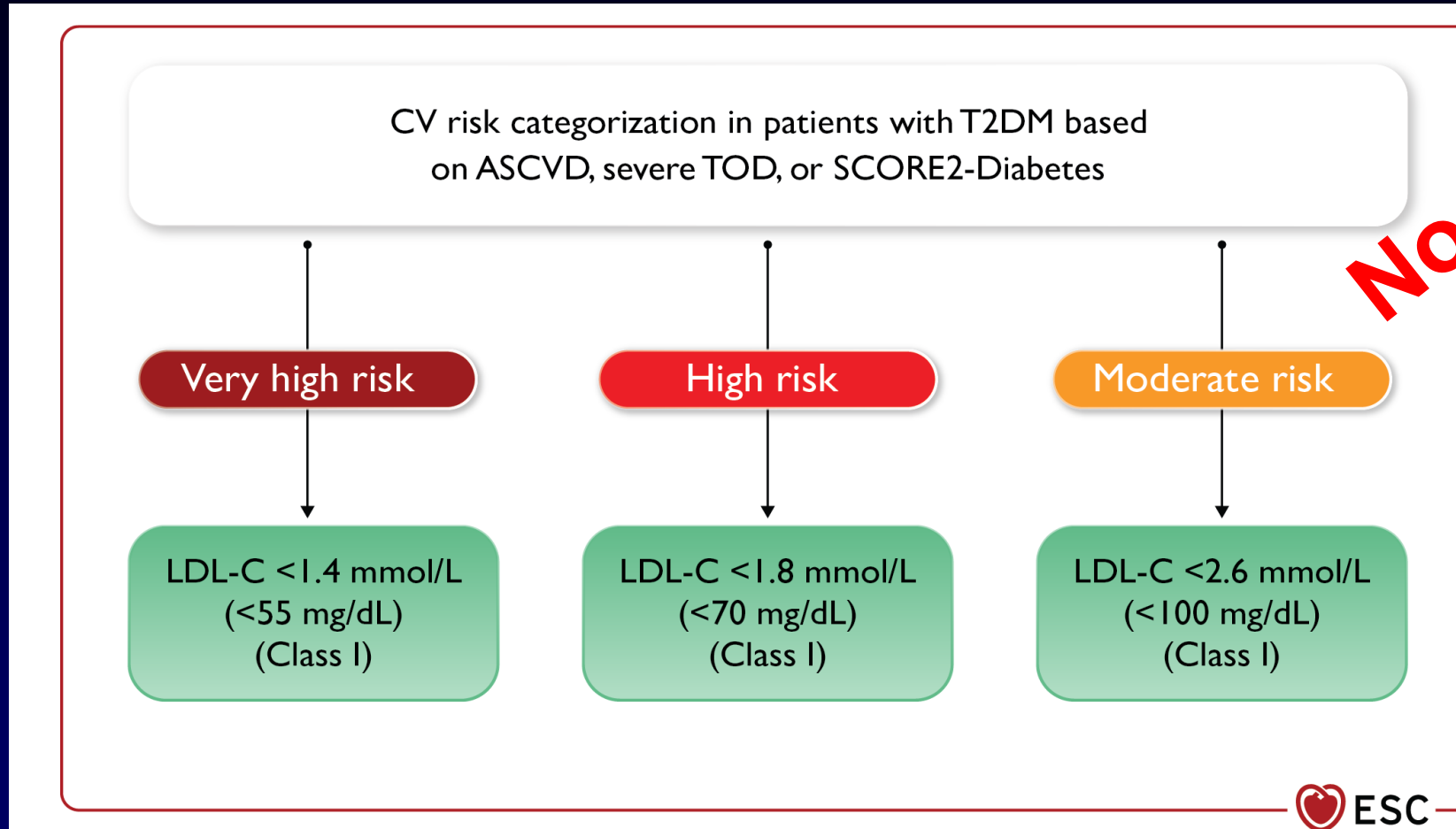
## Score2 Diabetes ≥20%

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!!!**

# Treatments for LDL-cholesterol

| Recommendations                                                                                                                                                                                                                                                         | Class | Level |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|
| <b><i>Lipid-lowering treatment</i></b>                                                                                                                                                                                                                                  |       |       |
| 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     |

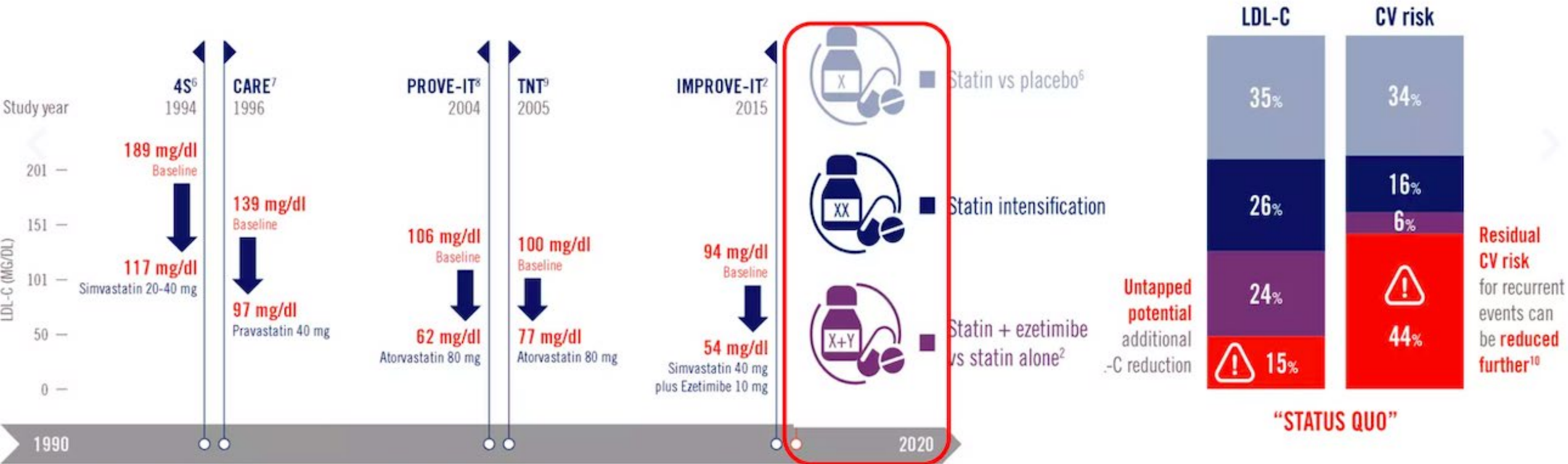
# Residual Risk

**Why?**

# STATINS ALONE LOWER LDL-C, BUT SOMETIMES NOT ENOUGH

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

Results of lipid-lowering trials<sup>‡</sup>



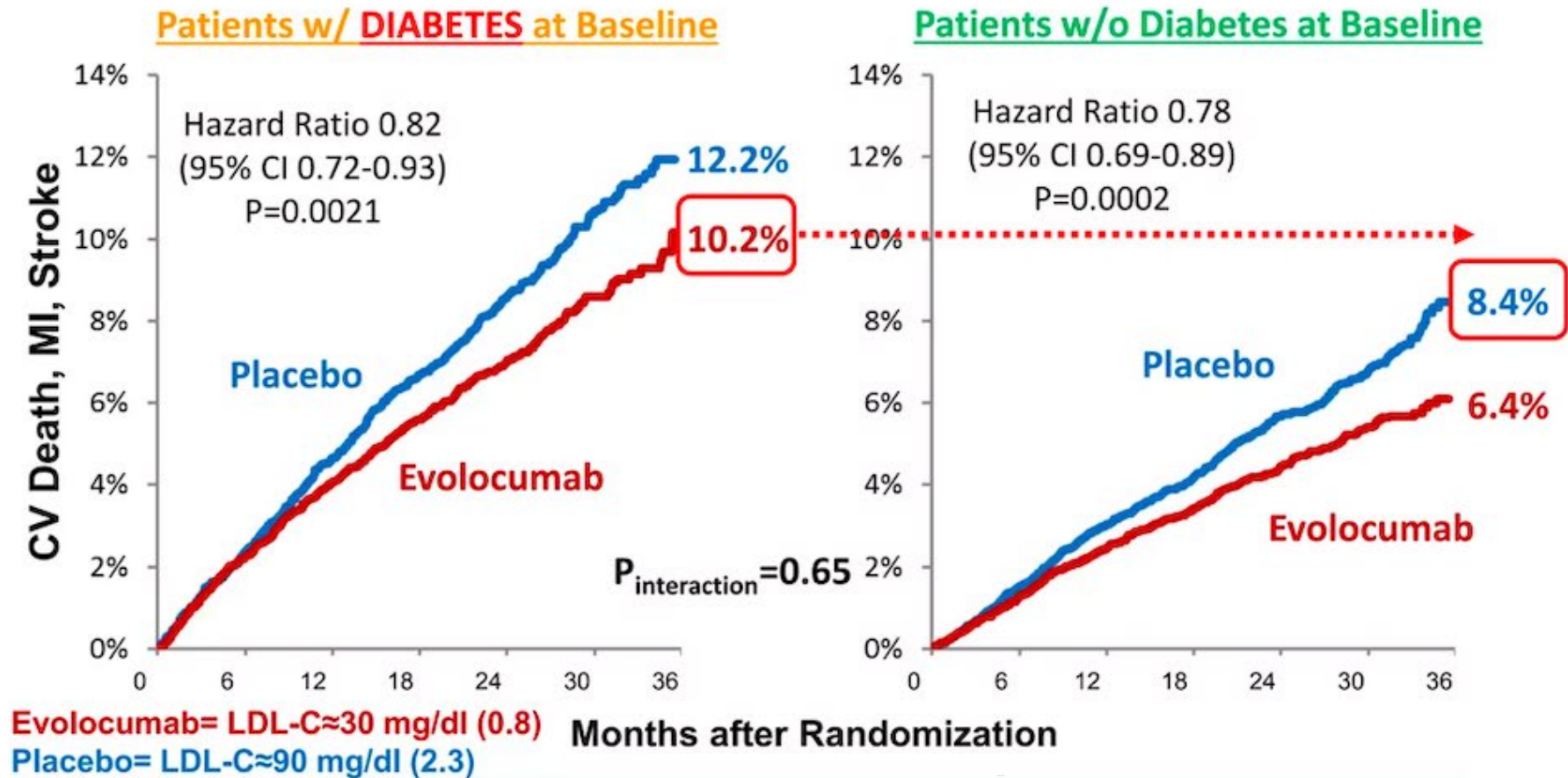
# Treatments for LDL-cholesterol

| Recommendations                                                                                                                                                                                                                                                         | Class | Level |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|
| <b><i>Lipid-lowering treatment</i></b>                                                                                                                                                                                                                                  |       |       |
| 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     |
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| If the target LDL-C is not reached with statins, combination therapy with ezetimibe is recommended.                                                                                                                                                                     | I     | B     |

# Especially - if you have T2DM!

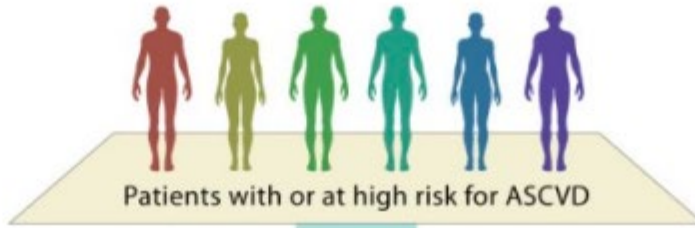


## Effect of Evolocumab on Key Secondary Endpoint



Sabatine MS et al N Engl J Med, 2017

# ASCVD RESIDUAL RISK



Despite contemporary evidence-based therapies\*, residual risk of ASCVD events persists

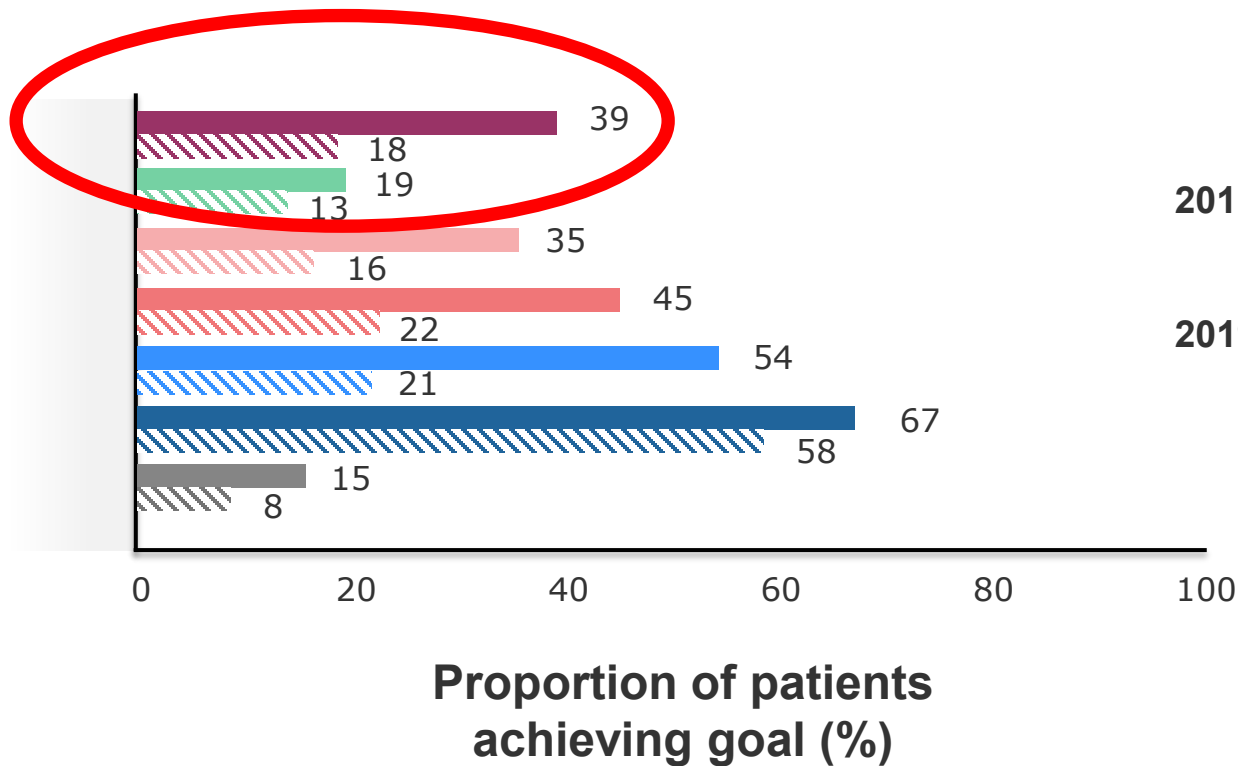
| Biological Issue          | Residual Cholesterol Risk                 | Residual Inflammatory Risk             | Residual Thrombotic Risk          | Residual Triglyceride Risk      | Residual Lp(a) Risk      | Residual Diabetes Risk                                                     |
|---------------------------|-------------------------------------------|----------------------------------------|-----------------------------------|---------------------------------|--------------------------|----------------------------------------------------------------------------|
|                           |                                           |                                        |                                   |                                 |                          |                                                                            |
| Critical Biomarker        | LDL-C $\geq 100$ mg/dL                    | hsCRP $\geq 2$ mg/L                    | No simple biomarker               | TG $\geq 150$ mg/dL             | Lp(a) $\geq 50$ mg/dL    | HbA1c<br>Fasting glucose                                                   |
| Potential Intervention    | Targeted LDL/Apo B Reduction              | Targeted Inflammation Reduction        | Targeted Antithrombotic Reduction | Targeted Triglyceride Reduction | Targeted Lp(a) Reduction | SGLT2 Inhibitors<br>GLP-1 Agonists                                         |
| Randomized Trial Evidence | IMPROVE-IT<br>FOURIER<br>SPIRE<br>ODYSSEY | CANTOS<br>COLCOT<br>LoDoCo2<br>OASIS-9 | PEGASUS<br>COMPASS<br>THEMIS      | REDUCE-IT<br>PROMINENT          | Planned                  | EMPA-REG<br>CANVAS<br>DECLARE<br>CREDENCE<br>LEADER<br>SUSTAIN-6<br>REWIND |

## Open questions

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

# 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)

# 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-cho

- CETP inhibitors (Obicetrapib)

## LDL-cho

- 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

# 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 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



# Acknowledgments



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### UNIMIB

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## Youngest UNIMIB

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Michela Vergani  
Matteo Conti  
Mariangela Rizzo



# Risk stratification

|                          |                                                                                                                                                                                                            |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Very high CV risk</b> | Patients with T2DM with: <ul style="list-style-type: none"><li>• Clinically established ASCVD or</li><li>• Severe TOD or</li><li>• 10-year CVD risk <math>\geq 20\%</math> using SCORE2-Diabetes</li></ul> |
| <b>High CV risk</b>      | Patients with T2DM not fulfilling the very high-risk criteria and a: <ul style="list-style-type: none"><li>• 10-year CVD risk 10 to <math>&lt;20\%</math> using SCORE2-Diabetes</li></ul>                  |
| <b>Moderate CV risk</b>  | Patients with T2DM not fulfilling the very high-risk criteria and a: <ul style="list-style-type: none"><li>• 10-year CVD risk 5 to <math>&lt;10\%</math> using SCORE2-Diabetes</li></ul>                   |
| <b>Low CV risk</b>       | Patients with T2DM not fulfilling the very high-risk criteria and a: <ul style="list-style-type: none"><li>• 10-year CVD risk <math>&lt;5\%</math> using SCORE2-Diabetes</li></ul>                         |

?

Majority

Some/many

few

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

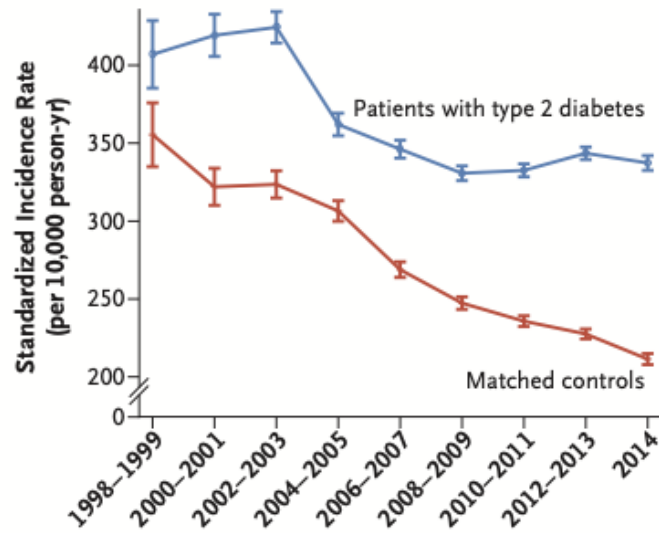


# CVD, CAD & T2DM (Europe)

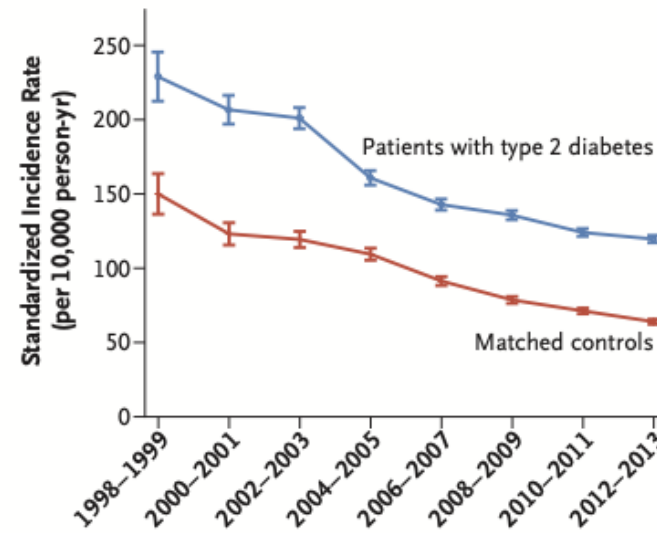
Swedish National Diabetes Register  
271,174 patients with T2DM vs.  
1,355,870 matched controls on the  
basis of age, sex, and county

Follow-up 5.7 years  
175,345 deaths occurred

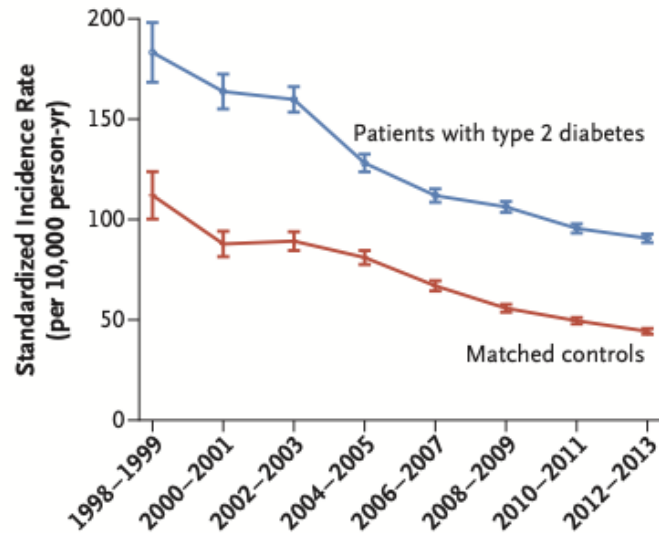
**A** Death from Any Cause



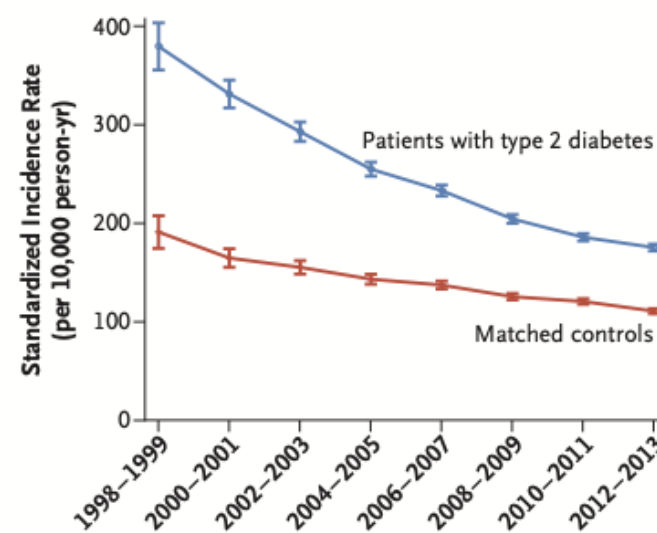
**B** Death from Cardiovascular Disease



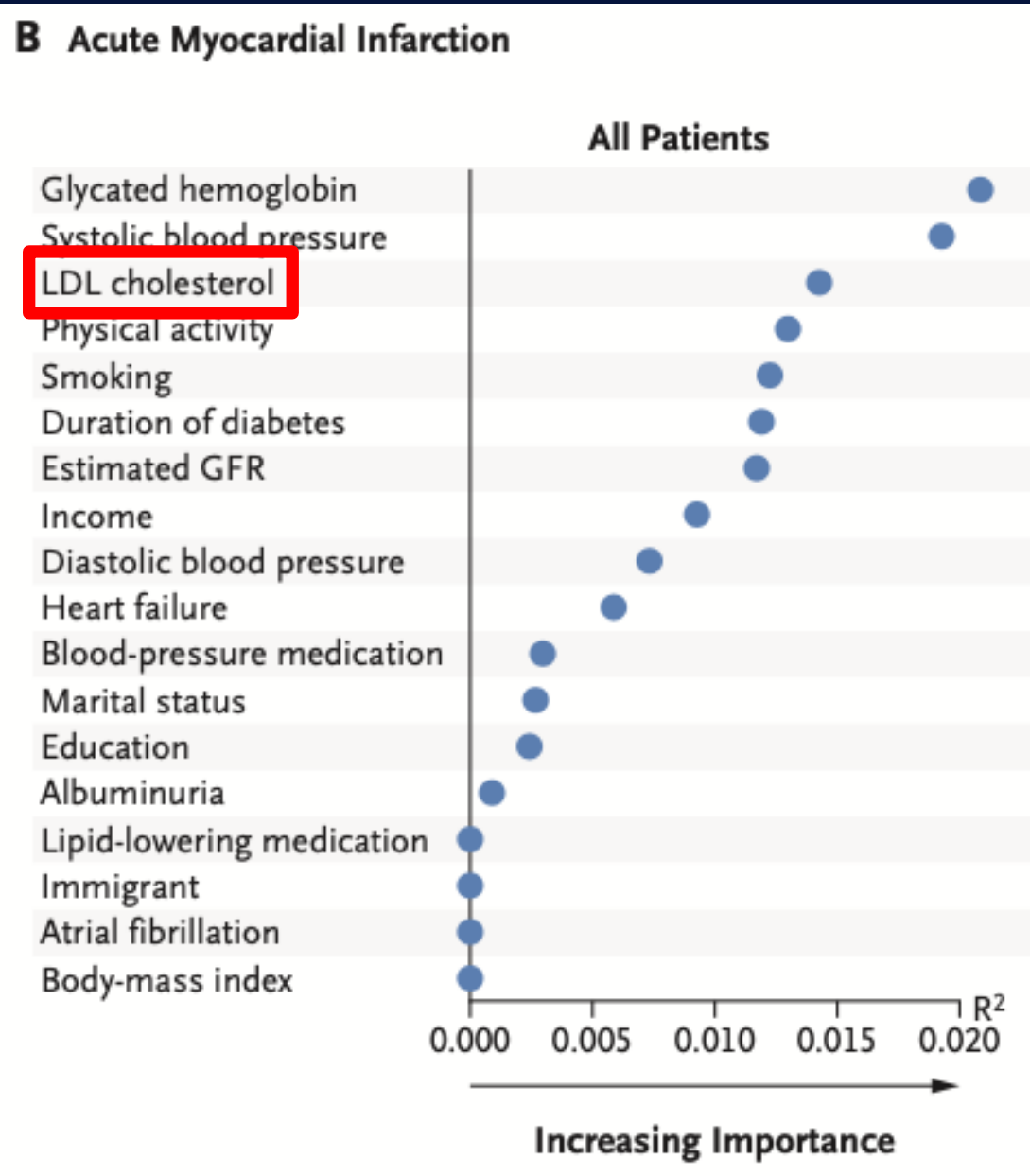
**C** Death from Coronary Heart Disease



**D** Hospitalization for Cardiovascular Disease



# 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

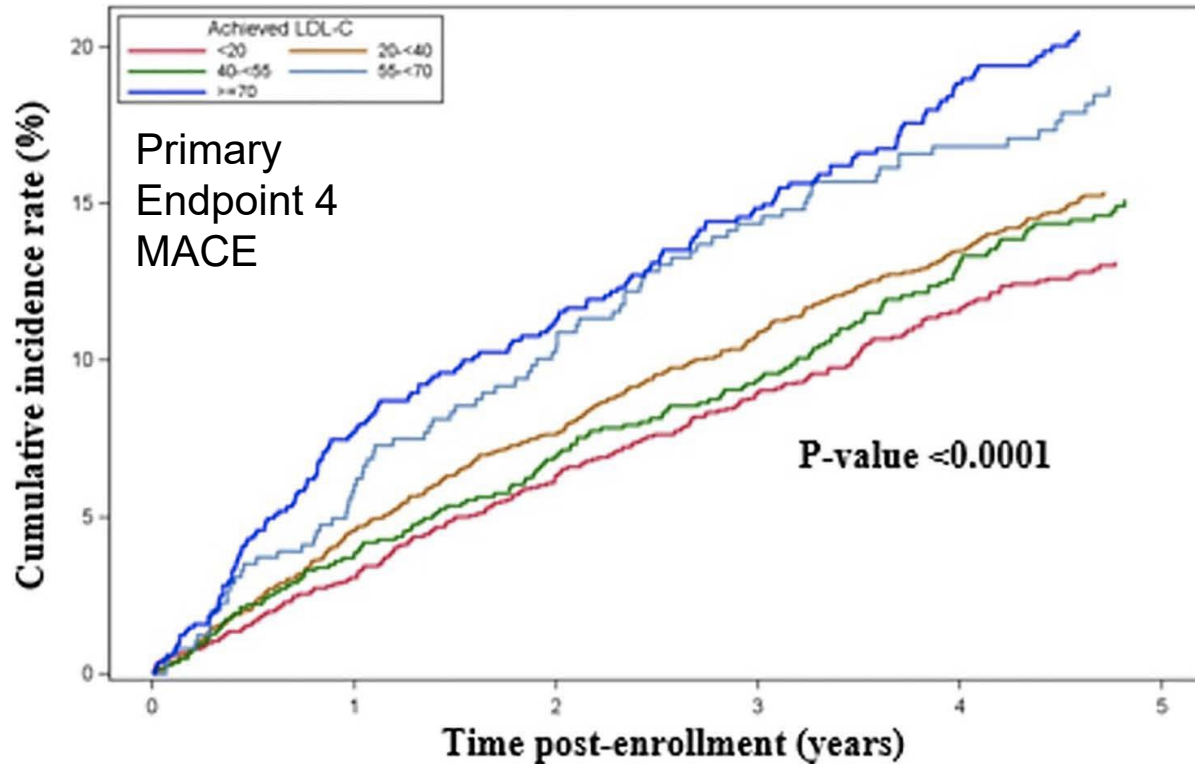
Risk factors:

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

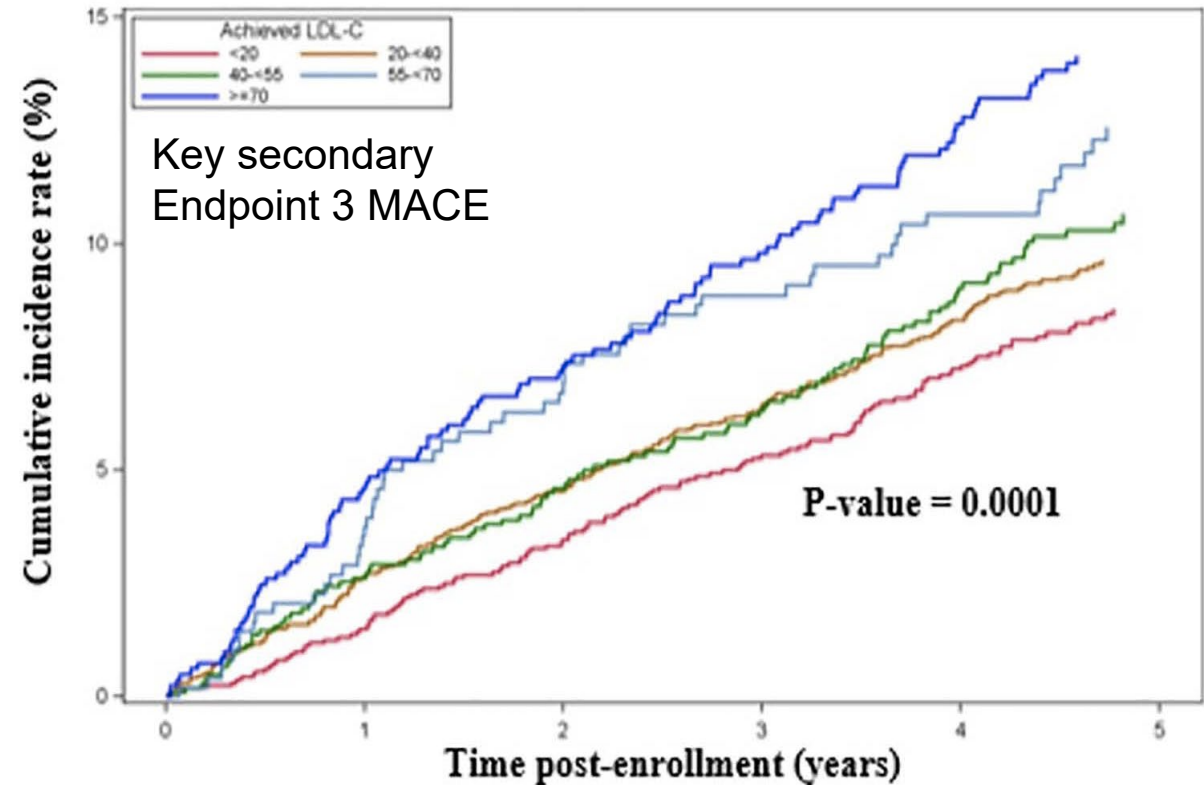
**Rawshani A et al N Engl J Med, 2018**

# Evolocumab and Long-Term Cardiovascular and Safety Outcomes

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



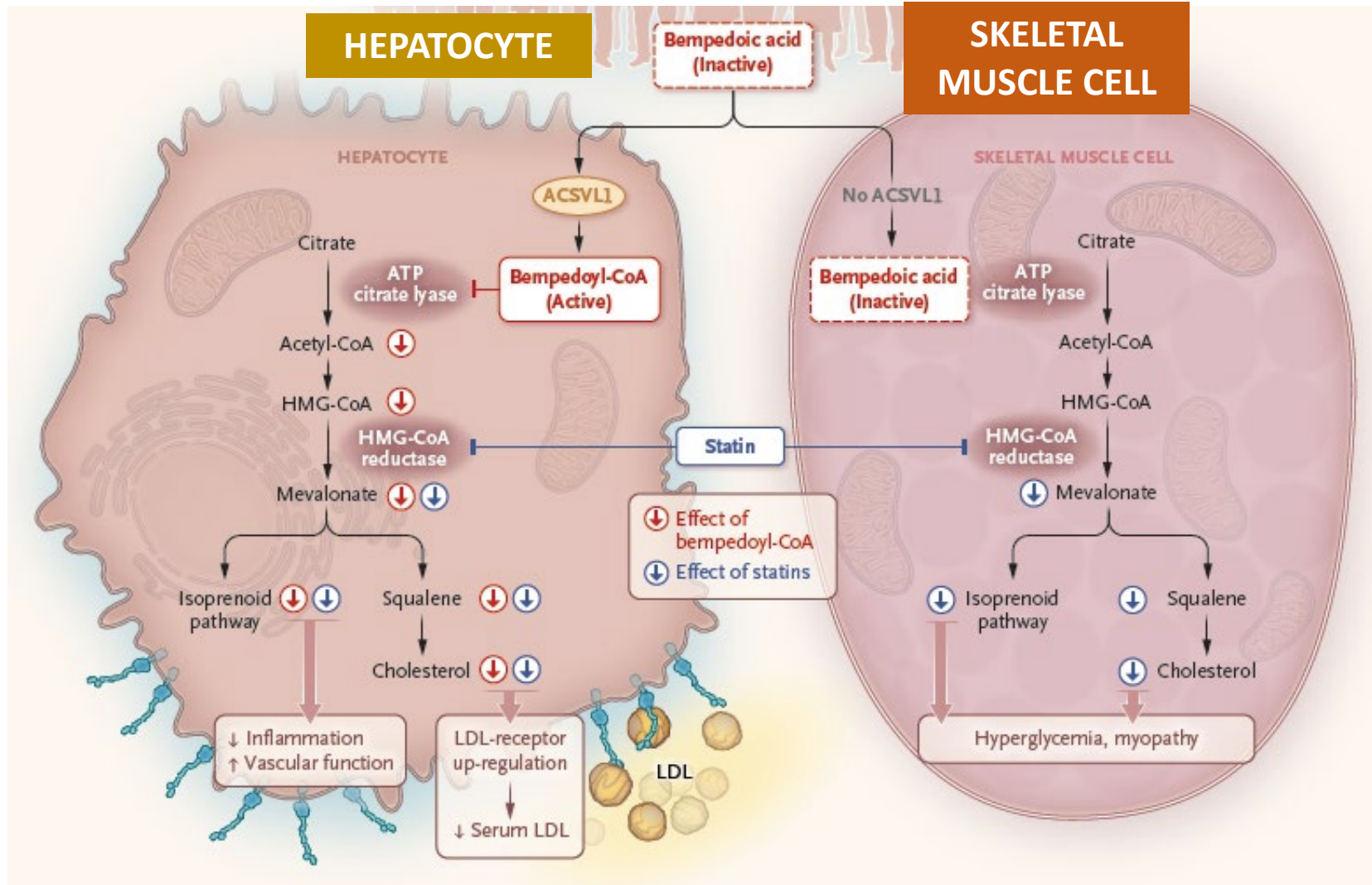
**B** CV death, MI, stroke



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.

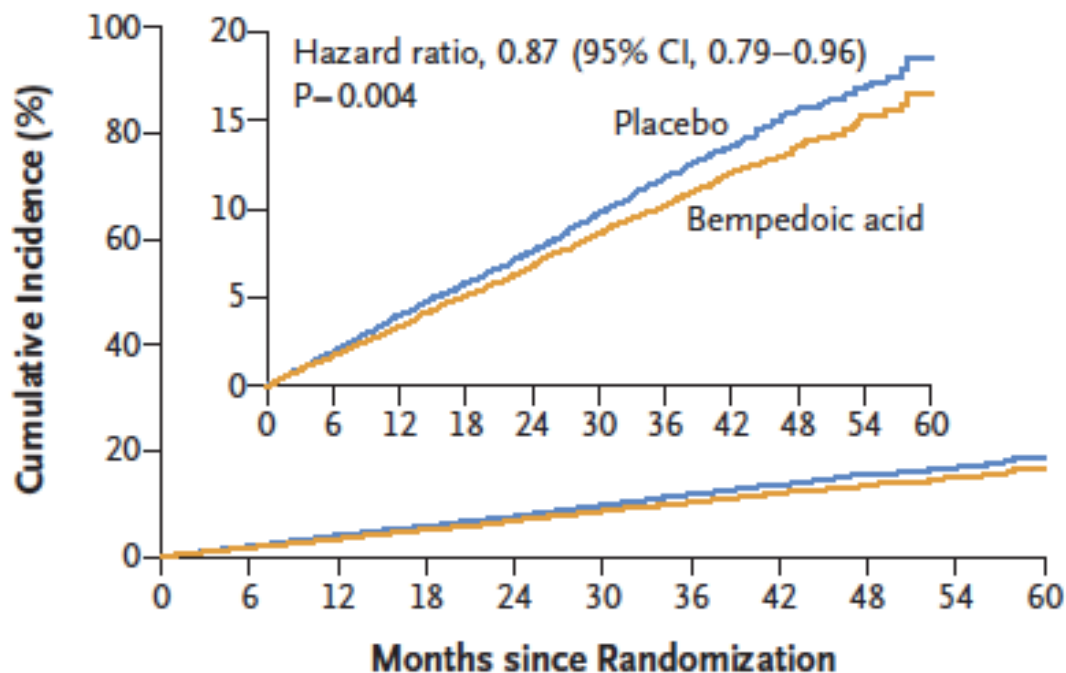
# Very-long-chain acyl-CoA synthetase 1 (ASCVL1) is required to activate bempedoic acid



# Bempedoic Acid and CVOT in Statin-Intolerant Patients

## The CLEAR trial

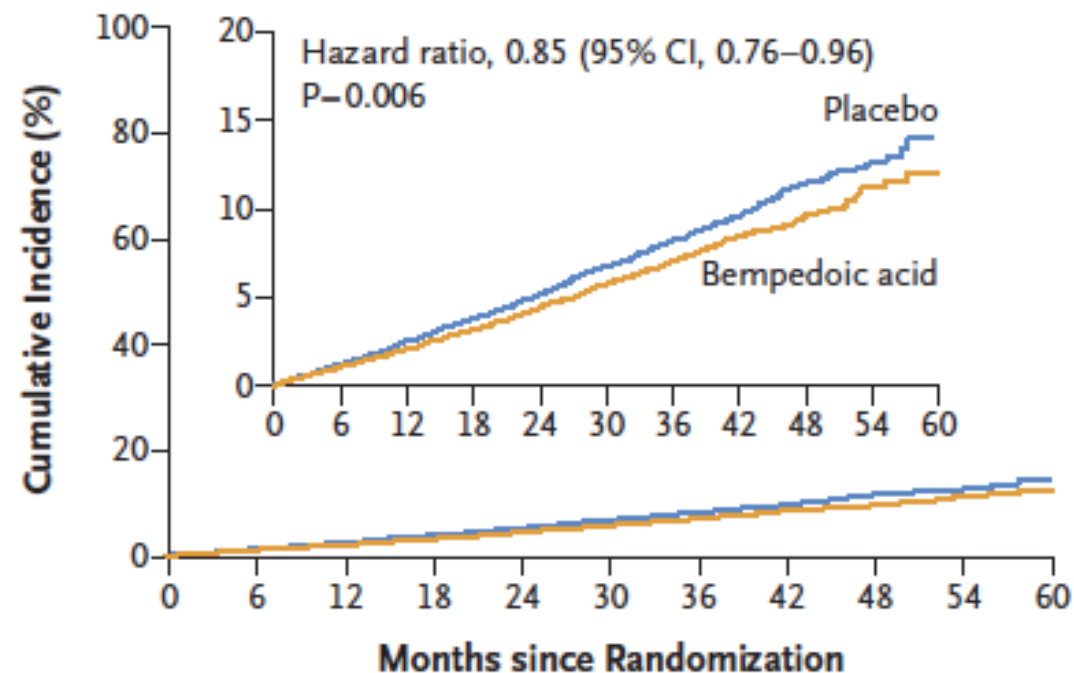
**A Four-Component MACE (Primary End Point)**



**No. at Risk**

|                |      |      |      |      |      |      |      |      |      |     |    |
|----------------|------|------|------|------|------|------|------|------|------|-----|----|
| Placebo        | 6978 | 6779 | 6579 | 6401 | 6206 | 5995 | 5105 | 2524 | 1207 | 513 | 55 |
| Bempedoic acid | 6992 | 6816 | 6654 | 6472 | 6293 | 6106 | 5257 | 2601 | 1240 | 556 | 74 |

**B Three-Component MACE**

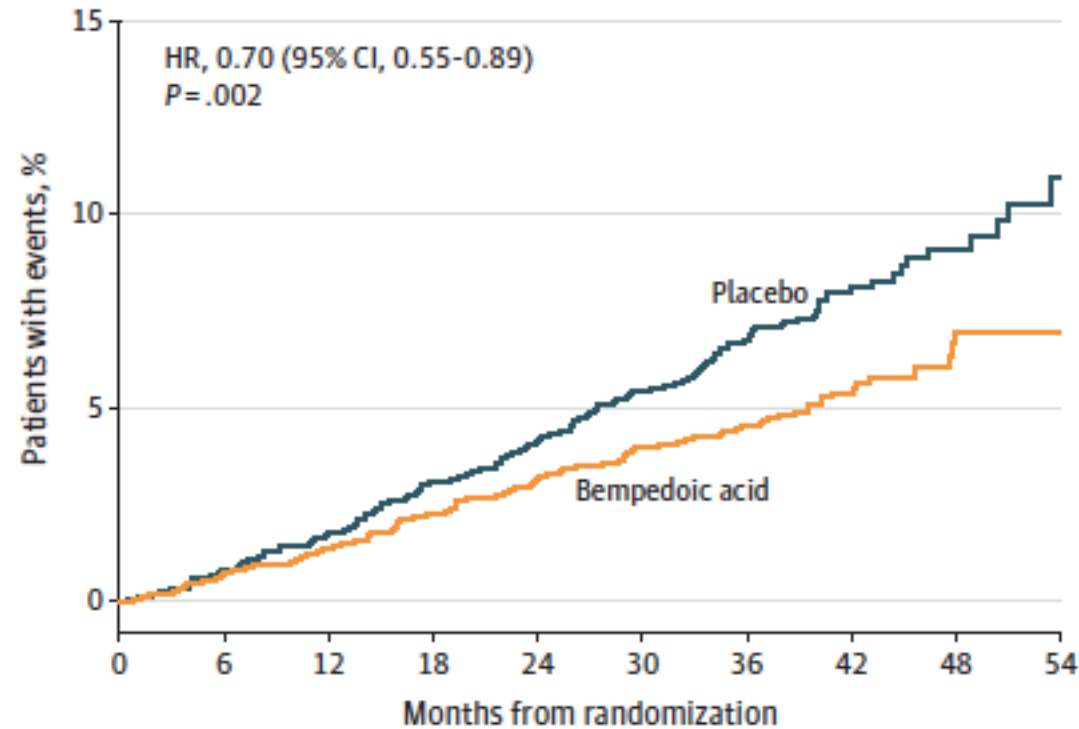


**No. at Risk**

|                |      |      |      |      |      |      |      |      |      |     |    |
|----------------|------|------|------|------|------|------|------|------|------|-----|----|
| Placebo        | 6978 | 6828 | 6883 | 6536 | 6368 | 6193 | 5321 | 2649 | 1279 | 554 | 62 |
| Bempedoic acid | 6992 | 6859 | 6745 | 6604 | 6457 | 6298 | 5453 | 2724 | 1317 | 591 | 80 |

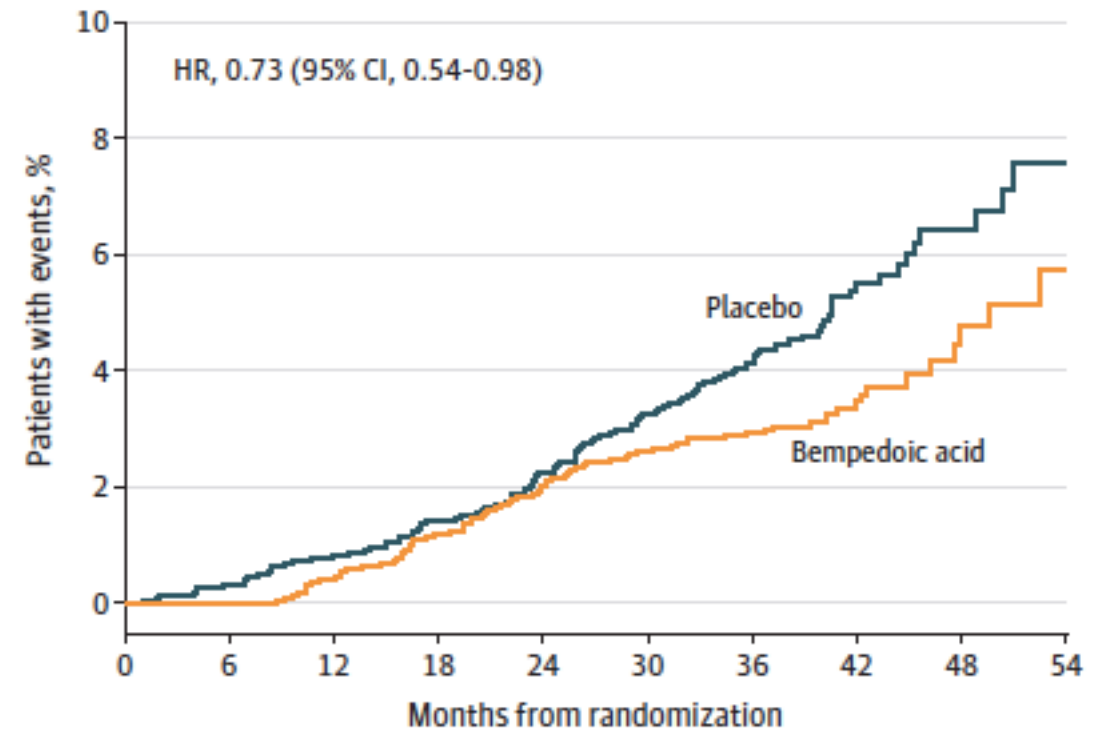
# Bempedoic Acid for Primary Prevention of CVOT in Statin-Intolerant Patients

**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)

