היפרליפידמיה בנשים בעידן החדש – מניעה ראשונית ומשנית

ד"ר רפי ביצור

מרכז שטרסבורגר לליפידים

המרכז הרפואי ע"ש שיבא, תל-השומר

Women and Men are Different…
But Also Have a Lot in Common

AHA Scientific Statement

Preventing and Experiencing Ischemic Heart Disease as a Woman: State of the Science

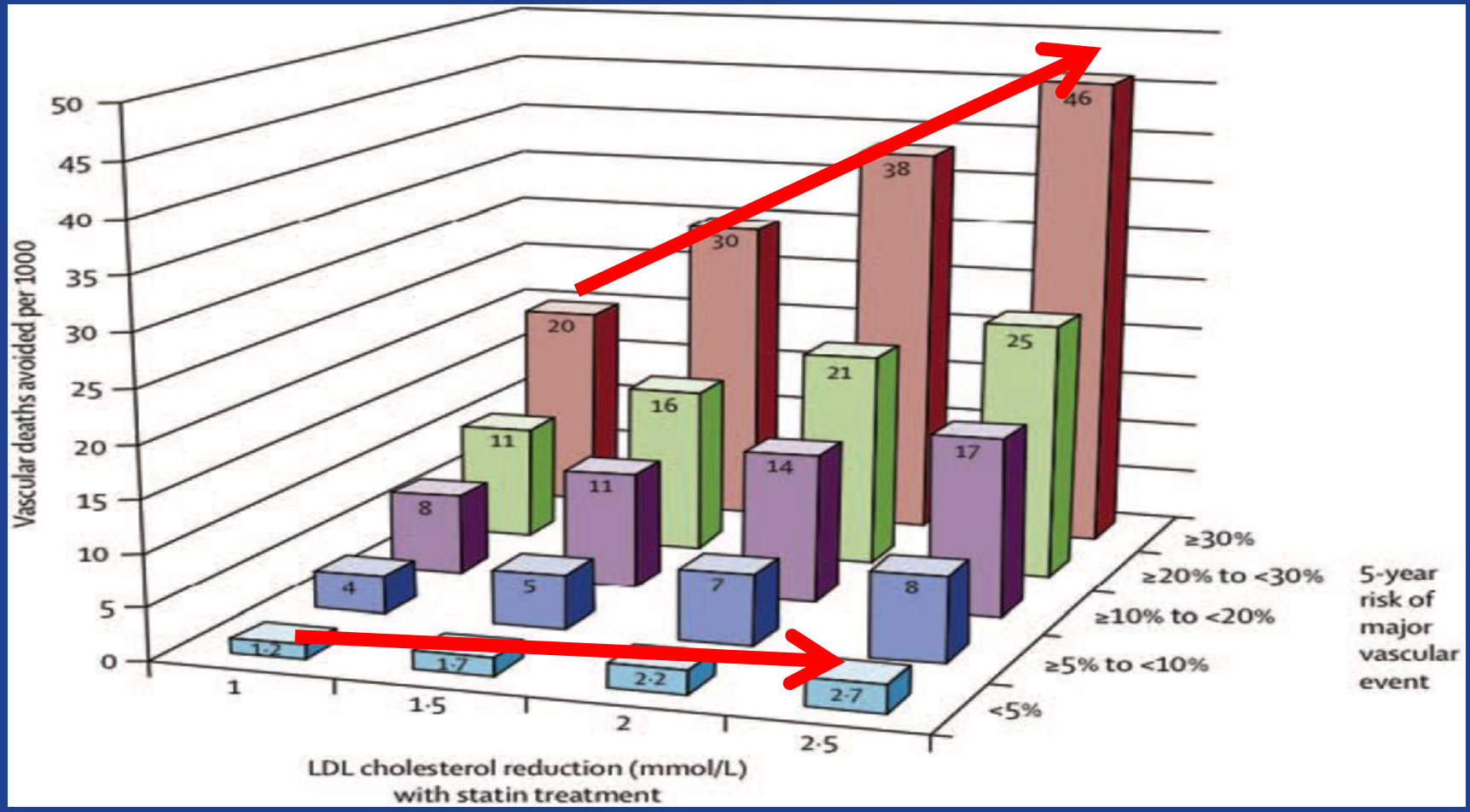
A Scientific Statement From the American Heart Association

Circulation 2016;133:1302-1331

לפום צערא אגרא

משנה, מסכת אבות, פרק ה', משנה כ"ג

Predicted Vascular Deaths Avoided Over 5 Years From Reductions in LDL-C With Statins at Different Levels of CVD Risk



Circulation. 2013;127:1929-1931

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- **IHD prevalence rate lower for women vs. men.**

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AHA STATISTICAL UPDATE

Heart Disease and Stroke Statistics 2018 Update

Coronary Heart Disease

Population Group	Prevalence, CHD, 2011–2014 Age ≥20 y	Prevalence, MI, 2011–2014 Age ≥20 y
Both sexes	16 500 000 (6.3%)	7 900 000 (3.0%)
Males	9 100 000 (7.4%)	4 700 000 (3.8%)
Females	7 400 000 (5.3%)	3 200 000 (2.3%)

Circulation. 2018;137:e67-e492

AHA Scientific Statement

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- IHD prevalence rate lower for women vs. men.
- **After age 45 for men and 55 for women, the risk for IHD increases similarly in both groups.**

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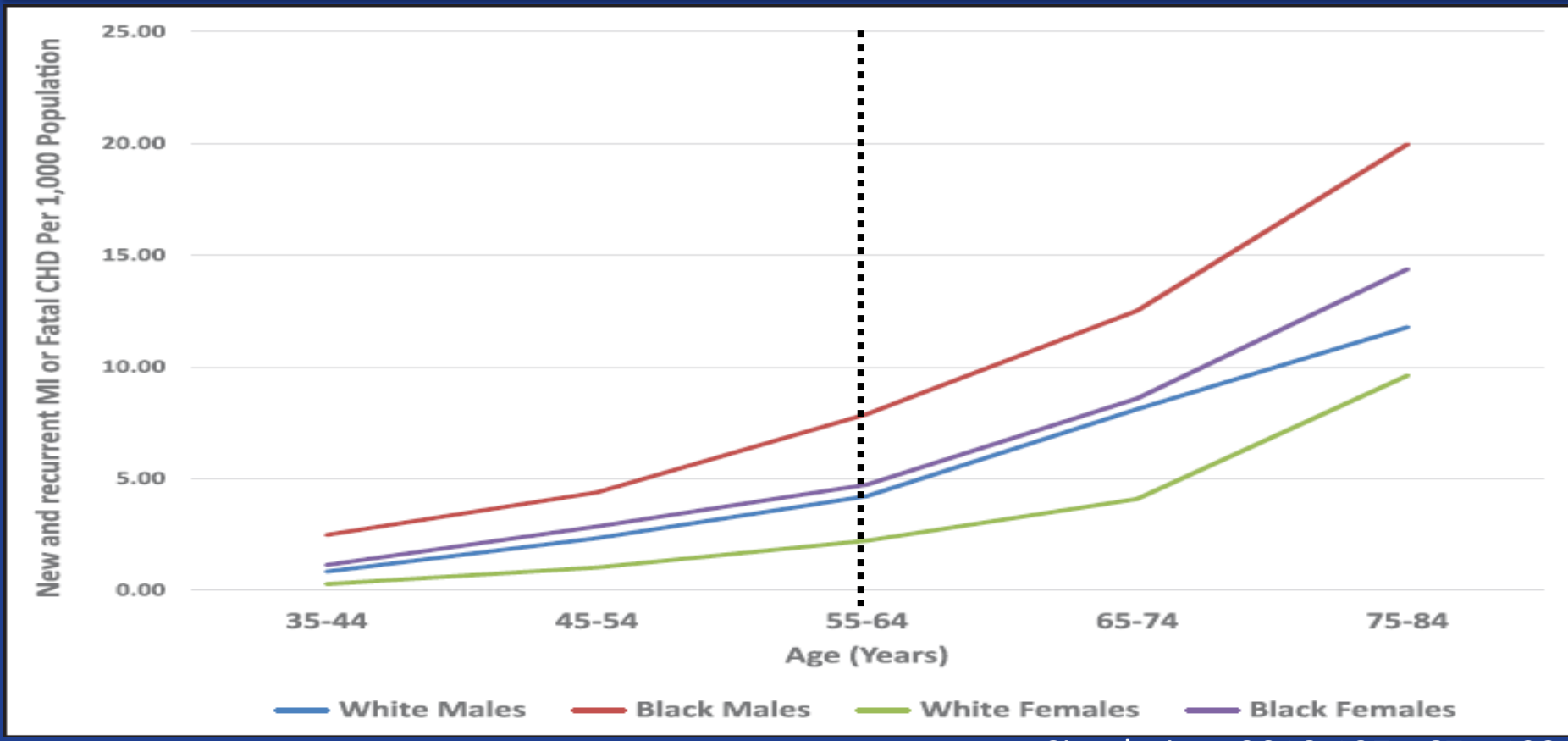
AHA STATISTICAL UPDATE

Heart Disease and Stroke Statistics 2018 Update

Incidence of MI or fatal CHD by age, sex, and race (ARIC Surveillance 2005–2014)



Circulation. 2018;137:e67-e492

AHA Scientific Statement

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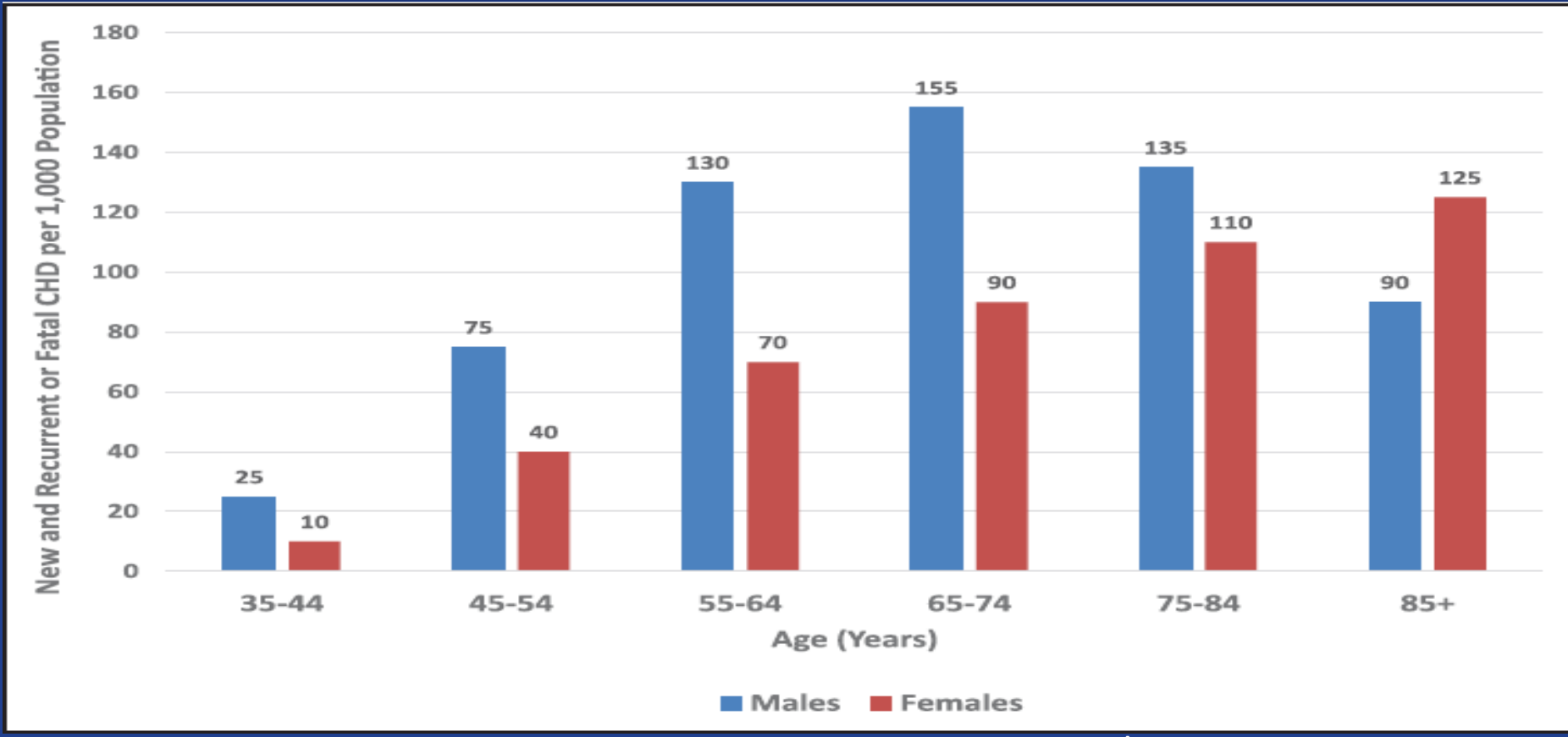
- IHD prevalence rate lower for women vs. men.
- After age 45 for men and 55 for women, the risk for IHD increases similarly in both groups.
- **Life expectancy for women is greater than that of men, leading to an aged female population with greater IHD risk**

Circulation 2016;133:1302-1331

AHA STATISTICAL UPDATE

Heart Disease and Stroke Statistics 2018 Update

Annual number of adults per 1000 having diagnosed MI or fatal CHD by age and sex (ARIC 2005–2014 and CHS).



Circulation. 2018;137:e67-e492

AHA Scientific Statement

Preventing and Experiencing Ischemic Heart Disease as a Woman: State of the Science

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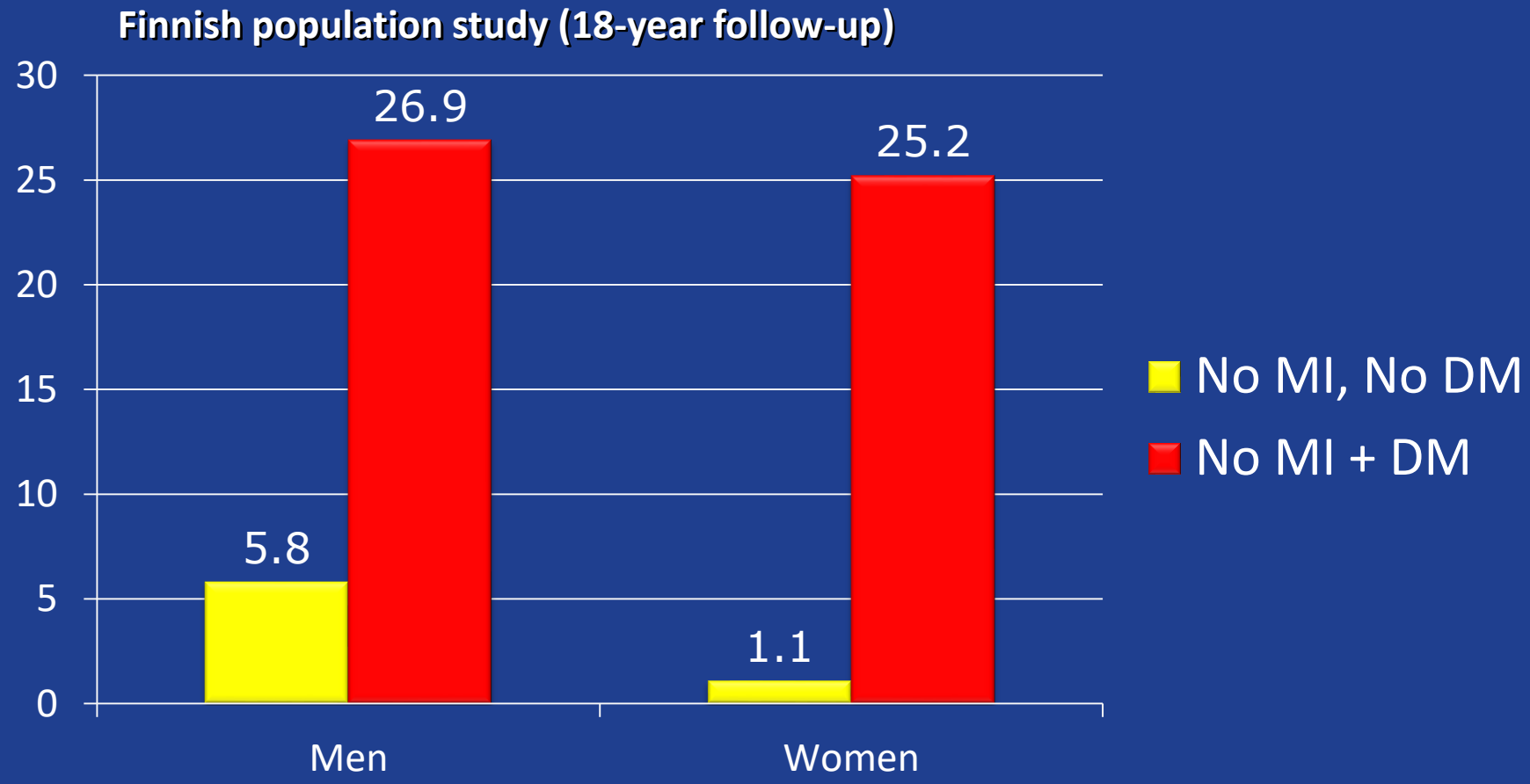
- IHD prevalence rate lower for women compared with men.
- After age 45 for men and 55 for women, the risk for IHD increases similarly in both groups.
- Life expectancy for women is greater than that of men, leading to an aged female population with greater IHD risk
- **IHD death rate in younger women 35-44 years of age continues to increase, while it is decreasing in their male counterparts**

Circulation 2016;133:1302-1331

Loss of Gender Benefit for CHD Mortality in Diabetic Women Without Prior MI



Numbers on bars represent number of persons in category at baseline.
*P<0.001, †P<0.05 vs persons without diabetes.

Diabetes Care 2005;28:2901-2907

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Heart Disease and Stroke Statistics 2018 Update

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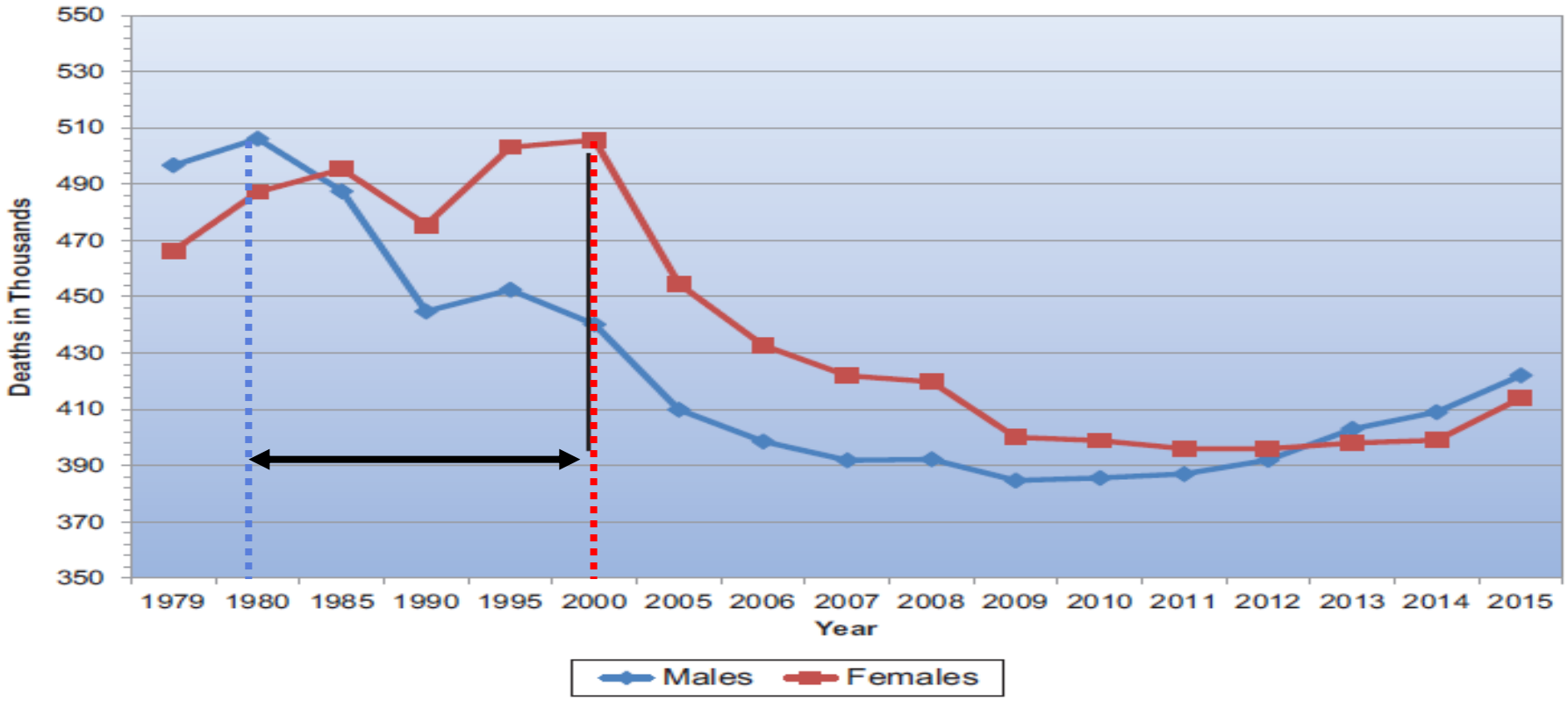
Circulation. 2018;137:e67-e492

Heart Disease and Stroke Statistics 2018 Update

CVD Mortality Trends for Males and Females (United States: 1979–2015)



Circulation. 2018;137:e67-e492

Mail Online

DO STATINS WORK AS WELL FOR WOMEN?

CONTROVERSY surrounds whether women get the same benefit from statins as men. Some researchers claim trials do not give a definitive answer – because most of the subjects were middle-aged men.

Although research shows that death rates appear to drop more markedly in men taking the drugs after surviving a first heart attack or stroke, recurrence rates fell for both genders.

There is no biological reason why statins should not work in both sexes – and five years' use leads to the same heart benefits, studies have shown.

However, younger women have natural protection against heart disease because of the hormone oestrogen, which they lose during the menopause. It means women over 50 are more likely to benefit when their risk rises to match older men.

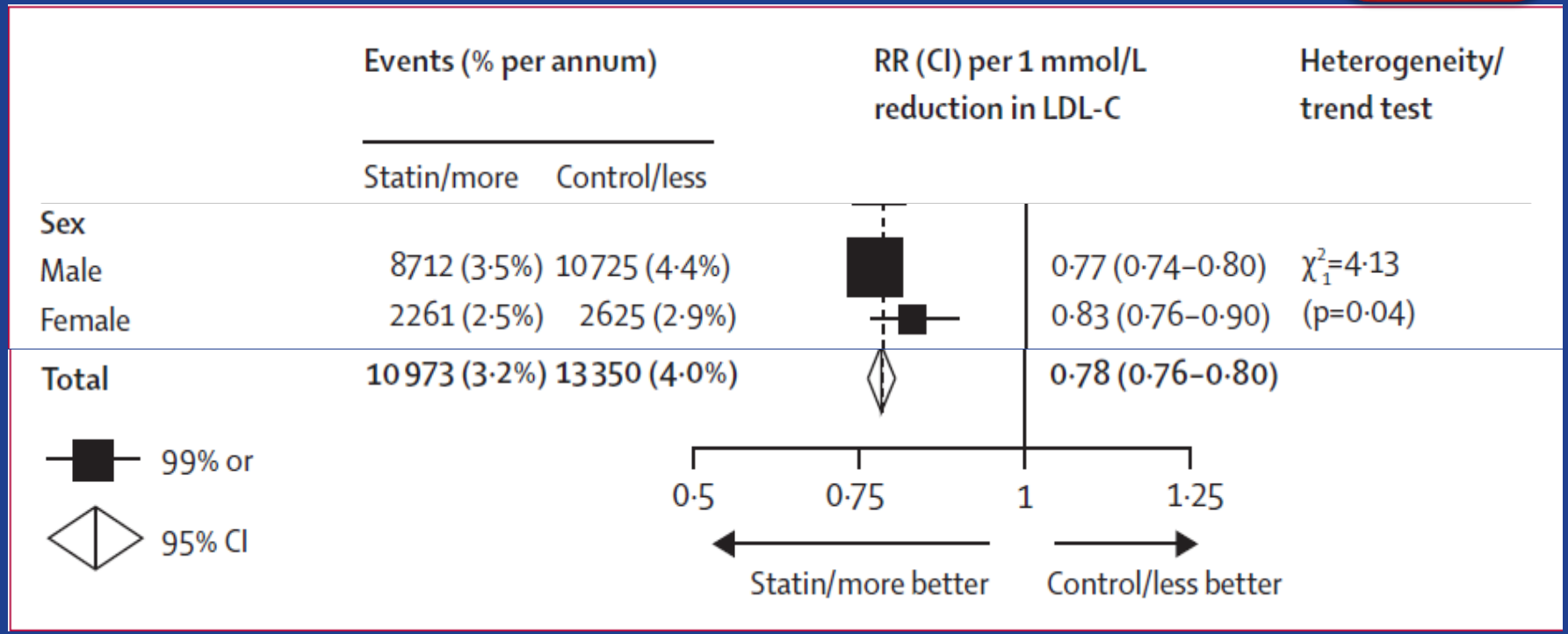
Researchers from Harvard Medical School re-analysed eight major studies in 2007 and concluded there was no evidence that statins worked as primary prevention for women.

Although some researchers disagree, most accept that women taking statins appear to suffer more side-effects that impact on their quality of life.

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**

	Number of patients	Treatment comparison (mg per day)	Median follow-up in survivors (years)*	Baseline LDL-C (mmol/L)	LDL-C difference at 1 year (mmol/L)	Women (%)
Total (26 trials)	169138	NA	4·9‖	NA	NA	45495 (27%)



Lancet 2010;376:1670-1681

Meta-Analysis of Statin Effects in Women Versus Men

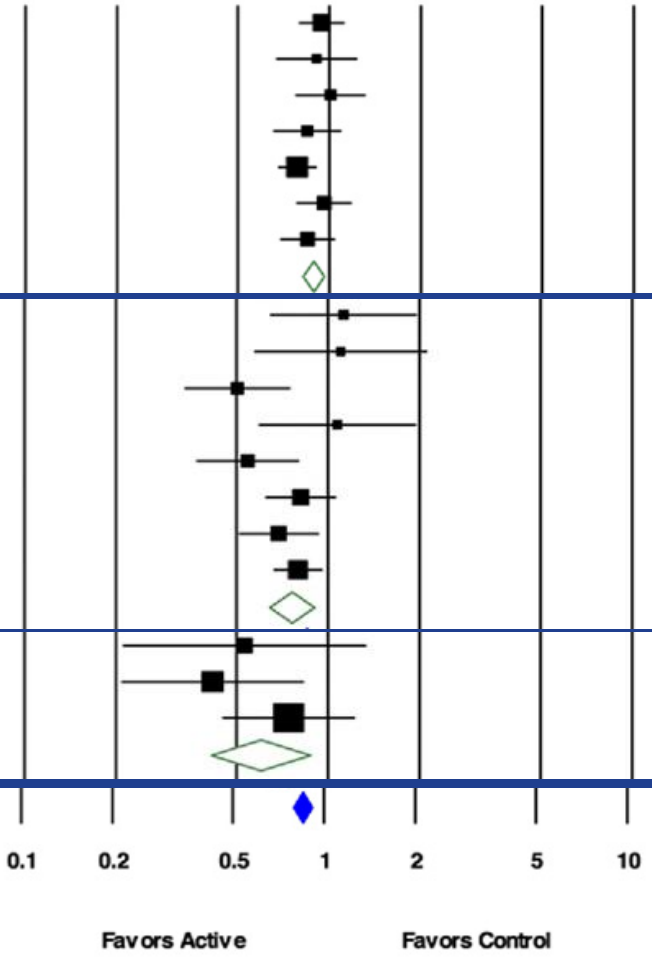
- 18 RCTs of statins with sex-specific outcomes (N=141,235)
  - 40,275 **women (28.5%)**, 21,468 CV events.
- **CV event rate was lower among those randomized to statin** than in those randomized to control (low-dose statin in 4 studies, placebo in 11 studies, usual care in 3 studies) and **similar in women and men**
- **All-cause mortality was also lower with statin** both in women and men without significant interaction by sex

JACC 2012;59:572-82

Meta-Analysis of Statin Effects in Women Versus Men

Primary Event by Level of Risk in Each Study in Women

Group by Risk 3 Way		Subgroup within study	Odds ratio	Lower limit	Upper limit	p-Value
HIGH	ALLHAT-LLT	WOMEN	0.94	0.79	1.13	0.5253
HIGH	ATCZ	WOMEN	0.91	0.66	1.24	0.5508
HIGH	AURORA	WOMEN	1.01	0.77	1.32	0.9549
HIGH	CORONA	WOMEN	0.85	0.65	1.10	0.2130
HIGH	HPS	WOMEN	0.78	0.67	0.91	0.0015
HIGH	PROSPER	WOMEN	0.96	0.77	1.19	0.7117
HIGH	SEARCH	WOMEN	0.85	0.68	1.05	0.1284
HIGH			0.88	0.81	0.95	0.0014
MEDIUM	4S	WOMEN	1.12	0.64	1.97	0.6866
MEDIUM	ASCOT-LLA	WOMEN	1.10	0.57	2.13	0.7745
MEDIUM	CARE	WOMEN	0.50	0.33	0.76	0.0009
MEDIUM	GISSI-P	WOMEN	1.07	0.59	1.96	0.8191
MEDIUM	JUPITER	WOMEN	0.54	0.37	0.81	0.0025
MEDIUM	LIPID	WOMEN	0.81	0.62	1.07	0.1374
MEDIUM	PROVE-IT	WOMEN	0.69	0.51	0.94	0.0176
MEDIUM	TNT	WOMEN	0.80	0.66	0.96	0.0192
MEDIUM			0.75	0.64	0.89	0.0011
LOW	AF-TEXCAPS	WOMEN	0.53	0.21	1.34	0.1807
LOW	GREACE	WOMEN	0.42	0.21	0.84	0.0141
LOW	MEGA	WOMEN	0.74	0.45	1.23	0.2481
LOW			0.59	0.41	0.87	0.0066
Overall			0.84	0.79	0.91	0.0000

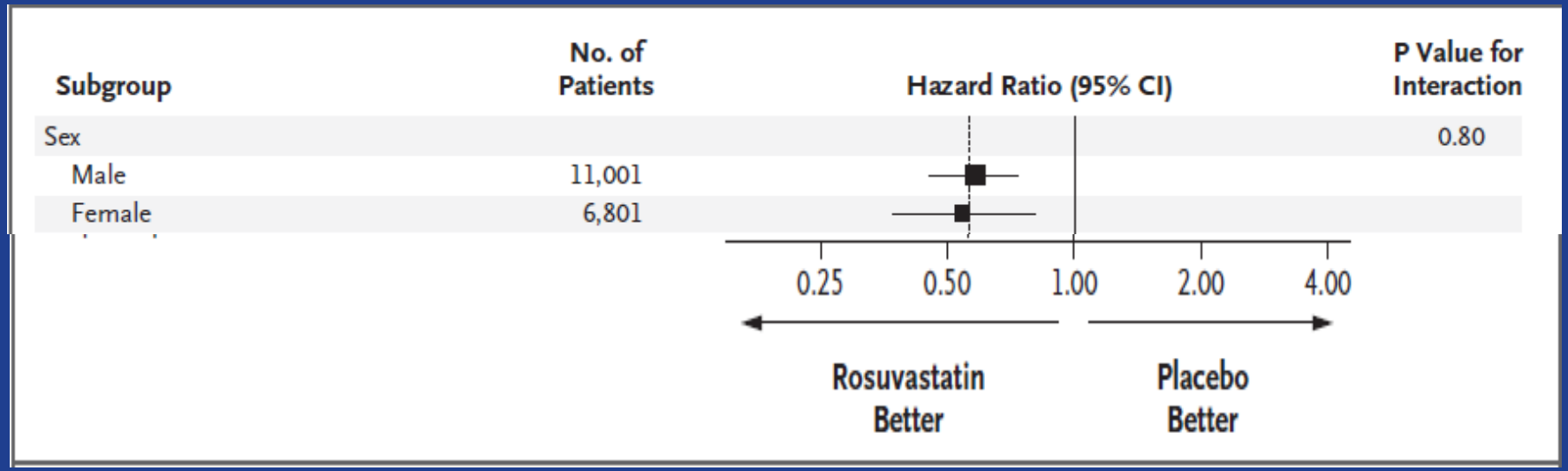


JACC 2012;59:572-82

JUPITER: Rosuvastatin for Primary Preventoion with Elevated CRP

Table 1. Baseline Characteristics of the Trial Participants, According to Study Group.*

Characteristic	Rosuvastatin (N=8901)	Placebo (N=8901)
Age — yr		
Median	66.0	66.0
Interquartile range	60.0–71.0	60.0–71.0
Female sex — no. (%)	3426 (38.5)	3375 (37.9)



N Engl J Med 2008;359:2195-207

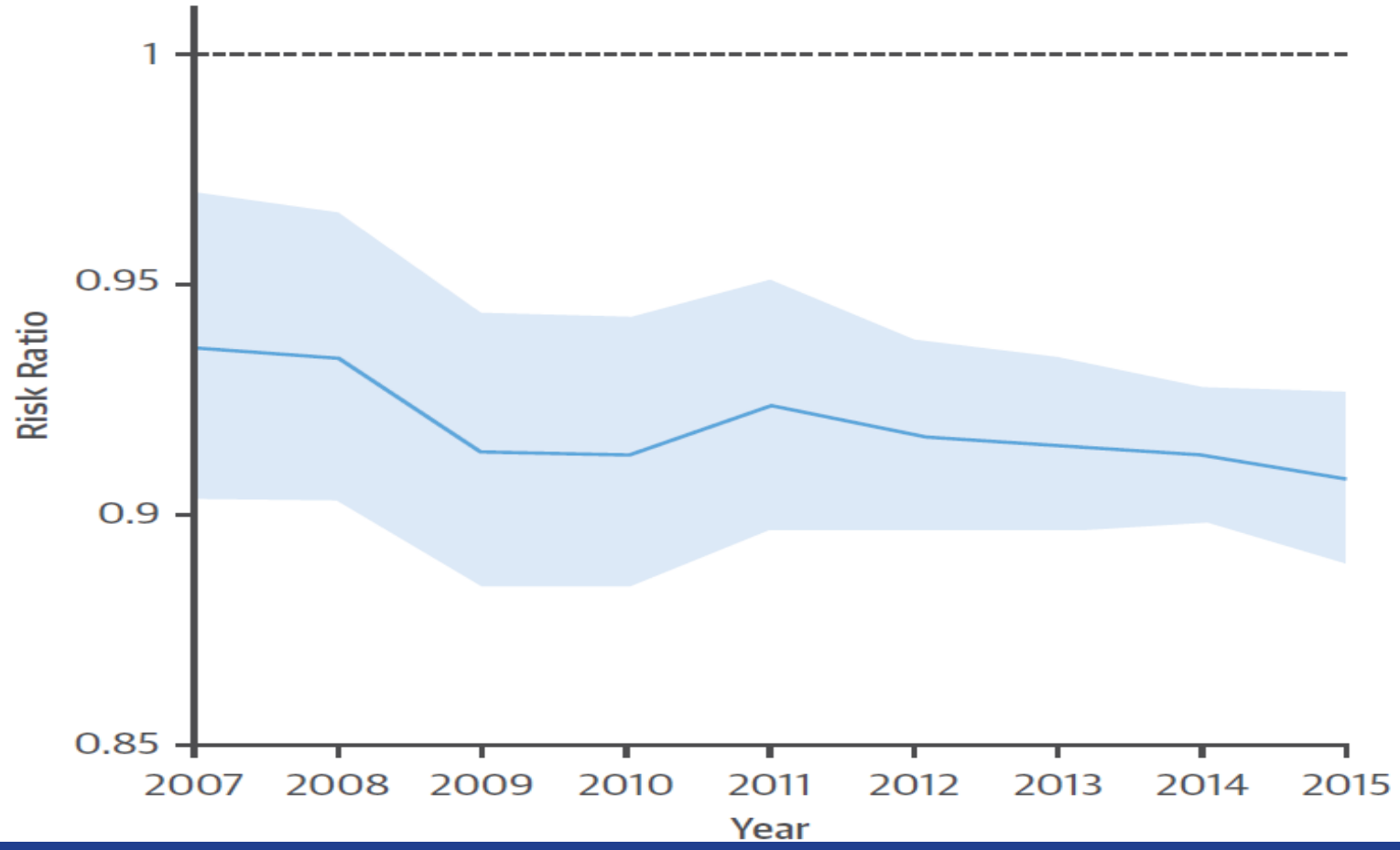
Statins for the primary prevention of cardiovascular disease (Review)

- Men and women, all appear to benefit.
- These findings counter earlier opinion that the evidence is insufficient to support use of statins in primary prevention for women

Cochrane Database of Systematic Reviews 2013, Issue 1

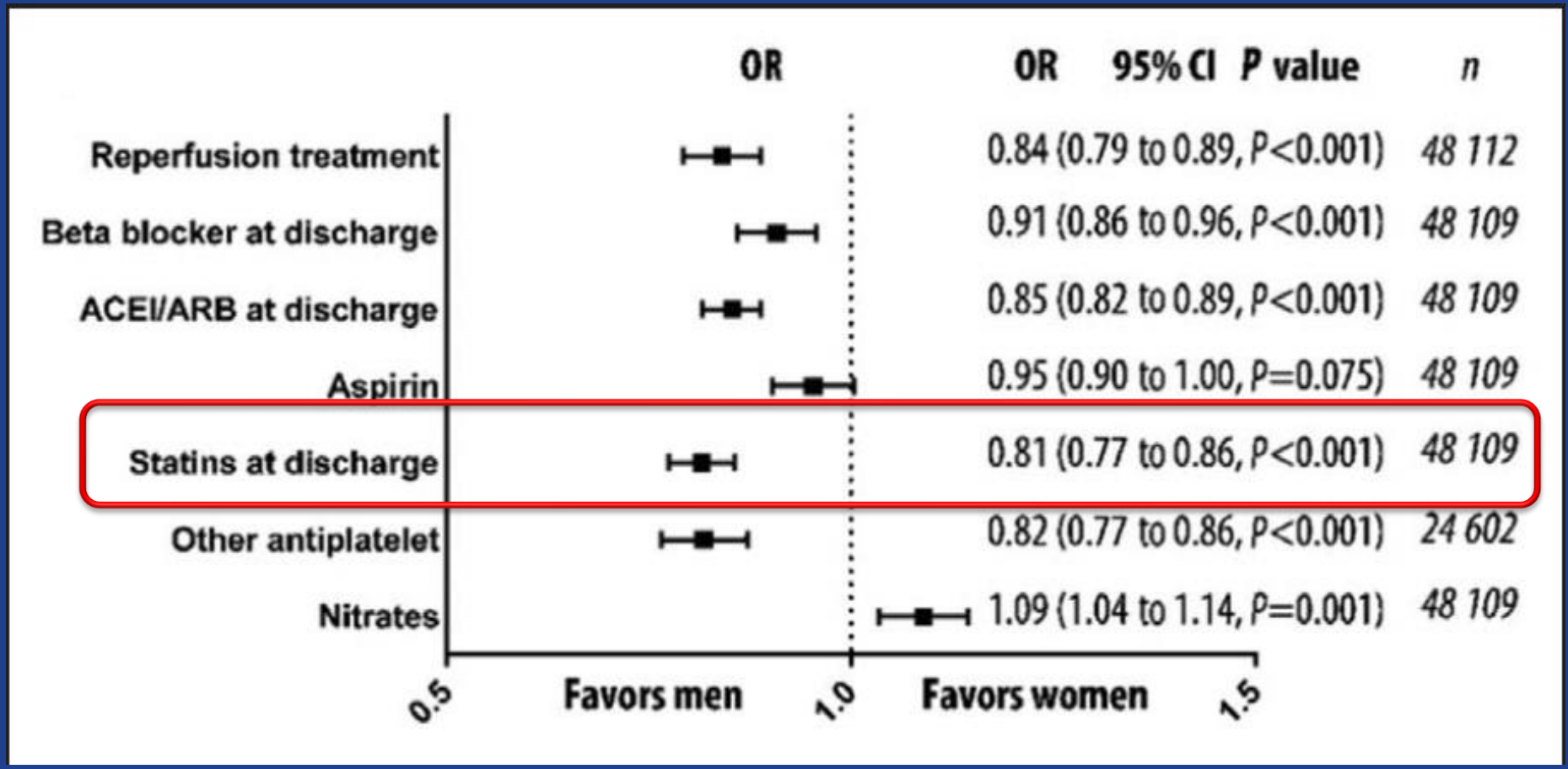
Sex Differences in High-Intensity Statin Use Following Myocardial Infarction

FIGURE 2 Risk Ratios (95% Confidence Intervals) for Filling a High-Intensity Statin Prescription Among Women Versus Men Between 2007 and 2015



J Am Coll Cardiol 2018;71:1729-37

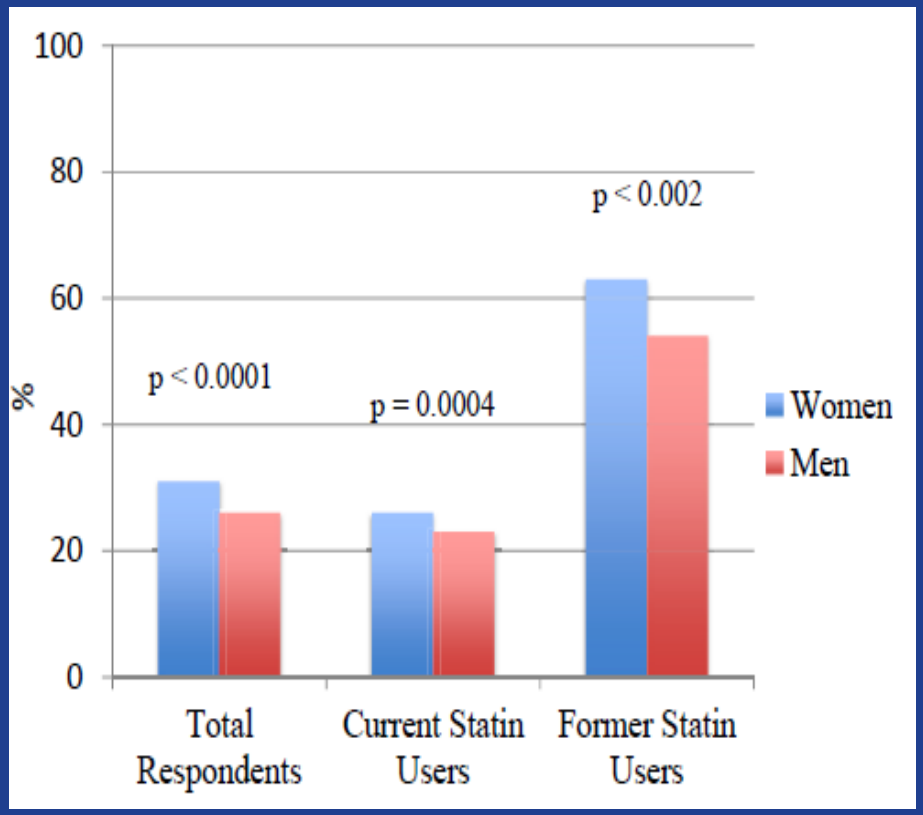
Likelihood of Receiving Evidence-Based Treatment After Acute MI by Sex



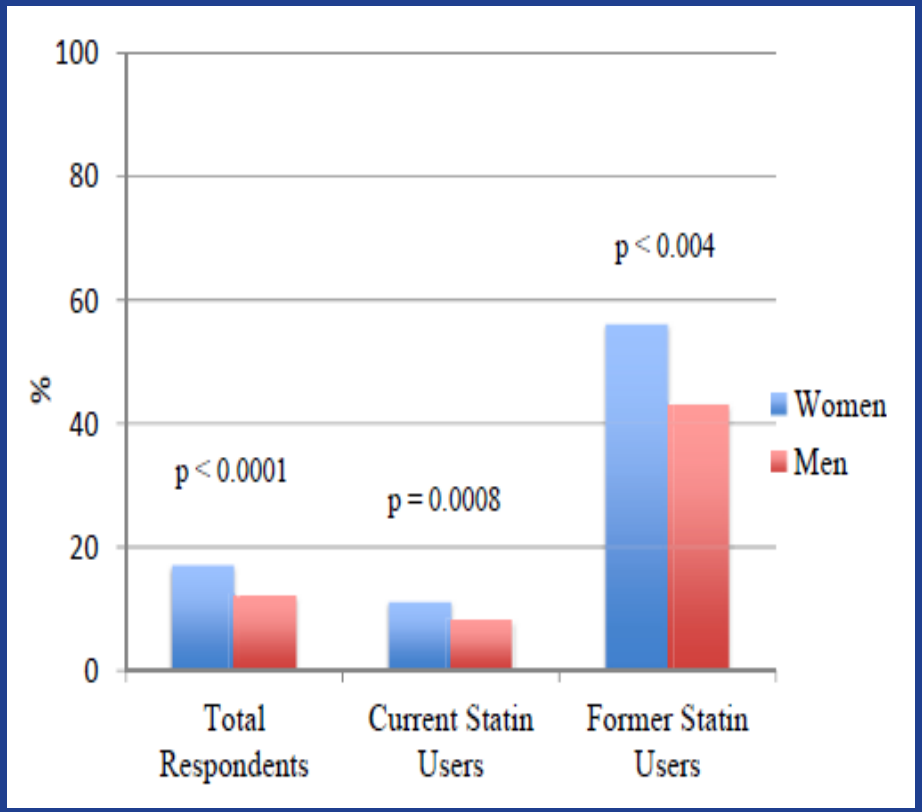
Circ Cardiovasc Qual Outcomes. 2018;11:e004437

Gender Differences in Side Effects and Attitudes Regarding Statin Use In The USAGE Study

New and/or worsening muscle symptoms while taking a statin.

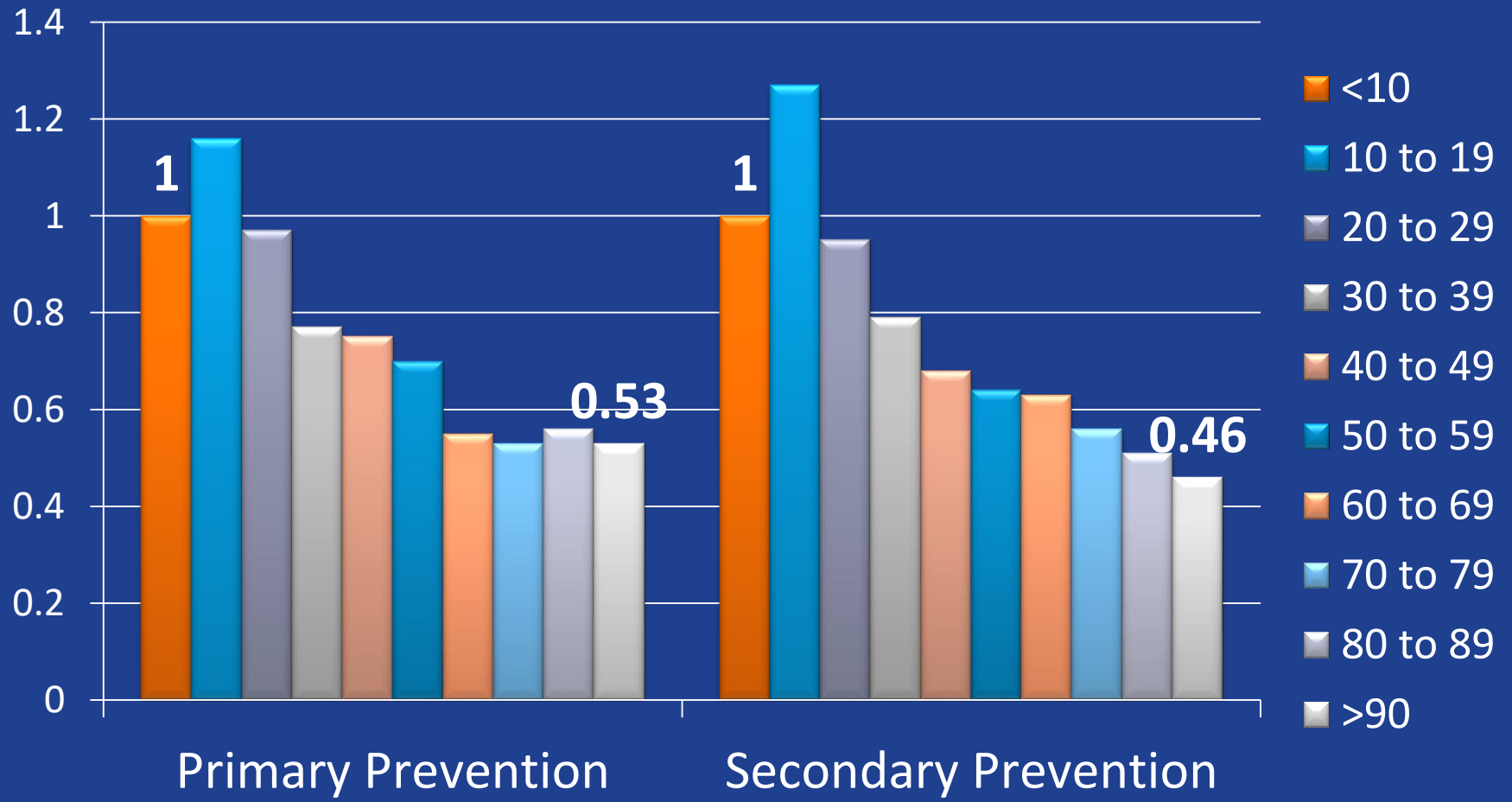


Stopped a statin due to muscle symptoms



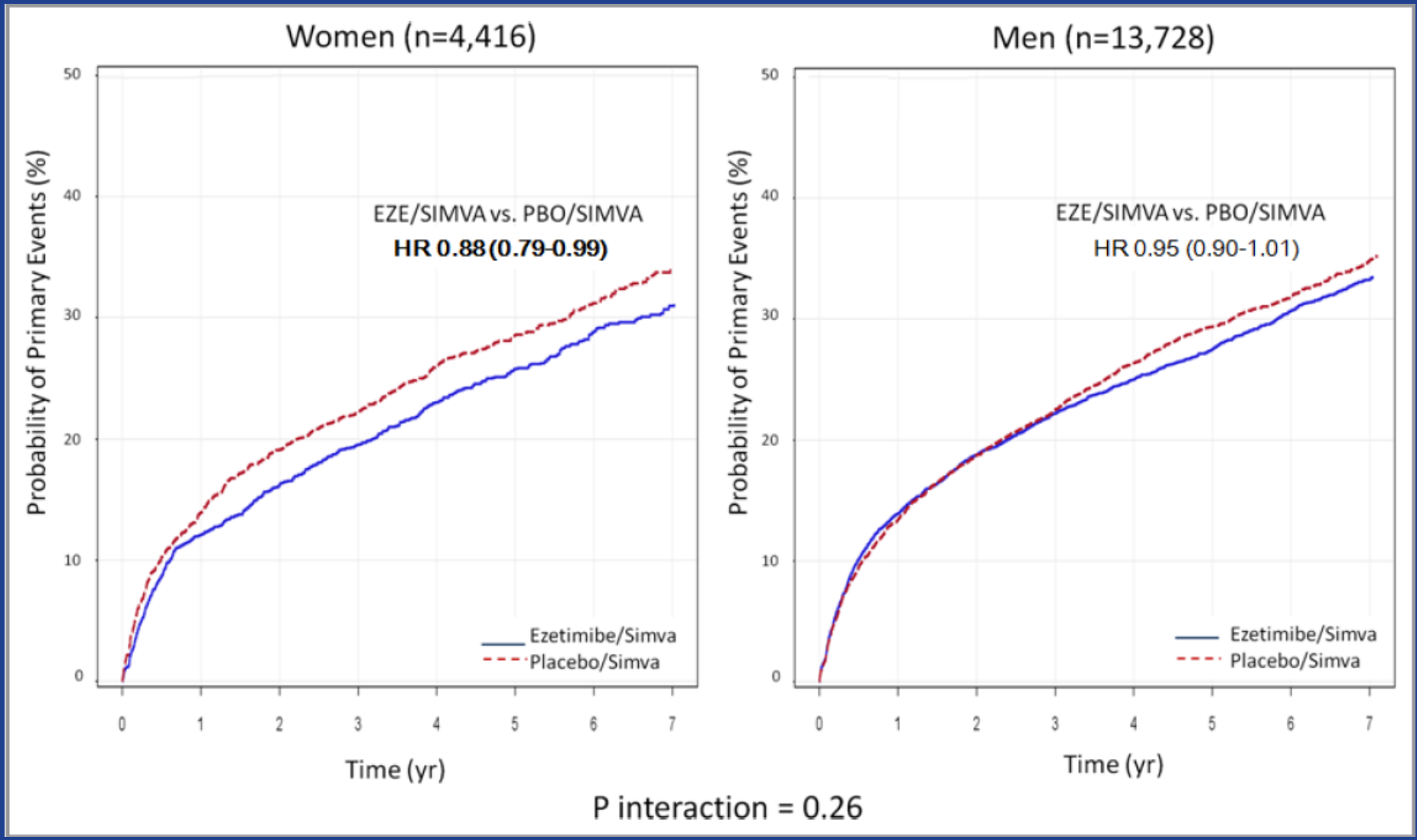
J Clin Lipidol 2016;10:833-841

Statin Proportion of Days Covered and All-Cause Mortality in Israel



Arch Intern Med. 2009;169:260-268

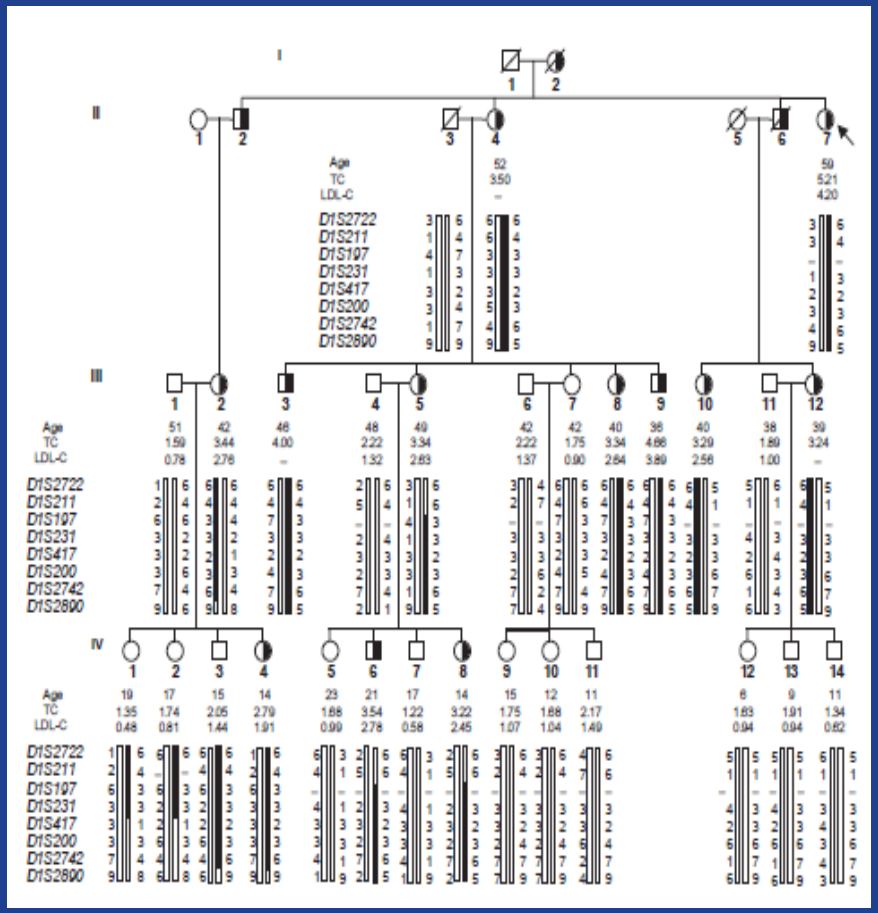
IMPROVE-IT: Ezetimibe Added to Statin after ACS



N Engl J Med 2015;372:2387-97

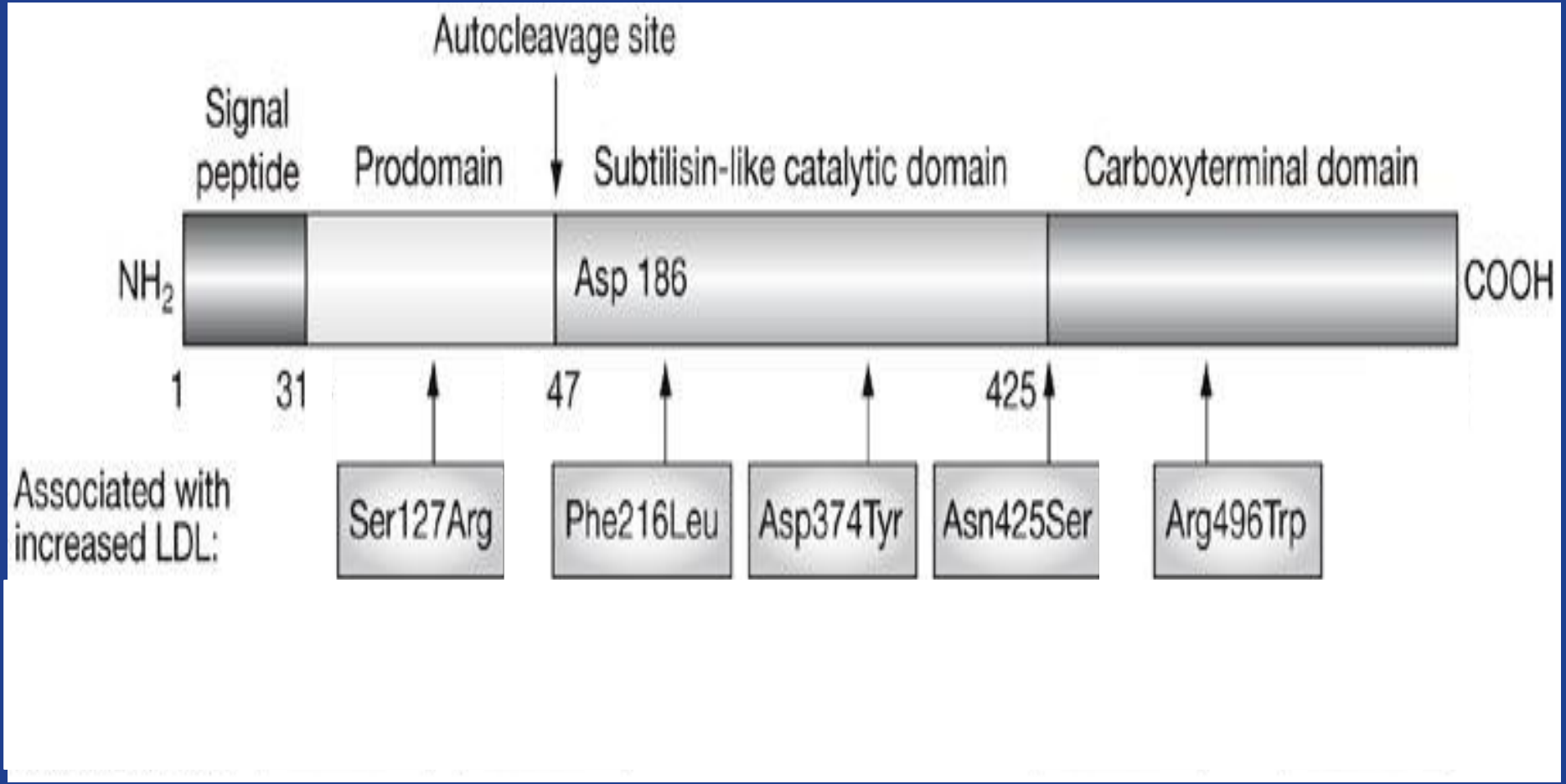
A New Gene Mutated in a Family with FH Phenotype

- Tendon xanthomas
- Early MI and stroke
- LDL-C > 250 mg/dL
- Autosomal dominant
- No mutations in LDL-R or ApoB genes



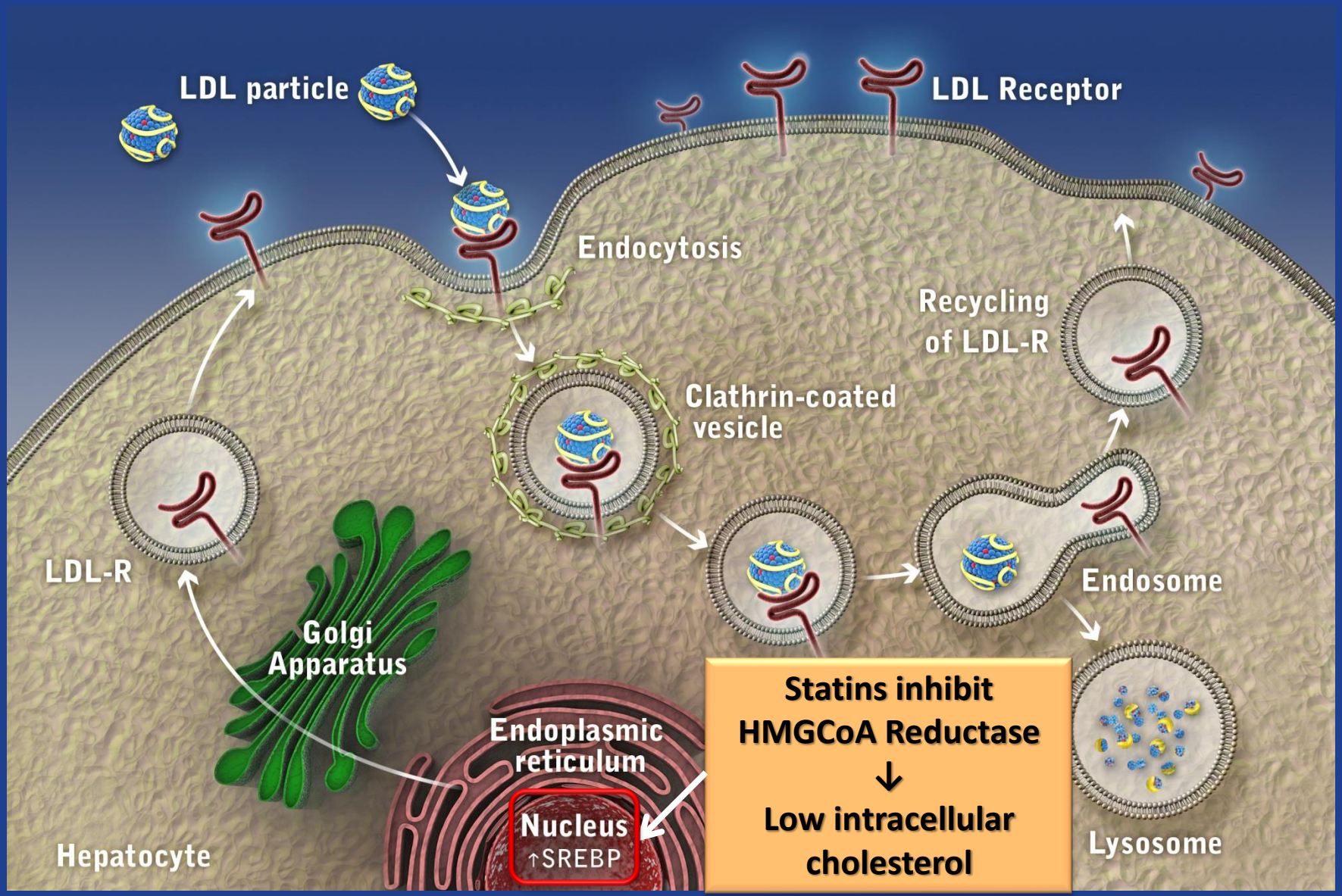
Nat Genet 2003;34:154-6

PCSK9 Gene
proprotein convertase subtilisin-like/kexin type 9

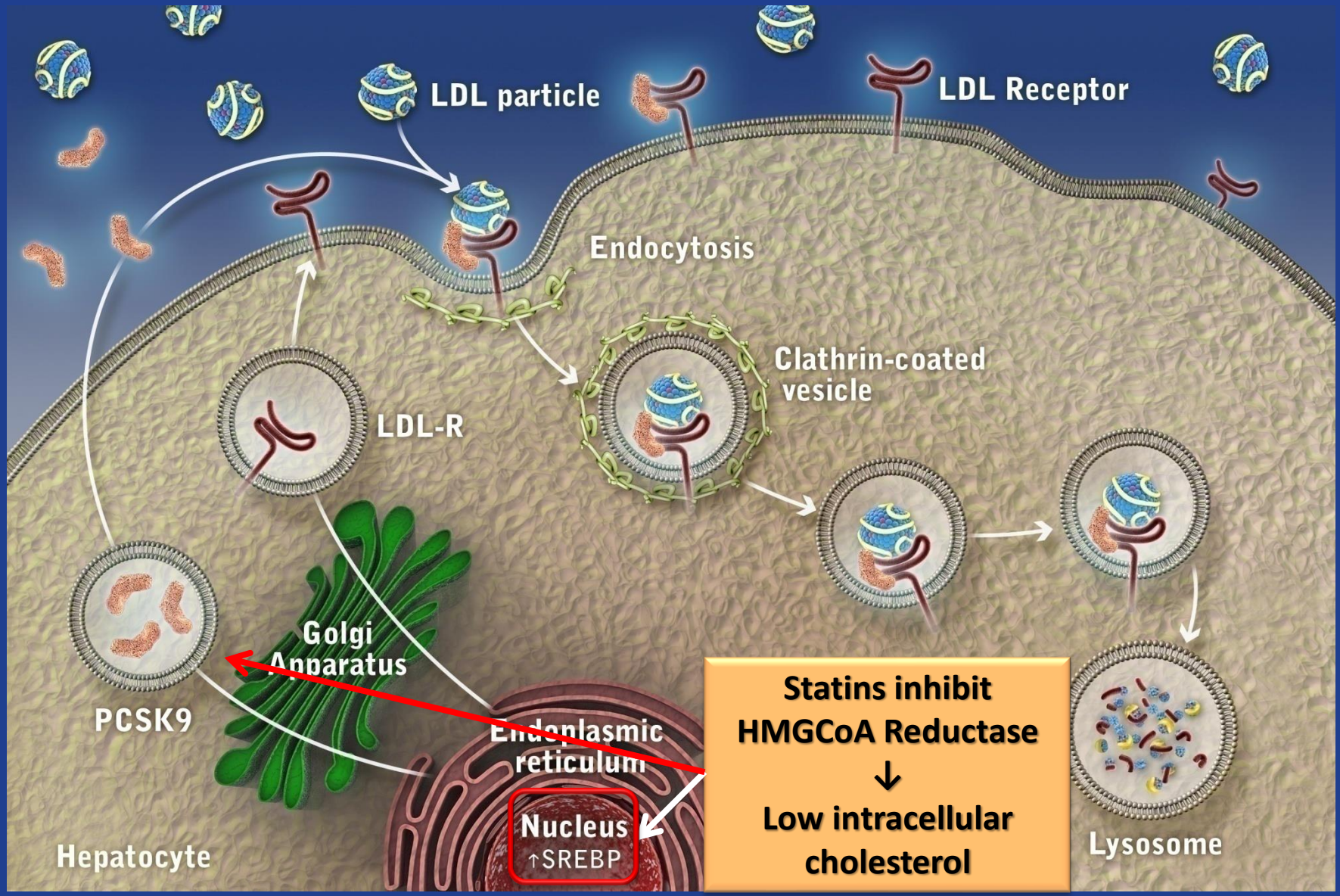


Nat Clin Pract Cardiovasc Med 2007;4: 214–225

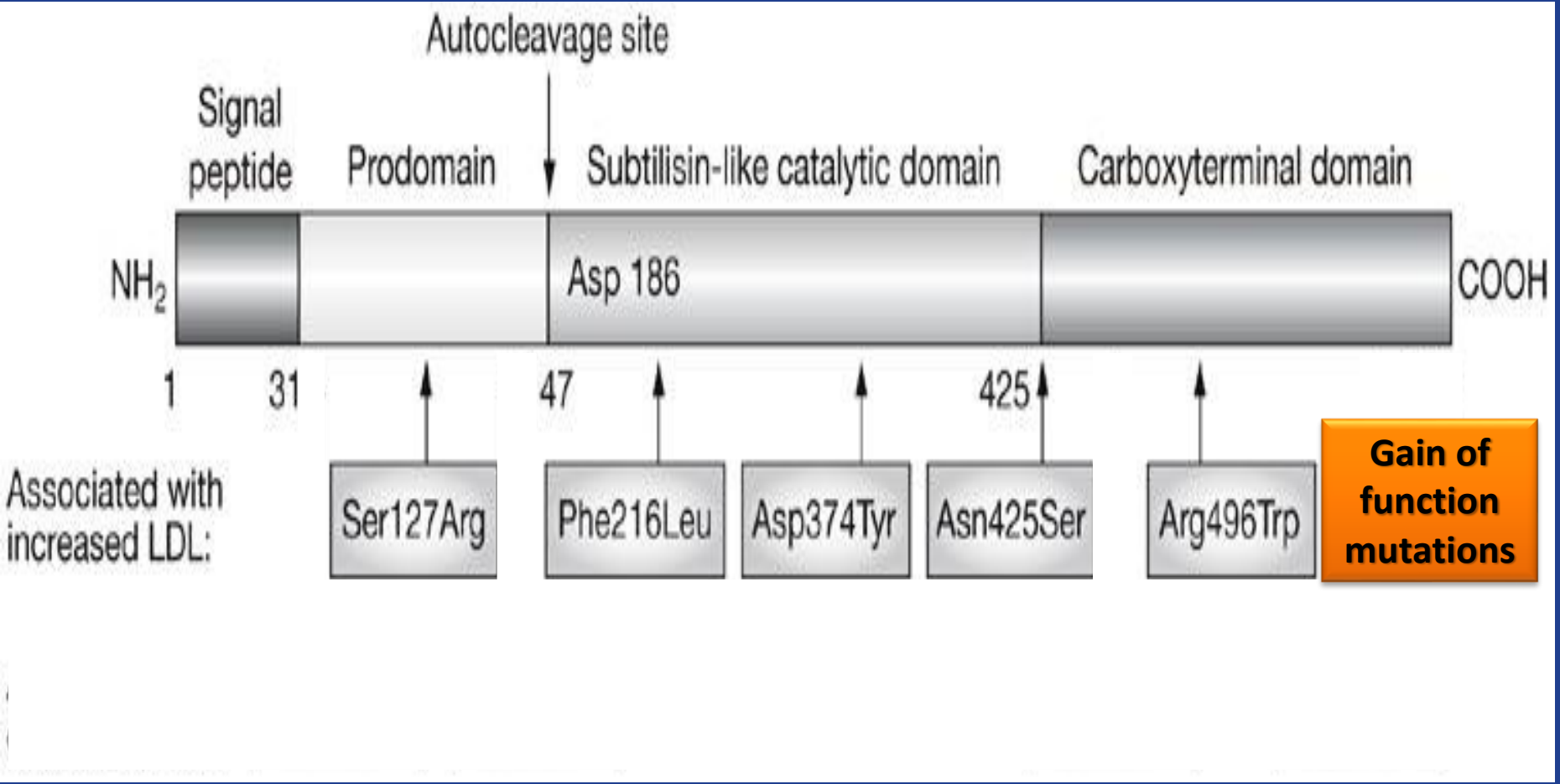
LDL Receptor Function and Life Cycle



The Role of PCSK9 in the Regulation of LDL Receptor Expression

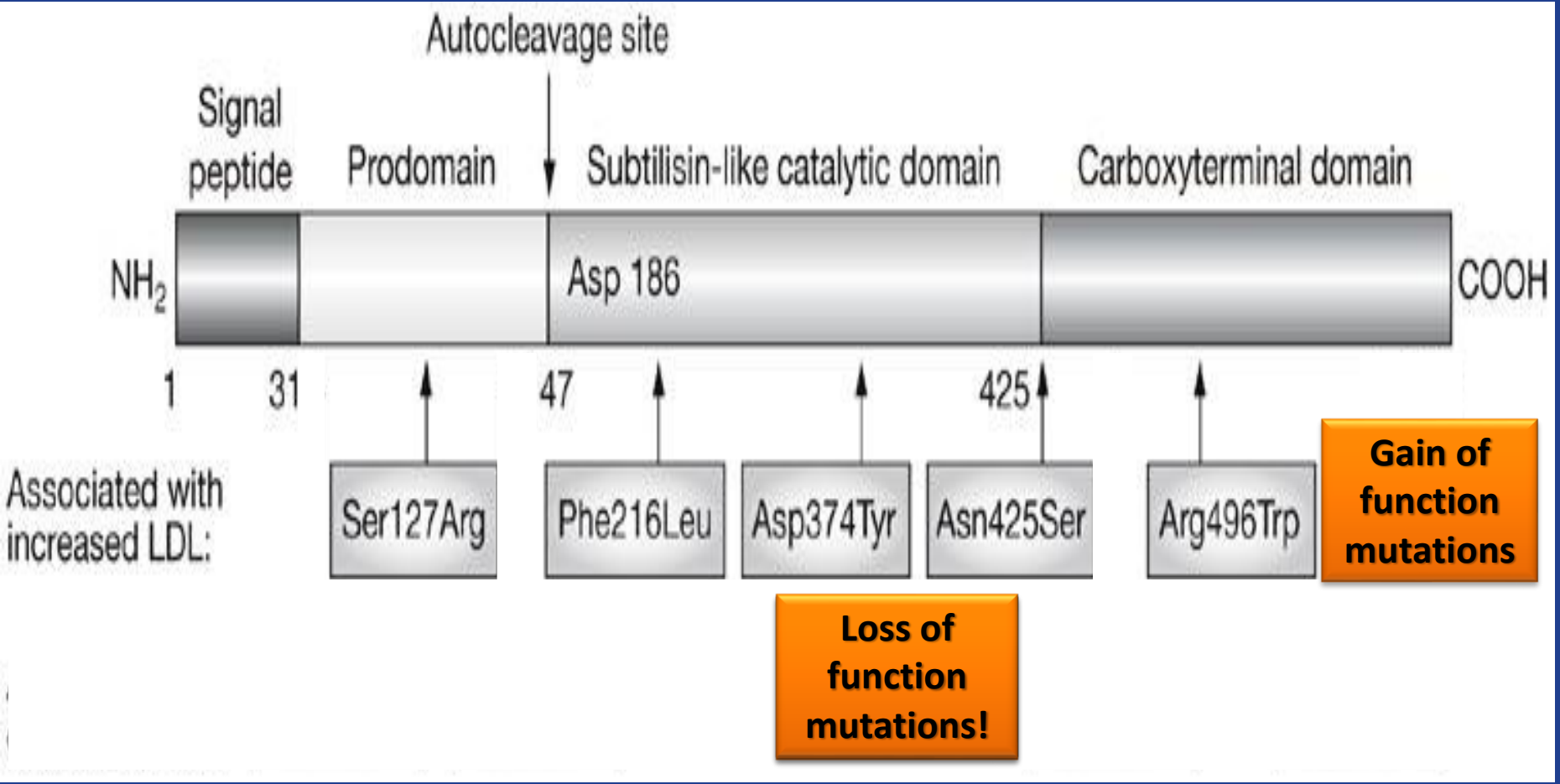


PCSK9 Gene



Nat Clin Pract Cardiovasc Med 2007;4: 214–225

PCSK9 Gene



Nat Clin Pract Cardiovasc Med 2007;4: 214–225

Population Studies of PCSK9 Loss of Function Mutations

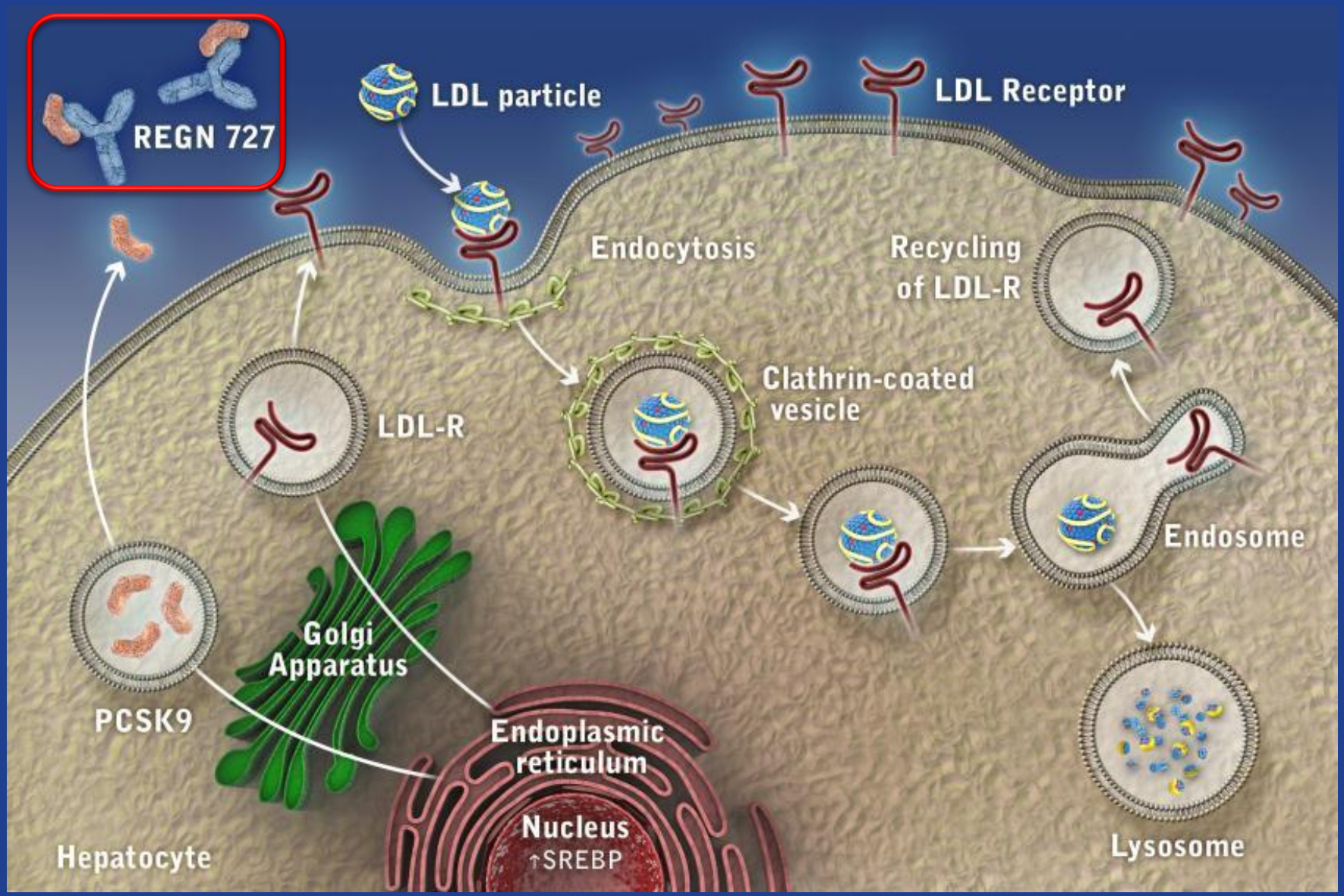
Patients with loss-of-function mutations in *PCSK9* or total lack of PCSK9

- Have naturally low levels of LDL-C and reduced coronary heart disease (→ efficacy)
- Are not associated with other detectable abnormalities (→ safety)

	PCSK9 Mutation	LDL-C Reduction	CHD Reduction	Population
Benn M, et al [1]	R46L	12%	46%	Copenhagen City Heart Study Copenhagen General Population Study Copenhagen Ischemic Heart Disease Study
Cohen JC, et al [2]	R46L	15%	47%	Atherosclerosis Risk in Community Study (US)
	Y142X or C679X	28%	88%	

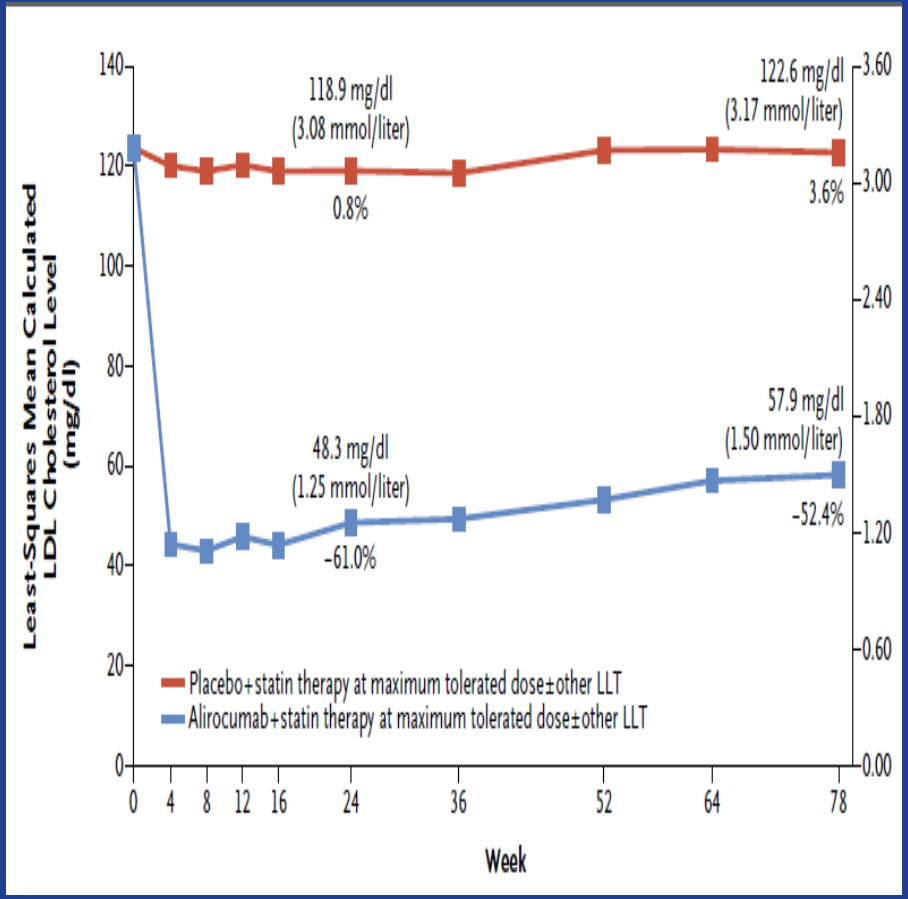
[1]JACC 2010;55:2833-42
[2]NEJM 2006;354:1264-72

Impact of an PCSK9 mAb on LDL Receptor Expression



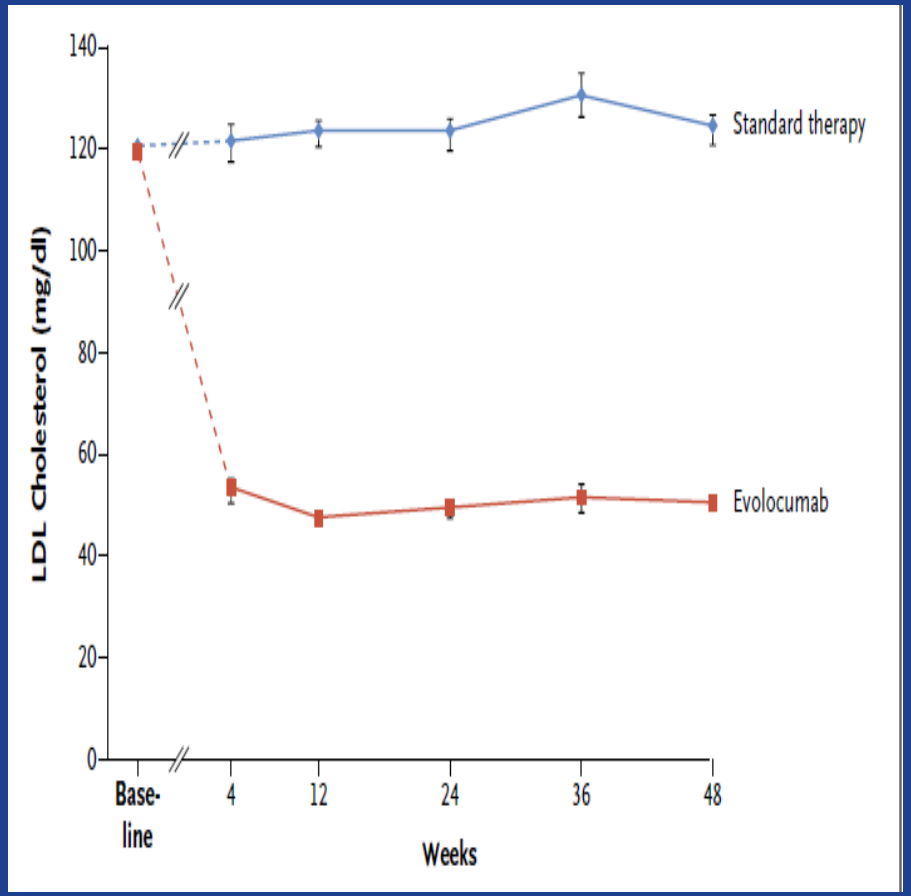
Long Term Studies With PCSK9 Inhibitors

Alirocumab: ODYSSEY Long term



N Engl J Med 2015;372:1489-99

Evolocumab: OSLER



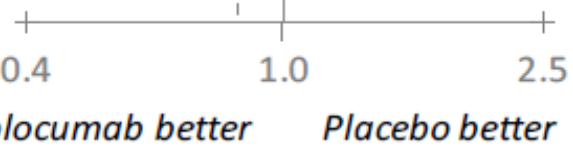
N Engl J Med 2015;372:1500-9

FOURIER: Evolocumab in Patients with CVD

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Evolocumab (N=13,784)	Placebo (N=13,780)
Age — yr	62.5±9.1	62.5±8.9
Male sex — no. (%)	10,397 (75.4)	10,398 (75.5)

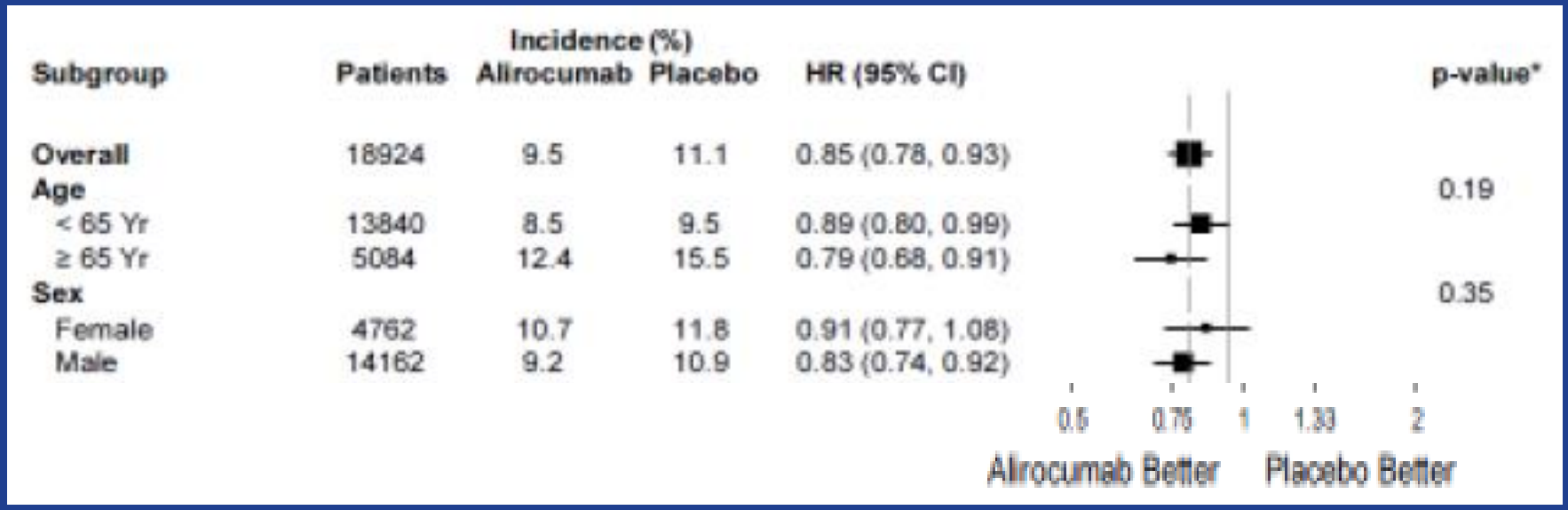
Subgroup	Patients	Evo Mab	Pbo	(95% CI)	$P_{interaction}$
OVERALL	27564	12.6	14.6	0.85 (0.79-0.92)	
Age					0.90
<65	15310	12.6	14.6	0.86 (0.78-0.94)	
≥65	12254	12.6	14.6	0.85 (0.76-0.95)	
Sex					0.48
Female	6769	9.9	12.5	0.81 (0.69-0.95)	
Male	20795	13.5	15.3	0.86 (0.80-0.94)	



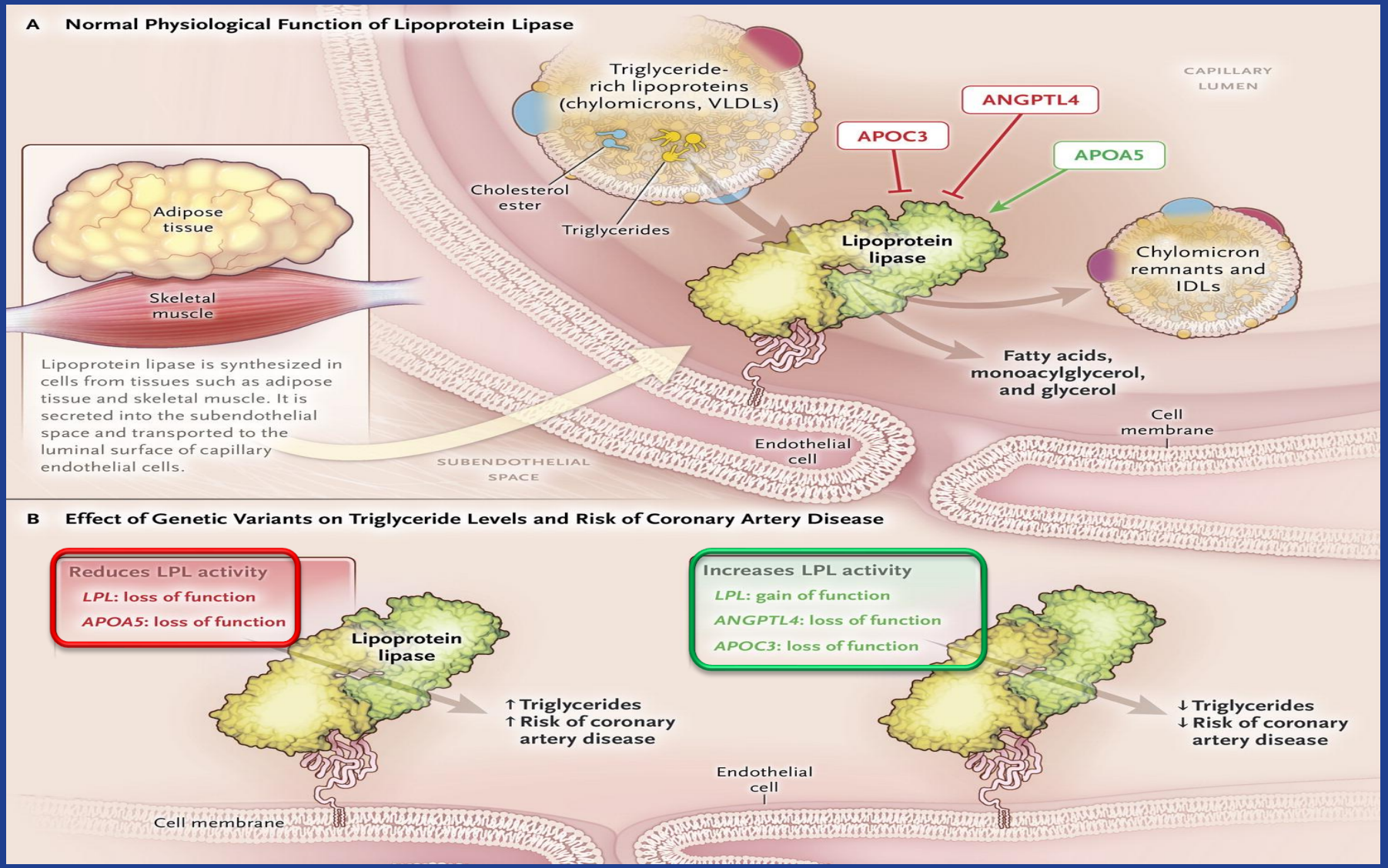
N Engl J Med 2017;376:1713-1722

ODYSSEY OTCOMES: Alirocumab in Post-ACS

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age, years, median (Q1–Q3)	58 (52–65)	58 (52–65)
Female, n (%)	2390 (25.3)	2372 (25.1)

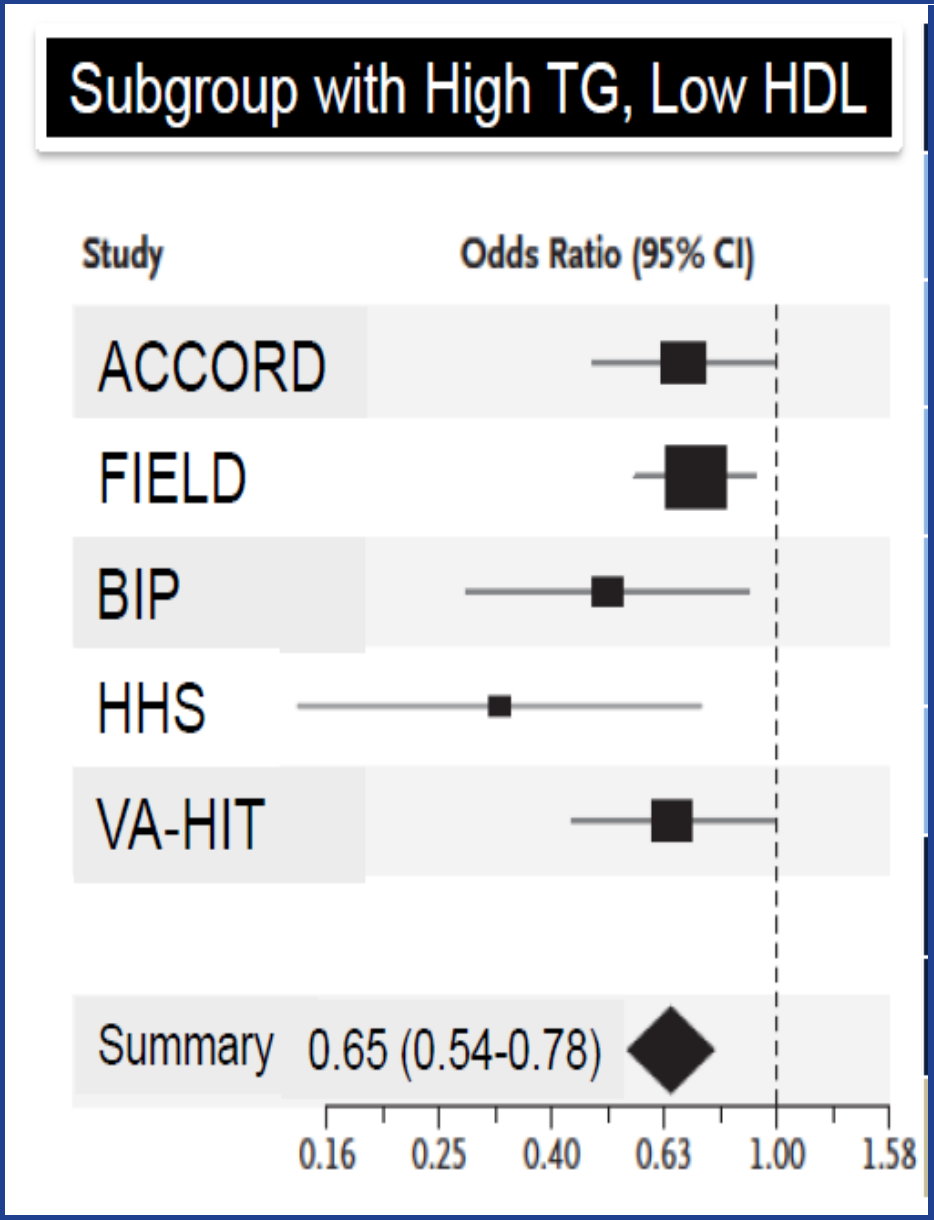


Mutations in Four LPL Pathway Genes Affect Plasma TG and CVD Risk



N Engl J Med 2016.374;1134-1144

CVD Prevention Trials with TG Lowering Agents

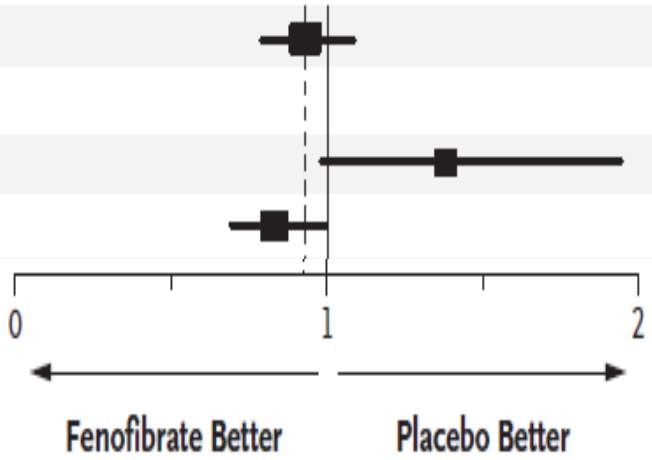


ACCORD: Fibreates for Women - Good or Bad?

Table 1. Baseline Characteristics of the Patients.*

Characteristic	All Patients (N=5518)	Fenofibrate (N=2765)	Placebo (N=2753)	P Value
Age — yr	62.3±6.8	62.2±6.7	62.3±6.9	0.69
Female sex — no. (%)	1694 (30.7)	851 (30.8)	843 (30.6)	0.90

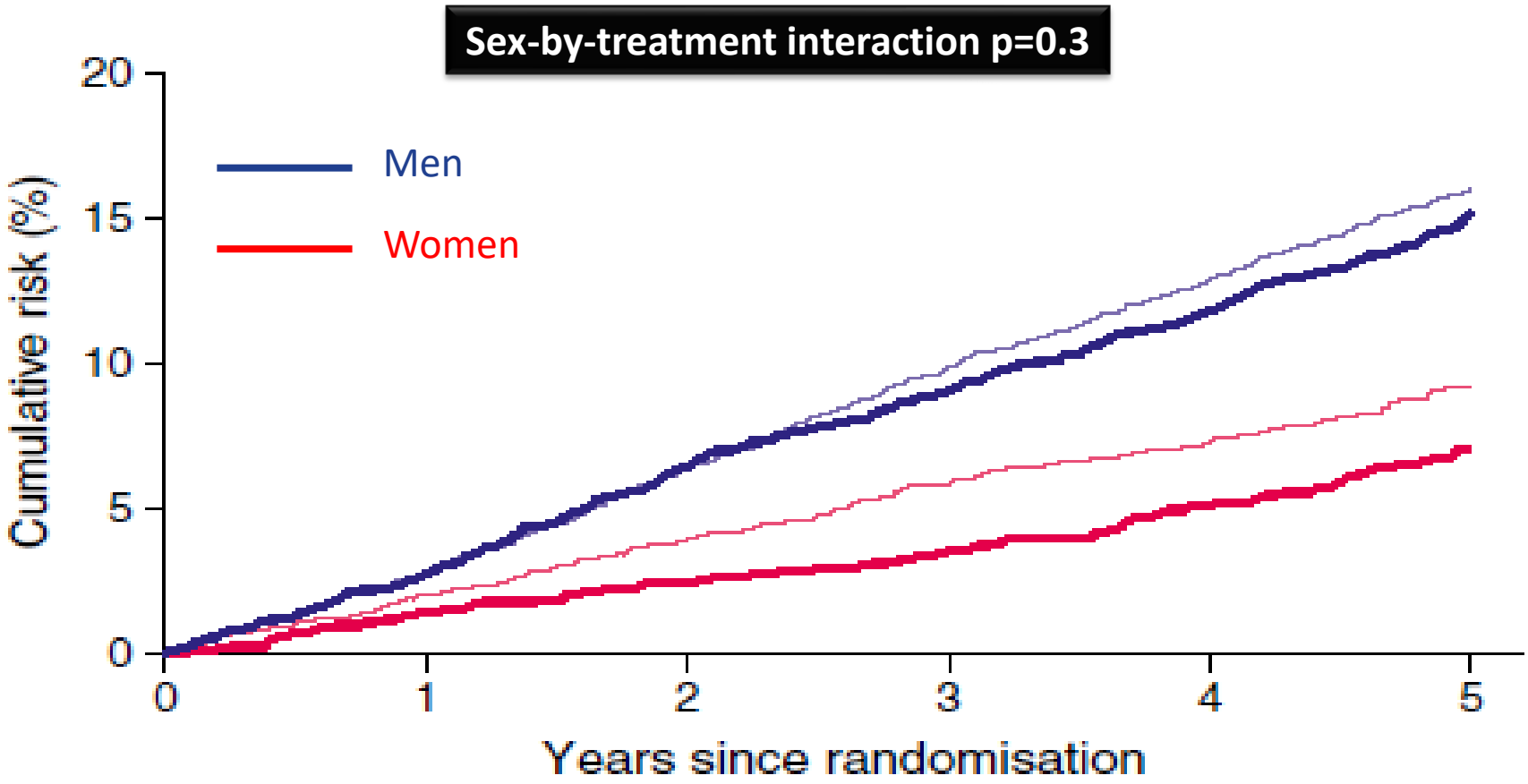
Subgroup	Fenofibrate	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	% of events (no. in group)			
Overall	10.52 (2765)	11.26 (2753)		
Sex				0.01
Female	9.05 (851)	6.64 (843)		
Male	11.18 (1914)	13.30 (1910)		



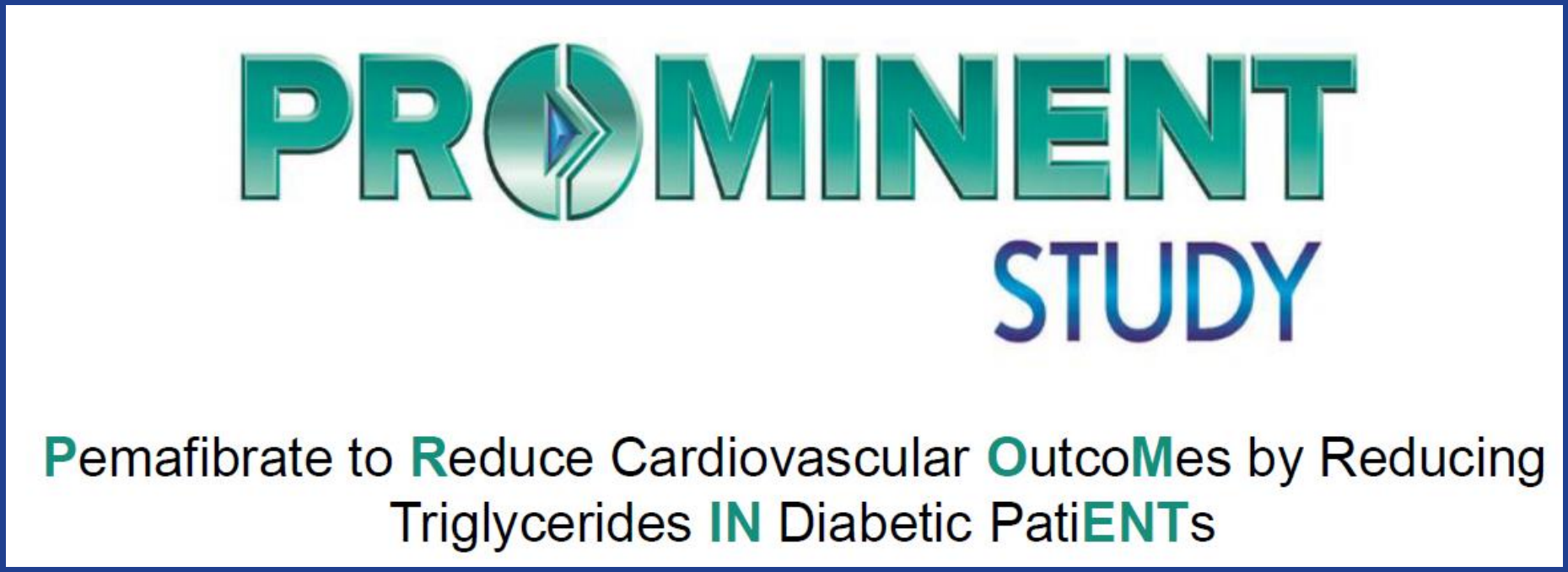
N Engl J Med 2010;362:1563-74

FIELD: Fenofibrate in 9795 people with type 2 DM

	Placebo (n=4900)	Fenofibrate (n=4895)
General characteristics		
Male	3067 (63%)	3071 (63%)



Lancet 2005;366:1849-61, Diabetologia 2014;57:2296-2303



- **Female Enrollment Target: 20-30%**
- **200 events in women before study may be terminated**

AHA/ACOG PRESIDENTIAL ADVISORY

Promoting Risk Identification and Reduction of Cardiovascular Disease in Women Through Collaboration With Obstetricians and Gynecologists

A Presidential Advisory From the American Heart Association and the American College of Obstetricians and Gynecologists

An optimal well-woman OB/GYN visit should include a thorough family history, screening for and targeted review of CV risk factors (including those unique to women), and lifestyle counseling to improve CV risk factors with the goal of preventing future CV events.

Circulation. 2018;137:e843-e852

Conclusions