Weigh the benefit of statin treatment: LDL & Beyond

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FOURIER

Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

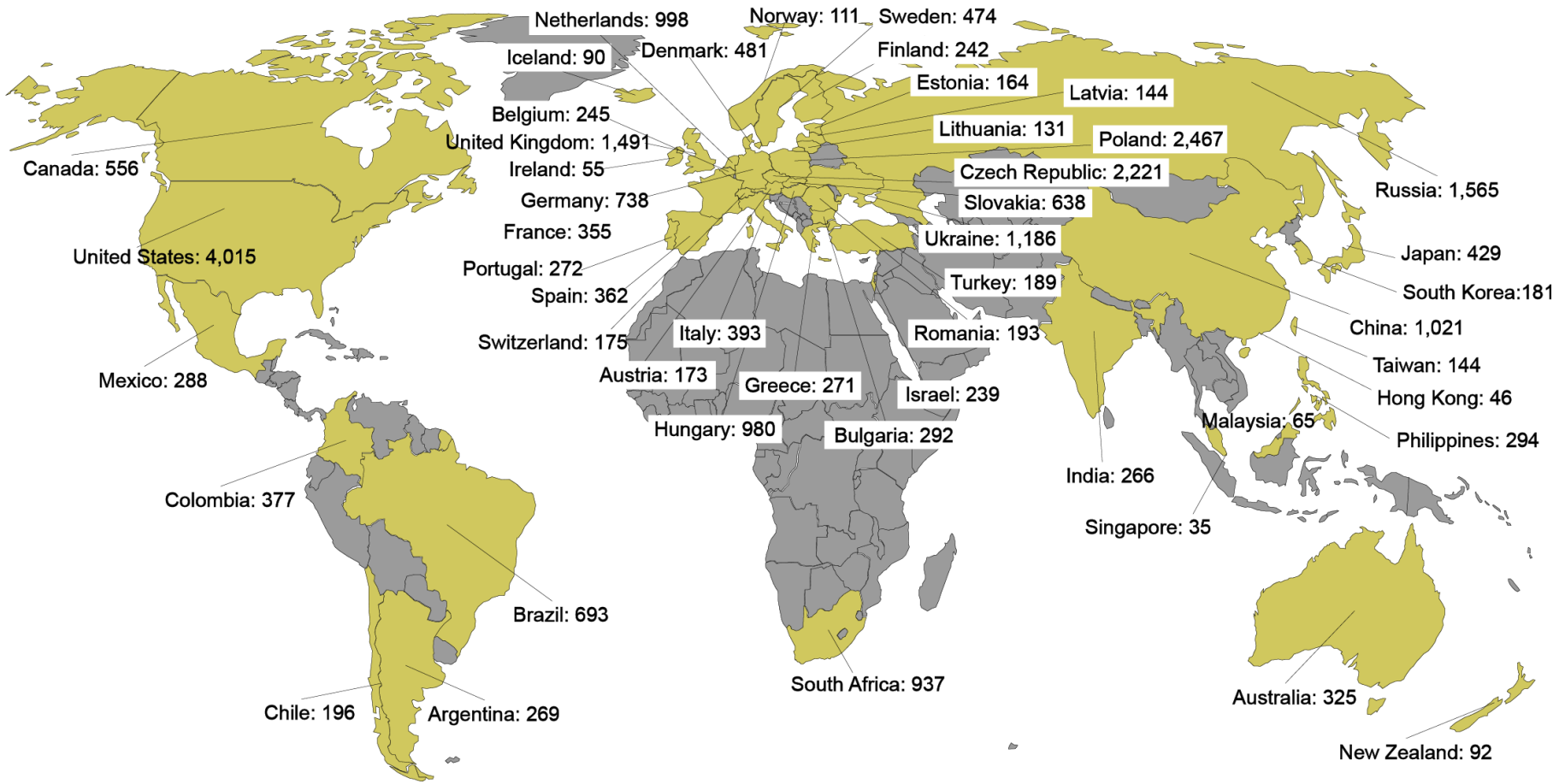
MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017

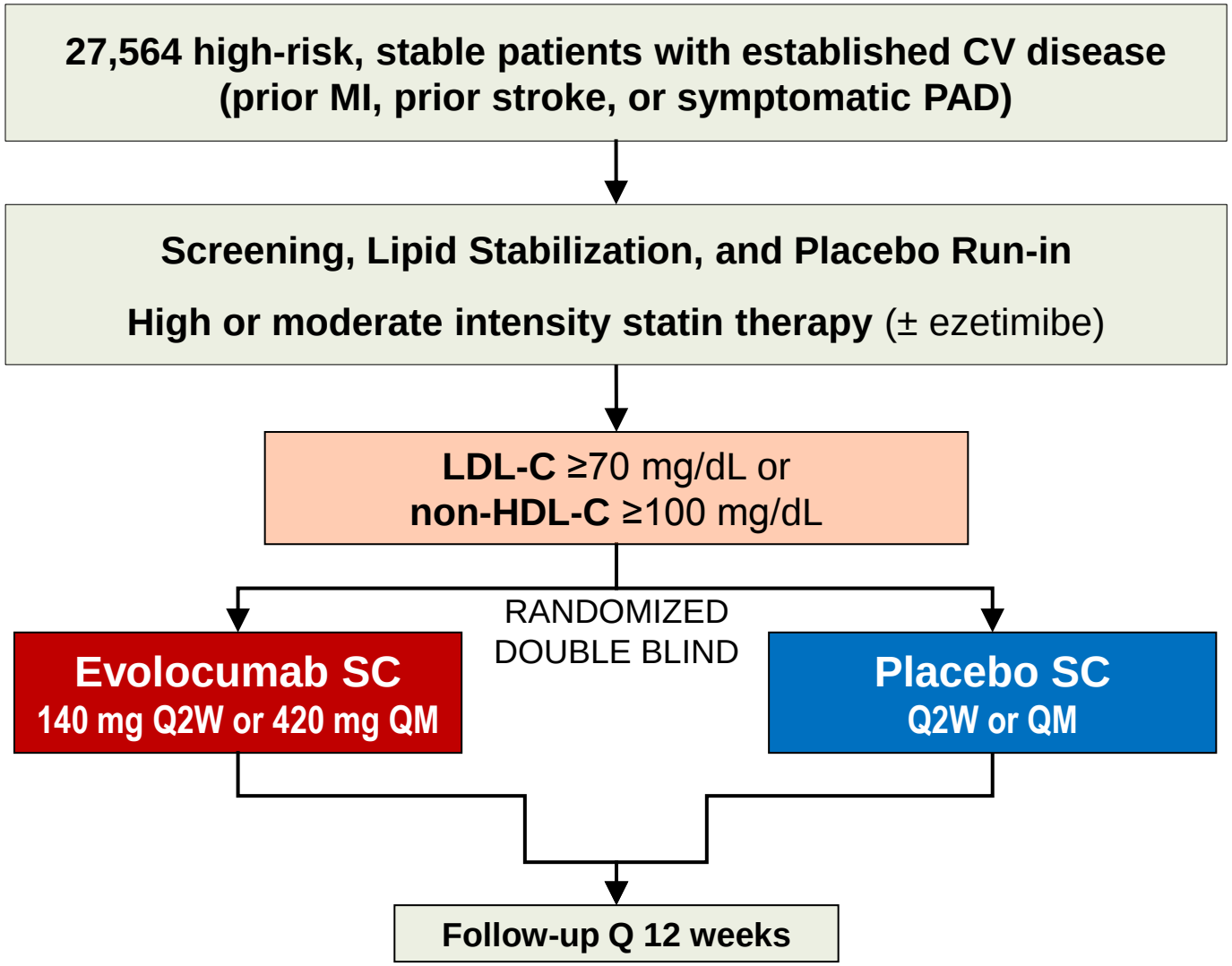
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Global Enrollment

27,564 patients randomized at 1242 sites
in 49 countries between 2/2013 – 6/2015



Trial Design



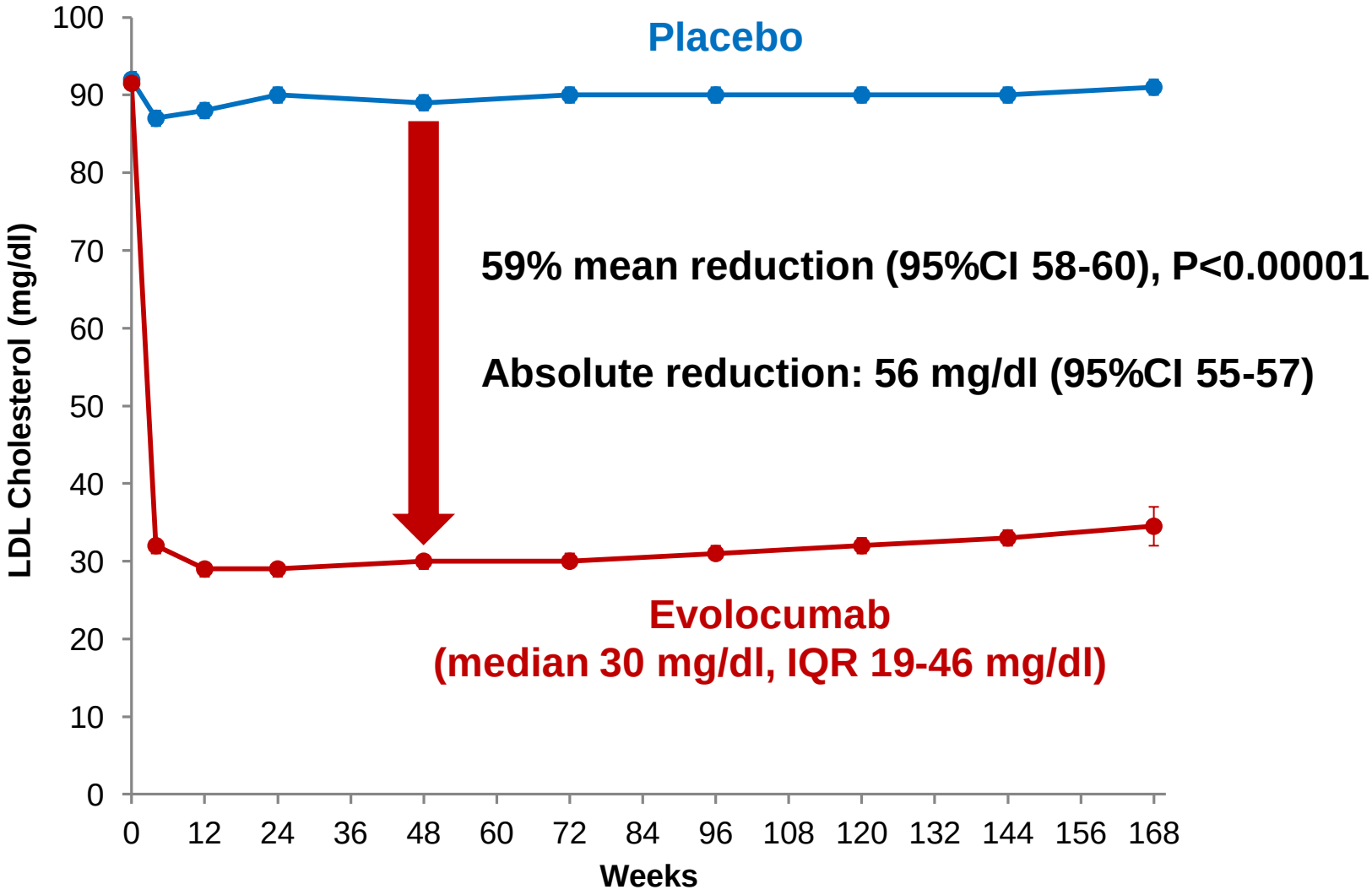
Sabatine MS et al. *Am Heart J* 2016;173:94-101

Endpoints

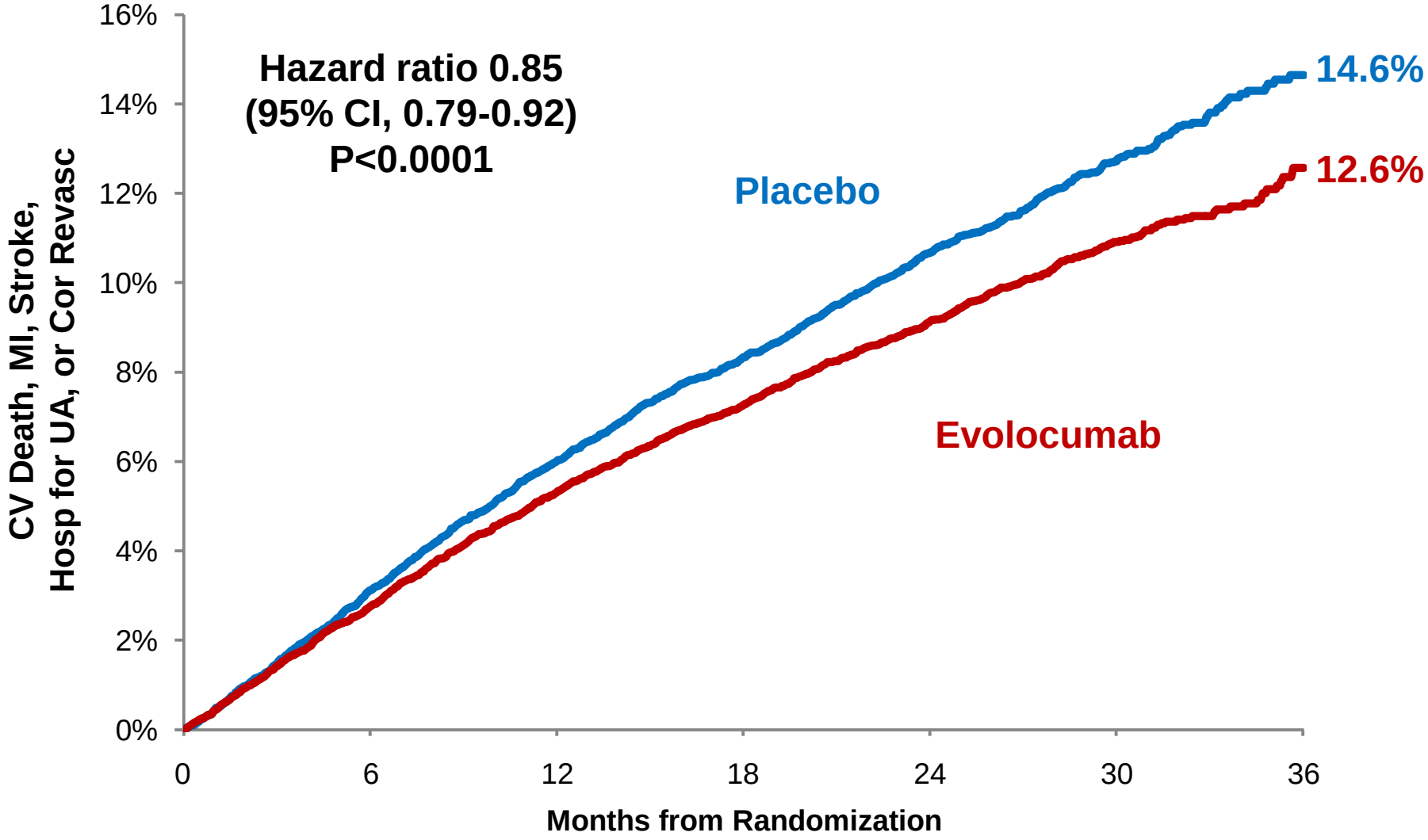
- **Efficacy**
  - **Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc**
  - **Key secondary: CV death, MI or stroke**
- **Safety**
  - **AEs/SAEs**
  - **Events of interest incl. muscle-related, new-onset diabetes, neurocognitive**
  - **Development of anti-evolocumab Ab (binding and neutralizing)**
- **TIMI Clinical Events Committee (CEC)**
  - **Adjudicated all efficacy endpoints & new-onset diabetes**
  - **Members unaware of treatment assignment & lipid levels**

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

LDL Cholesterol



Primary Endpoint

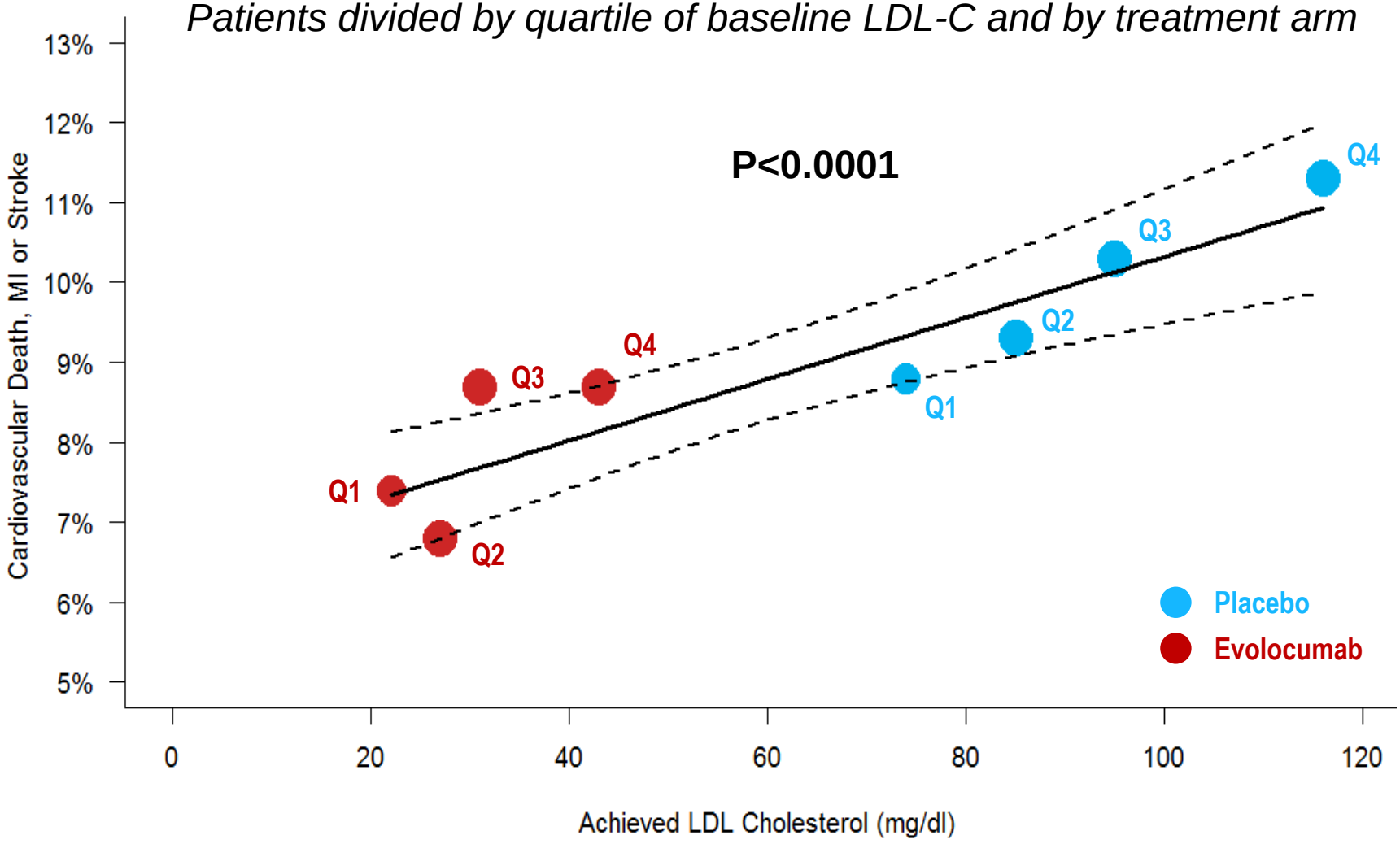


Types of CV Outcomes

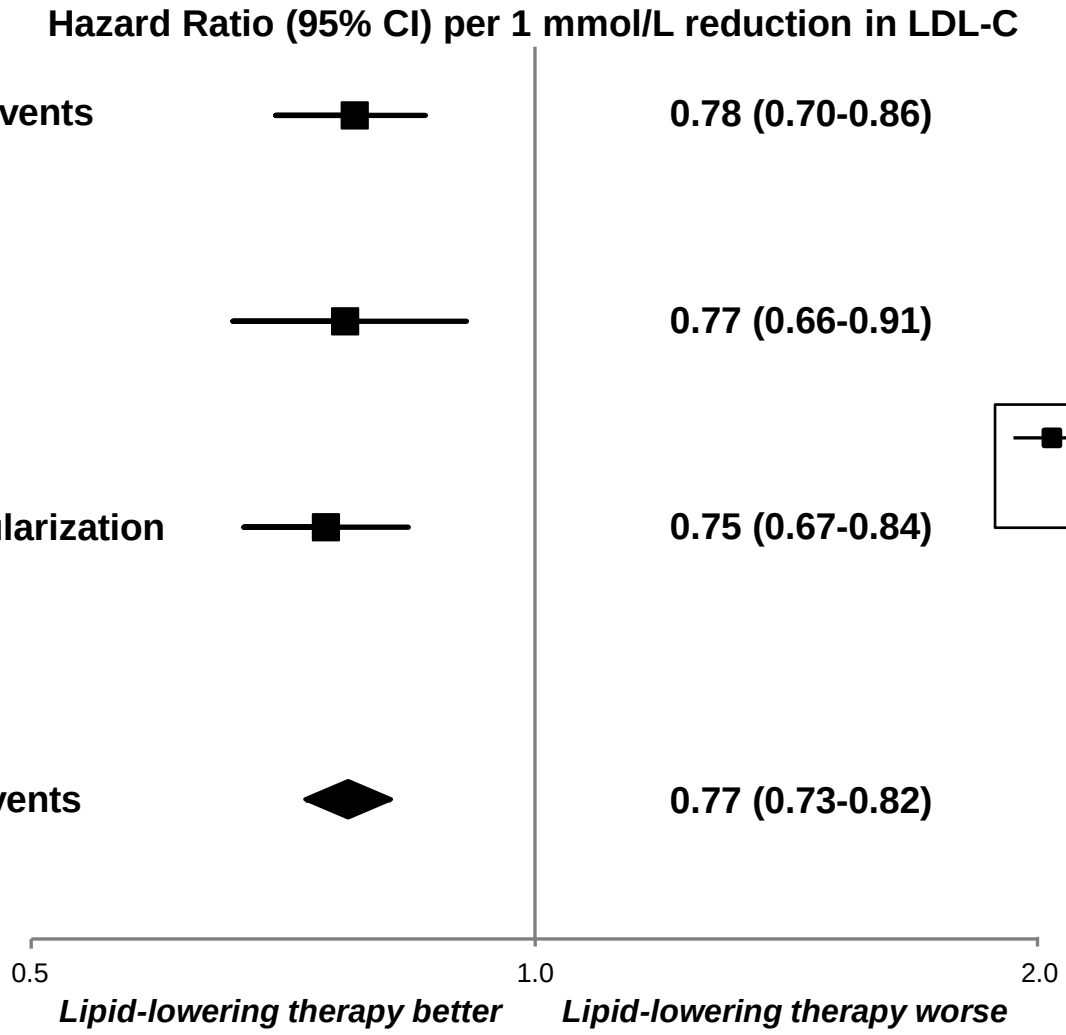
Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc	**12.6**	**14.6**	**0.85 (0.79-0.92)**
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**
Hosp for unstable angina	**2.2**	**2.3**	**0.99 (0.82-1.18)**
Coronary revasc	**7.0**	**9.2**	**0.78 (0.71-0.86)**
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	**4.8**	**4.3**	**1.04 (0.91-1.19)**

Lower LDL-C Is Better

Patients divided by quartile of baseline LDL-C and by treatment arm



Comparison to Cholesterol Treatment Trialists Collaboration



CTTC data from *Lancet* 2010;376:1670-81

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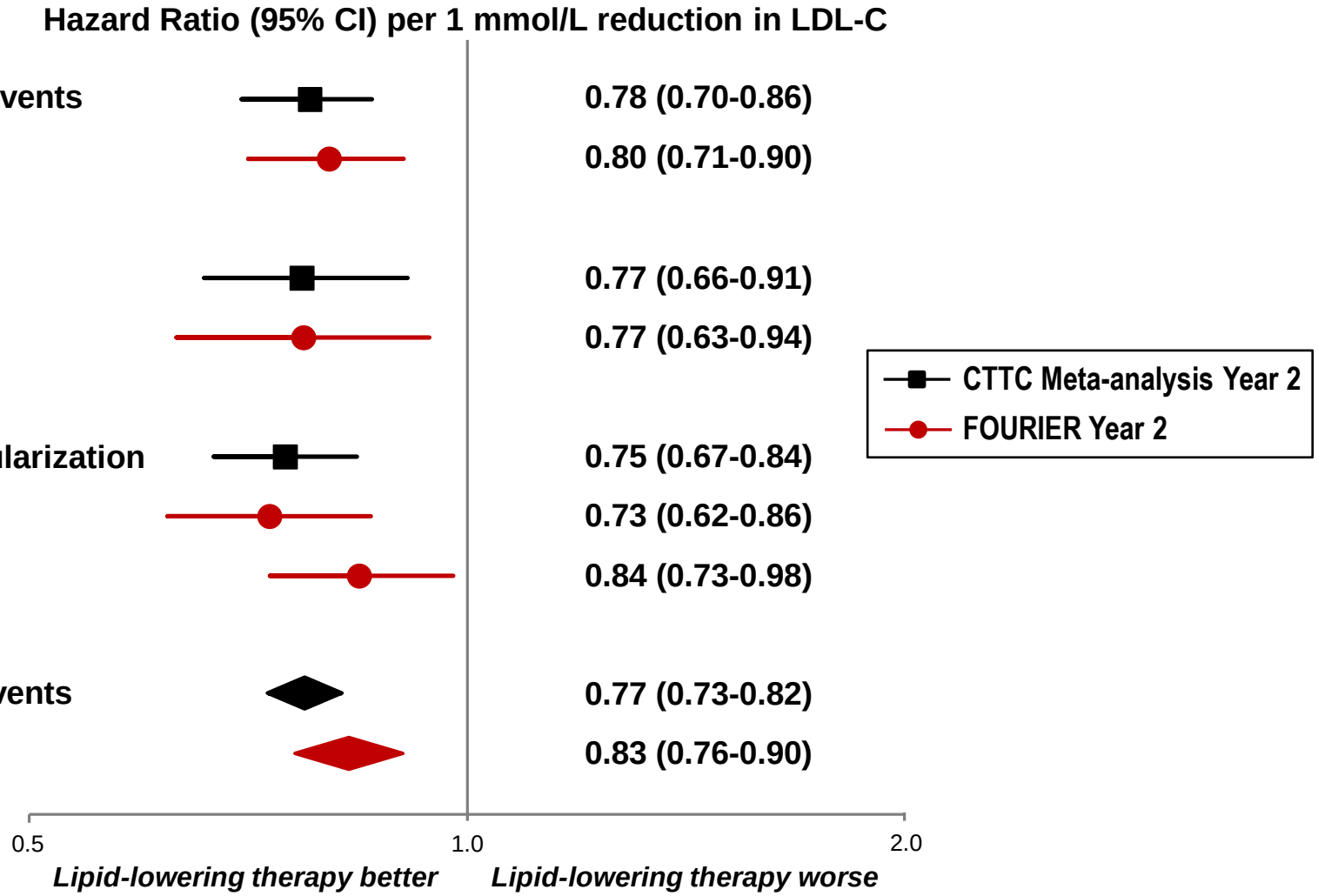


CTTC data from *Lancet* 2010;376:1670-81

Safety

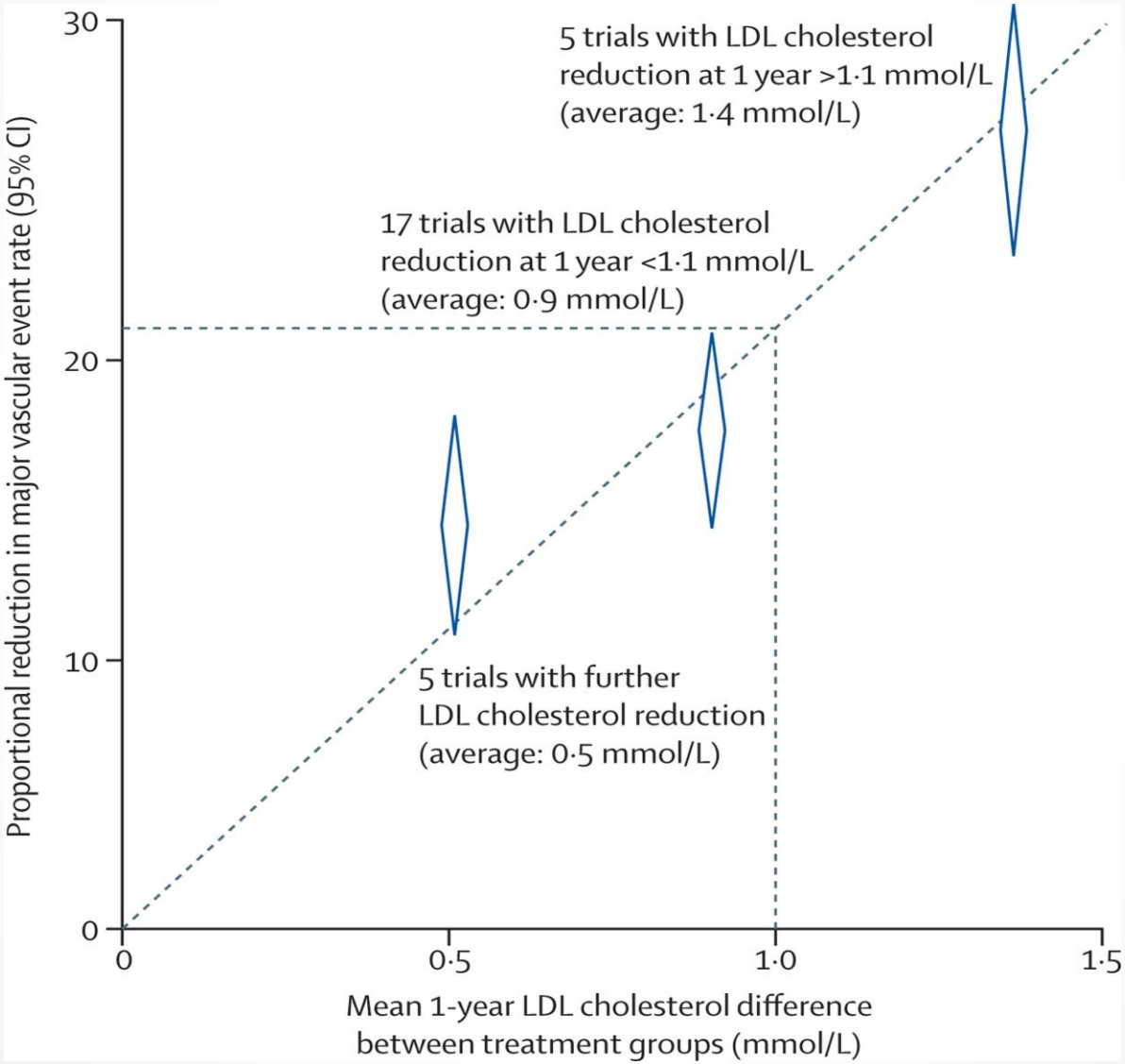
	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related and led to d/c of study drug	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC

Summary for Evolocumab

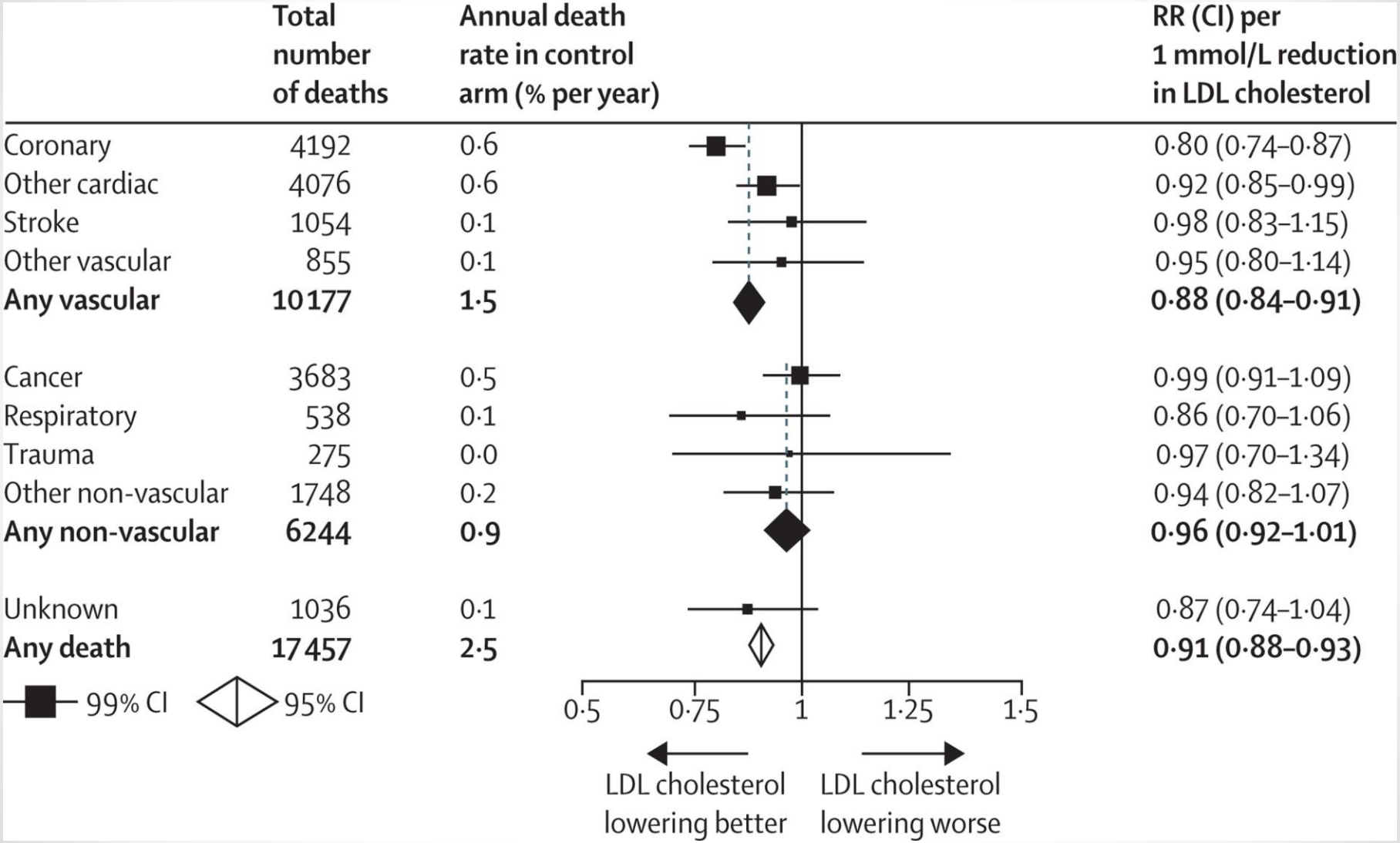
- **↓ LDL-C by 59%**
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)
- **↓ CV outcomes in patients already on statin therapy**
  - 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C
- **Safe and well-tolerated**
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed

LDL-C Reduction with Statins and CV Event Reduction



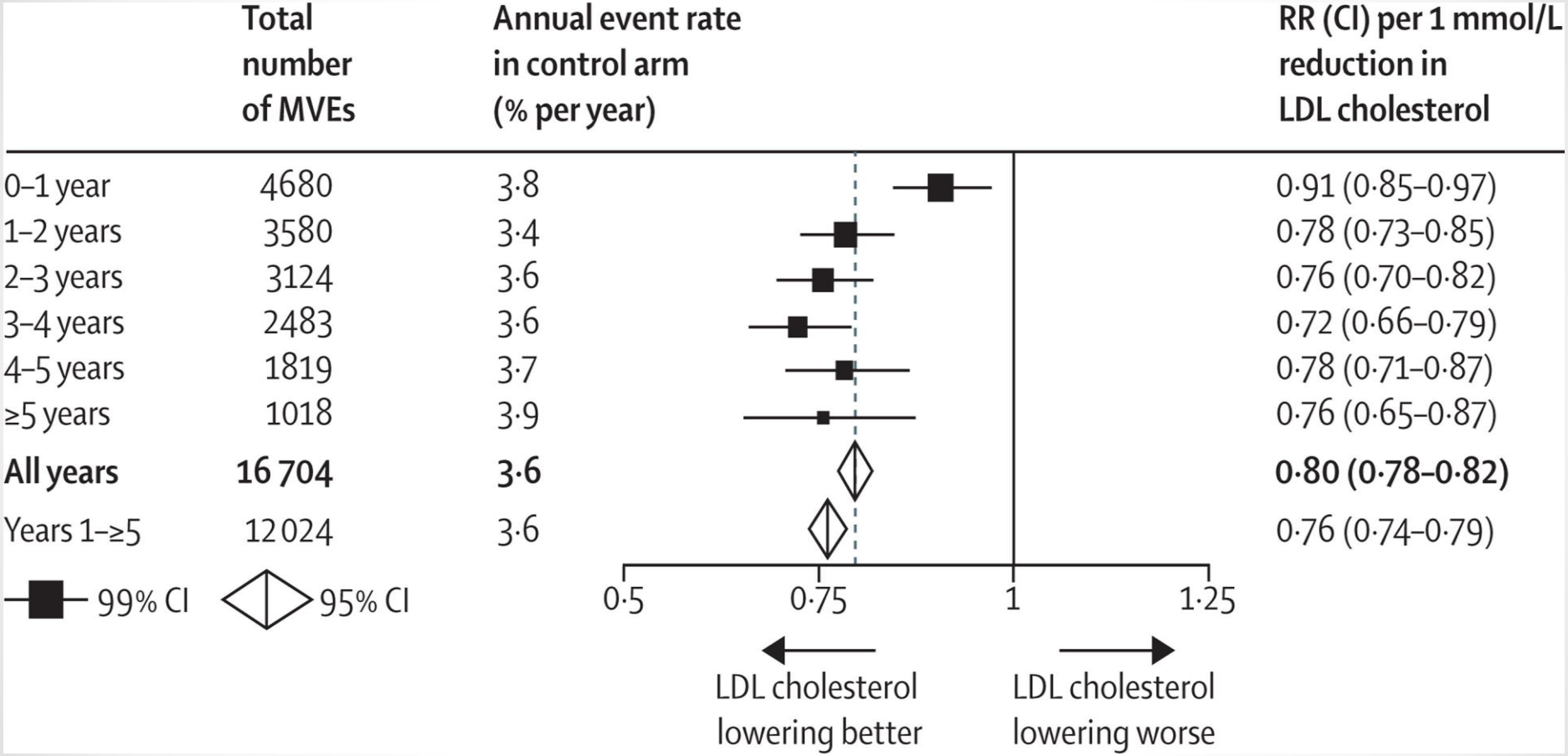
Collins R et al, *Lancet* epub Sept 9, 2016

Effect of LDL-C Lowering With Statins on Cause-Specific Mortality



Collins R et al, *Lancet* epub Sept 9, 2016

Reduction in CV Events Per Year of Statin Treatment



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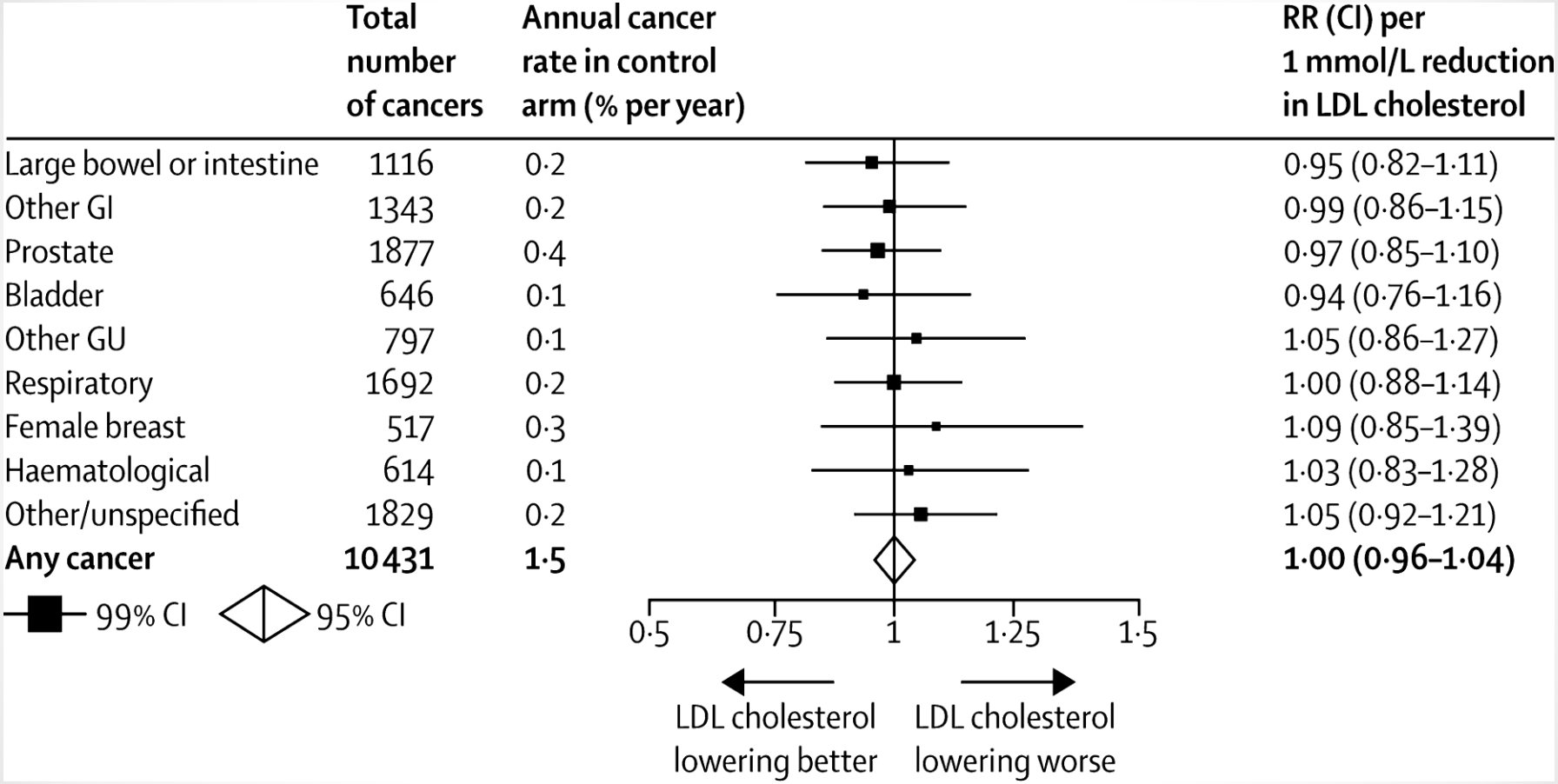
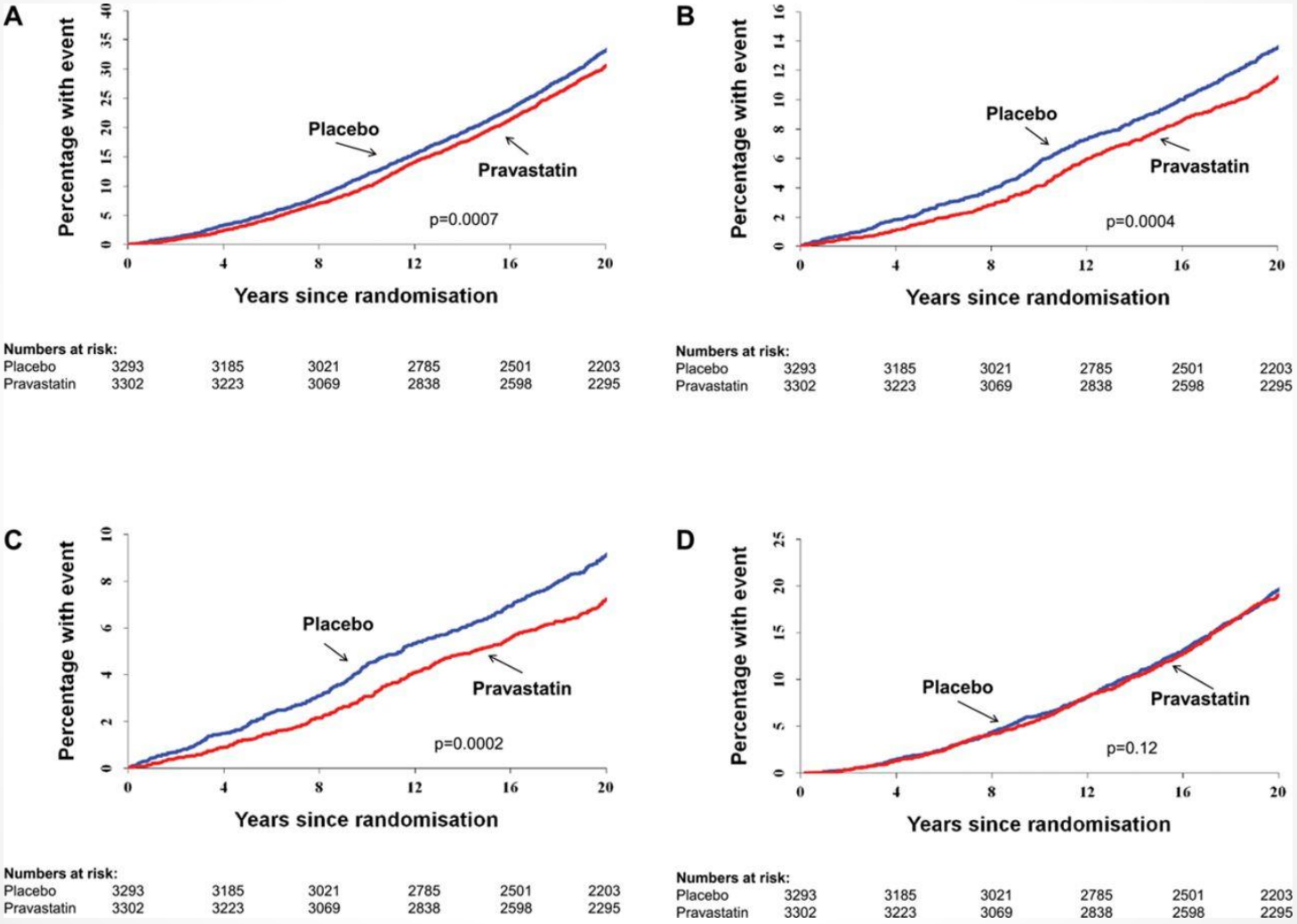
Effect of LDL-C Lowering With Statins on Cancer Incidence



Collins R et al, *Lancet* epub Sept 9, 2016

West of Scotland Study: 20-Year Follow-Up

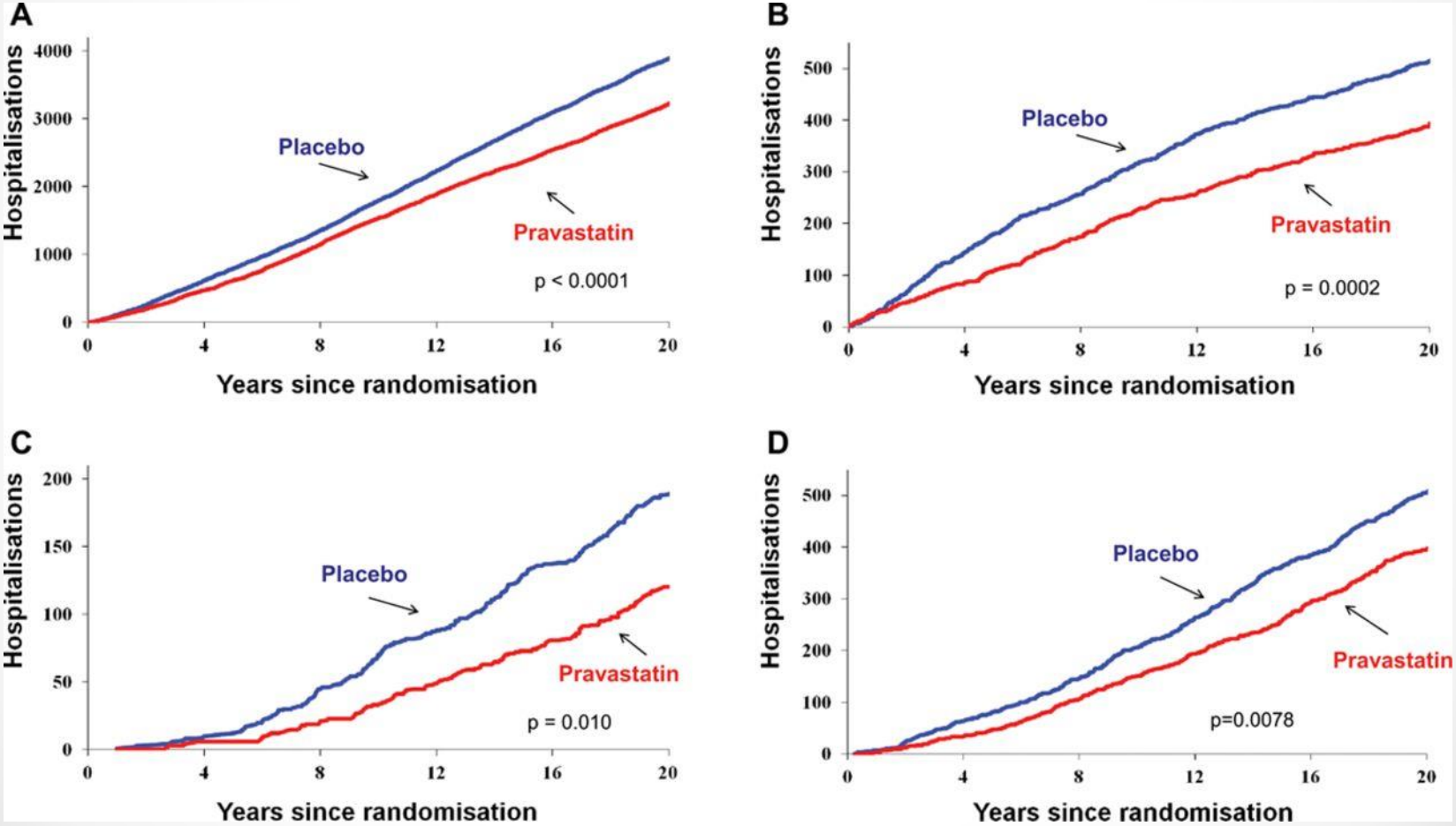
Mortality: (A) All Cause, (B) CV, (C) CHD, and (D) Non-CVD



Ford I et al, *Circulation* 2016;133:1073-80

West of Scotland Study: 20-Year Follow-Up

Cumulative hospitalizations for (A) CV disease, (B) MI, (C) heart failure, and (D) coronary revascularization

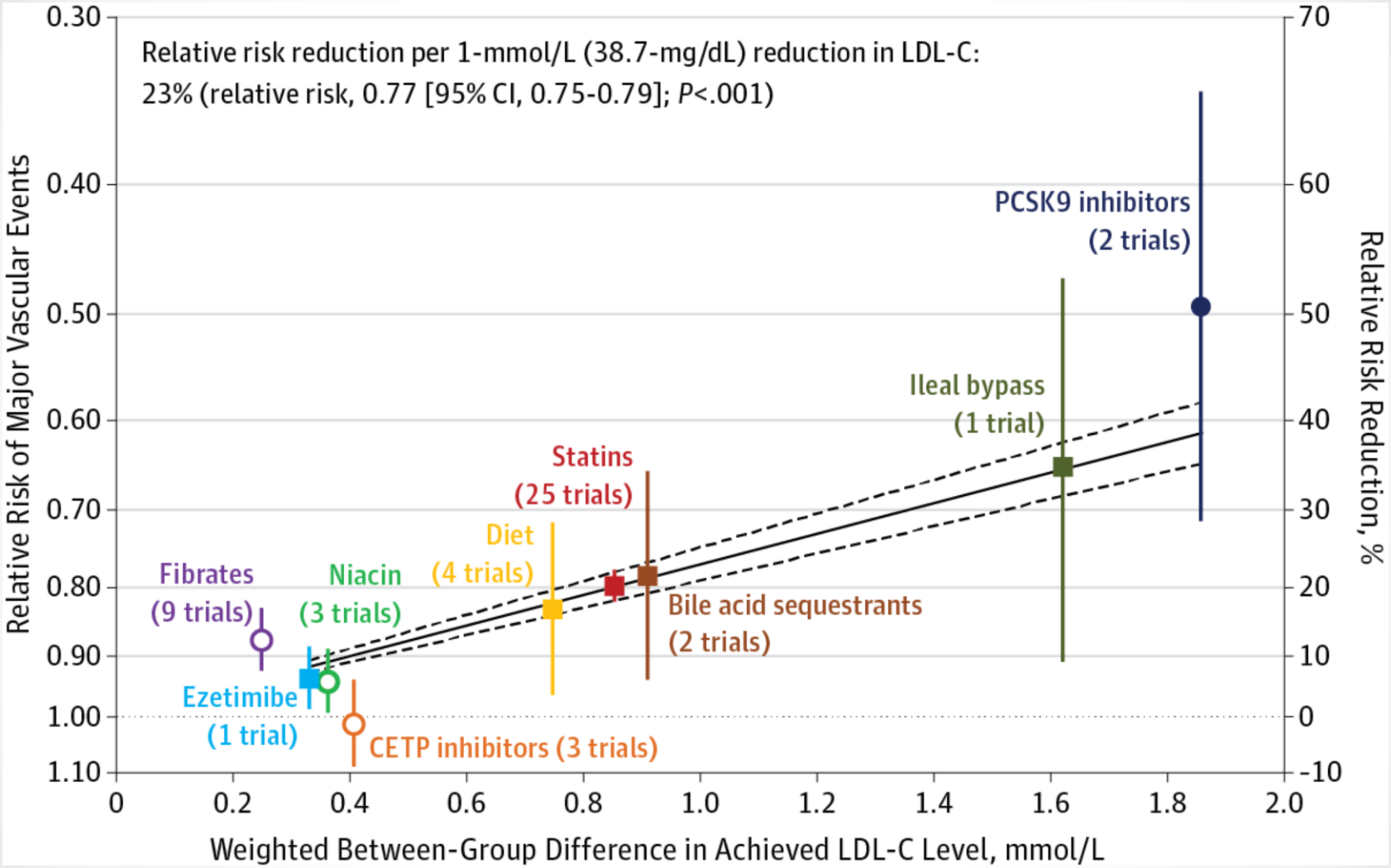


Ford I et al, *Circulation* 2016;133:1073-80

CV Event Reduction with Statins…

- **is proportional to LDL-C reduction**
- applies to a broad population
- is independent of baseline LDL-C
- is independent of baseline risk

LDL-C Lowering Drugs And CV Event Reduction



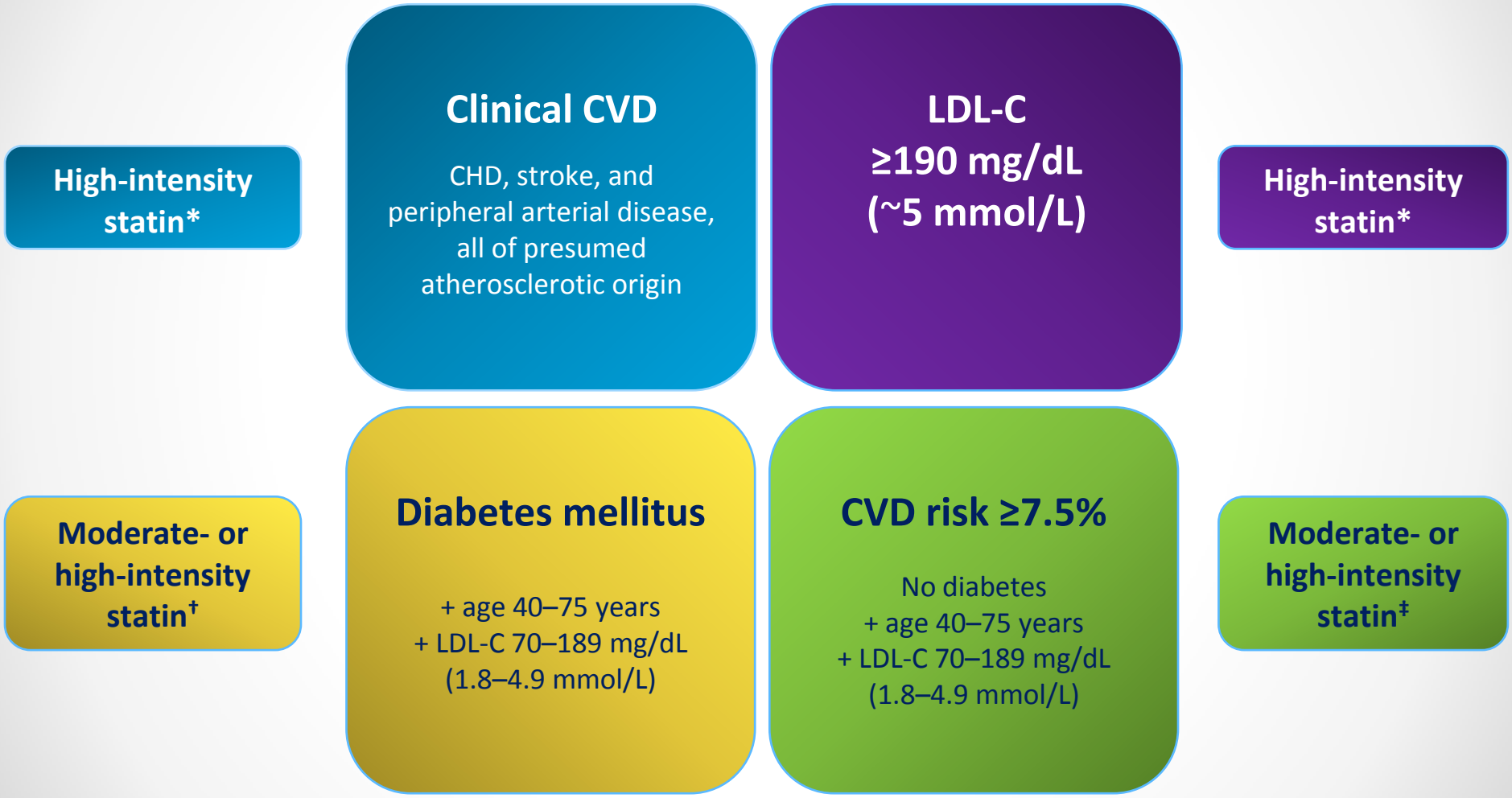
Silverman MG et al, *JAMA* 2016;316:1289-97

2016 European Guidelines

- Non-fasting blood samples allowed for screening
- *"lowering LDL-C beyond the goals that were set in the previous EAS/ESC guidelines is associated with fewer CV events. Therefore,* ***it seems appropriate to reduce LDL-C as low as possible, at least in patients at very high CV risk"***
- LDL-C targets include 50% reduction; so, for an untreated very high-risk patient with LDL-C 1.8-3.5 mmol/L, or an untreated high-risk patient with LDL-C 2.6-5.2 mmol/L, the new goal is a 50% LDL-C reduction
- Consider adding ezetimibe if target is not reached with highest tolerated statin dose (2b➔2a evidence)
- Consider adding a PCSK9 inhibitor for patients at very high risk with persistently high LDL-C despite therapy

Eur Heart J 2016, published on-line August 27, 2016

2014 ACC/AHA guidelines



- *Moderate intensity for selected patients
- †High intensity if ASCVD risk ≥7.5%
- ‡Choice according to individual patient factors

- Stone NJ, et al. J Am Coll Cardiol 2014;63:2889–2934

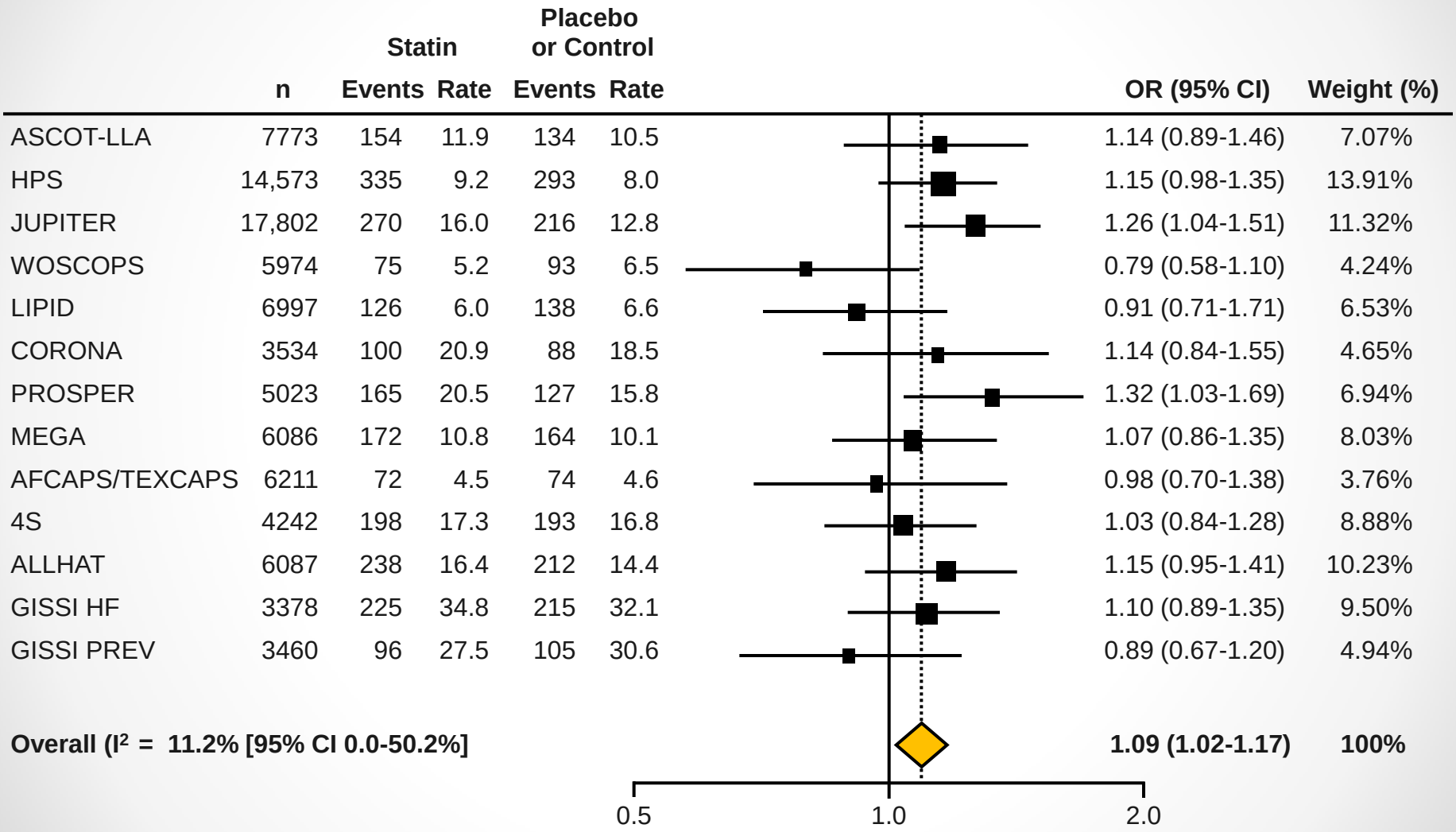
Intensity of Statin Therapy

High	Moderate	Low
LDL-C ≥50%	LDL-C 30 to <50%	LDL-C <30%
Atorva 40-80 mg **Rosuva 20-40 mg**	Atorva 10 mg Rosuva 10 mg Simva 20-40 mg Pravas 40 mg Lova 40 mg Fluva XL 80 mg Fluva 40 mg bid Pitava 2-4 mg	Simva 10 mg Prava 10-20 mg Lova 20 mg Fluva 20-40 mg Pitava 1 mg

Statins in bold were evaluated in randomized controlled trials; those in italics were not

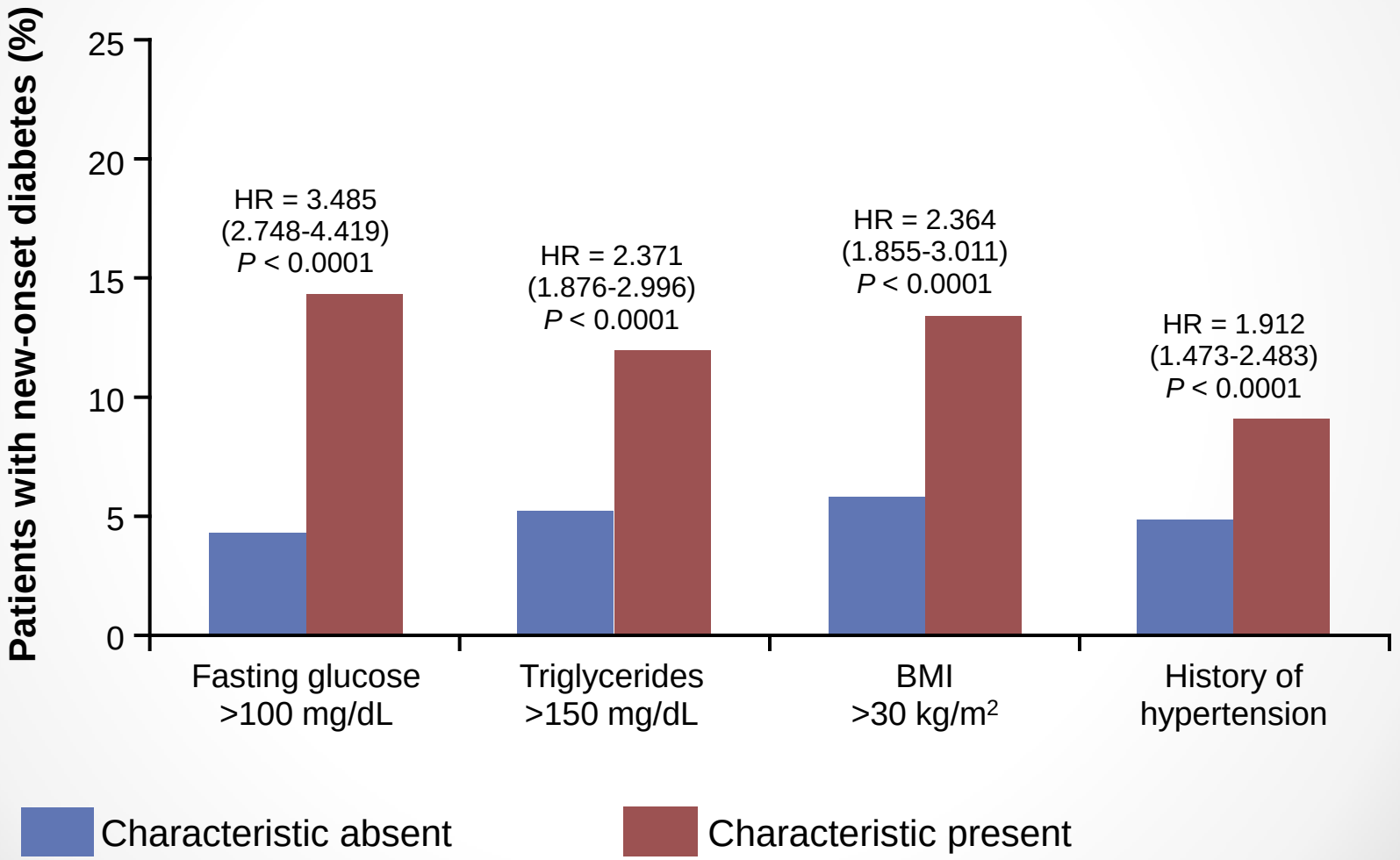
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, p 34

Statin Therapy and Incident Diabetes



Sattar N et al. *Lancet* 2010;375:735-42

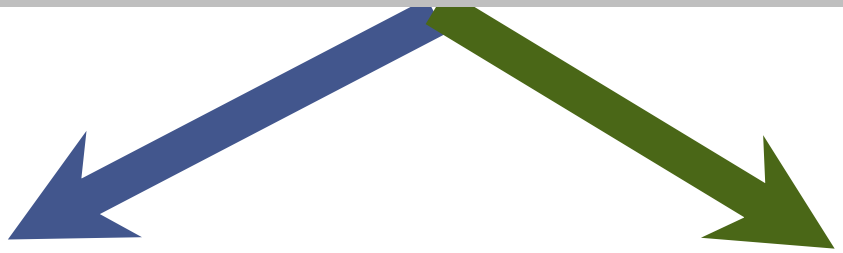
Incident Diabetes in the SPARCL Trial According to Baseline Clinical Predictors



Waters DD et al. *JACC* 2011;57:1535-45

Side effects vs CVD Risk Reduction by Statin Tx

10,000 patients treated by
Atorvastatin 40mg for 5 years



LDL-C 77mg/dL ↓
then, 10% for secondary prevention ↓
5% for primary prevention ↓
of vascular disease

0.05% case of Myopathy
1~0.5% Case of DM onset
0.1~0.05% Case of Hemorrhagic stroke

"Concern that exaggerated claims about side-effect rates with statin therapy may be responsible for its under-use among individuals at increased risk of cardiovascular events."

Collins R et al, *Lancet* 2016, epub Sept 8

Atorvastatin: Clinical Trials

Successful Trials

AVERT - ACS
MIRACL - ACS
CARDS - diabetes
ASCOT-LLA - hypertension
PROVE-IT – ACS
GREACE - CAD*
ALLIANCE – managed care
TNT – stable CAD
SPARCL – stroke/TIA

Unsuccessful Trials

ASPEN – diabetes*
4D – diabetes + dialysis
IDEAL – post-MI**
LEADe – Alzheimer's dementia

* Poor trial design
** Mainly positive endpoints

Safety of Atorvastatin 80 mg in Clinical Trials

	Follow-up	Patients	↑ALT/AST >3x ULN*	↑CK >10x ULN*
Newman et al+	variable	4,798	26 (0.6%)	2 (0.06%)
PROVE-IT	2 years	2,099	69 (3.3%)	NA
TNT	4.9 years	4,995	60 (1.2%)	0
IDEAL	4.8 years	4,439	61 (1.38%)	0
SPARCL	4.9 years	2,365	51 (2.2%)	2 (0.08%)
Total	variable	18,696	267 (1.43%)	4 (0.021%)

How Safe Is Atorvastatin in Asians?

- 67,637 patients in 55 atorvastatin trials included only 2,445 Asians
- No increased incidence of adverse events in Asians
- No case of rhabdomyolysis observed in atorvastatin-treated Asian patients
- Myalgias were reported by 2.3% of Asians (57 of 2,445) and 5.0% of non-Asians (2,235 of 44,793)
- The incidence of elevated hepatic enzymes was similar in Asians and non-Asians
- CAVEAT: only 106 Asian patients took the 80 mg dose
- CONCLUSION: safety profile of atorvastatin 10–80 mg is similar in Asians and non-Asians.

Chen J et al, from the 23rd Great Wall International Congress of Cardiology & the Asia Pacific Heart Congress, October, 2012; Beijing, China

Conclusions

- Newer guidelines (ESC, ACC/AHA and NICE) recommend that statins should be offered to a wider range of patients at risk
- High-intensity statin treatment is recommended for most patients and moderate-intensity for the rest
- Use statins to treat risk, not cholesterol
- Benefit outweights over the harm
- Atorvastatin reduced CV events in 9 trials covering a broad spectrum of patients, and is safe at the 80 mg dose (albeit with limited data in Asians)