# The Effect of EVolocumab in PatiEntS at High CArdiovascuLar RIsk WithoUt Prior Myocardial Infarction or Stroke:

## High-Risk Diabetes Subgroup Analysis

**Lawrence A. Leiter, MD FACE FAHA FACC**
**University of Toronto**

***On behalf of the VESALIUS-CV Investigators***

***American Diabetes Association 2026 Scientific Sessions***

American Diabetes Association. 2026 SCIENTIFIC SESSIONS

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TIMI

# Presenter Disclosure

- **Lawrence A. Leiter**
  - Advisory Panel: Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics, Merck, Novartis, Novo Nordisk, Regeneron
  - Research Support: Amgen, AstraZeneca, Eli Lilly, Novartis
  - Provided CME on behalf of: Abbott, Amgen, Eli Lilly, GSK, HLS Therapeutics, Merck, Novartis, Novo Nordisk

- **Study Sponsored by Amgen**

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# Background

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- Individuals living with diabetes are at increased CV risk
- LDL-C lowering with statins improves CV outcomes in individuals living with diabetes, including in those with and without ASCVD
- Studies demonstrating CV benefit of more intensive LDL-C lowering with non-statin Rx, including PCSK9 inhibitors, in individuals living with DM has been limited to high-risk groups with *a prior, major ASCVD event of MI or stroke*.

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# ASCVD Continuum

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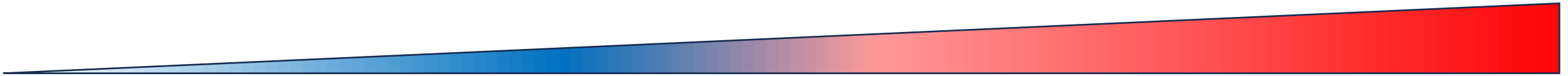
**No Known ASCVD** | **Known ASCVD**

*Increasing risk for development of ASCVD* → *Increasing severity of ASCVD* →



| Low-CV Risk (w/o known ASCVD) | High-CV Risk (w/o known ASCVD) | Atherosclerosis w/o Prior Event | Major ASCVD Event |
|---|---|---|---|
| | Diabetes + risk enhancer | Coronary, Cerebrovascular, or Peripheral artery disease, + Diabetes or other risk enhancer *No MI or Stroke* | Prior MI Prior Stroke Symptomatic PAD + Diabetes or other risk enhancer |

**VESALIUS-CV**

**FOURIER and ODYSSEY-OUTCOMES**

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# Trial Design

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***N= 12,257***

**Stable patients at high-risk for CV events but no prior MI or stroke***

**LDL-C ≥ 90 mg/dL or non-HDL-C ≥ 120 mg/dL or ApoB ≥ 80mg/dL**

**On optimized statin therapy (± ezetimibe)**

**1:1 Randomization**

**Evolocumab SC 140 mg Q2W**

**Placebo SC Q2W**

**Dual Primary Endpoints:**

Time to coronary heart disease death, MI, or ischemic stroke (3-P MACE)

Time to 3-P MACE plus ischemia-driven arterial revascularization (4-P MACE)

**Event & f/up driven trial:**

- 3-P MACE ≥ 751 events
- 4-P MACE ≥ 1,254 events
- Median f/up ≥ 4.5yrs

****At least one of the following:***

- CAD *without MI*
- CVD *without stroke*
- PAD
- High-risk diabetes mellitus
  - Microvascular disease
  - Chronic insulin use
  - Duration ≥ 10 years

Bohula EA, et al. *Am Heart J.* 2024;269:179-190.

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High-Risk DM subgroup

# Baseline Characteristics

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| Demographics | High-Risk DM N=6,002 |
|---|---|
| Age (years) | 66 [60, 71] |
| Female | 50% |
| White | 92% |
| Hispanic | 22% |

| Qualifying Disease Categories* | |
|---|---|
| Any qualifying athero | 33% |
| CAD w/o MI | 21% |
| CVD w/o stroke | 4% |
| PAD | 11% |

| Lipid Lowering Therapy (LLT) | High-Risk DM N=6,002 |
|---|---|
| Any LLT | 91% |
| High-intensity LLT regimen | 71% |
| Any statin† | 87% |
| High-intensity statin | 66% |
| Ezetimibe | 16% |

| Lipid Values (mg/dL) | |
|---|---|
| LDL-C | 125 [104, 151] |
| Non-HDL-C | 158 [135, 187] |
| Apolipoprotein-B | 104 [91, 125] |
| Triglycerides | 170 [122, 242] |
| HDL-C | 46 [39, 55] |

*% or median and interquartile range.*
**Qualification for CAD CVD, and PAD are not mutually exclusive*
*No difference between randomized treatment arms*

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High-Risk DM subgroup

# Baseline Characteristics

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| High-Risk DM Criteria | High-Risk DM N=6,002 |
|---|---|
| Microvascular disease | 30% |
| Duration ≥ 10 years | 88% |
| Chronic insulin use | 42% |

| Glucose Lowering Medication (GLM) | High-Risk DM N=6,002 |
|---|---|
| Any GLM | 96% |
| Metformin | 74% |
| Insulin | 42% |
| SFU | 24% |
| DPP4 inhibitor | 15% |
| SGLT2 inhibitor | |
| At baseline | 17% |
| At any time during study | 30% |
| GLP-1 RA | |
| At baseline | 11% |
| At any time during study | 19% |

*No difference between randomized treatment arms*

*SFU, sulfonylurea; DDP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2; GLP-1 RA, glucagon-like peptide-1 receptor agonists*

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High-Risk DM subgroup

# LDL-C Over Time

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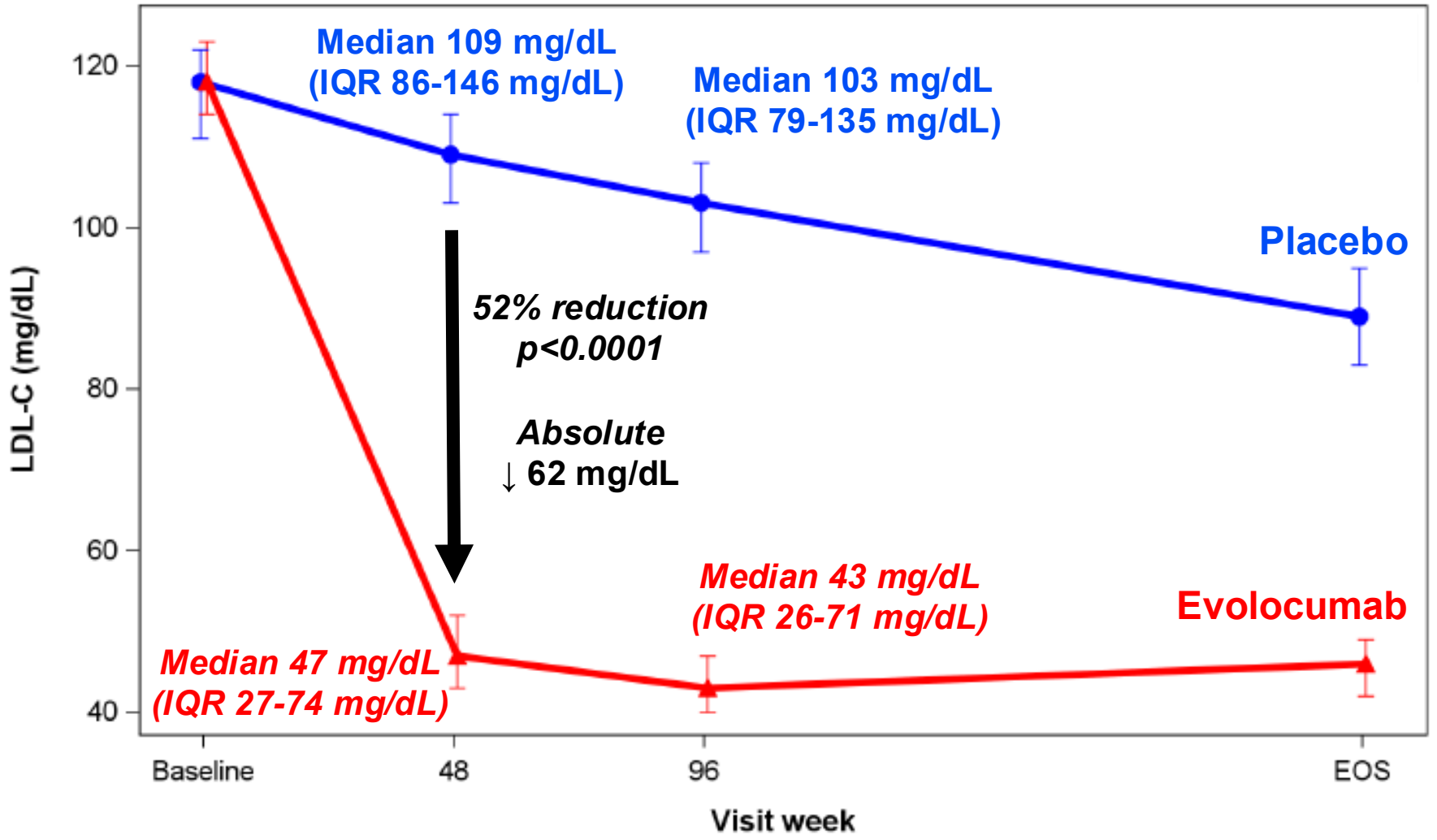
**Baseline**
**Median 118 mg/dL**
**(IQR 94-145 mg/dL)**






*Lipid sub-study in N=898 with high-risk DM*

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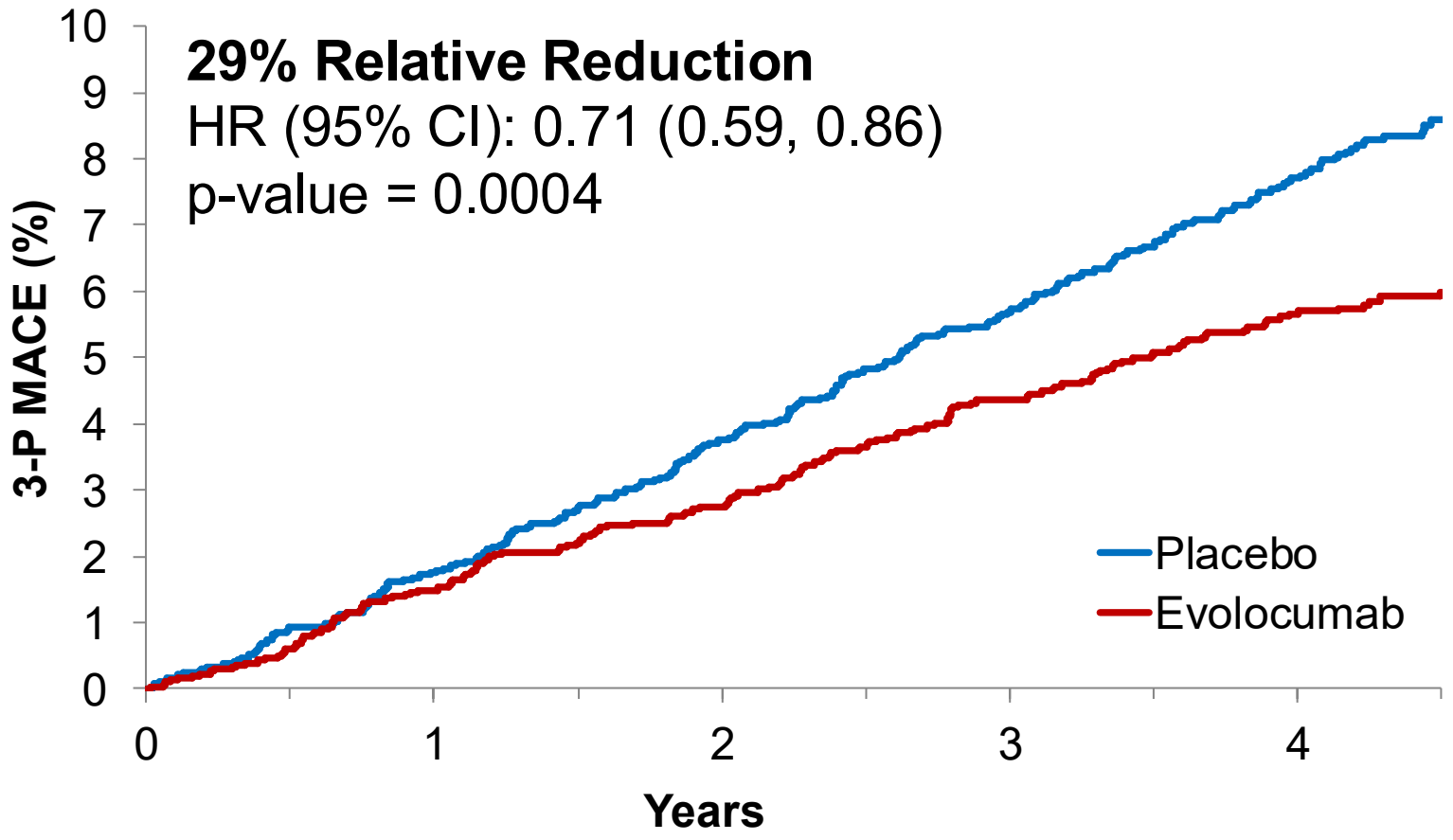
High-Risk DM subgroup

# Dual Primary Endpoint

## 3-P MACE (CHD death, MI, or ischemic stroke)






*CHD, coronary heart disease*

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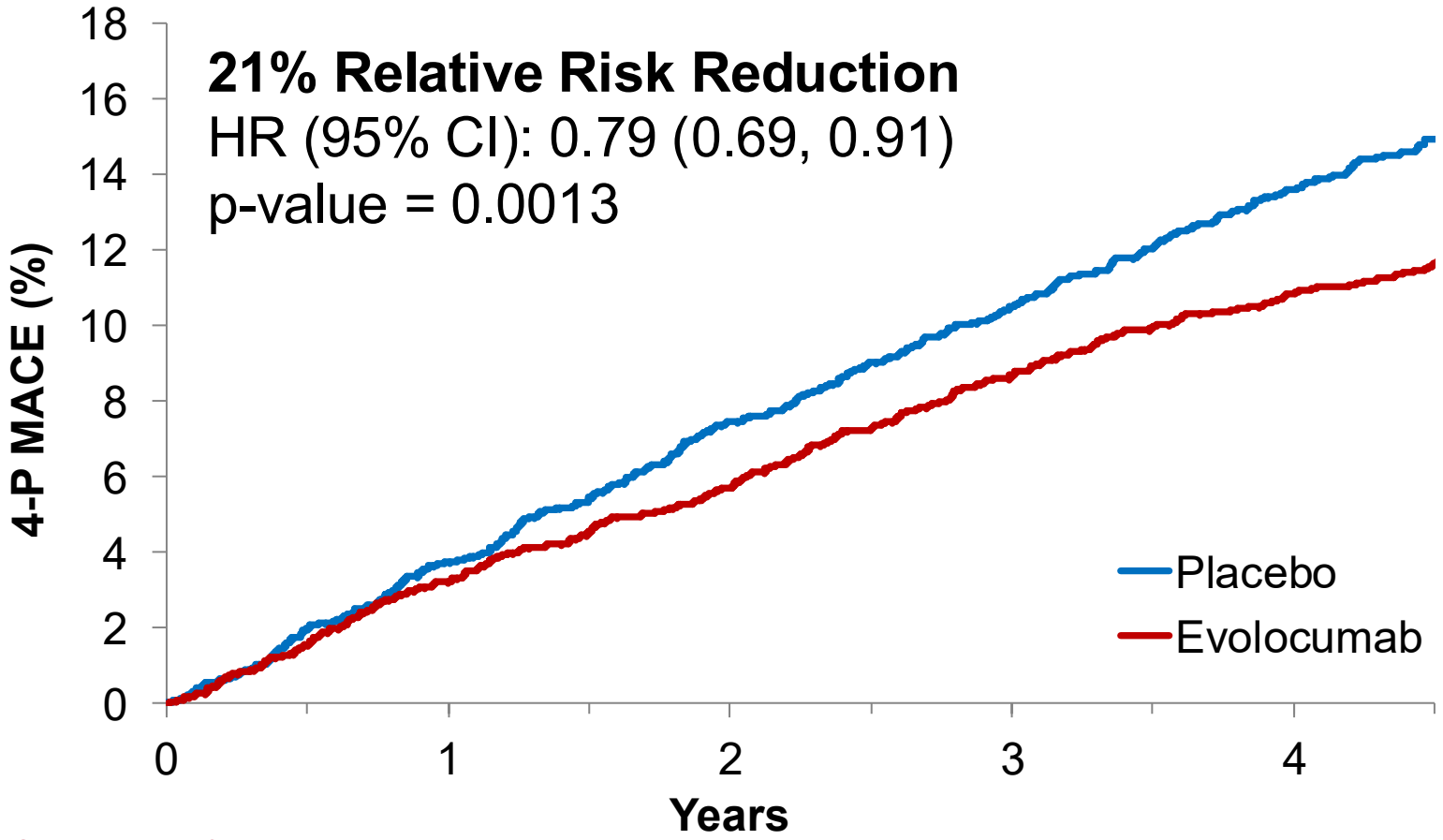
# Dual Primary Endpoint

## 4-P MACE (CHD death, MI, ischemic stroke, or IDR)






*CHD, coronary heart disease; IDR, ischemia-driven arterial revasc*

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High-Risk DM subgroup

# Primary & Key Secondary EPs

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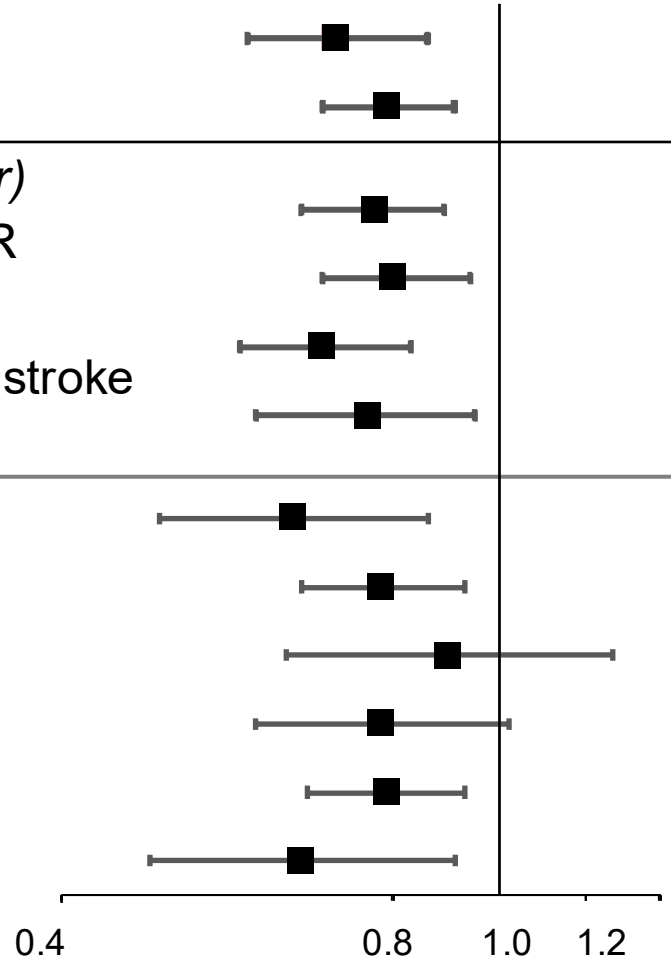
| | | HR (95% CI) |
|---|---|---|
| **Dual Primary Endpoints** | | |
| | 3-P MACE | 0.71 (0.59, 0.86) |
| | 4-P MACE | 0.79 (0.69, 0.91) |
| **Key Secondary Endpoints** *(in testing order)* | | |
| Composite Endpoints | MI, ischemic stroke, or IDR | 0.77 (0.66, 0.89) |
| | CHD death, MI, or IDR | 0.80 (0.69, 0.94) |
| | CV death, MI, or ischemic stroke | 0.69 (0.58, 0.83) |
| | CHD death or MI | 0.76 (0.60, 0.95) |
| Individual Endpoints | MI | 0.65 (0.49, 0.86) |
| | IDR | 0.78 (0.66, 0.93) |
| | CHD death | 0.90 (0.64, 1.27) |
| | CV death | 0.78 (0.60, 1.02) |
| | All-cause death | 0.79 (0.67, 0.93) |
| | Ischemic stroke | 0.66 (0.48, 0.91) |




*CHD, coronary heart disease*
*IDR, ischemia-driven arterial revasc*

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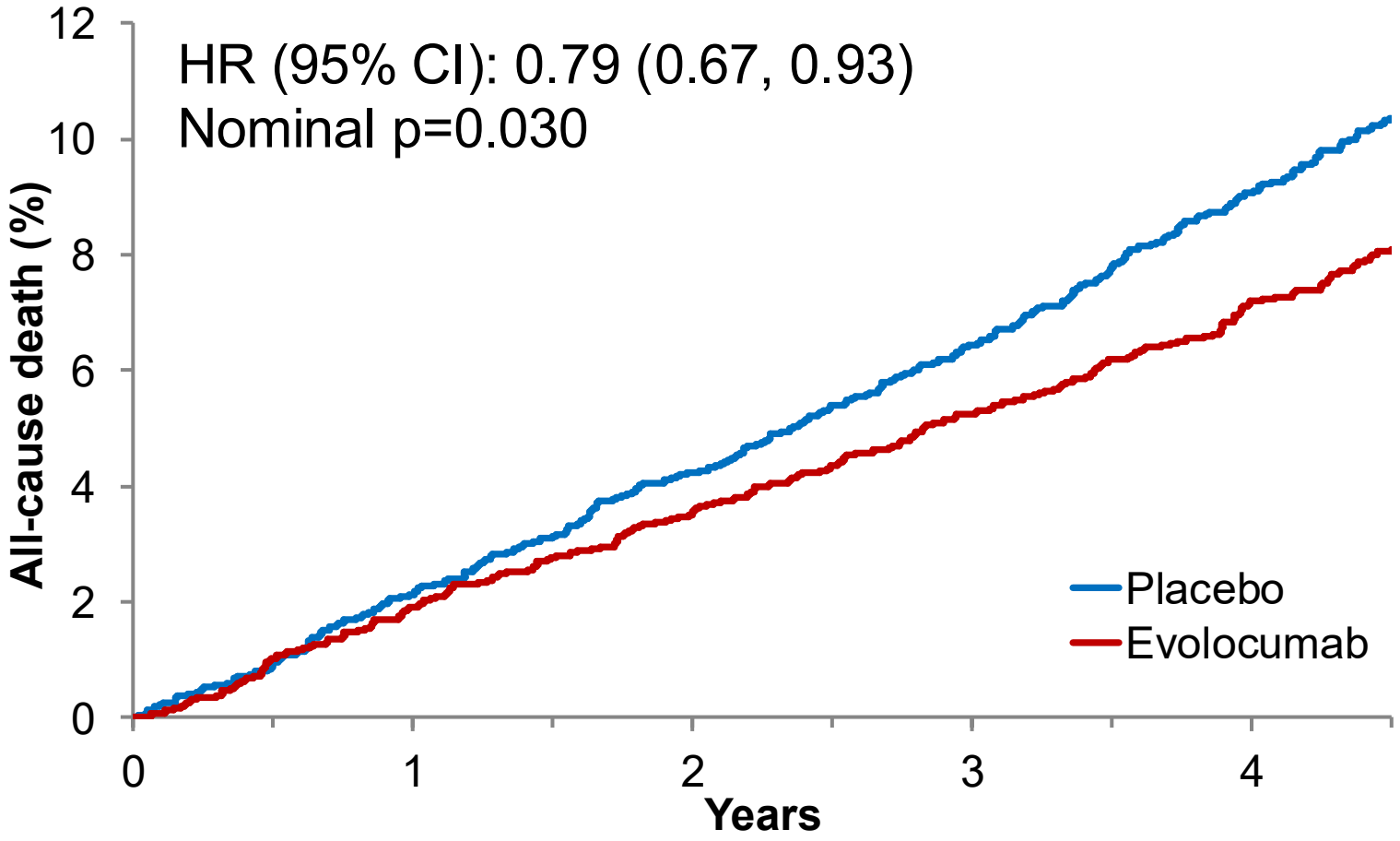
High-Risk DM subgroup

# All-Cause Death



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High-Risk DM subgroup

# Key Subgroups

| Subgroup | N | 3-P MACE Evo (%) | 3-P MACE Pbo (%) | 3-P MACE HR | 3-P MACE P-int | 4-P MACE Evo (%) | 4-P MACE Pbo (%) | 4-P MACE HR | 4-P MACE P-int |
|---|---|---|---|---|---|---|---|---|---|
| **Overall** | 6002 | 6.1 | 8.4 | 0.71 | - | 11.7 | 14.5 | 0.79 | - |
| **No. High-Risk DM Criteria*** | | | | | | | | | |
| 3 | 755 | 7.2 | 17.4 | 0.36 | 0.006 | 18.9 | 25.5 | 0.68 | 0.35 |
| 2 | 2089 | 7.7 | 9.4 | 0.81 | | 13.2 | 15.9 | 0.81 | |
| 1 | 3158 | 4.8 | 5.5 | 0.87 | | 9.1 | 10.8 | 0.84 | |
| **Lipid Related** | | | | | | | | | |
| **Baseline LDL-C (mg/dL)** | | | | | | | | | |
| 1st quartile (≤104) | 1409 | 6.2 | 8.9 | 0.70 | 0.97 | 12.0 | 14.3 | 0.83 | 0.45 |
| 2nd quartile (>104-122) | 1591 | 6.4 | 8.3 | 0.77 | | 12.7 | 15.1 | 0.84 | |
| 3rd quartile (>122-149) | 1470 | 5.2 | 7.7 | 0.66 | | 11.4 | 13.8 | 0.80 | |
| 4th quartile (>149) | 1531 | 6.5 | 8.8 | 0.74 | | 10.7 | 14.7 | 0.72 | |
| **Statin Intensity** | | | | | | | | | |
| High intensity | 3991 | 5.2 | 8.3 | 0.62 | 0.079 | 10.4 | 13.2 | 0.77 | 0.67 |
| None or not high intensity | 2011 | 7.7 | 8.7 | 0.88 | | 14.3 | 17.1 | 0.82 | |
| **Other** | | | | | | | | | |
| Age < 65 | 2563 | 6.4 | 7.1 | 0.89 | 0.047 | 11.1 | 12.4 | 0.88 | 0.21 |
| Age ≥ 65 | 3439 | 5.9 | 9.4 | 0.61 | | 12.2 | 16.1 | 0.74 | |
| eGFR<60 | 1380 | 8.0 | 13.8 | 0.55 | 0.06 | 14.6 | 20.5 | 0.68 | 0.13 |
| eGFR≥60 | 4608 | 5.5 | 6.7 | 0.81 | | 11.0 | 12.7 | 0.85 | |
| Any qualifying atherosclerosis | 2001 | 8.2 | 11.7 | 0.69 | 0.83 | 18.7 | 22.1 | 0.82 | 0.48 |
| No qualifying atherosclerosis | 4001 | 4.9 | 6.8 | 0.71 | | 8.1 | 10.8 | 0.74 | |
| Any SGLT2i or GLP-1 RA | 1456 | 5.5 | 9.4 | 0.58 | 0.23 | 13.8 | 15.9 | 0.85 | 0.48 |
| No SGLT2i or GLP-1 RA | 4546 | 6.2 | 8.1 | 0.76 | | 11.0 | 14.1 | 0.77 | |


*%, n/N.*

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High-Risk DM subgroup

# CTTC Meta-Regression

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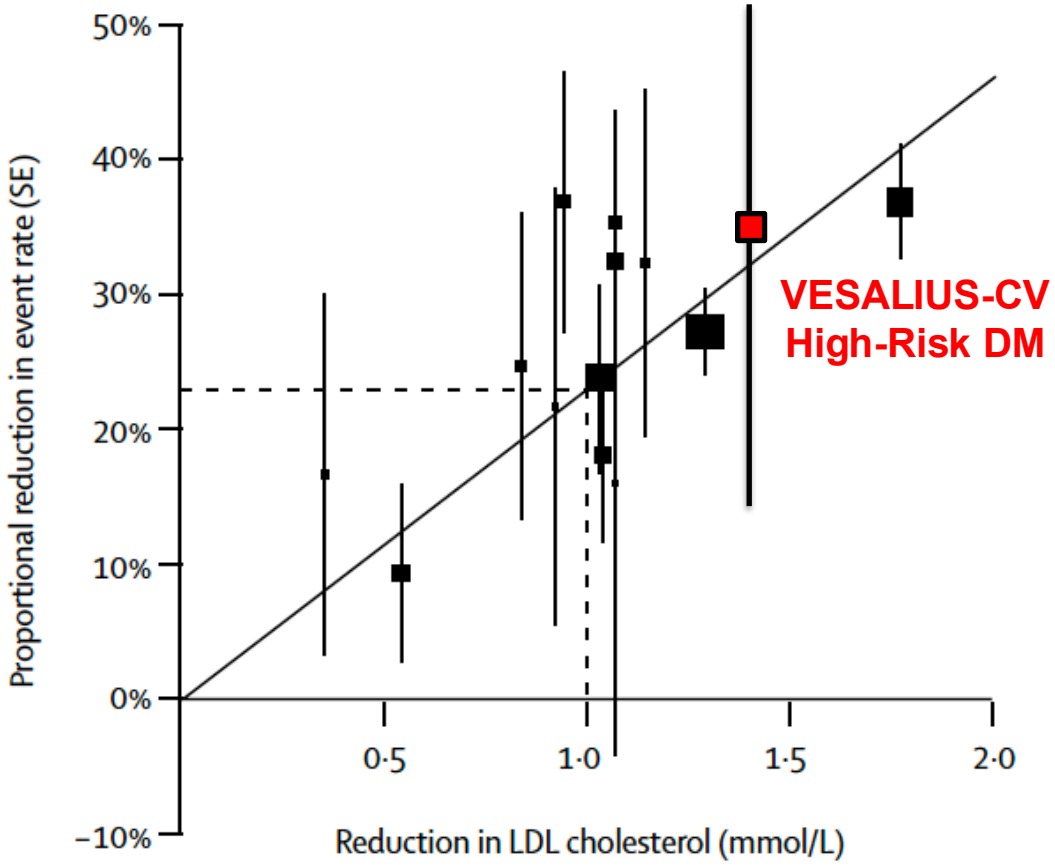
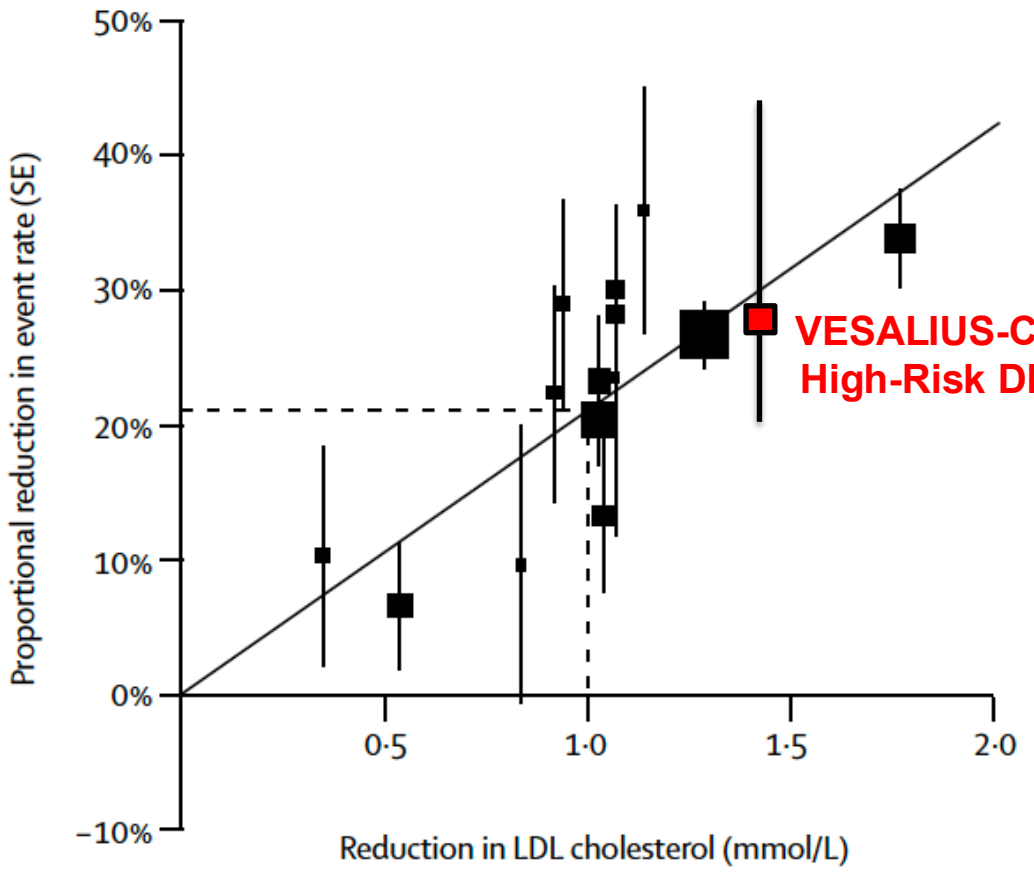
## Major Coronary Event [MCE]
*(Death due to AMI, MI)*




## Major Vascular Event [MVE]
*(MCE, fatal/non-fatal stroke, cor revasc)*




BWH

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

**CTTC** (Cholesterol Treatment Trialists' Collaboration)

*Lancet.* 2005;366:1267-78.
*Lancet.* 2010;376:1670-81.

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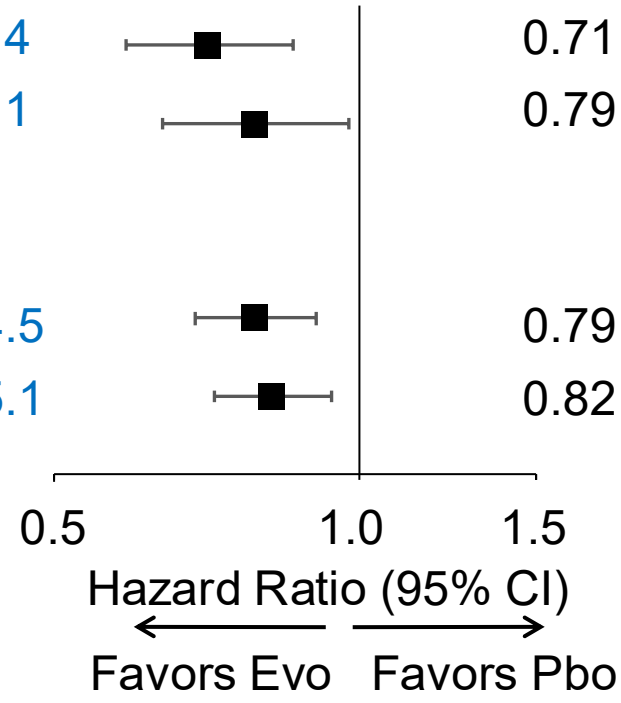
High-Risk DM subgroup

# With vs Without High-Risk DM

TIMI

| 3-P MACE | N | Evo (%) | Pbo (%) | HR (95% CI) | P-int |
|---|---|---|---|---|---|
| High-Risk Diabetes | 6,002 | 6.1 | 8.4 | 0.71 (0.59, 0.86) | 0.47 |
| No high-risk Diabetes | 6,255 | 4.9 | 6.1 | 0.79 (0.64, 0.98) | |
| **4-P MACE** | | | | | |
| High-Risk Diabetes | 6,002 | 11.7 | 14.5 | 0.79 (0.69, 0.91) | 0.73 |
| No high-risk Diabetes | 6,255 | 12.6 | 15.1 | 0.82 (0.72, 0.94) | |



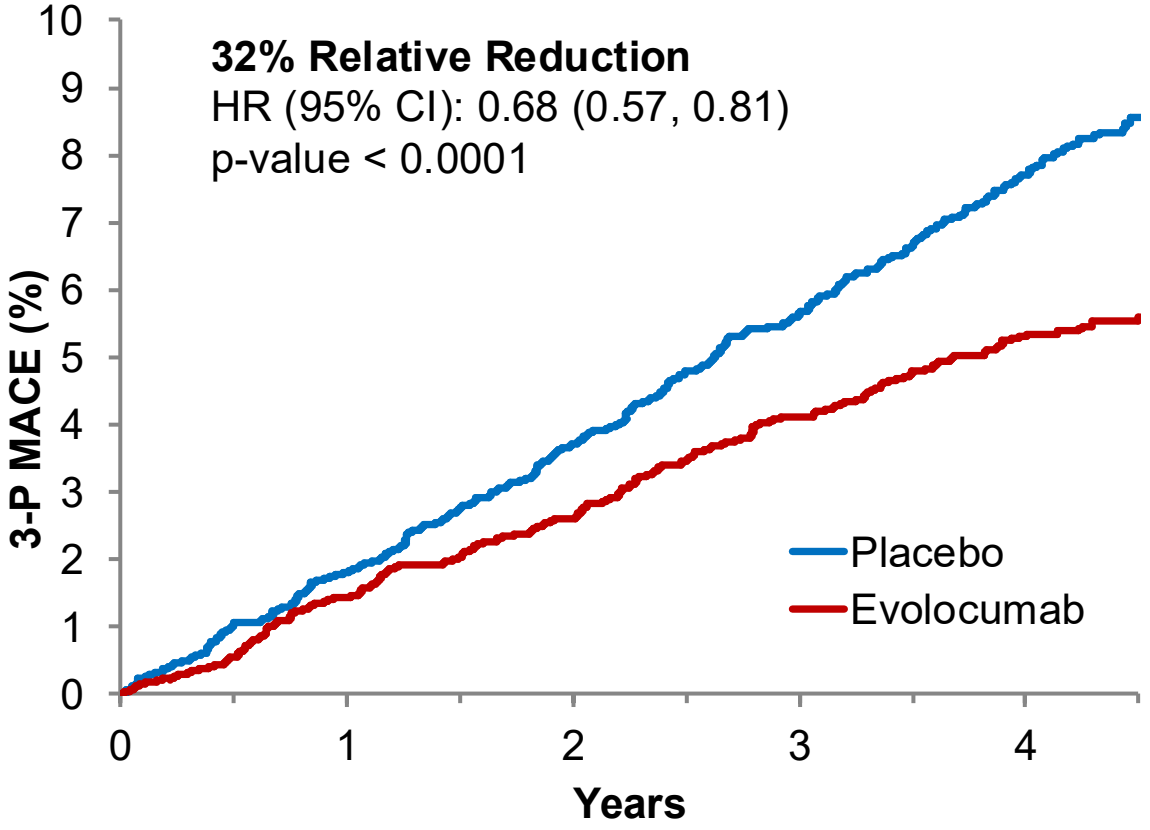



*%, n/N.*
*3-P MACE: Coronary heart disease death, MI, or ischemic stroke*
*4-P MACE: 3-P MACE plus ischemia-driven arterial revascularization*

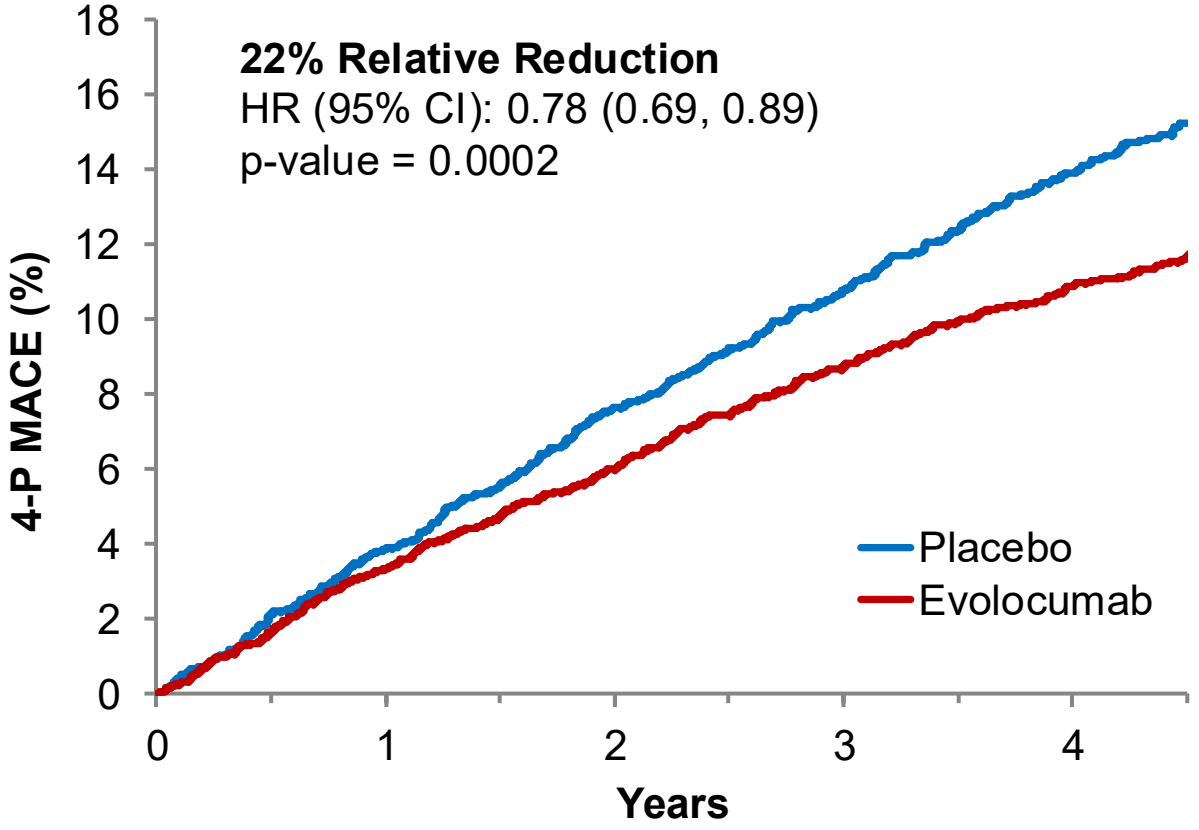
# All Patients with Diabetes

**Any DM (N=7,122)**

## 3-P MACE




## 4-P MACE



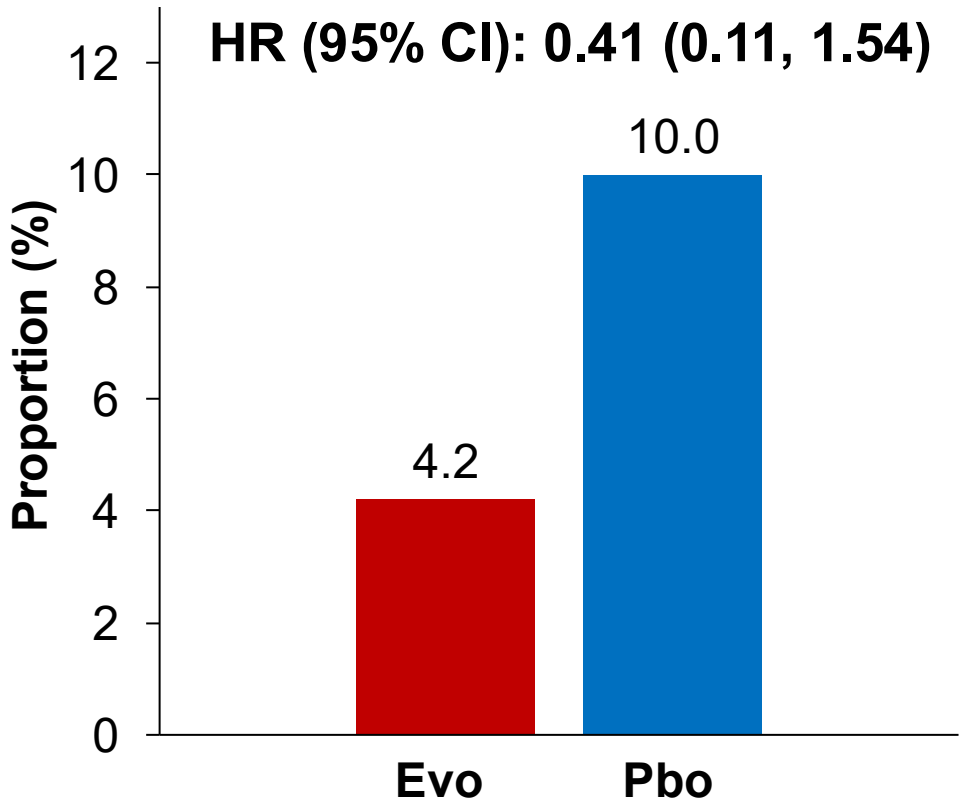



*Any DM includes high-risk and non-high-risk DM*

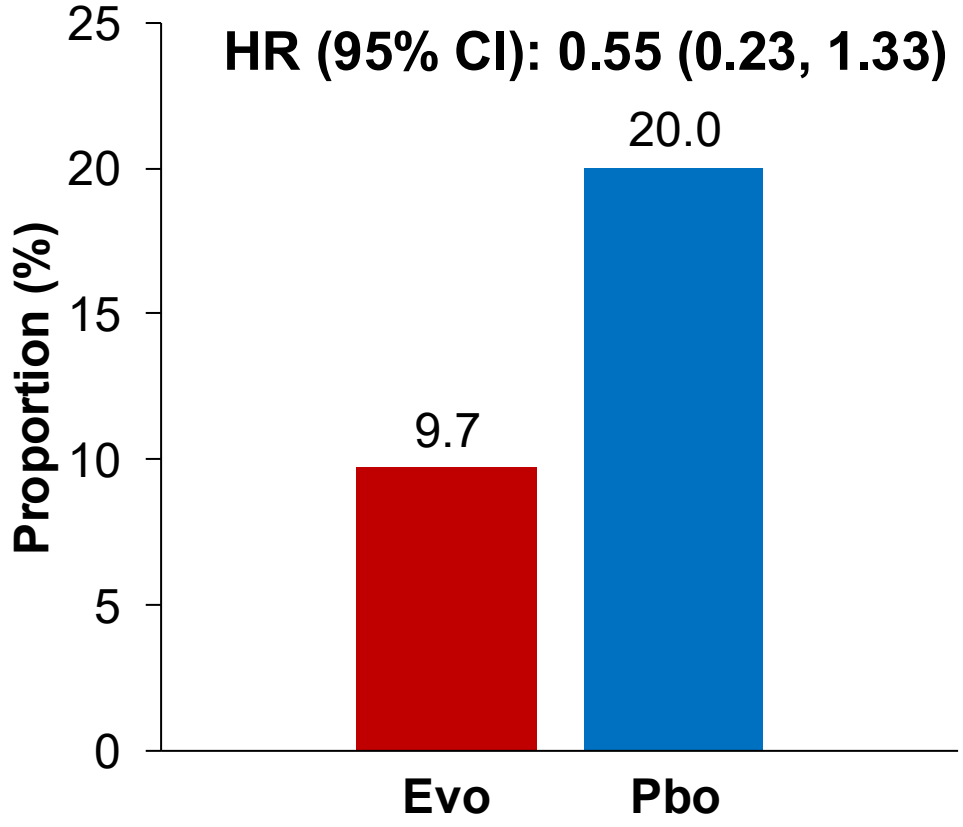
# Type 1 Diabetes

**Type 1 DM (N=162)**

## 3-P MACE




## 4-P MACE




%, n/N.

*3-P MACE: Coronary heart disease death, MI, or ischemic stroke*
*4-P MACE: 3-P MACE plus ischemia-driven arterial revascularization*

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High-Risk DM subgroup

# Safety

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| | Evolocumab (N = 3051) | Placebo (N = 2947) | P value |
|---|---|---|---|
| **Serious adverse events, n (%)** | 28.5 | 29.9 | 0.23 |
| **Adverse events leading to study drug discontinuation, n (%)** | 3.5 | 4.0 | 0.25 |
| **Thought to be related to study drug, n (%)** | 1.4 | 1.2 | 0.32 |



*N = number of randomized subjects who received at least 1 dose of investigational product*

# Limitations



- Glycemic parameters were not assessed at baseline or during the study
- Diabetes complications were not assessed during the study
- Used a practical definition of “high-risk diabetes” that may vary from other definitions; note that key findings similar in broader cohort with any diagnosis of diabetes
- Although the median baseline LDL-C was 125 mg/dL (~3.2 mmol/L), the observed CV benefits of evolocumab were consistent across quartiles of baseline LDL-C.

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High-Risk DM subgroup

# Summary

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**In high-risk diabetes patients w/o prior MI or stroke, addition of evolocumab to baseline LLRx resulted in:**

- Median achieved LDL-C of ~45 mg/dL
- 29% ↓ in 3-P MACE and 21% ↓ in 4-P MACE
- Nominal 21% ↓ in all-cause death
- Consistent benefits across subgroups, including in those without qualifying atherosclerosis or who were on an SGLT2 inhibitor or GLP1RA.
- Magnitude of benefit, normalized to amount of LDL-C lowering, was consistent with prior meta-regression for statin therapy

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High-Risk DM subgroup

# Conclusions

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***These data support a single LDL-C target for all high-risk individuals living with DM, regardless of where they are in the continuum of their ASCVD course.***

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High-Risk DM subgroup

TIMI

Diabetes Care
American Diabetes Association

# Evolocumab in Patients With High-Risk Diabetes: Results From the VESALIUS-CV Trial

Lawrence A. Leiter, Robert P. Giugliano, Nicholas A. Marston, Gaetano De Ferrari, Jose C. Nicolau, Ajay K. Bhatia, Marcoli Cyrille, Jeong-Gun Park, Julia F. Kuder, Sabina A. Murphy, Lyrica Liu, Emileigh Walsh, Huei Wang, Andrej Džupina, Jorge Ferreira, Ioanna Gouni-Berthold, Henrik K. Jensen, Johanna Kuusisto, Daniel Pella, Naveed Sattar, Konstantinos P. Tsioufis, Dragos Vinereanu, Gabriel Paiva da Silva Lima, Marc S. Sabatine, and Erin A. Bohula

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