Cardiovascular Efficacy & Safety of Evolocumab in Diabetes, and Risk of Development of Diabetes: An Analysis from the FOURIER Trial

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European Association for the Study of Diabetes – 53rd Annual Meeting
Clinical Trial Update
September 15, 2017

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

Disclosures

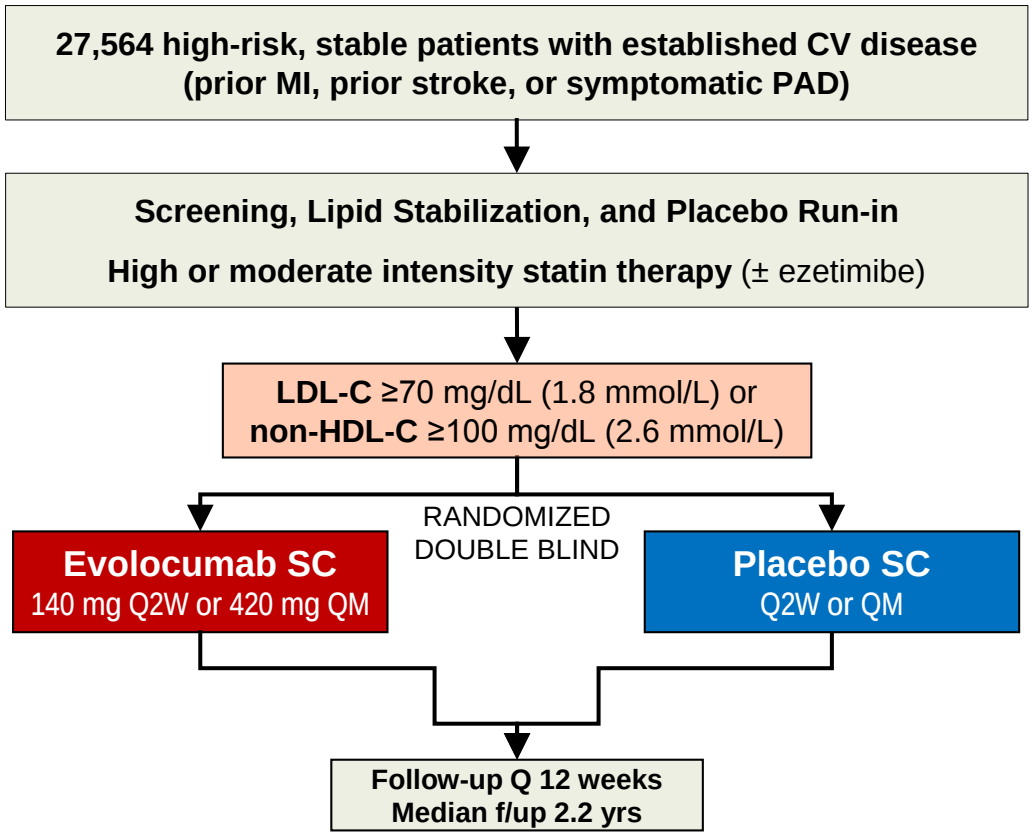
Research Grant Support through BWH:

Amgen; AstraZeneca; Daiichi-Sankyo; Eisai; GlaxoSmithKline; Intarcia; Janssen Research Development; Medicines Company; MedImmune; Merck; Novartis; Pfizer; Poxel; Takeda

Scientific Advisory Boards:

Amgen; CVS Caremark; Esperion; Intarcia; Janssen Research Development; MedImmune; Merck; Novartis

Trial Design



Sabatine MS et al. *Am Heart J* 2016;173:94-101

Overall Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	**63 (9)**
Male sex (%)	**75**
Weight, kg, mean (SD)	**85 (17)**
Type of cardiovascular disease (%)	
Myocardial infarction	**81**
Stroke (non-hemorrhagic)	**19**
Symptomatic PAD	**13**
Cardiovascular risk factor (%)	
Hypertension	**80**
Diabetes mellitus per patient hx	**37**
Current cigarette use	**28**

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms

Sabatine MS et al. *NEJM* 2017;376:1713-1722

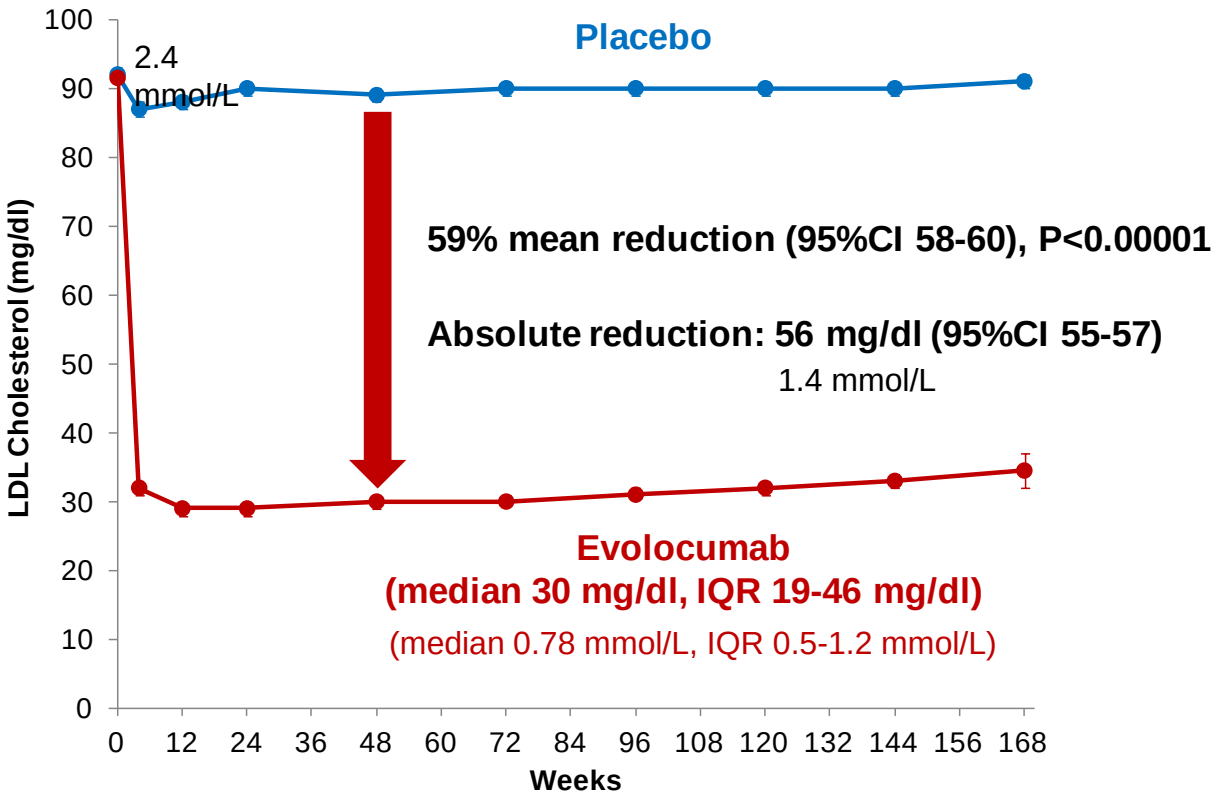
Overall Lipid Lowering Therapy & Lipid Levels at Baseline

Characteristic	Value	
Statin use (%)*		
High-intensity	**69**	
Moderate-intensity	**30**	
Ezetimibe use (%)	**5**	
Median lipid measures (IQR)	mg/dL	mmol/L
LDL-C	**92 (80-109)**	**2.4 (2.1-2.8)**
Total cholesterol	**168 (151-189)**	**4.3 (3.9-4.9)**
HDL-C	**44 (37-53)**	**1.1 (1.0-1.4)**
Triglycerides	**133 (100-182)**	**1.5 (1.1-2.1)**

*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.
Pooled data; no differences between treatment arms.

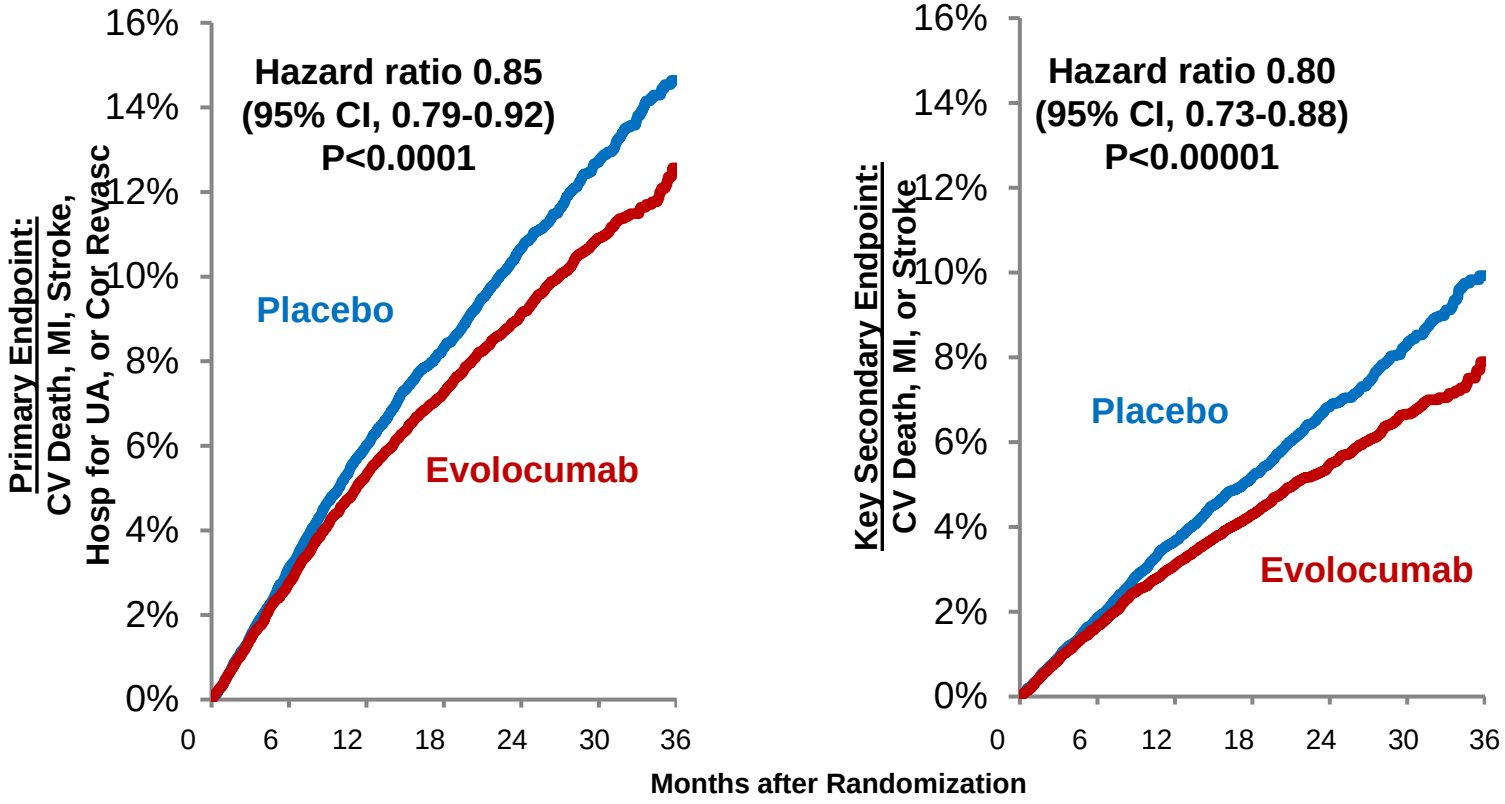
Sabatine MS et al. *NEJM* 2017;376:1713-1722

Overall Effects on LDL Cholesterol



Sabatine MS et al. *NEJM* 2017;376:1713-1722

Primary & Key Secondary Endpoints



Sabatine MS et al. *NEJM* 2017;376:1713-1722

Overall Safety

	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related and led to d/c of study drug	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Neurocognitive	1.6	1.5
Laboratory results (%)		
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a

Sabatine MS et al. *NEJM* 2017;376:1713-1722

Diabetes Substudy Objectives

- **Investigate the efficacy of evolocumab in patients with and without diabetes at baseline**
- **Investigate the safety profile of evolocumab, particularly with respect to glycemia and the development of new-onset diabetes**

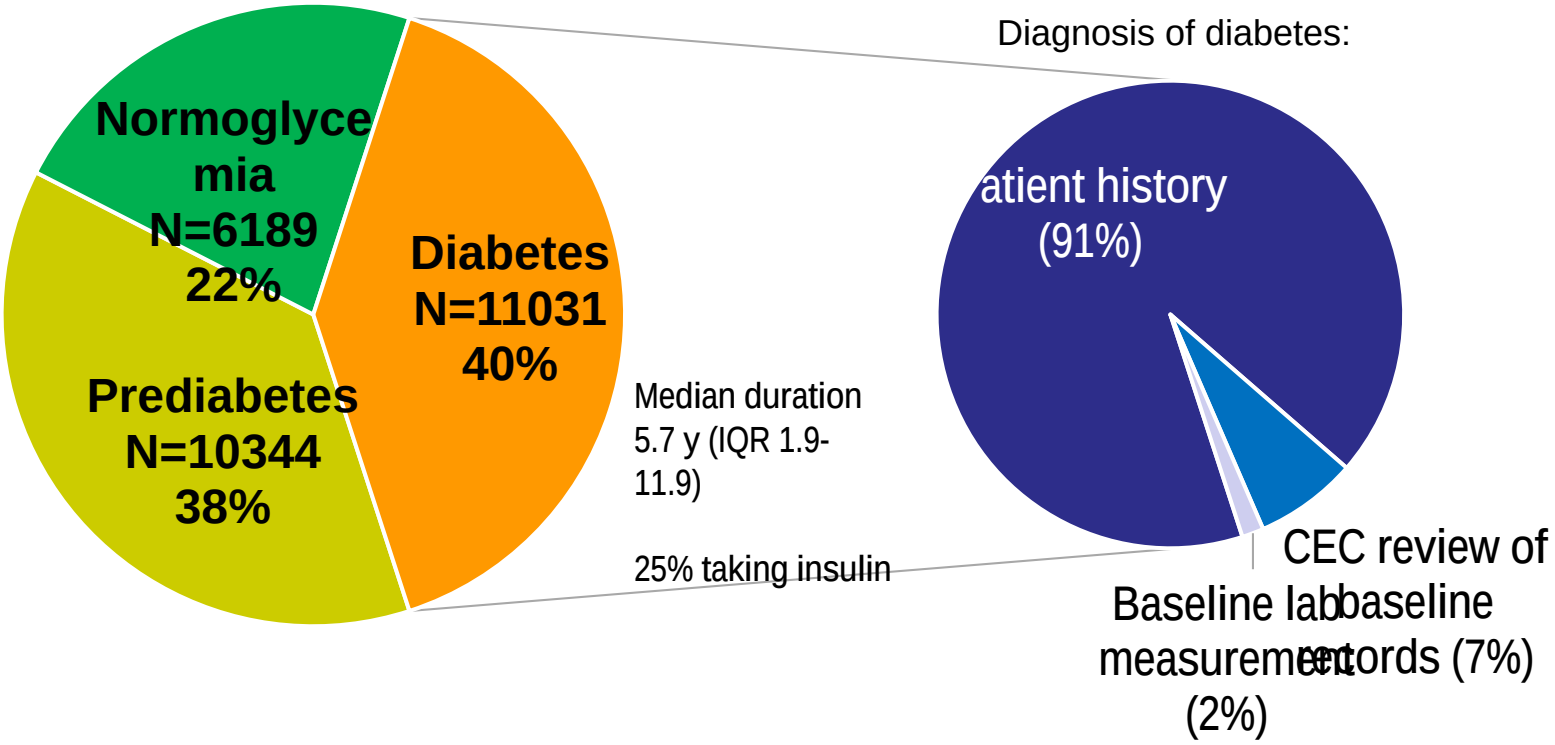
Methods

- **Baseline Diabetes Subgroups**
  - **<u>Diabetes</u>: either clinical history per patient; CEC review of baseline medical records; or baseline HbA1c ≥6.5% or FPG ≥126 mg/dL (7.0 mmol/L)**
  - **<u>No diabetes</u>**
    - ***Prediabetes*: baseline HbA1c 5.7-6.4% or FPG 100-125 mg/dL (5.5-6.9 mmol/L)**
    - ***Normoglycemia*: none of the above**
- **Outcomes**
  - **Primary endpoint: CV death, MI, stroke, hospitalization for UA, coronary revasc**
  - **Key secondary endpoint: CV death, MI, stroke**
  - **Adverse events in general; new-onset diabetes; glycemia**
- **TIMI Clinical Events Committee (CEC)**
  - **Adjudicated all efficacy endpoints & new-onset diabetes (per ADA definitions)**
  - **Members unaware of treatment assignment & lipid levels**

Analyses

- **Comparison of CV outcomes in patients w/ diabetes vs. w/o diabetes at baseline**
  - **Adjusted for: age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, high-intensity statin use**
- **Efficacy of evolocumab vs. placebo**
  - **Lipids**
  - **Clinical outcomes**
  - **In patients w/ and w/o diabetes at baseline**
- **Safety of evolocumab vs. placebo**
  - **New-onset diabetes in those w/o diabetes at baseline**
  - **Glycemia in patients w/ & w/o diabetes at baseline; weight**
  - **In patients w/ and w/o diabetes at baseline**

Diabetes at Baseline



Diabetes vs. No Diabetes

Characteristic	Diabetes (N=11,031)	No Diabetes (N=16,533)
Age, years, mean (SD)	**63 (9)**	**62 (9)**
Female sex (%)	**27**	**23**
White race (%)	**80**	**88**
Weight, kg, mean (SD)	**88 (19)**	**83 (16)**
Type of cardiovascular disease (%)		
Myocardial infarction	**79**	**83**
Stroke (non-hemorrhagic)	**22**	**18**
Symptomatic PAD	**15**	**12**
Cardiovascular risk factor (%)		
Hypertension	**87**	**75**
Current cigarette use	**22**	**32**
eGFR, mL/min per 1.73 m^2 (SD)	**75 (21)**	**76 (17)**

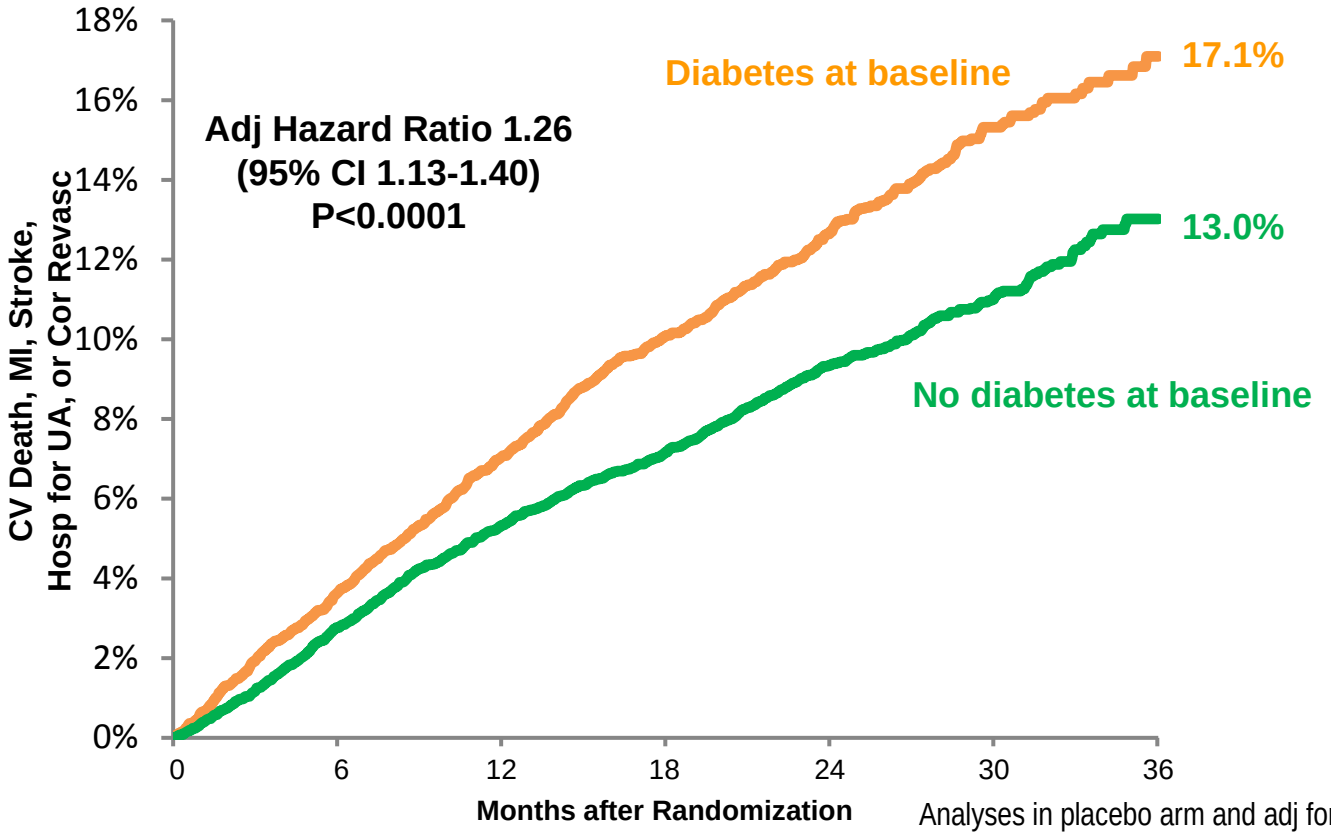
All P values <0.0001 apart from age (P=0.55)

Diabetes vs. No Diabetes

Characteristic	Diabetes (N=11,031)	No Diabetes (N=16,533)
Statin use (%)		
High-intensity	**67**	**71**
Moderate-intensity	**33**	**29**
Ezetimibe use (%)	**4**	**6**
Median lipid measures, mmol/L (IQR)		
LDL-C	**2.3 (2.0-2.8)**	**2.4 (2.1-2.8)**
Total cholesterol	**4.3 (3.9-4.8)**	**4.4 (3.9-4.9)**
HDL-C	**1.1 (0.9-1.3)**	**1.2 (1.0-1.4)**
Triglycerides	**1.7 (1.3-2.3)**	**1.4 (1.1-1.9)**

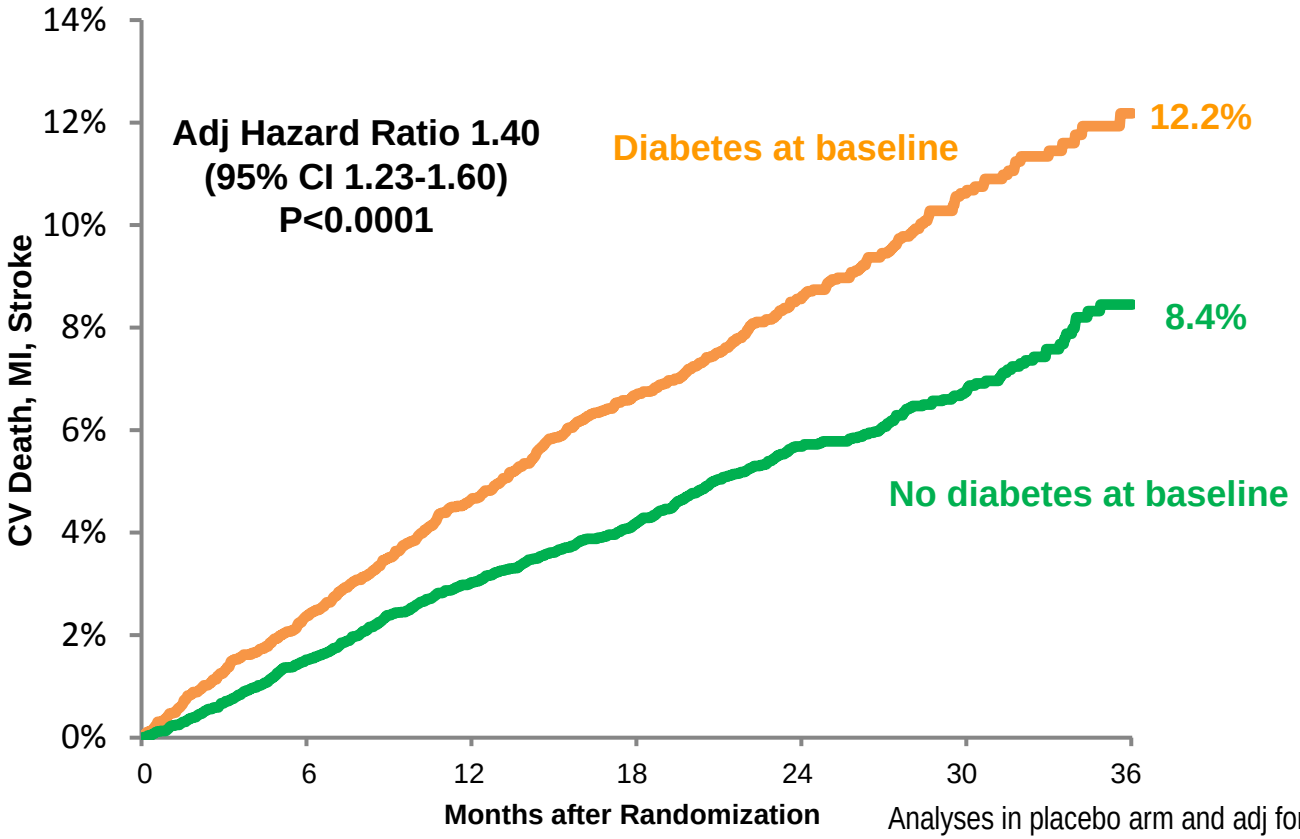
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines. All P values <0.0001

Risk of Primary Endpoint with Diabetes



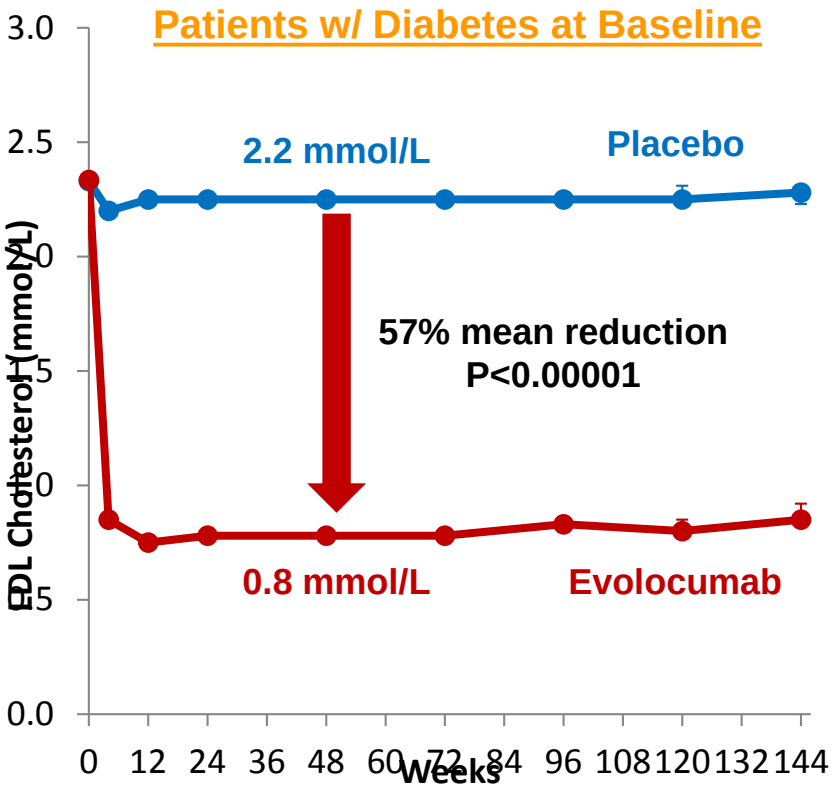
Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.

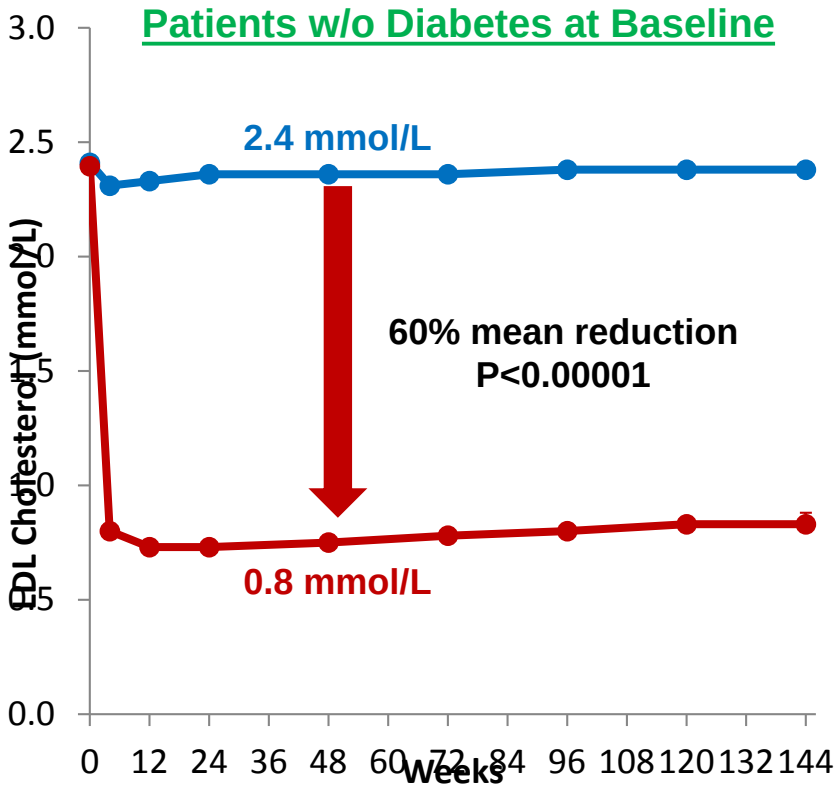
Risk of Key Secondary Endpoint with Diabetes



Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.

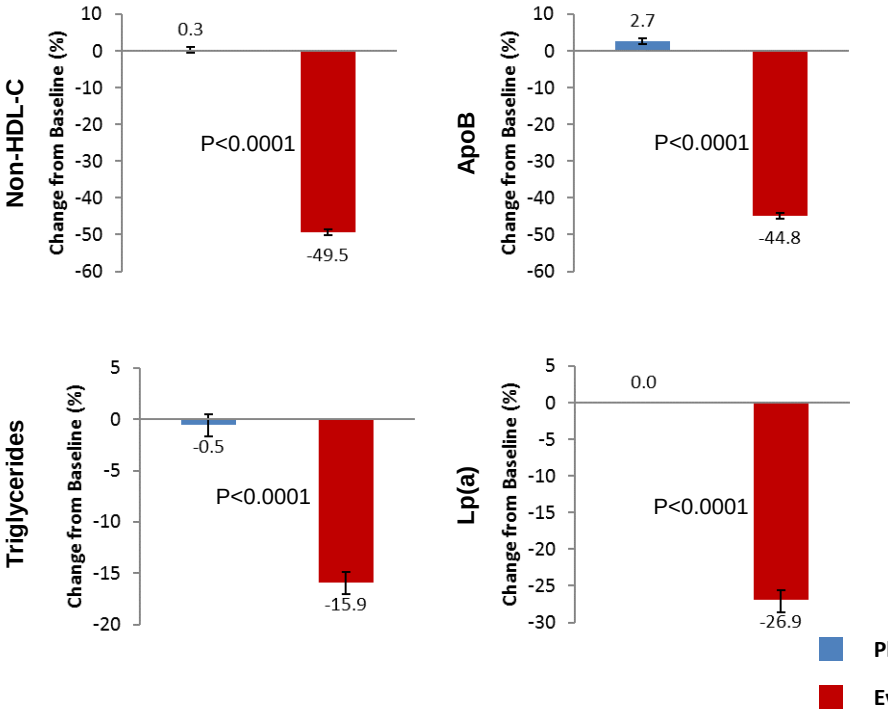
LDL-C Reduction with Evolocumab



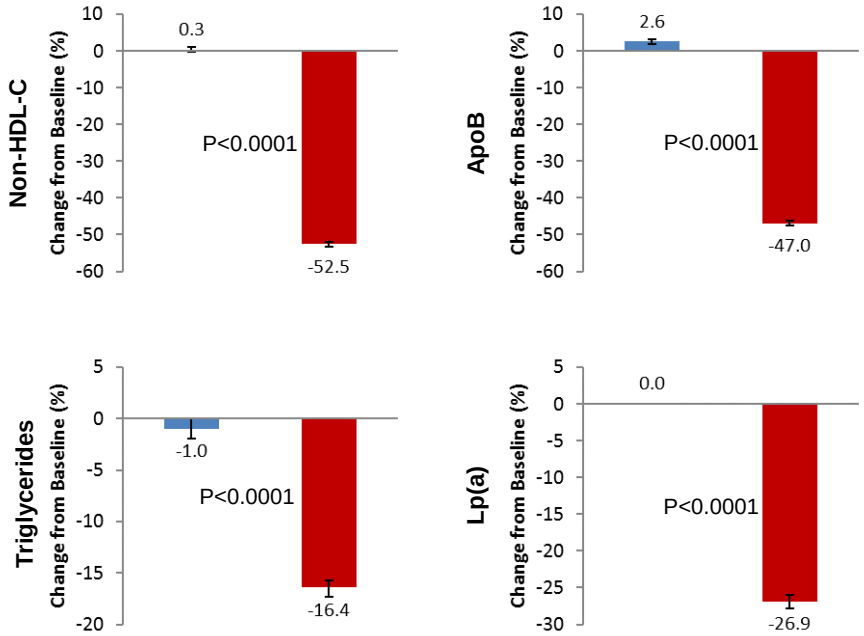


Effect of Evolocumab on Other Lipid Parameters

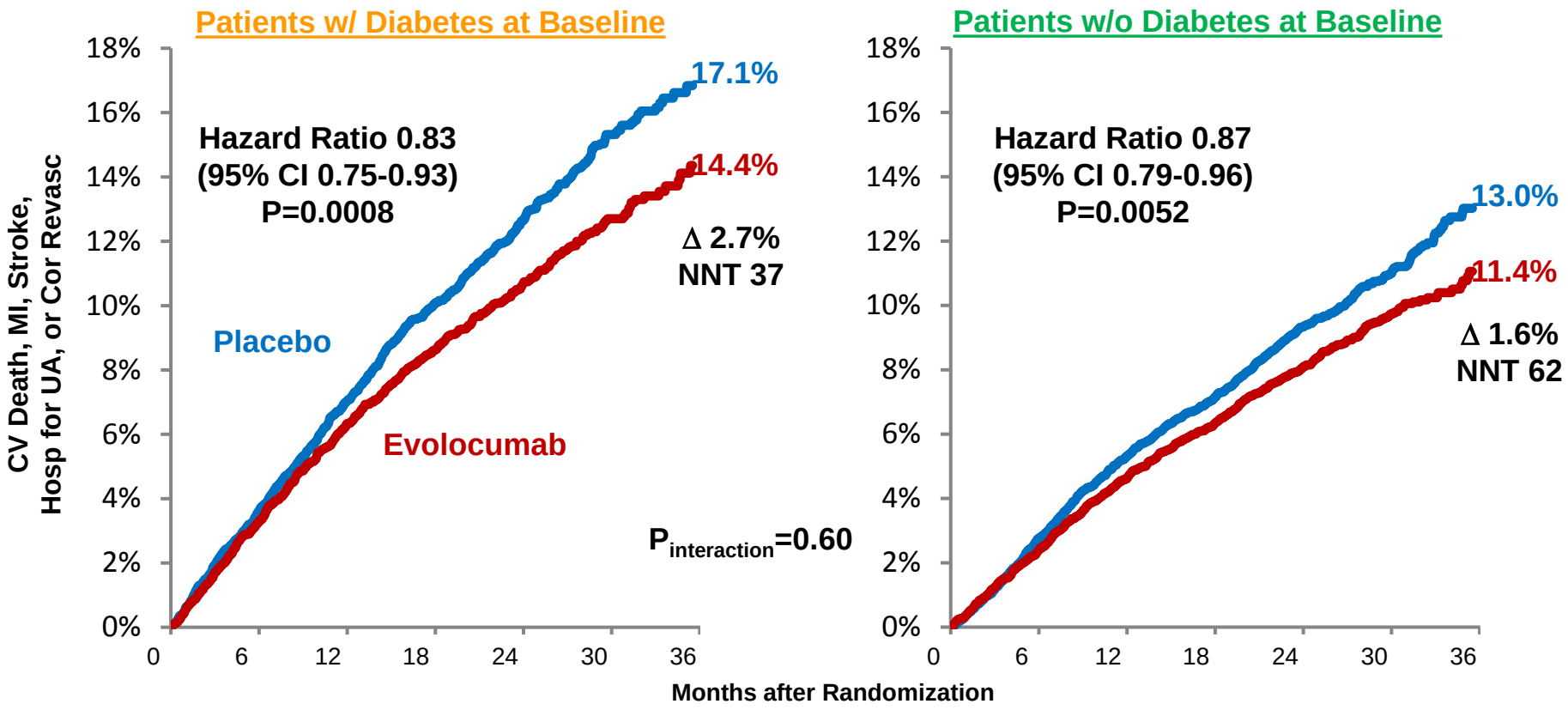
Patients w/ Diabetes at Baseline



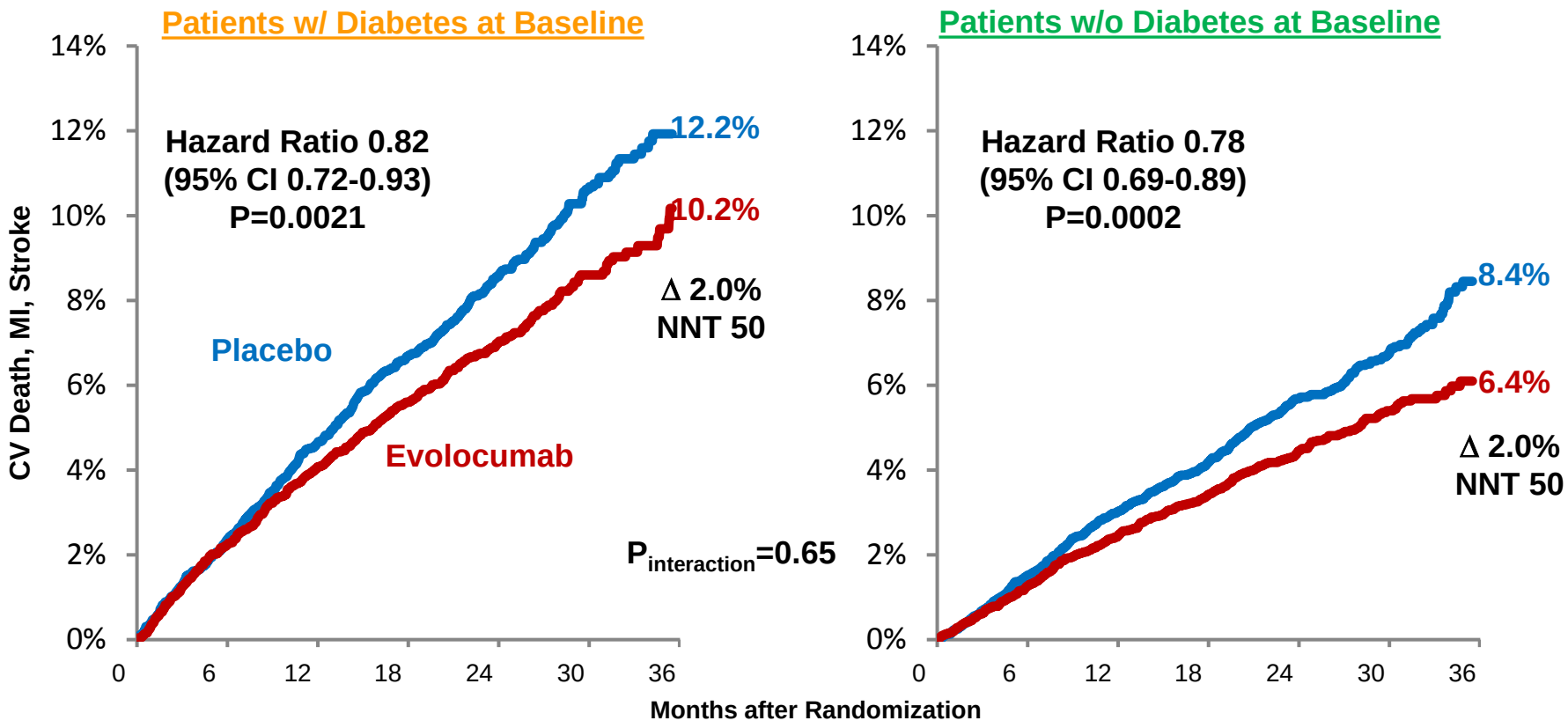
Patients w/o Diabetes at Baseline



Effect of Evolocumab on Primary Endpoint



Effect of Evolocumab on Key Secondary Endpoint

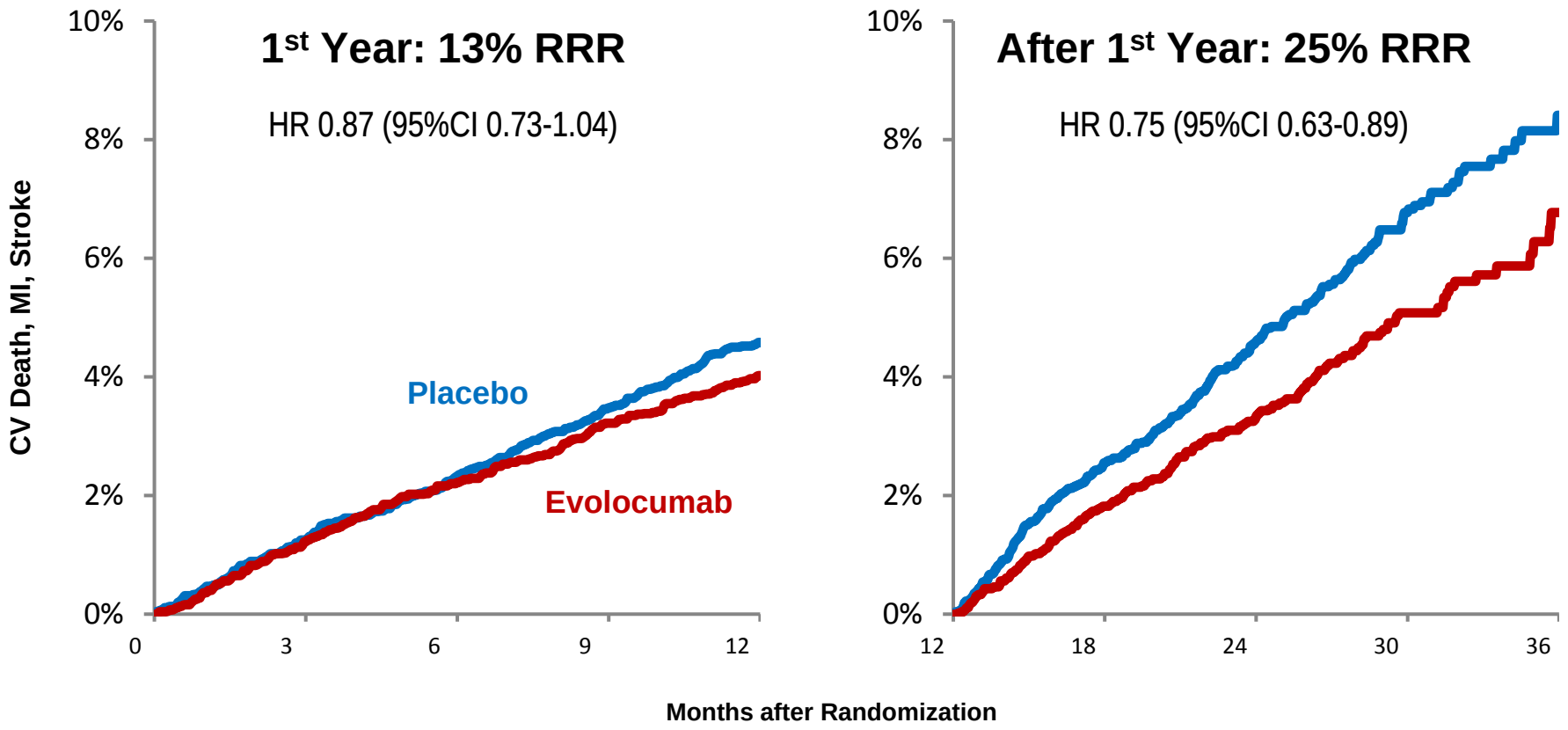


Individual CV Outcomes

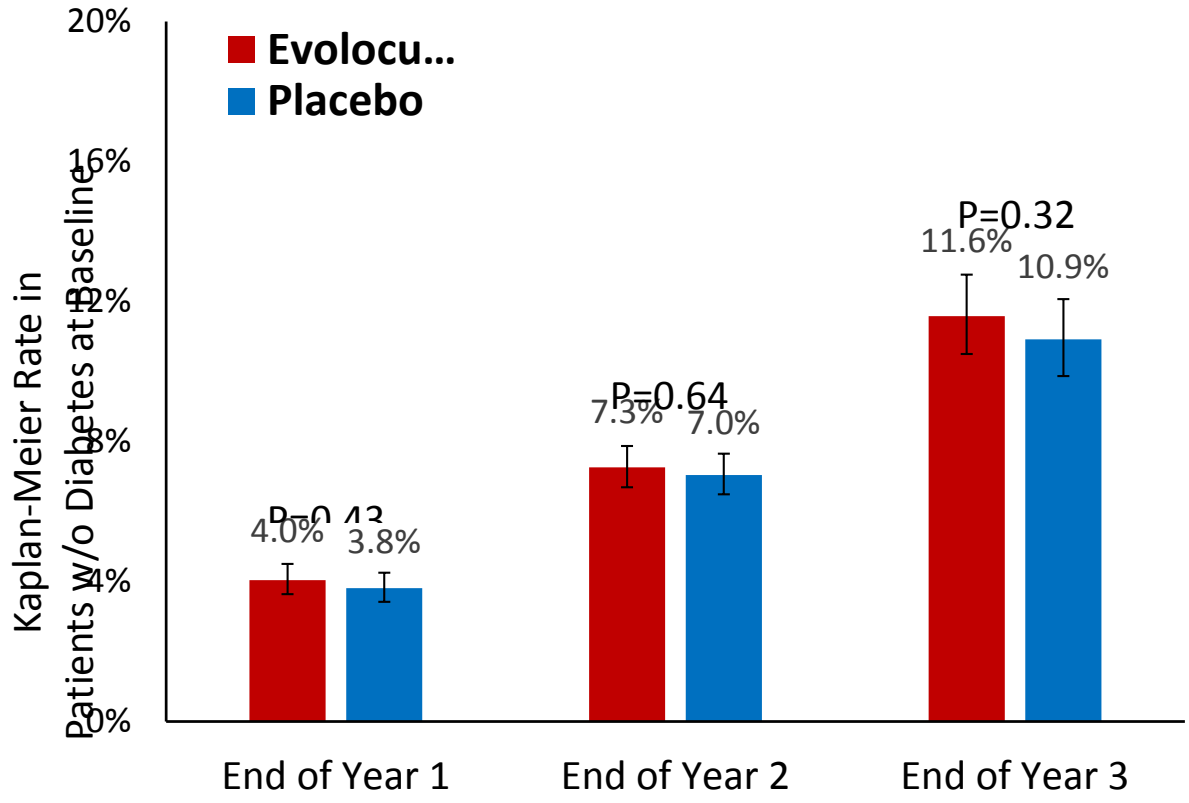
	Patients with Diabetes at Baseline			Patients without Diabetes at Baseline		
Endpoint	EvoMab (N=5515)	Placebo (N=5516)	HR (95% CI)	EvoMab (N=8269)	Placebo (N=8264)	HR (95% CI)
CVD, MI, stroke, UA, or revasc	14.4	17.1	0.83 (0.75-0.93)	11.4	13.0	0.87 (0.79-0.96)
CV death, MI, or stroke	10.2	12.2	0.82 (0.72-0.93)	6.4	8.4	0.78 (0.69-0.89)
Cardiovascular death	3.6	3.5	1.05 (0.83-1.34)	1.8	1.7	1.04 (0.80-1.35)
MI	5.5	7.5	0.77 (0.65-0.92)	3.7	5.5	0.69 (0.58-0.81)
Stroke	2.9	3.2	0.79 (0.62-1.01)	1.7	2.2	0.79 (0.60-1.03)
Hosp for Unstable Angina	2.3	2.4	0.93 (0.70-1.22)	2.2	2.3	1.04 (0.82-1.31)
Coronary revasc	7.4	10.0	0.77 (0.66-0.88)	6.8	8.6	0.79 (0.70-0.90)

KM rates at 3 years

Landmark Analysis
in Patients w/ Diabetes at Baseline



New-Onset Diabetes



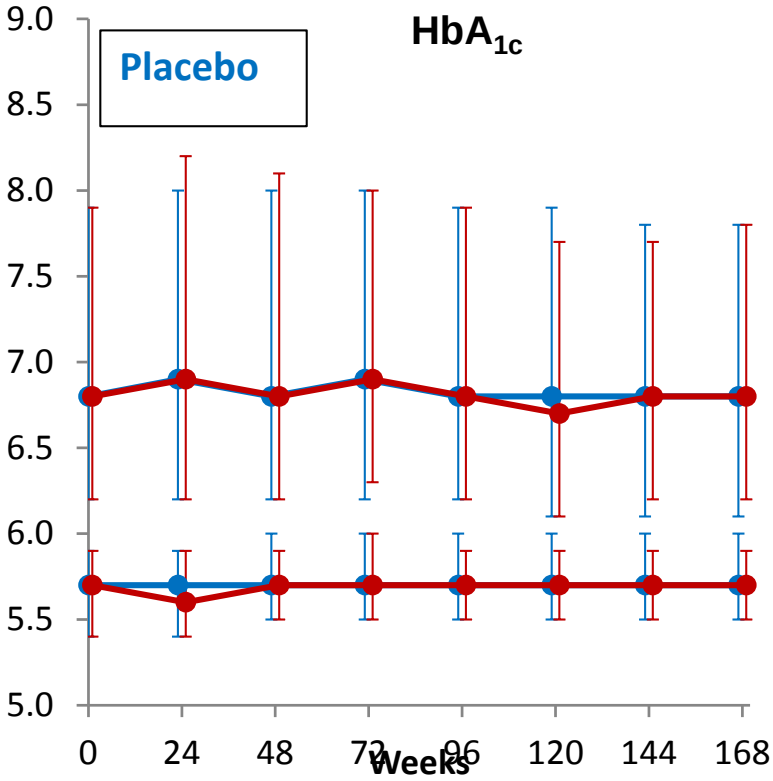
In all patients w/o diabetes at baseline (1294 incident cases in 16,510 patients):

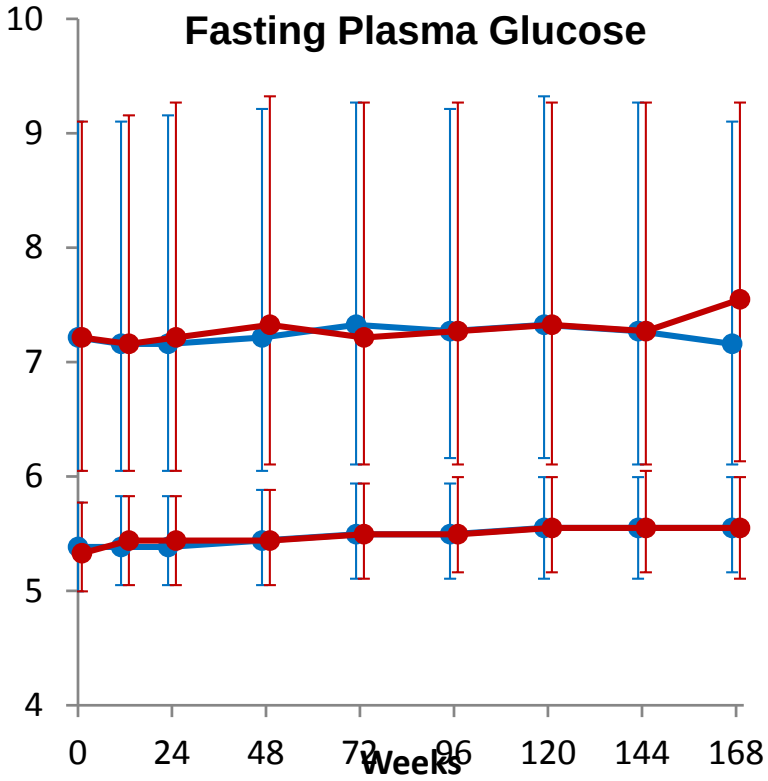
HR 1.05 (95% CI 0.94-1.17)

In patients w/ prediabetes at baseline (1163 incident cases in 10,338 patients):

HR 1.00 (95% CI 0.89-1.13)

Glycemic Parameters



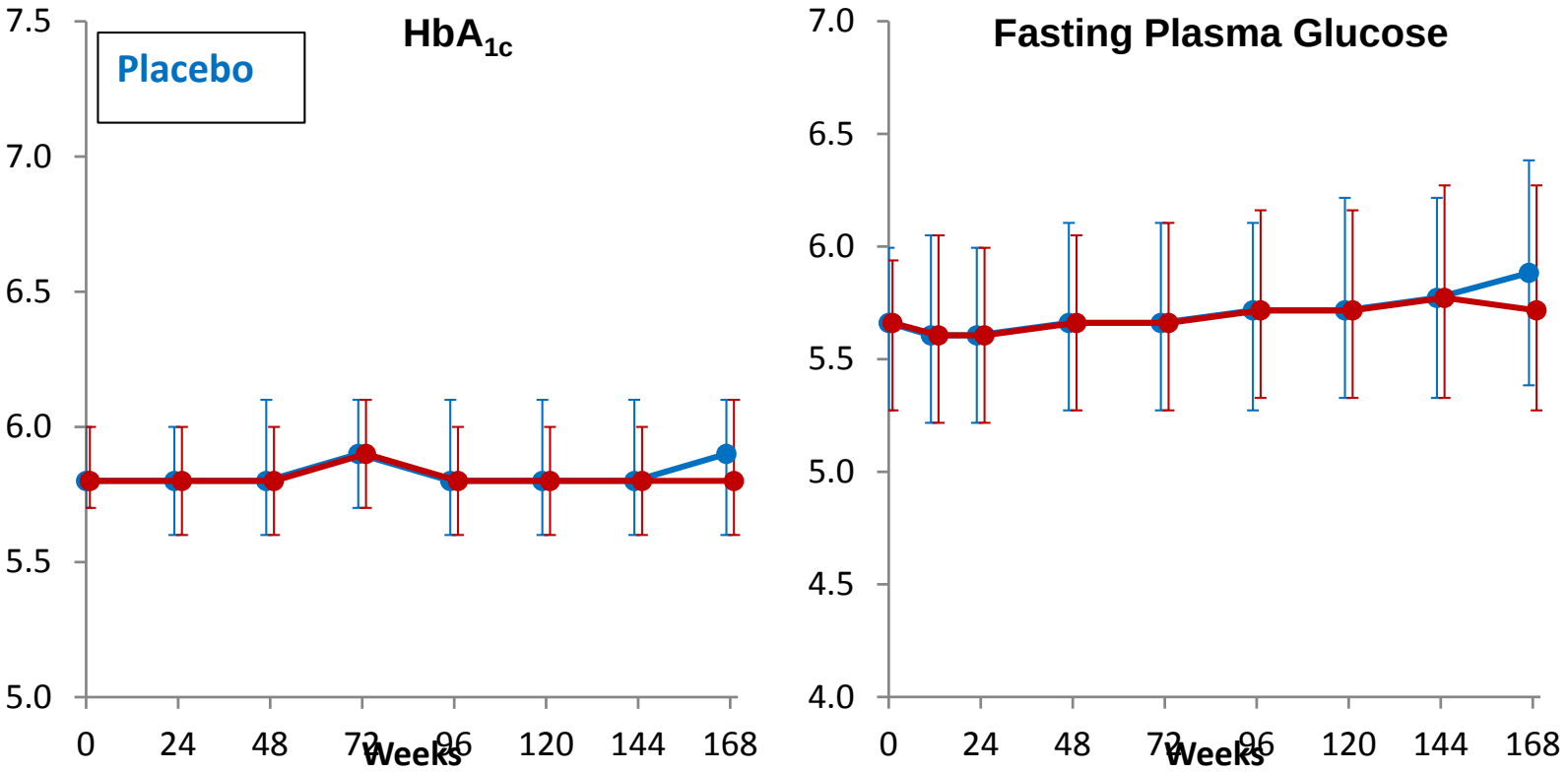


Diabetes at baseline

No diabetes at baseline

Values are median (IQR)

Glycemic Parameters in Prediabetes



Values are median (IQR)

Change in bodyweight

Subgroup	Evolocumab	Placebo
Patients with diabetes	**-0.1 (-2.1, 1.6)**	**-0.1 (-2.0, 1.7)**
Patients without diabetes	**0.3 (-1.3, 2.0)**	**0.3 (-1.3, 2.0)**
Patients with prediabetes	**0.2 (-1.4, 2.0)**	**0.3 (-1.4, 2.0)**
Patients with normoglycemia	**0.3 (-1.3, 2.0)**	**0.3 (-1.3, 2.0)**

Bodyweight in kg. Values are median (IQR) of time-weighted average for post-baseline measurements.

Strengths & Limitations

- **Largest trial of PCSK9i**
- **~3× # of events (CV and new-onset diabetes) than prior studies**
- **CV events and new-onset DM adjudicated**
- **Serial glycemia measurements**

- **Median trial duration 2.2 years**
- **All patients on background statin therapy**
- **No glucose tolerance testing**

Summary

- **Patients w/ diabetes at substantially higher risk of CV events**
- **Evolocumab efficacious in ASCVD patients w/ & w/o diabetes**
  - 57-60% ↓ in LDL-C
  - 18-22% relative risk reductions in CVD/MI/stroke; benefit ↑ over time
  - Given higher baseline risk, larger absolute risk reduction in CV events with evolocumab in patients with diabetes (particularly coronary revasc)
- **Evolocumab safe and well-tolerated**
  - No increased risk of diabetes, even in patients with prediabetes
  - No worsening of glycemia

Conclusion

Use of evolocumab is particularly clinically efficacious in ASCVD patients with diabetes, and evolocumab does not cause diabetes or worsen glycemia in patients with or without diabetes in the timeframe we studied.

Further Details

THE LANCET
Diabetes & Endocrinology

Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ioanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen

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