Role of PCSK9 Inhibitors in patients with Diabetes
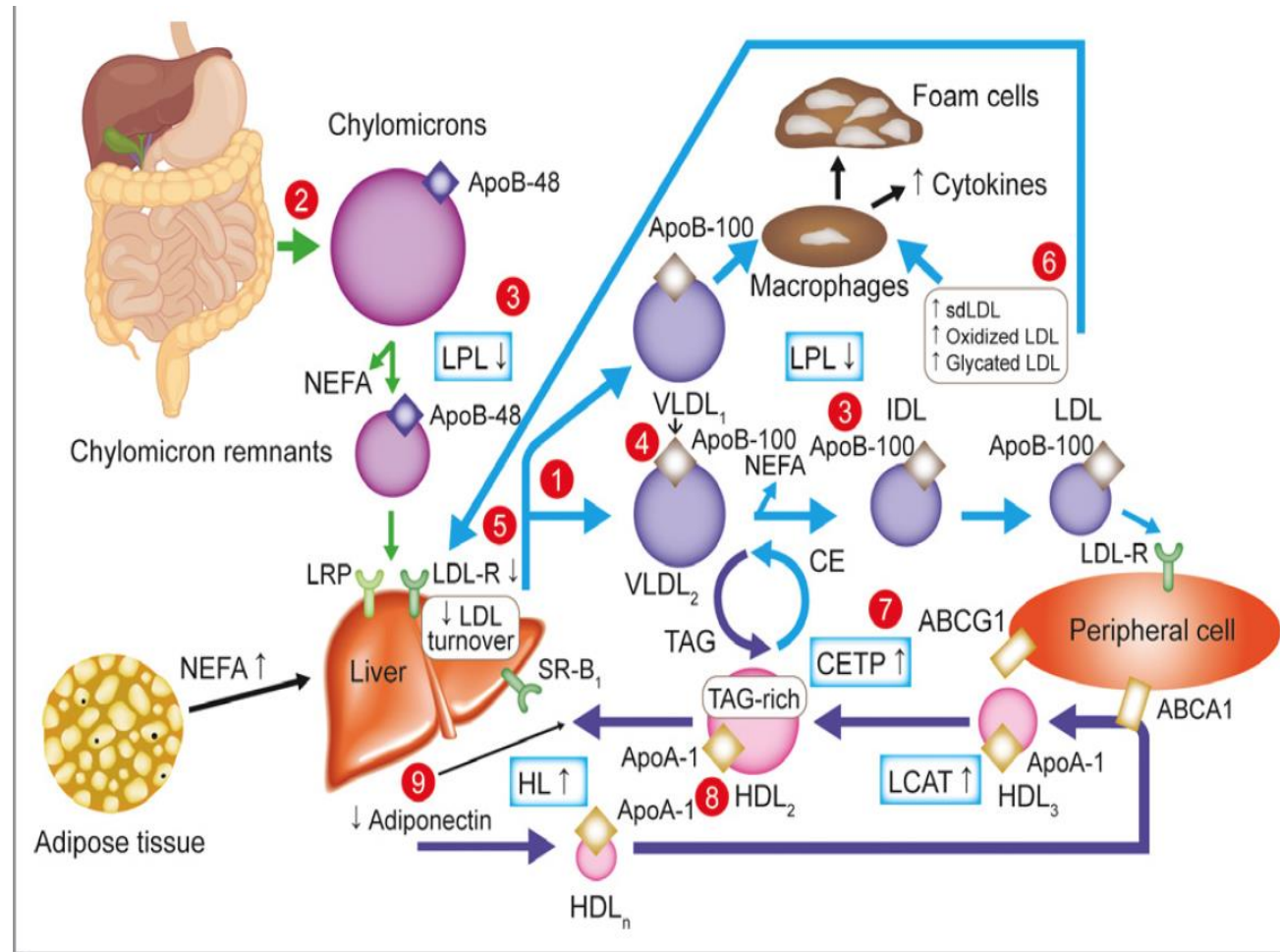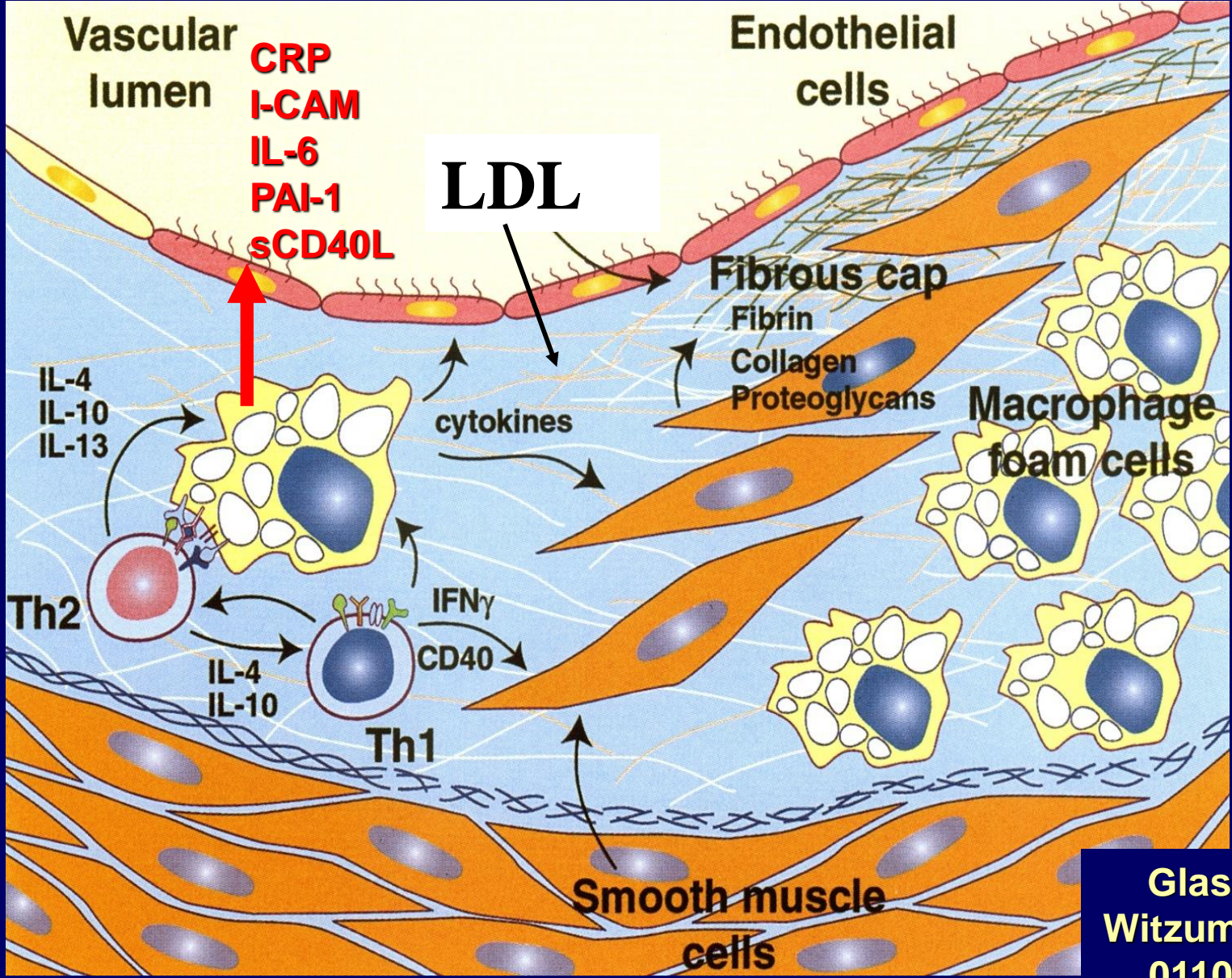
Prakash Deedwania, MD,FACC,FACP,FAHA,FESC,FHFSA

**Professor of Medicine, UCSF School of Medicine, San Francisco,
Director, Cardiovascular Research, UCSF Program, Fresno, CA
Clinical Professor of Medicine, Stanford University, Palo Alto, CA**

Lipid Abnormalities in Diabetics

Cell Biology of Atherosclerosis

Glass and Witzum,Cell,20 01104,530

# Lowering LDL Cholesterol is a central Tenet of Clinical Practice

.Ecologic,Evolutionary,Epidemiologic and Experimental Studies have shown that LDL-C has a Causative role in ASCVD

RCTs have shown that lowering LDL-C with Statins consistently reduces ASCVD events

CARDS: Primary Endpoint

- The primary endpoint consisted of the first of the following: acute CHD event (MI including silent infarction, UA, acute CHD death, resuscitated cardiac arrest), coronary revascularization procedures, or stroke
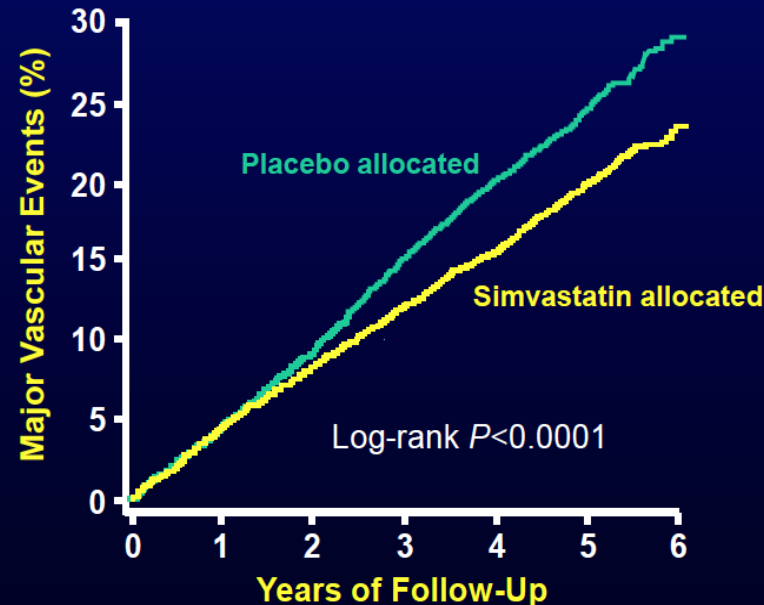
Primary Endpoint: Major CV Events

RR=-37%
(95% CI, -52 to -17, *P*=0.001)

Placebo
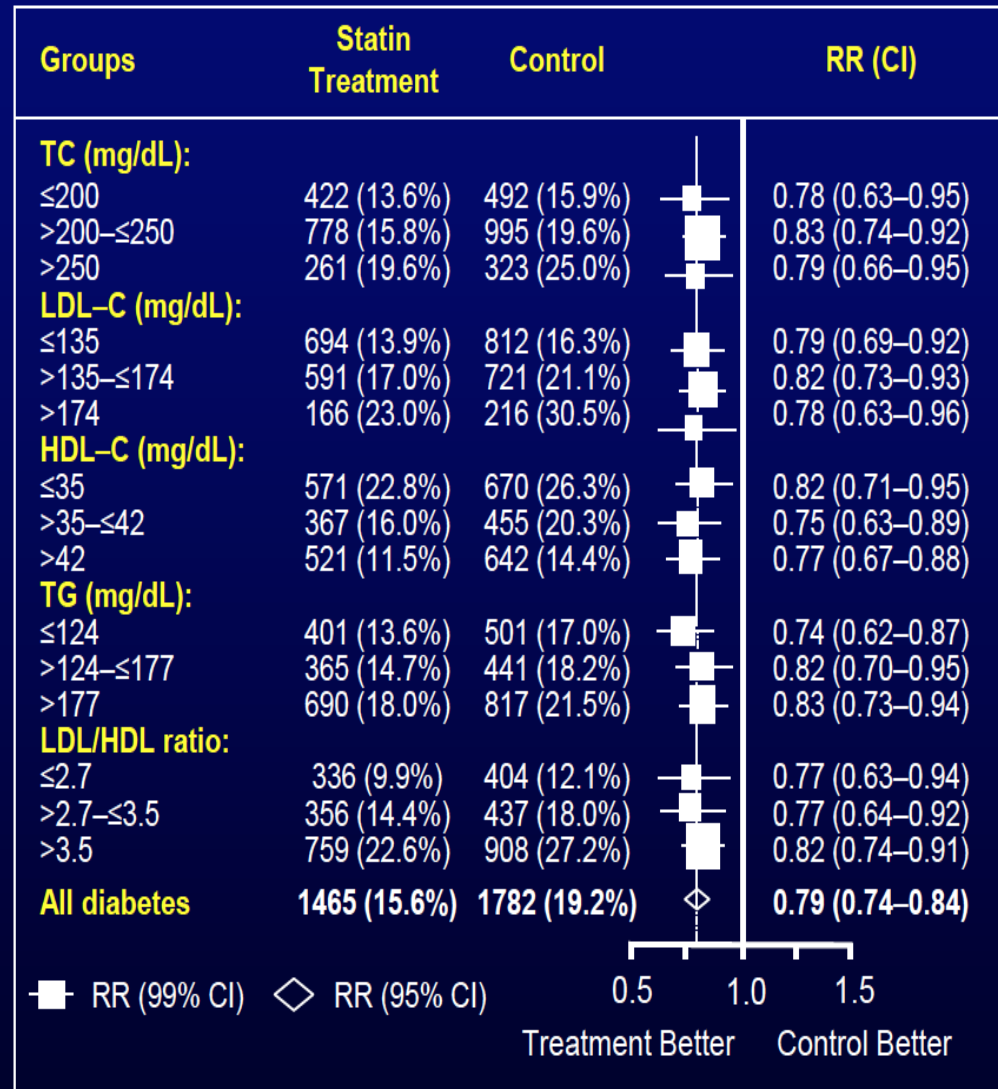Atorvastatin
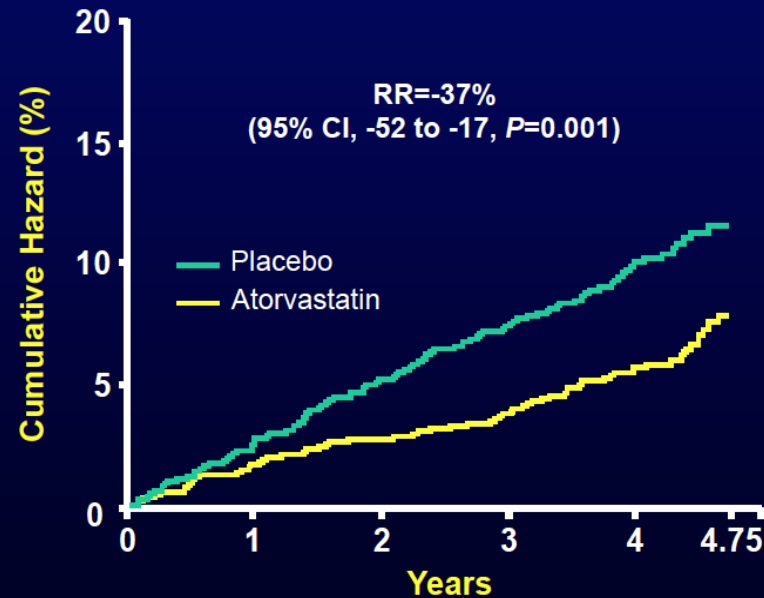
HPS: Primary Endpoint

- Assessments of the effects of treatment were based on first major coronary event (nonfatal MI or death from coronary disease) and first major vascular event (major coronary event, stroke of any type, and coronary or noncoronary revascularization)

Life-Table Plot of Effects of Simvastatin Allocation on Percentages of Patients With DM Having Major Vascular Events

Placebo allocated

Simvastatin allocated

Log-rank $P < 0.0001$

Major Vascular Events (%) vs Years of Follow-Up

- The proportional reduction in major vascular events with statin therapy was approximately a fifth per mmol/L (38.6 mg/dL) reduction of TC, LDL–C, HDL–C, TG, and LDL/HDL ratio

Proportional Effects on Major Vascular Events per mg/dL Reduction in LDL–C by Baseline Lipid Profile in Patients With DM*

Groups	Statin Treatment	Control		RR (CI)
TC (mg/dL):				
≤200	422 (13.6%)	492 (15.9%)		0.78 (0.63–0.95)
>200–≤250	778 (15.8%)	995 (19.6%)		0.83 (0.74–0.92)
>250	261 (19.6%)	323 (25.0%)		0.79 (0.66–0.95)
LDL–C (mg/dL):				
≤135	694 (13.9%)	812 (16.3%)		0.79 (0.69–0.92)
>135–≤174	591 (17.0%)	721 (21.1%)		0.82 (0.73–0.93)
>174	166 (23.0%)	216 (30.5%)		0.78 (0.63–0.96)
HDL–C (mg/dL):				
≤35	571 (22.8%)	670 (26.3%)		0.82 (0.71–0.95)
>35–≤42	367 (16.0%)	455 (20.3%)		0.75 (0.63–0.89)
>42	521 (11.5%)	642 (14.4%)		0.77 (0.67–0.88)
TG (mg/dL):				
≤124	401 (13.6%)	501 (17.0%)		0.74 (0.62–0.87)
>124–≤177	365 (14.7%)	441 (18.2%)		0.82 (0.70–0.95)
>177	690 (18.0%)	817 (21.5%)		0.83 (0.73–0.94)
LDL/HDL ratio:				
≤2.7	336 (9.9%)	404 (12.1%)		0.77 (0.63–0.94)
>2.7–≤3.5	356 (14.4%)	437 (18.0%)		0.77 (0.64–0.92)
>3.5	759 (22.6%)	908 (27.2%)		0.82 (0.74–0.91)
All diabetes	**1465 (15.6%)**	**1782 (19.2%)**		**0.79 (0.74–0.84)**

■ RR (99% CI) ◇ RR (95% CI)

0.5   1.0   1.5

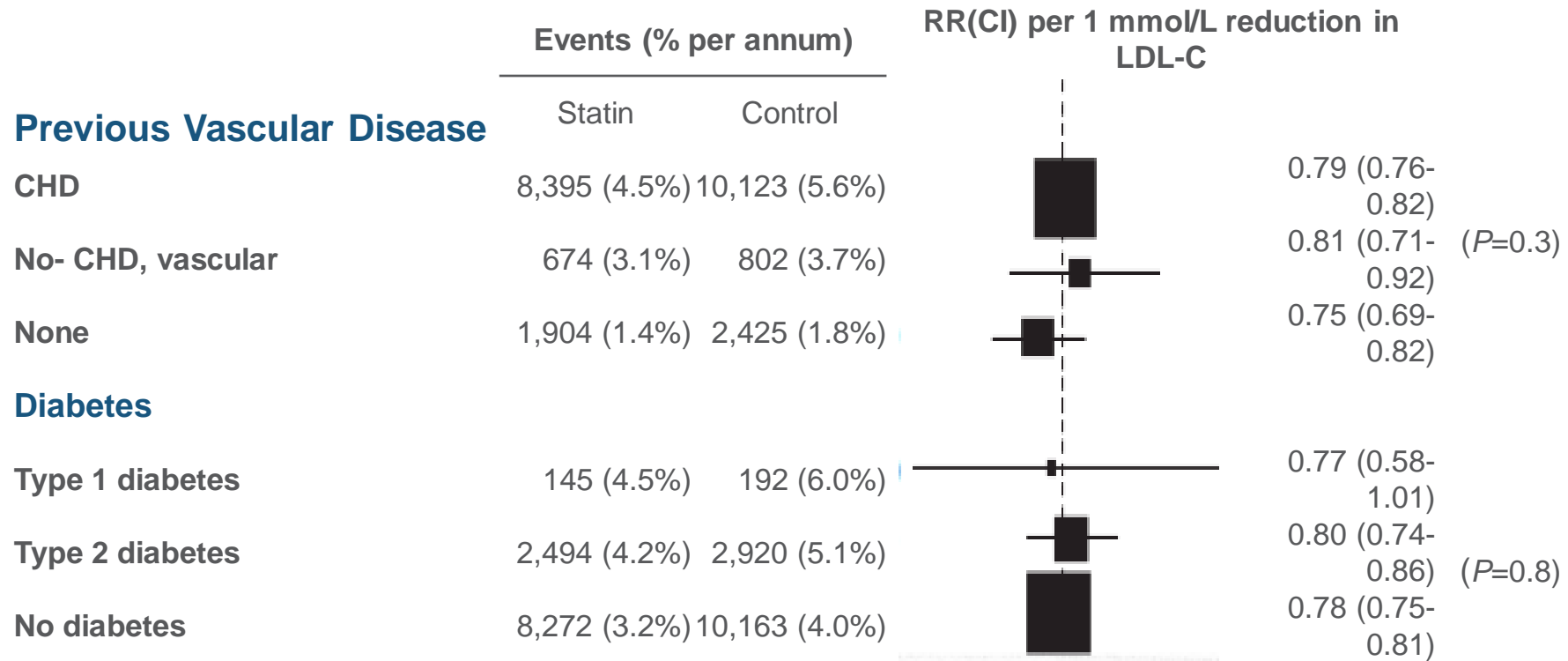Treatment Better   Control Better

* TC, LDL–C, and HDL–C values were converted from mmol/L to mg/dL using the conversion factor of 1 mmol/L to 38.6 mg/dL. TG values were converted from mmol/L to mg/dL using the conversion factor 1 mmol/L to 88.5 mg/dL.

CI=confidence interval; DM=diabetes mellitus; HDL=high-density lipoprotein; HDL–C=high-density lipoprotein–cholesterol; LDL=low-density lipoprotein; LDL–C=low-density lipoprotein–cholesterol; RR=rate ratio; TC=total cholesterol; TG=triglycerides.

Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet*. 2008;371:117-125.

# Cholesterol Treatment Trialists' Collaboration: Effect on CHD and Diabetes Primary Prevention

1 mmol/L = 38.6 mg/dL

	Events (% per annum)		RR(CI) per 1 mmol/L reduction in LDL-C	
Previous Vascular Disease	Statin	Control		
CHD	8,395 (4.5%)	10,123 (5.6%)		0.79 (0.76-0.82)
No- CHD, vascular	674 (3.1%)	802 (3.7%)		0.81 (0.71-0.92) (*P*=0.3)
None	1,904 (1.4%)	2,425 (1.8%)		0.75 (0.69-0.82)
Diabetes				
Type 1 diabetes	145 (4.5%)	192 (6.0%)		0.77 (0.58-1.01)
Type 2 diabetes	2,494 (4.2%)	2,920 (5.1%)		0.80 (0.74-0.86) (*P*=0.8)
No diabetes	8,272 (3.2%)	10,163 (4.0%)		0.78 (0.75-0.81)

Abbreviation: CHD: coronary heart disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; RR: relative risk.

Baigent C, et al. *Lancet*. 2010;376:1670-1681.

Effects of Intensive LLT in Diabetes over past 10 years
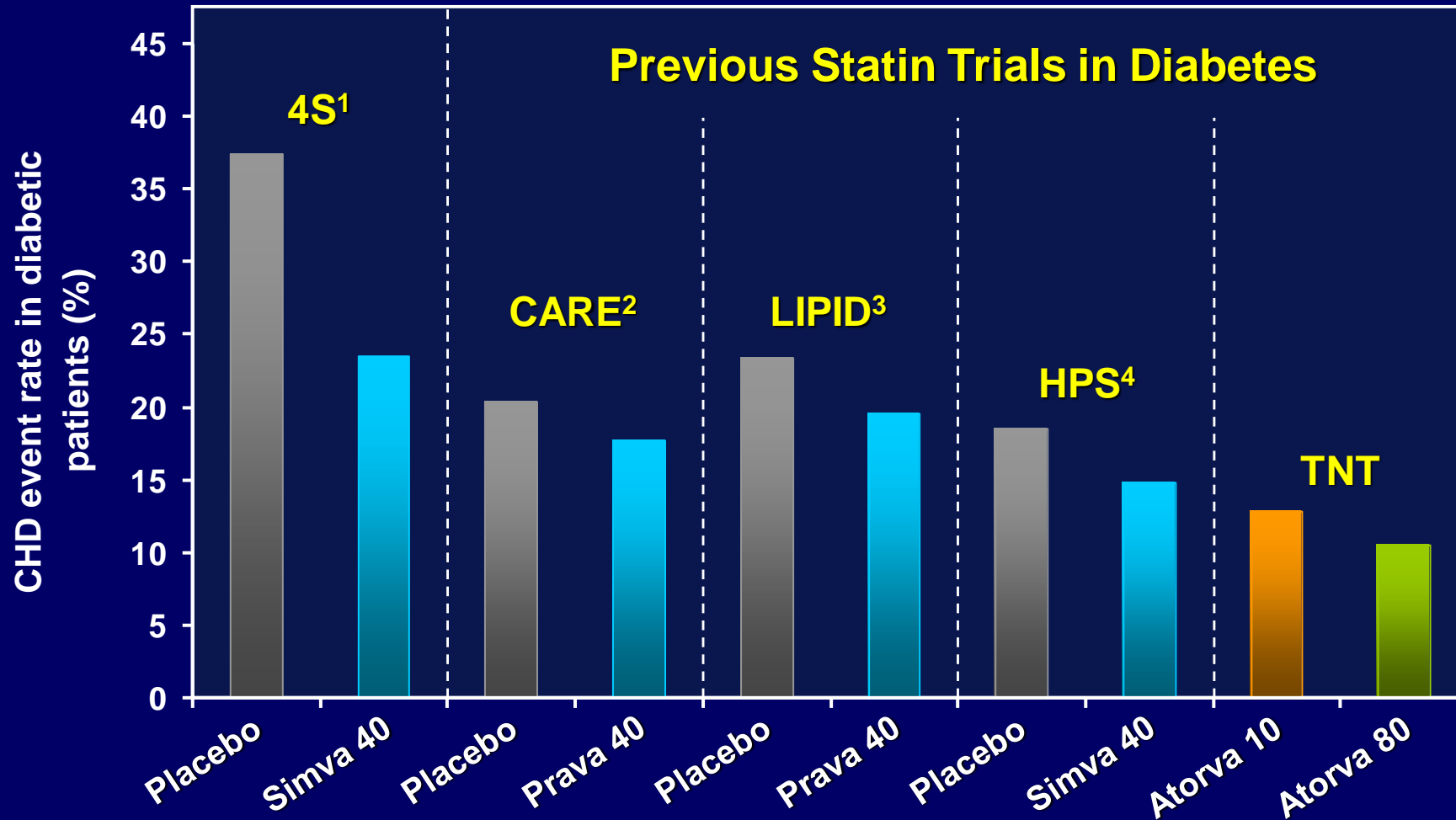
1. Haffner SM, et al. Arch Intern Med. 1999;159:2661-67
2. Goldberg RB, et al. Circulation. 1998;98 :2513-19
3. Keech A, et al. Diabetes Care. 2003;26:2713-21
4. HPS Collaborative Group. Lancet. 2003;361:2005-16

Secondary Prevention and Statins in Diabetics

Study (year of primary publication)	Comparison	Subjects	Subjects with diabetes (%)	Diabetes results
4S (1994)	Simvastatin 20–40 mg vs placebo	4,444	202 (5%) 483 (11%)	No significant reduction in total mortality, significant 55% reduction in major coronary events
CARE (1996)	Pravastatin 40 mg vs placebo	4,159	586 (14%)	No significant reduction in major coronary events, significant 25% reduction in expanded coronary endpoint
LIPID (1998)	Pravastatin 40 mg vs placebo	9,014	1,077 (12%)	No significant reduction in major coronary events, significant 21% reduction in any cardiovascular event
HPS (2002)	Simvastatin 40 mg vs usual care	20,536	5,963 (28%), 3,051 secondary prevention	Significant reduction in defined endpoint for subcategories
4D (2005)	Atorvastatin 20 mg vs placebo	1,255	1,255 (100%)	No significant reduction in MACE
SPARCL (2006)	Atorvastatin 80 mg vs placebo	4,731	794 (17%)	No significant reduction in strokes, significant reduction in major coronary events and MACE

Ezetimibe in Addition to a Statin Reduces CV Risk in Patients With Diabetes Mellitus

IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial)[1,2]

- Included patients ≥50 years of age hospitalized with an ACS event in the preceding 10 days; 27% had DM

- Ezetimibe in addition to a statin significantly reduced major adverse CV events in the diabetic patient population

Reduction in 7-Year Event Rate in Patients With DM
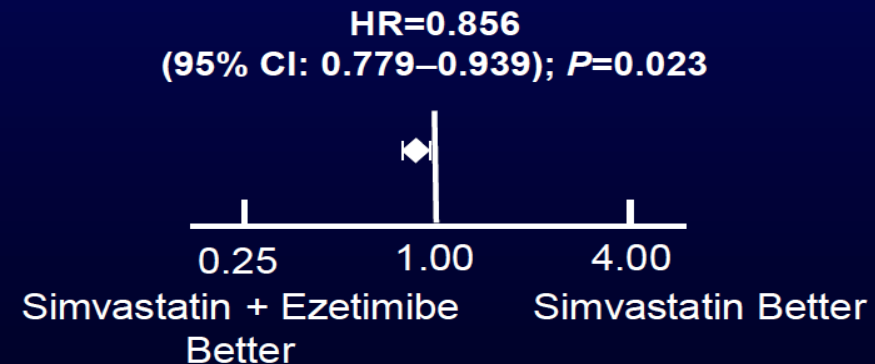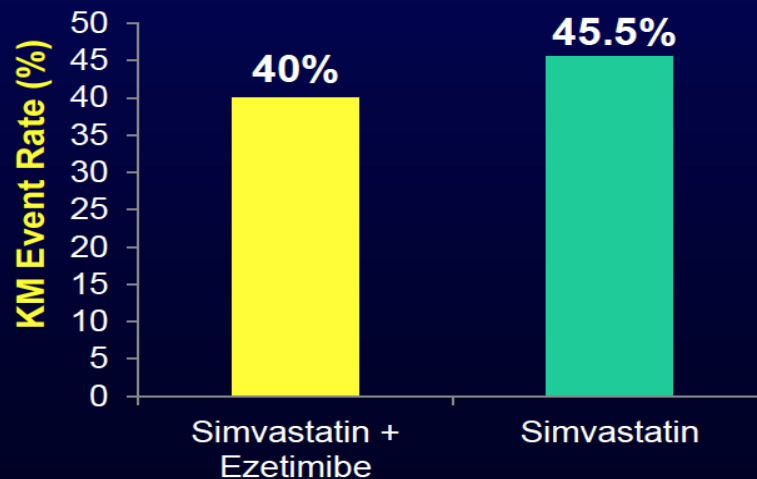
HR=0.856
(95% CI: 0.779–0.939); *P*=0.023

Simvastatin + Ezetimibe Better

Simvastatin Better

IMPROVE-IT TRIAL
DIABETICS vs Non-Diabetics

▼ Primary Endpoint (P value for interaction = 0.023)
- ezetimibe vs. placebo in diabetics: 40.0% vs. 45.5%; HR 0.86, CI 0.78-0.94
- ezetimibe vs. placebo in non-diabetics: 30.2% vs. 30.8%, HR 0.98, CI 0.91-1.04

▼ Myocardial Infarction (P value for interaction = 0.028)
- diabetes: 16.4% vs. 20.8%
- non-diabetes: 12.0% vs. 12.7%

▼ Stroke (P value for interaction = 0.031)
  - diabetes: 3.8% vs. 6.5%
- non-diabetes: 3.2% vs. 3.4%

How Low Should We Go?

Lower Is Better

PCSK9 Inhibitor Outcome Trials

PCSK9 Inhibition with a Monoclonal Antibody
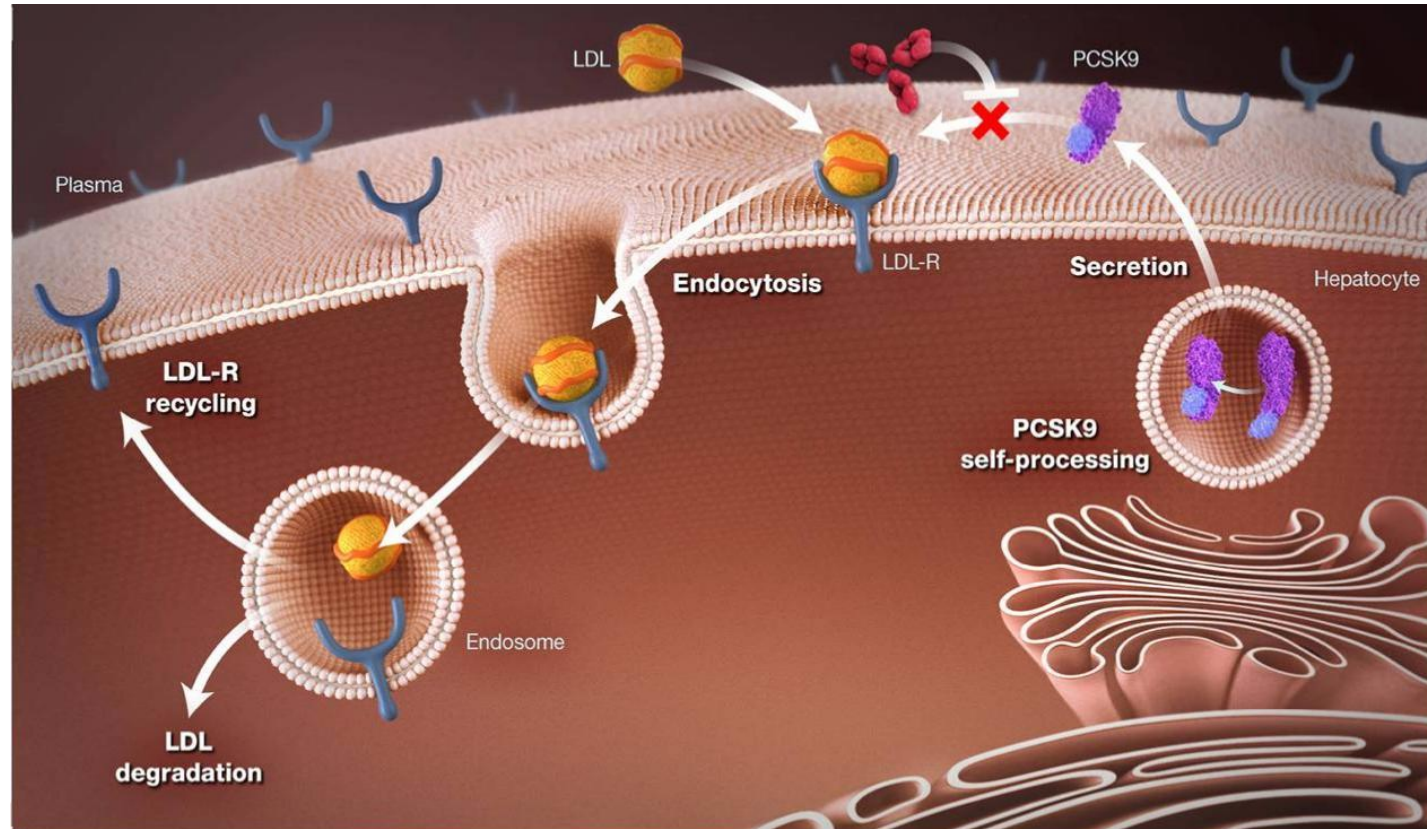
Qian YW, Schmidt RJ, Zhang Y, et al. *J Lipid Res.* 2007;48:1488-1498
Horton JD, Cohen JC, Hobbs HH. *J Lipid Res.* 2009;50(suppl):S172-S177
Rashid S et al. *PNAS* 2005;102:5374-5379
Chan JC, Piper DE, Cao Q, et al. *Proc Natl Acad Sci U S A.* 2009;106:9820-9825

Anti-PCSK9 mAb and LDL-c

Anti-PCSK9 mAb and MACE

Primary endpoints: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, UA requiring hospitalisation
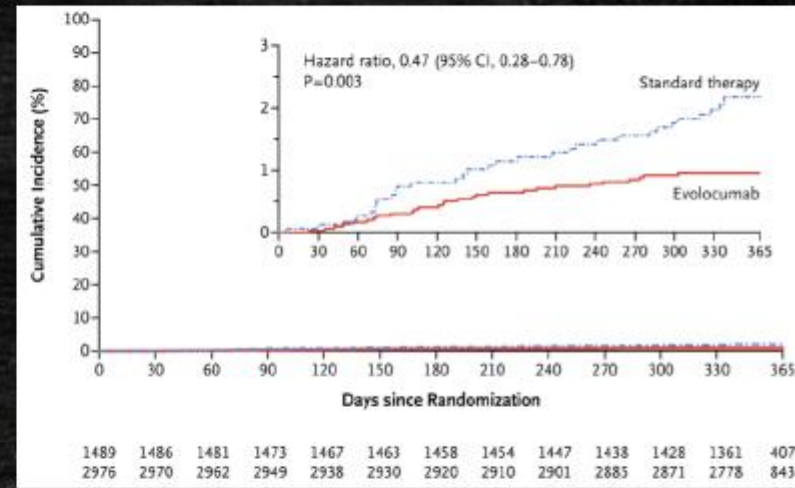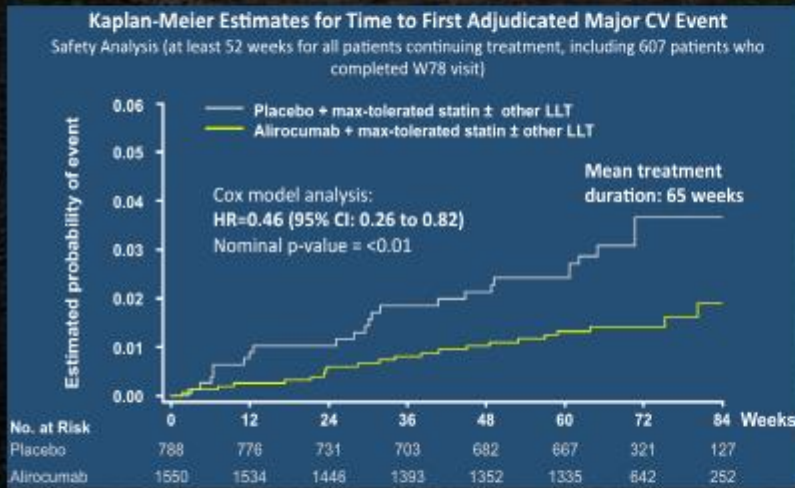
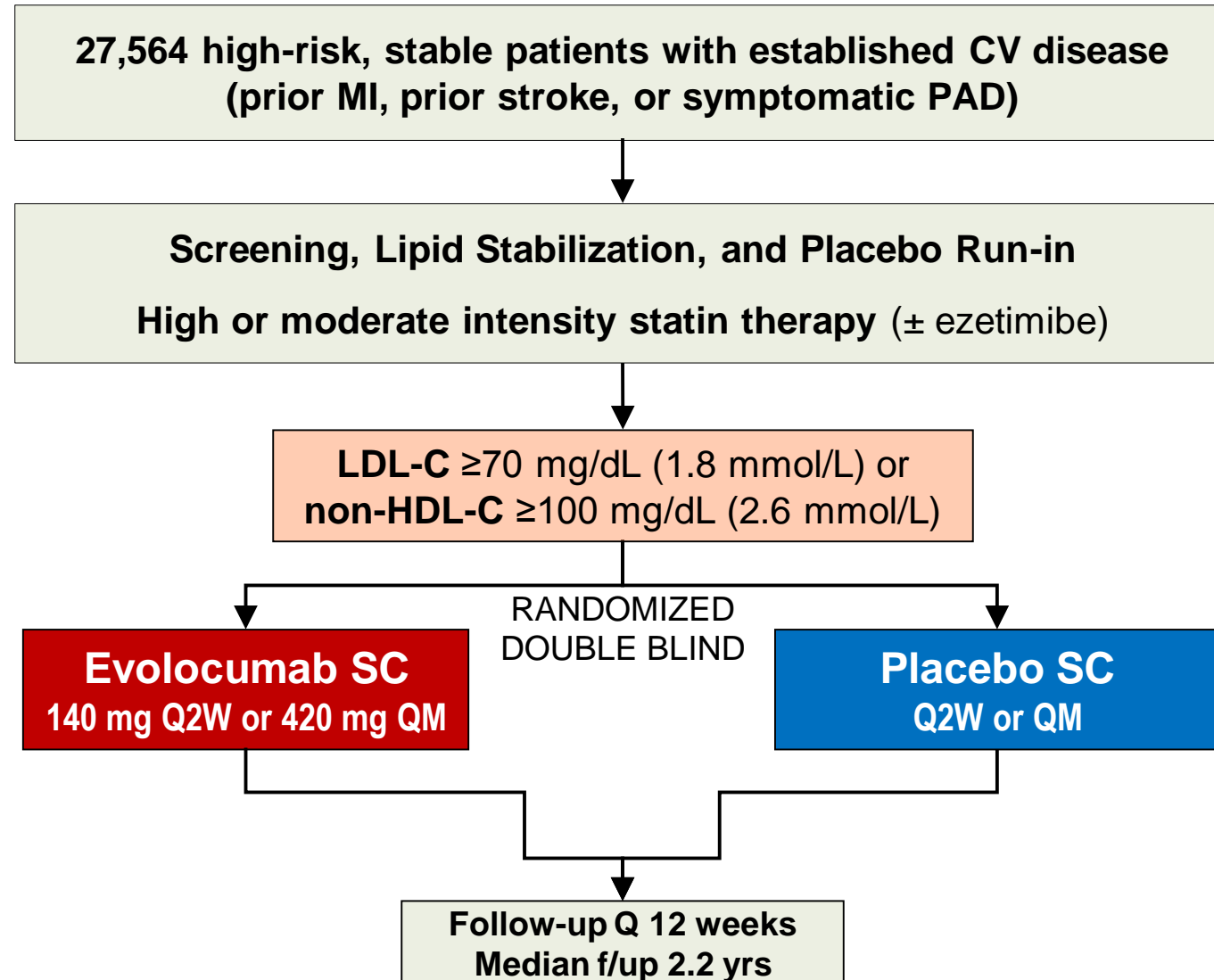*ESC Late Clinical Breaking Trial 2014*

New Engl J Med 2015;372:1500-9

Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in

High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL (1.8 mmol/L) or
non-HDL-C ≥100 mg/dL (2.6 mmol/L)

RANDOMIZED
DOUBLE BLIND

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks
Median f/up 2.2 yrs

Overall Effects on LDL Cholesterol

Sabatine MS et al. *NEJM* 2017;376:1713-1722
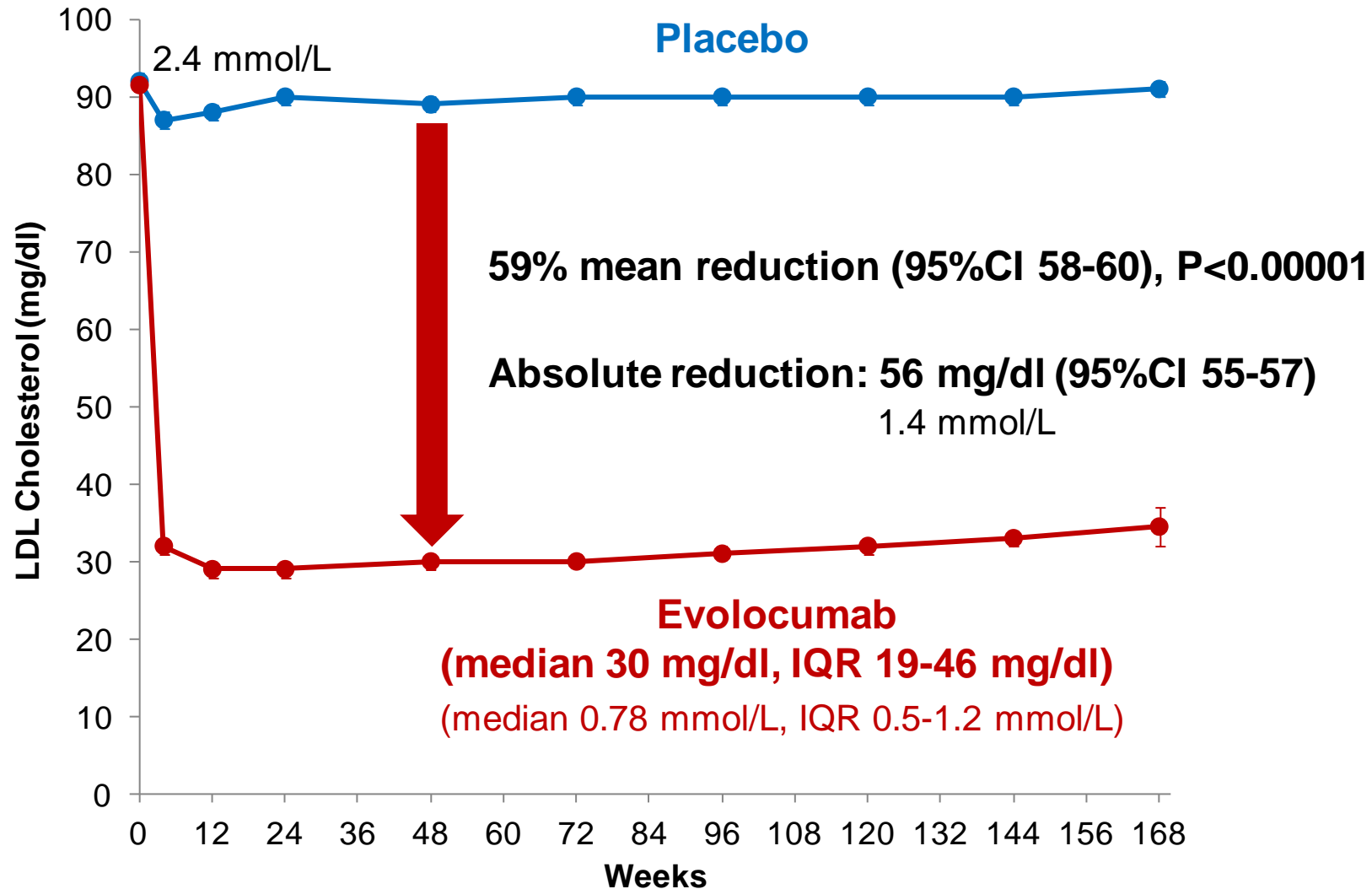
Primary & Key Secondary Endpoints

Primary Endpoint: CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

Placebo

Evolocumab

Key Secondary Endpoint: CV Death, MI, or Stroke

Hazard ratio 0.80
(95% CI, 0.73-0.88)
P<0.00001

Placebo

Evolocumab

Months after Randomization
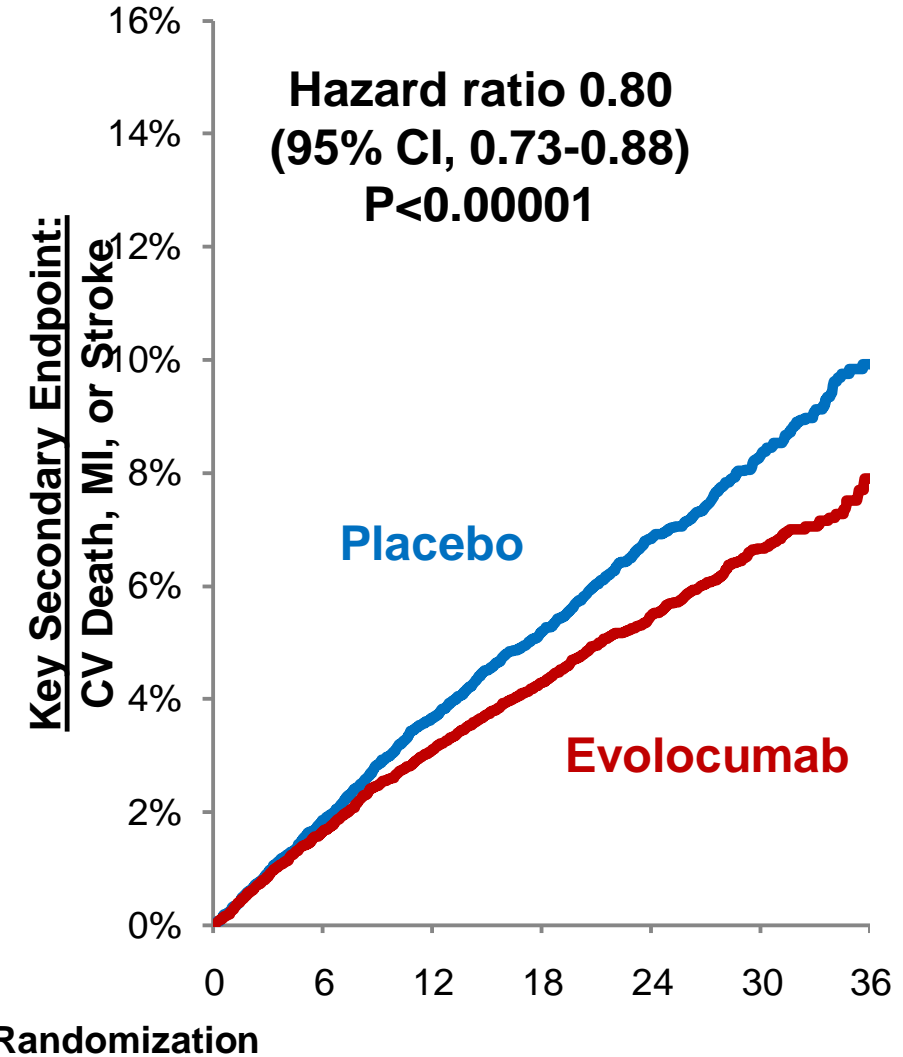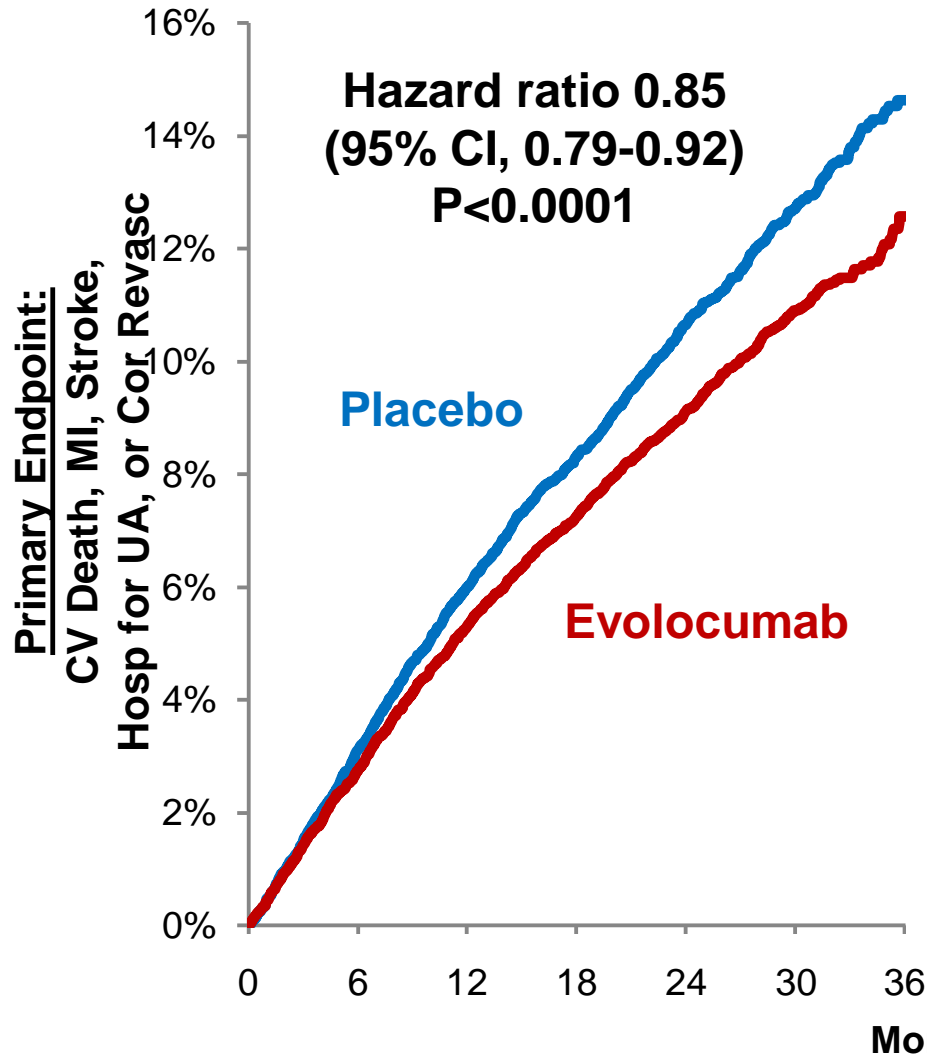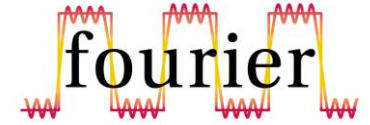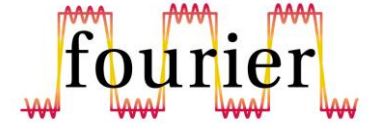
THE LANCET
Diabetes & Endocrinology

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

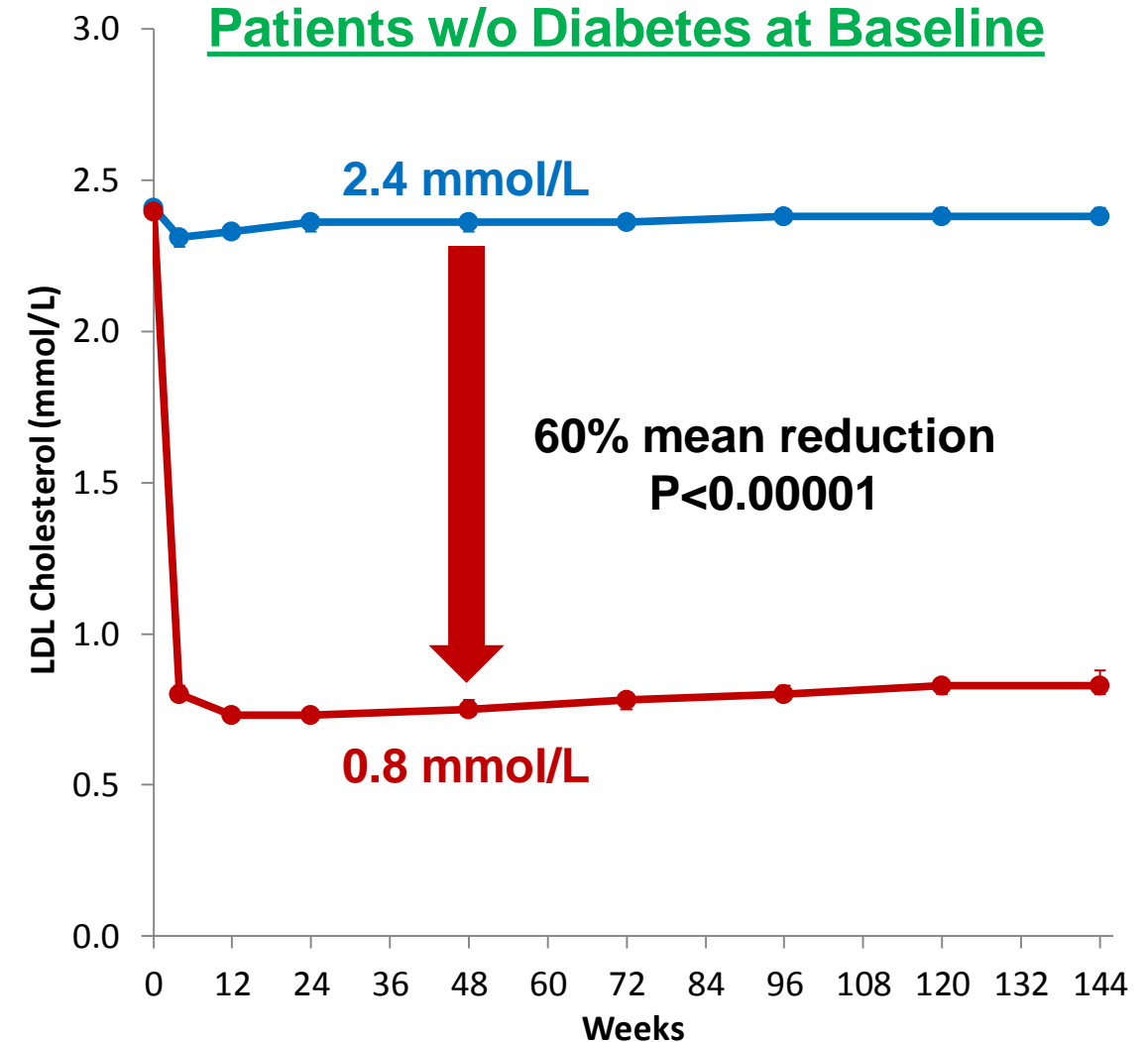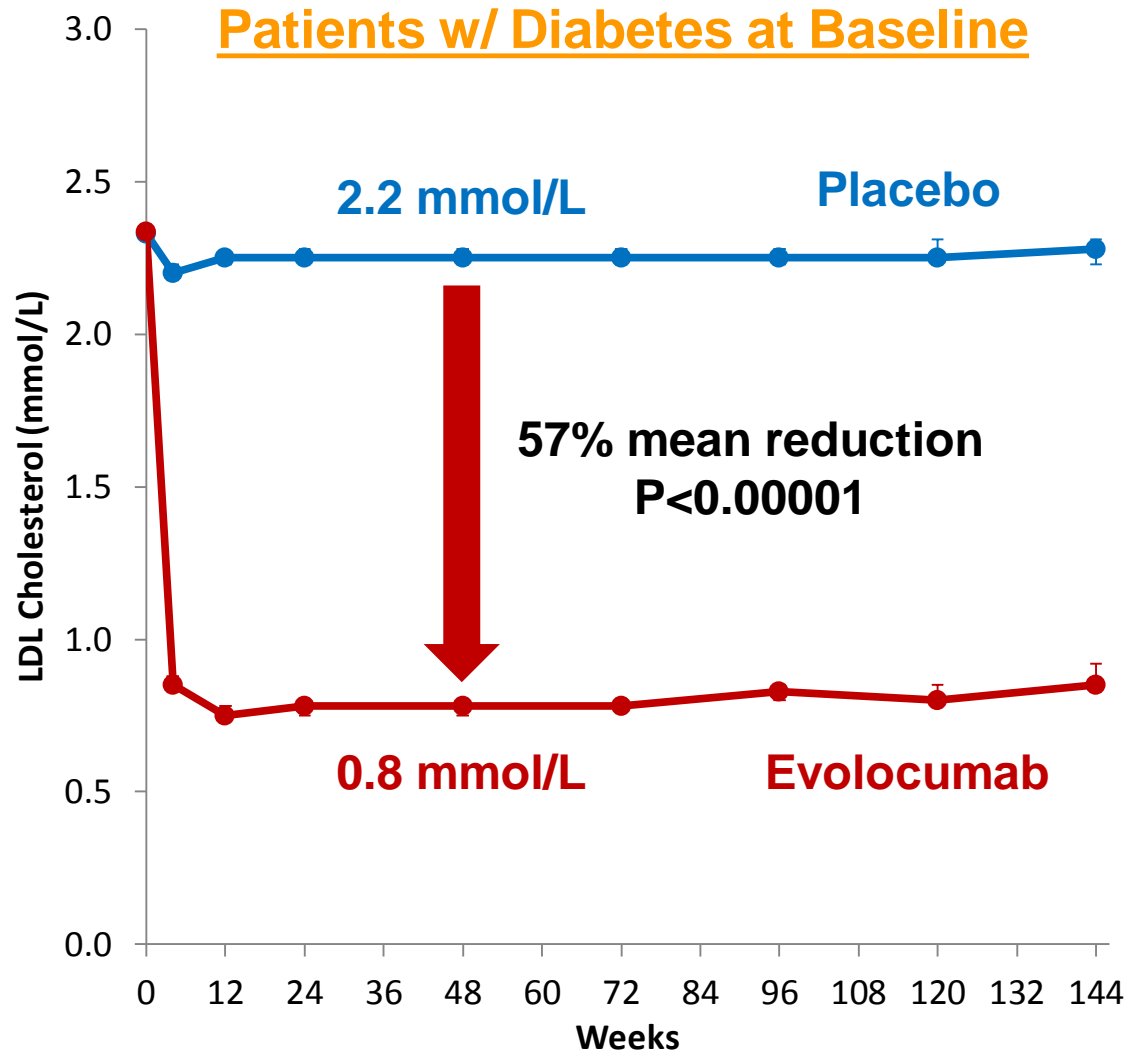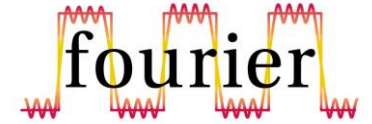*Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ioanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen*

Article available at http://www.thelancet.com/journals/landia/onlineFirst
Slides available at www.TIMI.org

Risk of Primary Endpoint with Diabetes

Adj Hazard Ratio 1.26
(95% CI 1.13-1.40)
P<0.0001

Diabetes at baseline — 17.1%

No diabetes at baseline — 13.0%

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

Months after Randomization

Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.
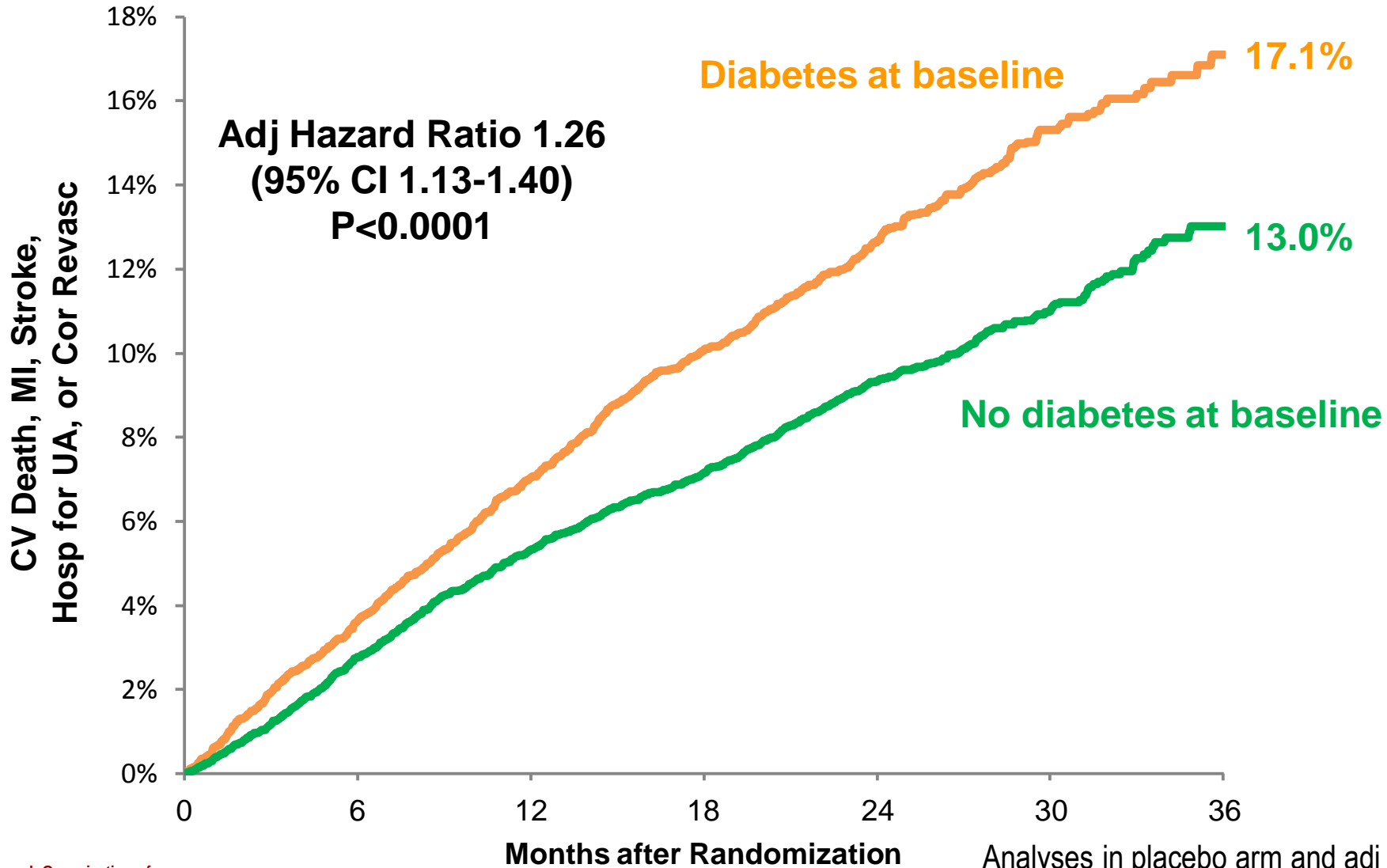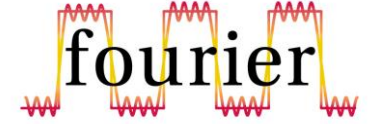
Risk of Key Secondary Endpoint in Diabetics vs Non-Diabetics

Adj Hazard Ratio 1.40
(95% CI 1.23-1.60)
P<0.0001

Diabetes at baseline — 12.2%

No diabetes at baseline — 8.4%

CV Death, MI, Stroke

Months after Randomization

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

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Effect of Evolcumab on Primary Endpoint

Patients w/ Diabetes at Baseline

Hazard Ratio 0.83
(95% CI 0.75-0.93)
P=0.0008

17.1%
14.4%

Δ 2.7%
NNT 37

Placebo

Evolocumab

Patients w/o Diabetes at Baseline

Hazard Ratio 0.87
(95% CI 0.79-0.96)
P=0.0052

13.0%
11.4%

Δ 1.6%
NNT 62

$P_{interaction}=0.60$

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

Months after Randomization

Effect of Evolocumab on Key Secondary Endpoint

Patients w/ Diabetes at Baseline

Hazard Ratio 0.82
(95% CI 0.72-0.93)
P=0.0021

Placebo

Evolocumab

12.2%

10.2%

Δ 2.0%
NNT 50

P$_{interaction}$=0.65

Patients w/o Diabetes at Baseline

Hazard Ratio 0.78
(95% CI 0.69-0.89)
P=0.0002

8.4%

6.4%

Δ 2.0%
NNT 50

CV Death, MI, Stroke

Months after Randomization
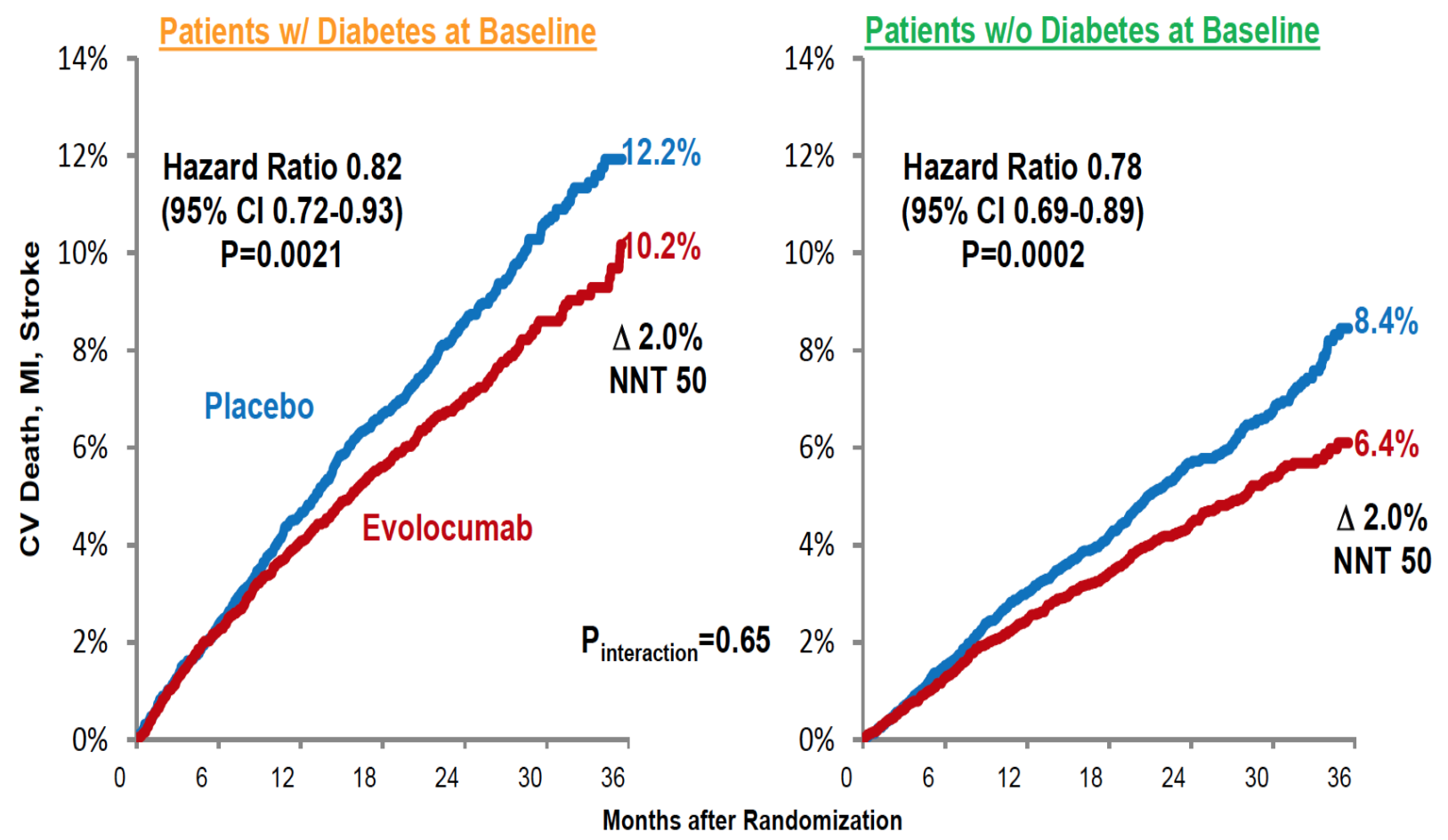
New-Onset Diabetes
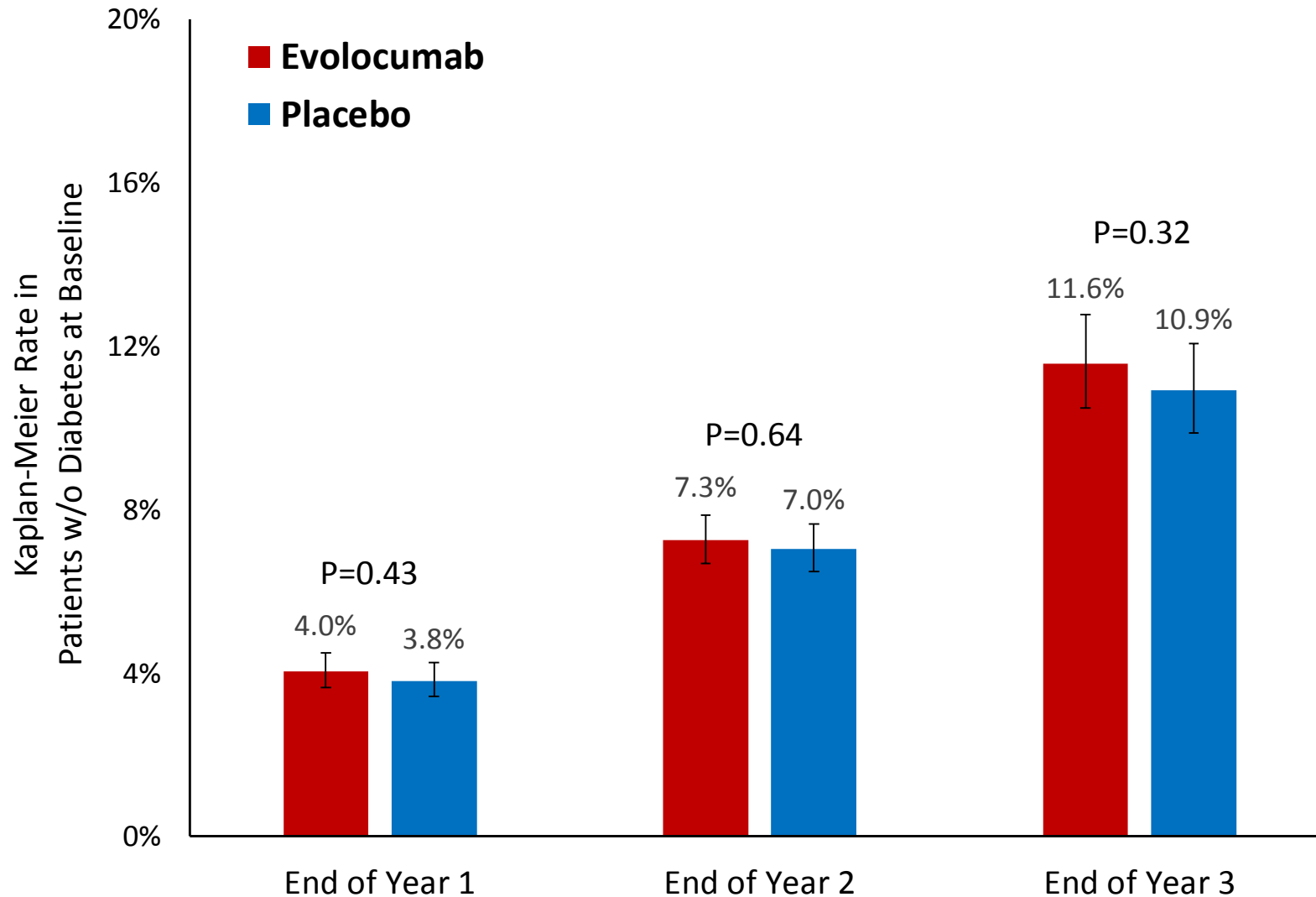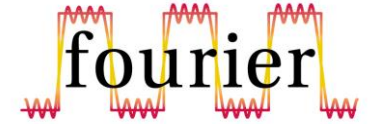
In all patients w/o diabetes at baseline (1294 incident cases in 16,510 patients):
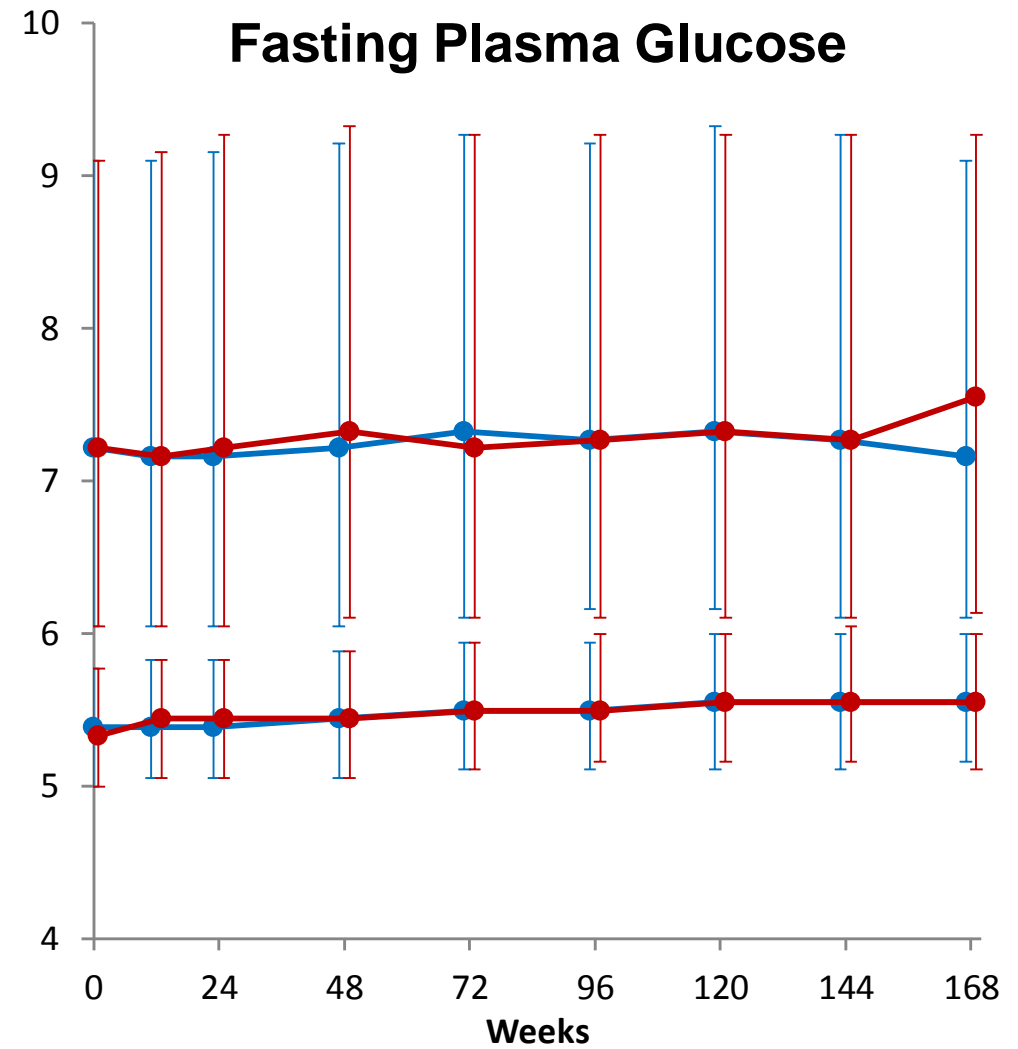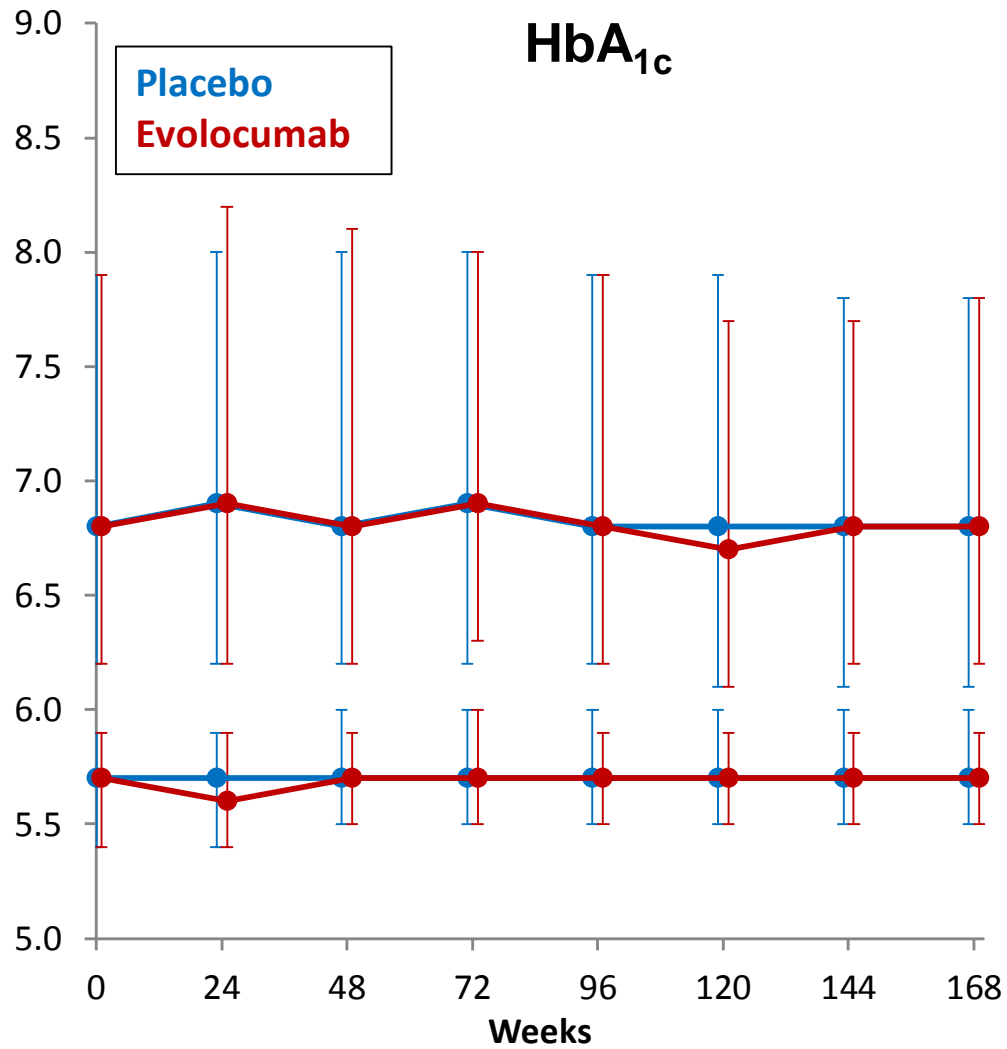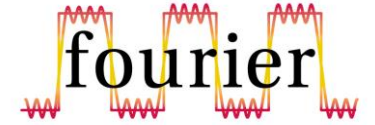
HR 1.05 (95% CI 0.94-1.17)

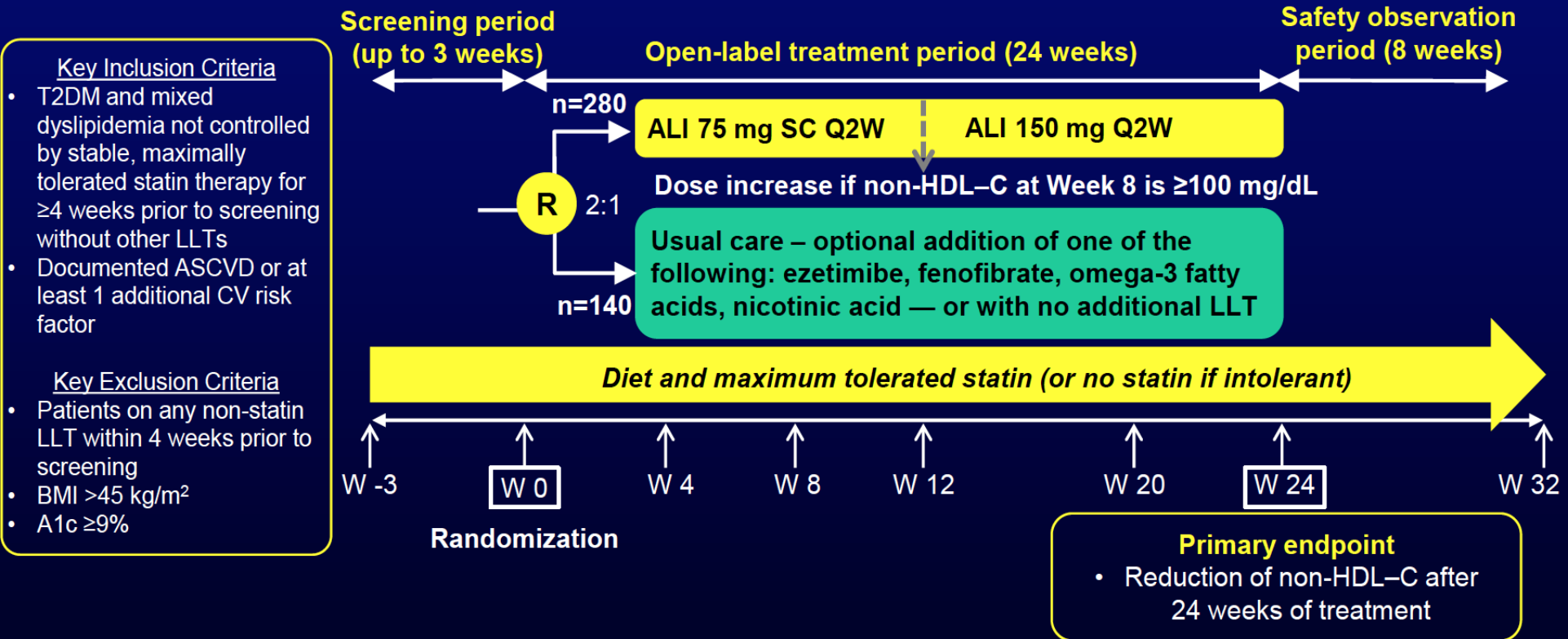In patients w/ prediabetes at baseline (1163 incident cases in 10,338 patients):

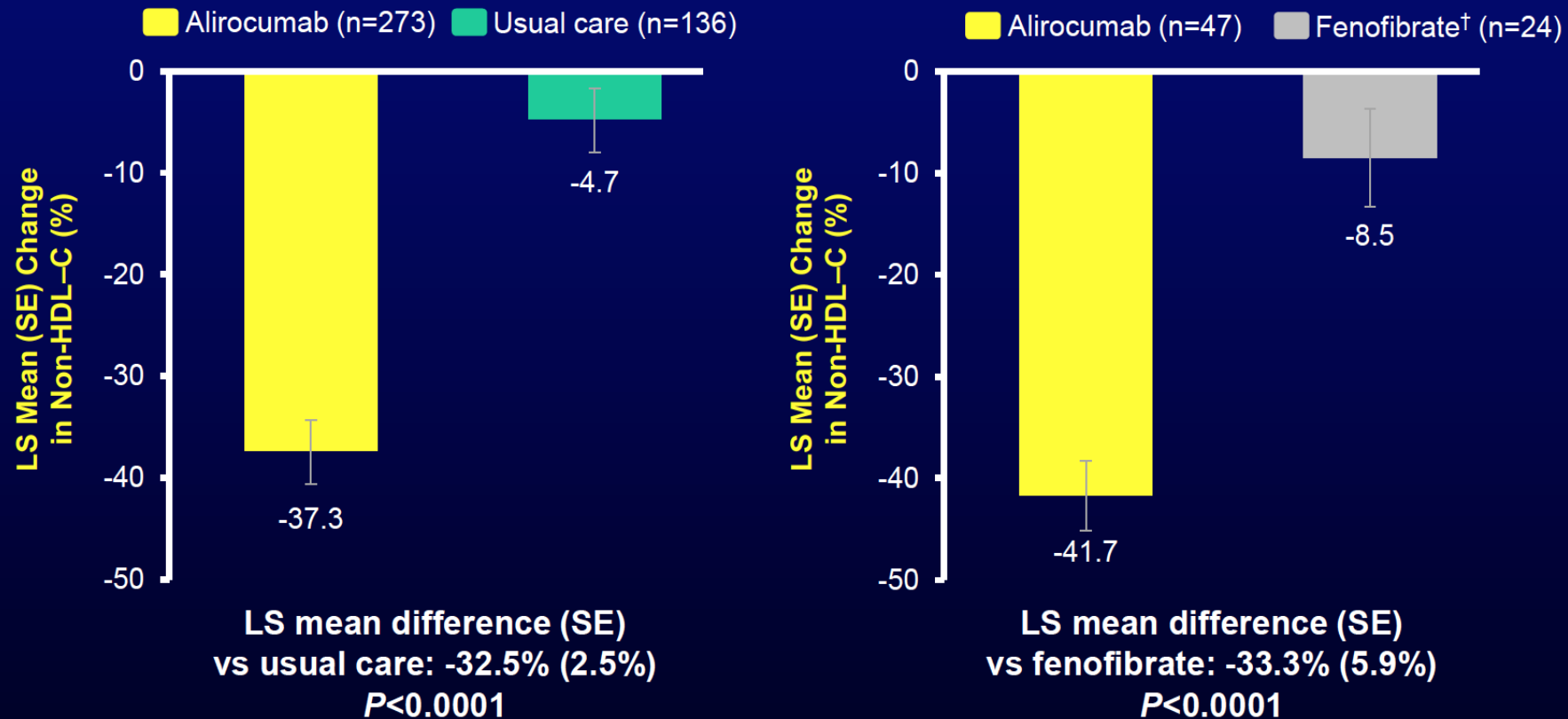**HR 1.00 (95% CI 0.89-1.13)**

ODYSSEY DM-DYSLIPIDEMIA
Study Design

- ODYSSEY DM-DYSLIPIDEMIA is a Phase 3b/4, randomized, open-label, parallel-group, multicenter, multinational clinical trial

Screening period (up to 3 weeks)

Open-label treatment period (24 weeks)

Safety observation period (8 weeks)

Key Inclusion Criteria
- T2DM and mixed dyslipidemia not controlled by stable, maximally tolerated statin therapy for ≥4 weeks prior to screening without other LLTs
- Documented ASCVD or at least 1 additional CV risk factor

Key Exclusion Criteria
- Patients on any non-statin LLT within 4 weeks prior to screening
- BMI >45 kg/m^2
- A1c ≥9%

n=280

R 2:1

ALI 75 mg SC Q2W   **ALI 150 mg Q2W**

Dose increase if non-HDL–C at Week 8 is ≥100 mg/dL

Usual care – optional addition of one of the following: ezetimibe, fenofibrate, omega-3 fatty acids, nicotinic acid — or with no additional LLT

n=140

Diet and maximum tolerated statin (or no statin if intolerant)

W -3   W 0   W 4   W 8   W 12   W 20   W 24   W 32

Randomization

Primary endpoint
- Reduction of non-HDL–C after 24 weeks of treatment

A1c=glycated hemoglobin; ALI=alirocumab; ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index; CV=cardiovascular; DM=diabetes mellitus; HDL–C=high-density lipoprotein–cholesterol; LLT=lipid-lowering therapy; Q2W=every 2 weeks; R=randomization; SC=subcutaneous; T2DM=type 2 diabetes mellitus; W=week.

Müller-Wieland D et al. *Cardiovasc Diabetol*. 2017. doi:10.1186/s12933-017-0552-4.

ODYSSEY DM-DYSLIPIDEMIA: Primary Endpoint

Percent Change in Non-HDL–C From Baseline to Week 24 (Primary Efficacy Endpoint*)

Alirocumab (n=273) Usual care (n=136)

Alirocumab (n=47) Fenofibrate[†] (n=24)

LS Mean (SE) Change in Non-HDL–C (%)

-4.7

-37.3

LS mean difference (SE) vs usual care: -32.5% (2.5%)
P<0.0001

-8.5

-41.7

LS mean difference (SE) vs fenofibrate: -33.3% (5.9%)
P<0.0001

* Intent-to-treat, mixed-effect model with repeated measures analysis. [†] Intent to prescribe.
DM=diabetes mellitus; HDL–C=high-density lipoprotein–cholesterol; LS=least squares; SE=standard error.

Alirocumab versus usual care in type 2 diabetes with mixed dyslipidemia – the ODYSSEY DM-DYSLIPIDEMIA study.
Presented at: European Association for the Study of Diabetes; 2017; Lisbon, Portugal.

Odyssey Outcomes Diabetic Sub-Study
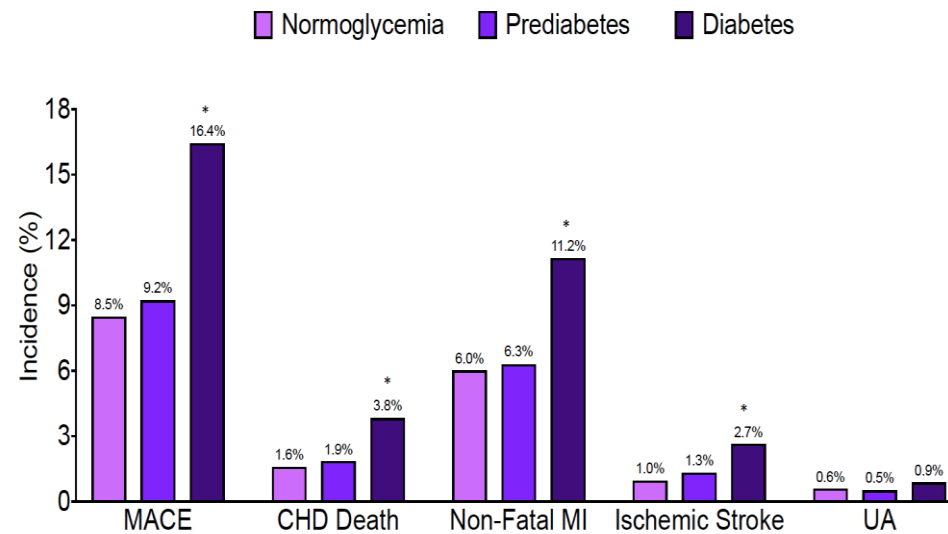

Lipids at 16 Weeks After Randomization*
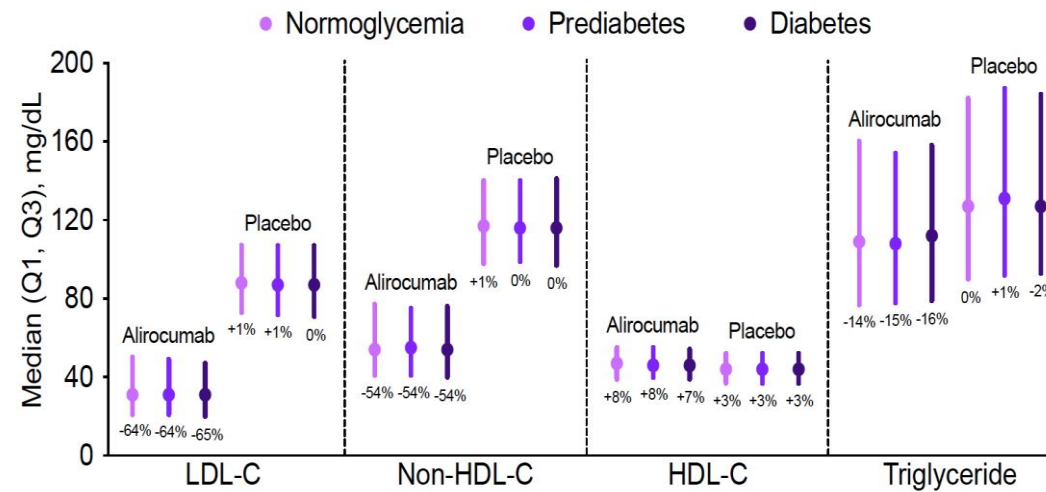
Median percent change from baseline presented below each bar
*Intention-to-treat analysis

Abstract Presentation ADA 2018

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Odyssey Outcomes Diabetic Sub-Study

ADA18

Incidence of CV Events in *Placebo Group* was Greater in Patients With vs Without Diabetes

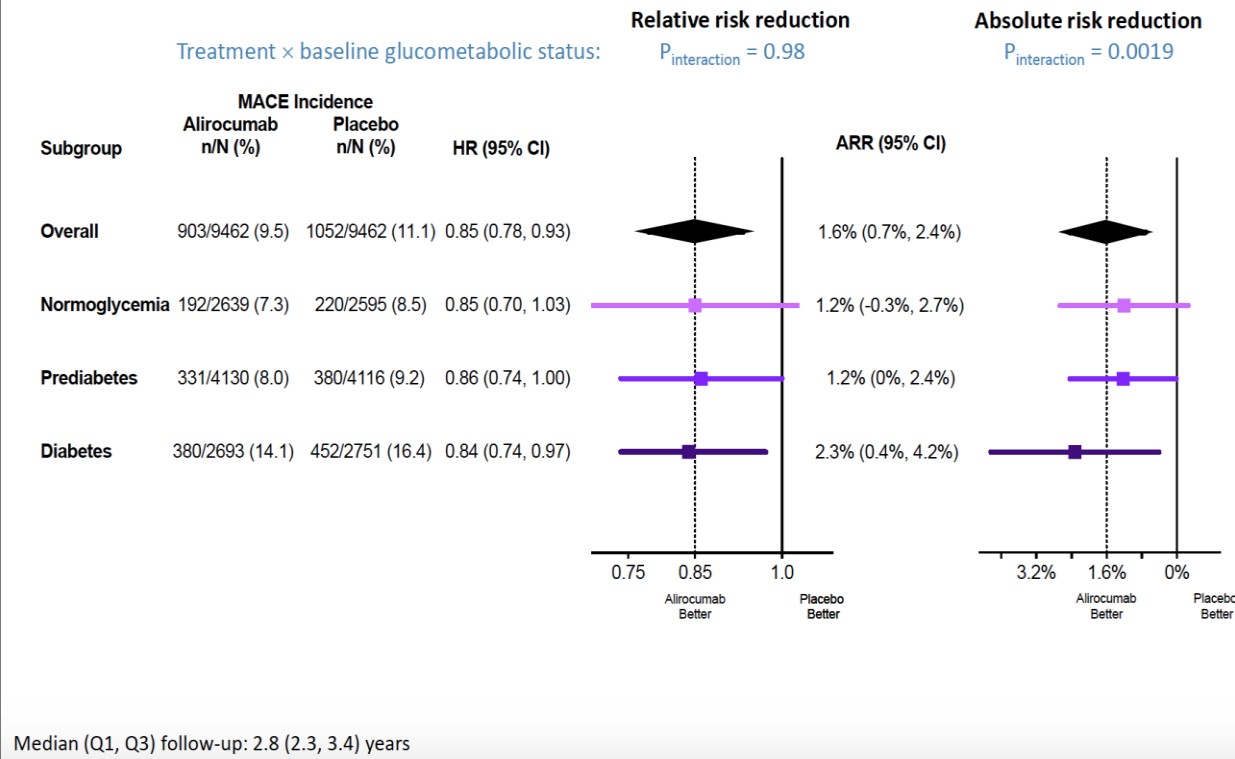Legend: Normoglycemia | Prediabetes | Diabetes

Median (Q1, Q3) follow-up: 2.8 (2.3, 3.4) years
*P<0.0001 for comparison of hazard in people with diabetes vs that in people with normoglycemia or prediabetes

Abstract Presentation ADA 2018

Odyssey Outcomes Diabetic Sub-Study

Relative and Absolute Risk Reduction with Alirocumab By Glucometabolic Status

Conclusions

➢ **LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i (<< 1 mM)**

➢ **A strong progressive relationship of achieved LDL-C and CV events seen in pts with DM**

➢ **No increase in NODM or changes in HgA1c with PCSK9i**

These data suggest that we should target considerably lower LDL-C than is currently recommended for our patients with DM and atherosclerotic CV disease to get Maximum CV Protection