

# **Dyslipidemia in women: Who should be treated and how ?**

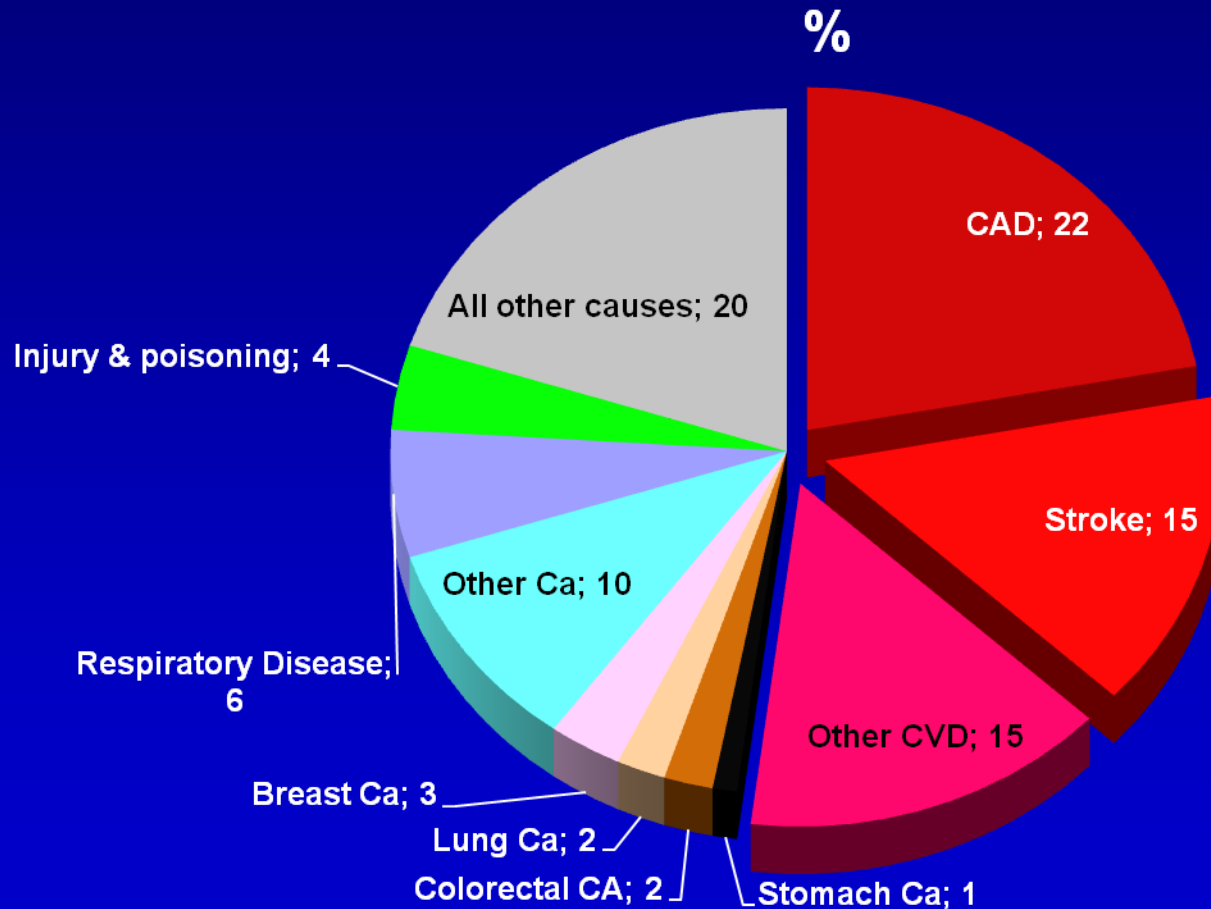
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**Professor of Cardiology**

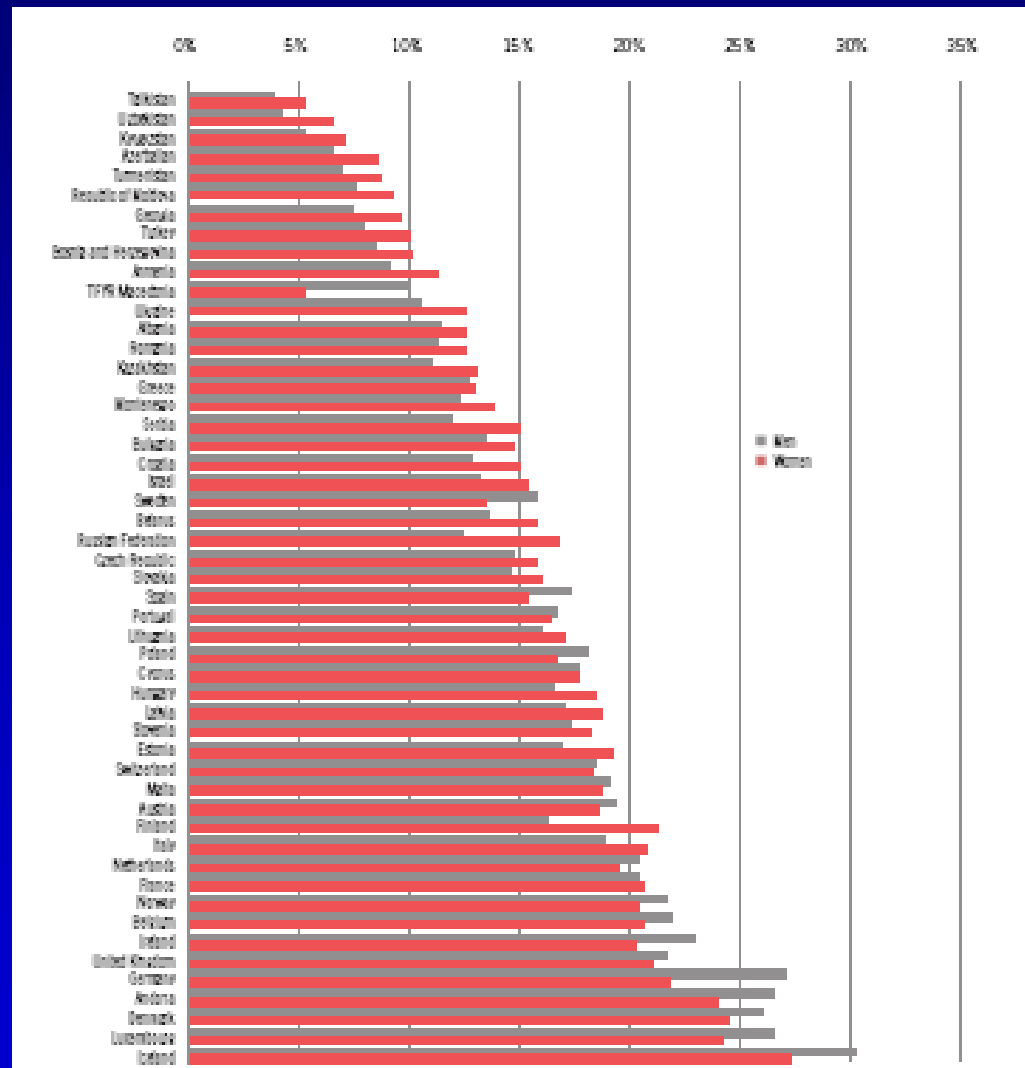
***Hacettepe University Faculty of Medicine***

***Ankara, Turkey.***

# Cause of Death in Women: European Cardiovascular Statistics 2012



# Prevalance of hypercholesterolemia above 6.2 mmol/l (240 mg/dl) by gender in Europe



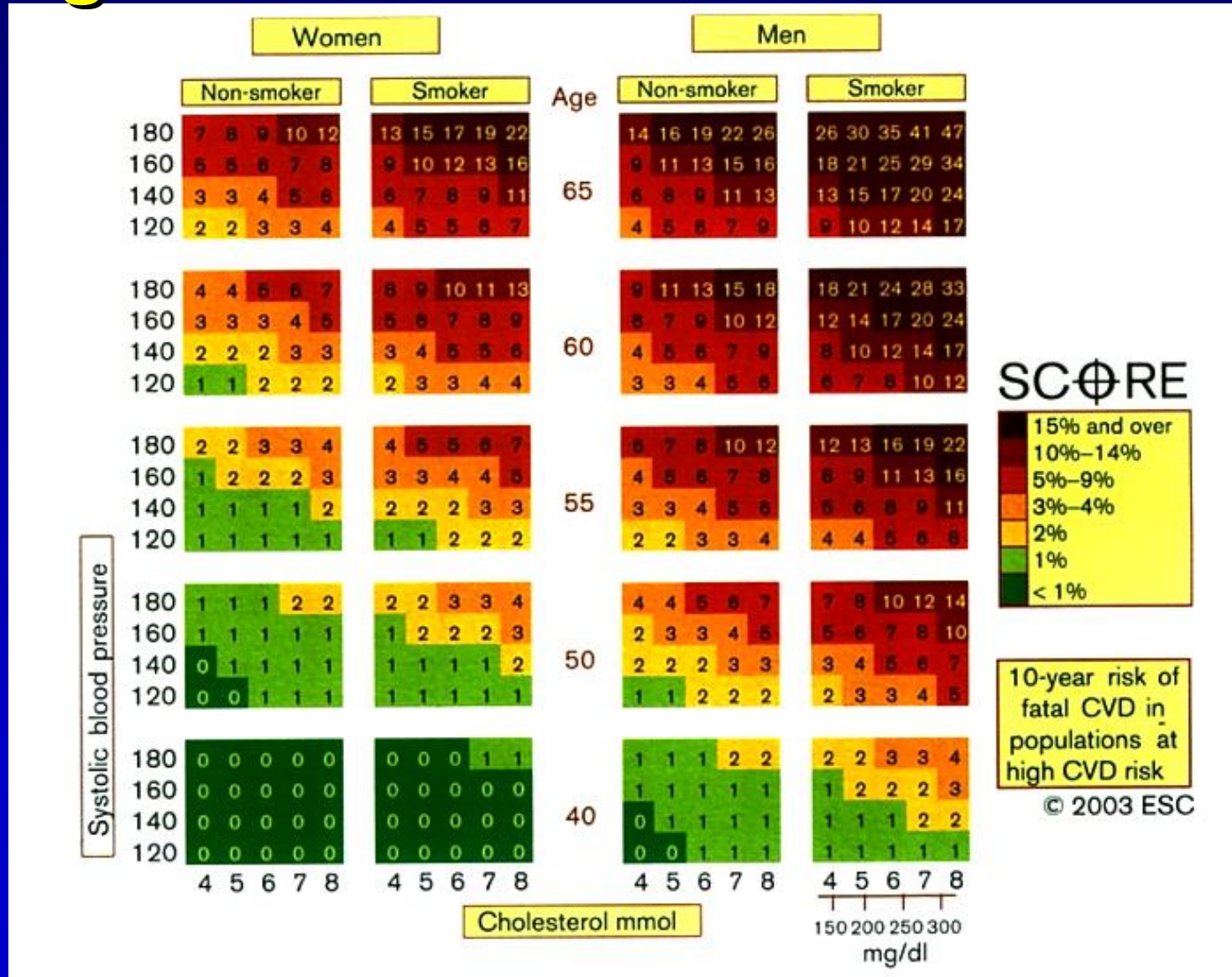
# Ranking and Magnitude of Risk Differs in Two Genders:

21 y FU Copenhagen City Heart Study  
(n=12077, women 6478)

Ranking by relative risk (RR)

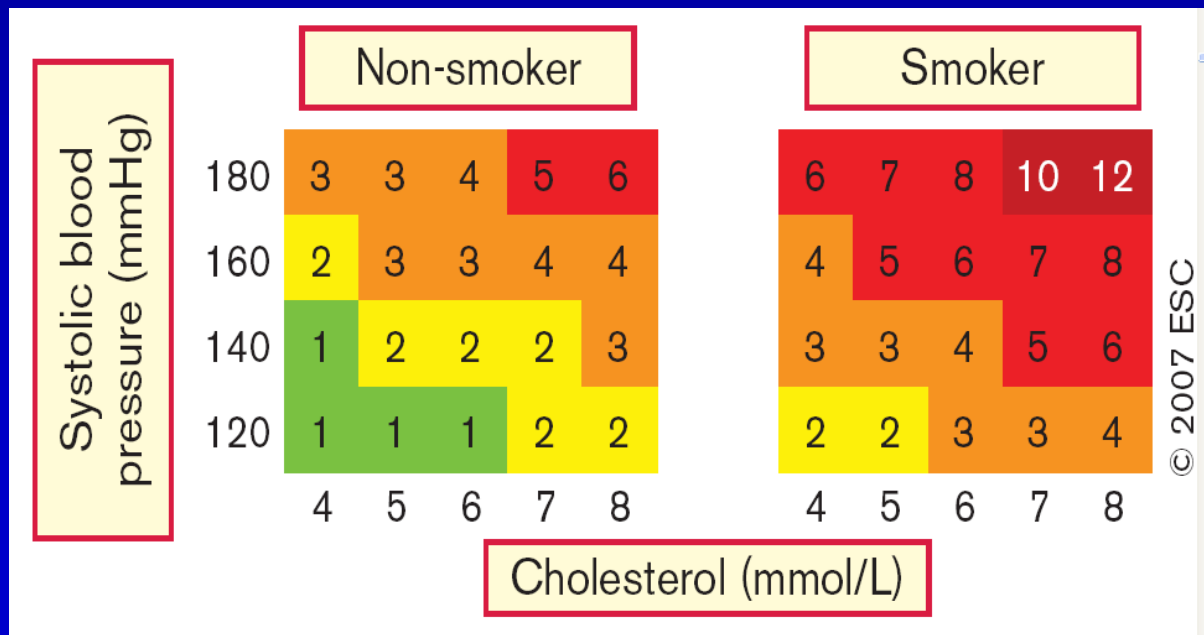
Men		RR	%	Women		RR	%
1	Diabetes	1.69	4	1	Diabetes	2.74	2
2	Hypertension	1.46	48	2	Smoking	2.02	58
3	Smoking	1.41	71	3	Hypertension	1.42	40
4	Physical inactivity	1.28	20	4	Physical inactivity	1.36	19
5	No daily alcohol intake	1.24	56	5	Hypertriglyceridemia	1.33	19
6	Hypercholesterolemia	1.22	47	6	Hypercholesterolemia	1.23	57
7	Obesity	1.20	57	7	Obesity	1.19	39
8	Low or middle income	1.14	78	8	School education ≤ 10 years	1.28	89
9	Hypertriglyceridemia	1.06	40	9	Low or middle income	1.22	82
10	School education ≤ 10 years	1.01	84	10	No daily alcohol intake	0.99	88

# Principles of risk estimation and management are same for both sexes



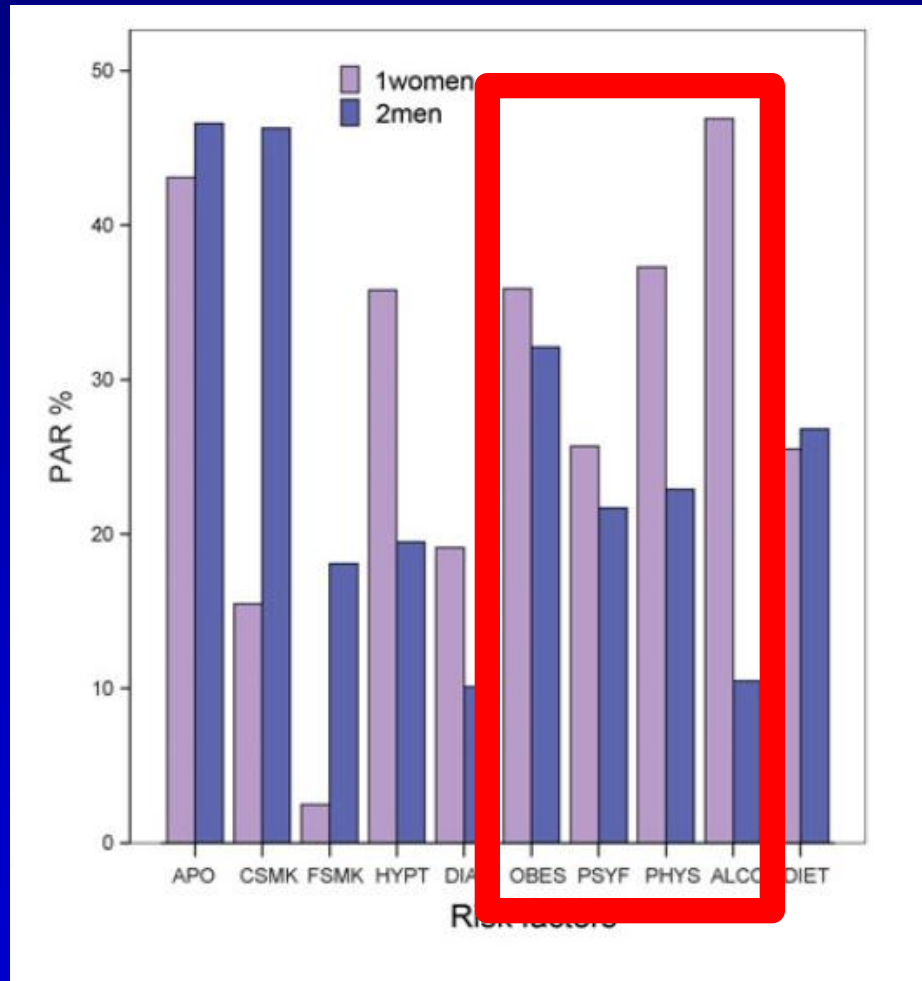
# A low absolute risk in a younger women may conceal a high relative risk:

- Extrapolate to older age
- Use relative risk chart
- Lifestyle advice to prevent risk



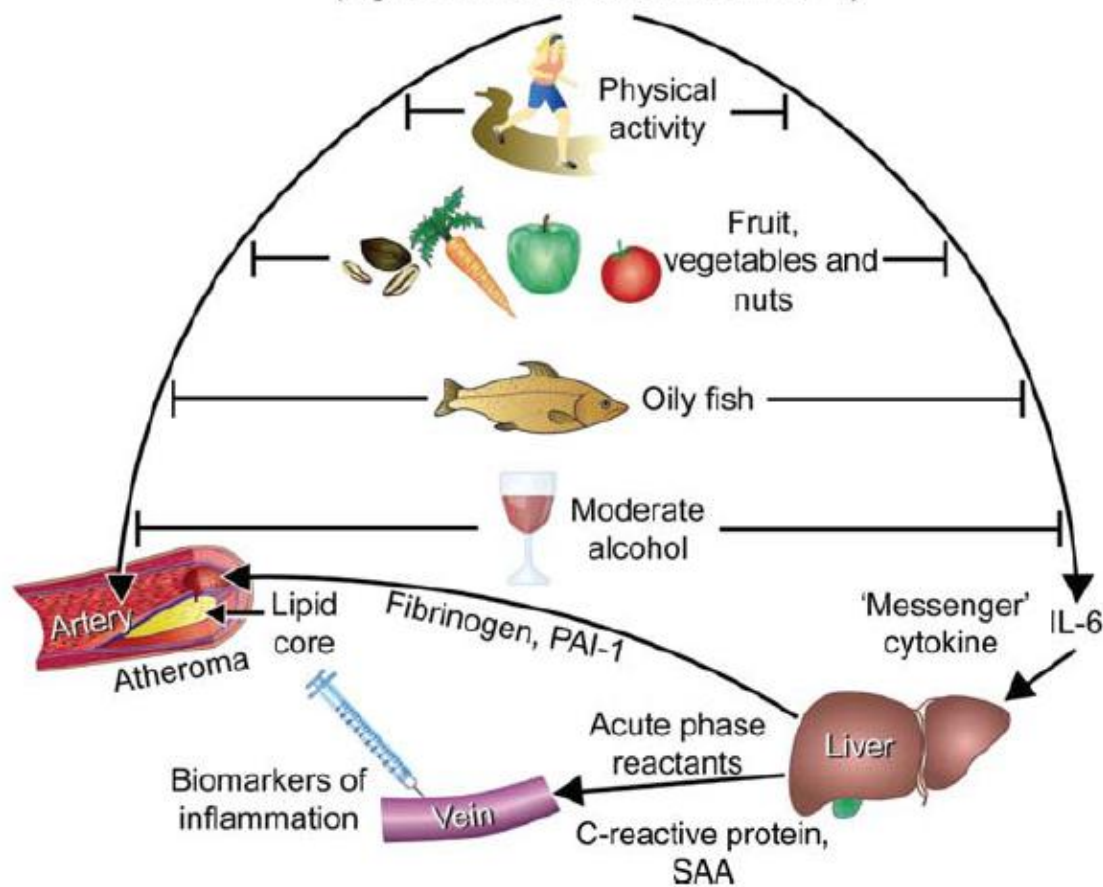
# INTERHEART:

## The PAR for Lifestyle Factors Significantly Higher in Women





Proinflammatory cytokines  
(e.g. IL-1, TNF, IL-18, CD40L, MCP-1)





# Canadian Dyslipidemia Guidelines

Target lipid levels		Primary targets	
Risk level	Initiate treatment if:	LDL-C	Alternate
High CAD, PVD, atherosclerosis* Most patients with diabetes FRS ≥20% RRS ≥20%	Consider treatment in all patients	<2 mmol/L or ≥50% ↓ LDL-C Class I, level A	apoB <0.80 g/L Class I, level A
Moderate FRS 10%–19%	LDL-C >3.5 mmol/L TC/HDL-C >5.0 hs-CRP >2 mg/L Men >50 years Women >60 years Family history and hs-CRP modulates risk (RRS)	<2 mmol/L or ≥50% ↓ LDL-C Class IIa, level A	apoB <0.80 g/L Class IIa, level A
Low FRS <10%	LDL-C ≥5.0 mmol/L	≥50% ↓ LDL-C Class IIa, level A	



# ESC/EAS Dyslipidemia Guideline: Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class <sup>a</sup> /Level <sup>b</sup>	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class <sup>a</sup> /Level <sup>b</sup>	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class <sup>a</sup> /Level <sup>b</sup>	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class <sup>a</sup> /Level <sup>b</sup>	IIa/A	IIa/A	I/A	I/A	I/A

# ESC/EAS Dyslipidemia Guidelines 2011

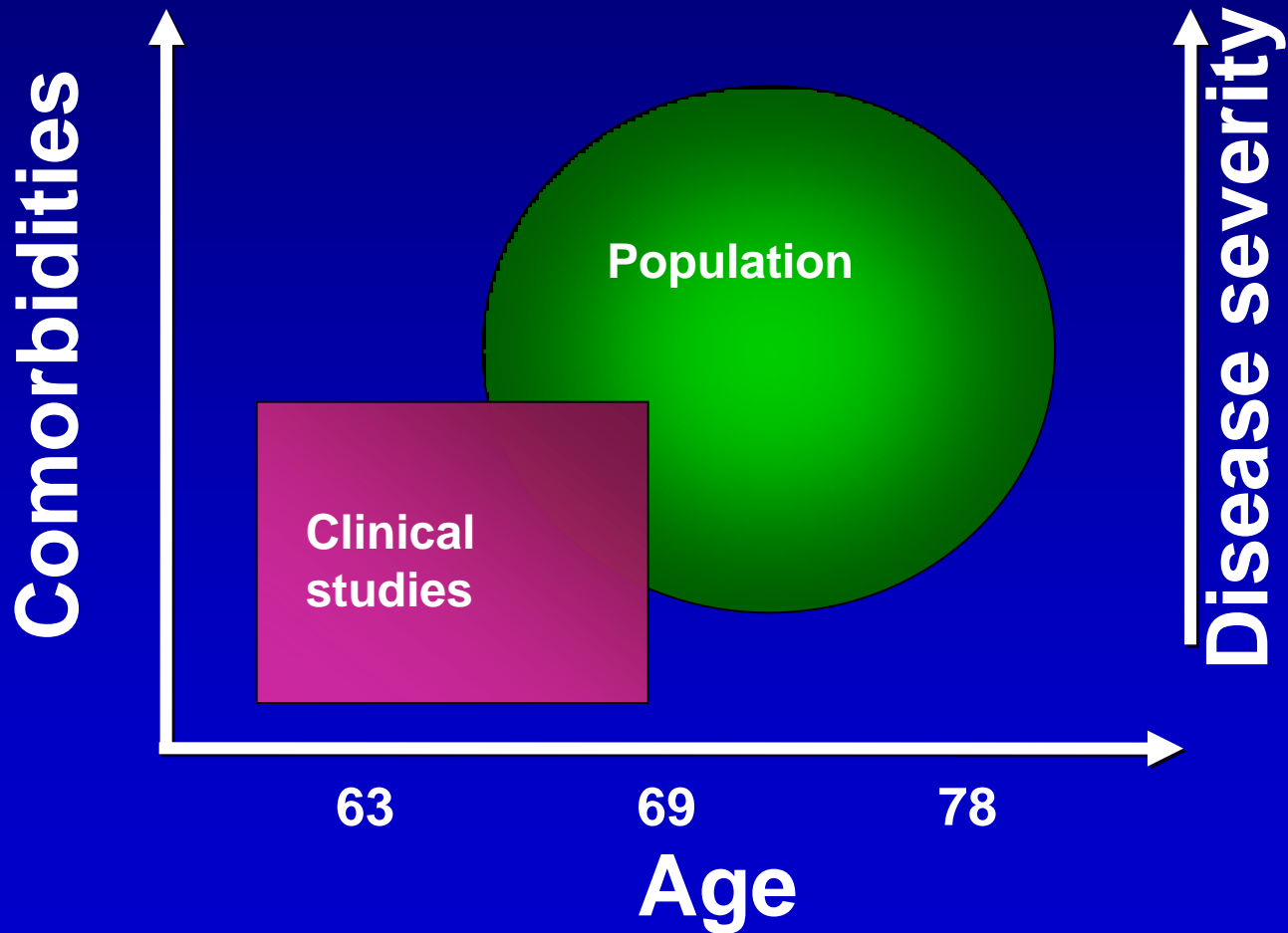
Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level $\geq 10\%$ ) the LDL-C goal is $< 1.8$ mmol/L (less than $\sim 70$ mg/dL) and/or $\geq 50\%$ LDL-C reduction when target level cannot be reached.	I	A
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level $\geq 5$ to $< 10\%$ ) an LDL-C goal $< 2.5$ mmol/L (less than $\sim 100$ mg/dL) should be considered.	IIa	A
In subjects at MODERATE risk (SCORE level $> 1$ to $\leq 5\%$ ) an LDL-C goal $< 3.0$ mmol/L (less than $\sim 115$ mg/dL) should be considered.	IIa	C

# **Same medications used, Response to Therapy in Women is Different**

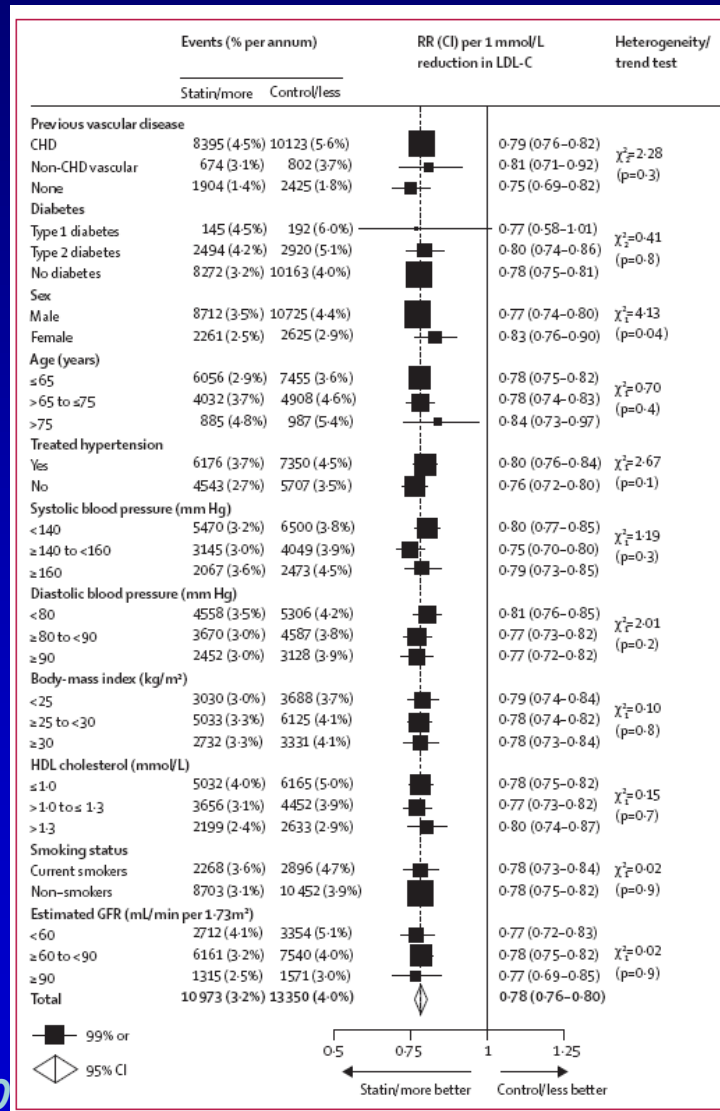
- **Lower body weight**
- **Higher proportion of fat**
- **Different endogenous hormone levels**
- **Differences in enzyme activities involved in drug metabolism**
- **Lower GFR**

**Are statins just as  
beneficial in women ?**

# Women are underrepresented in trials

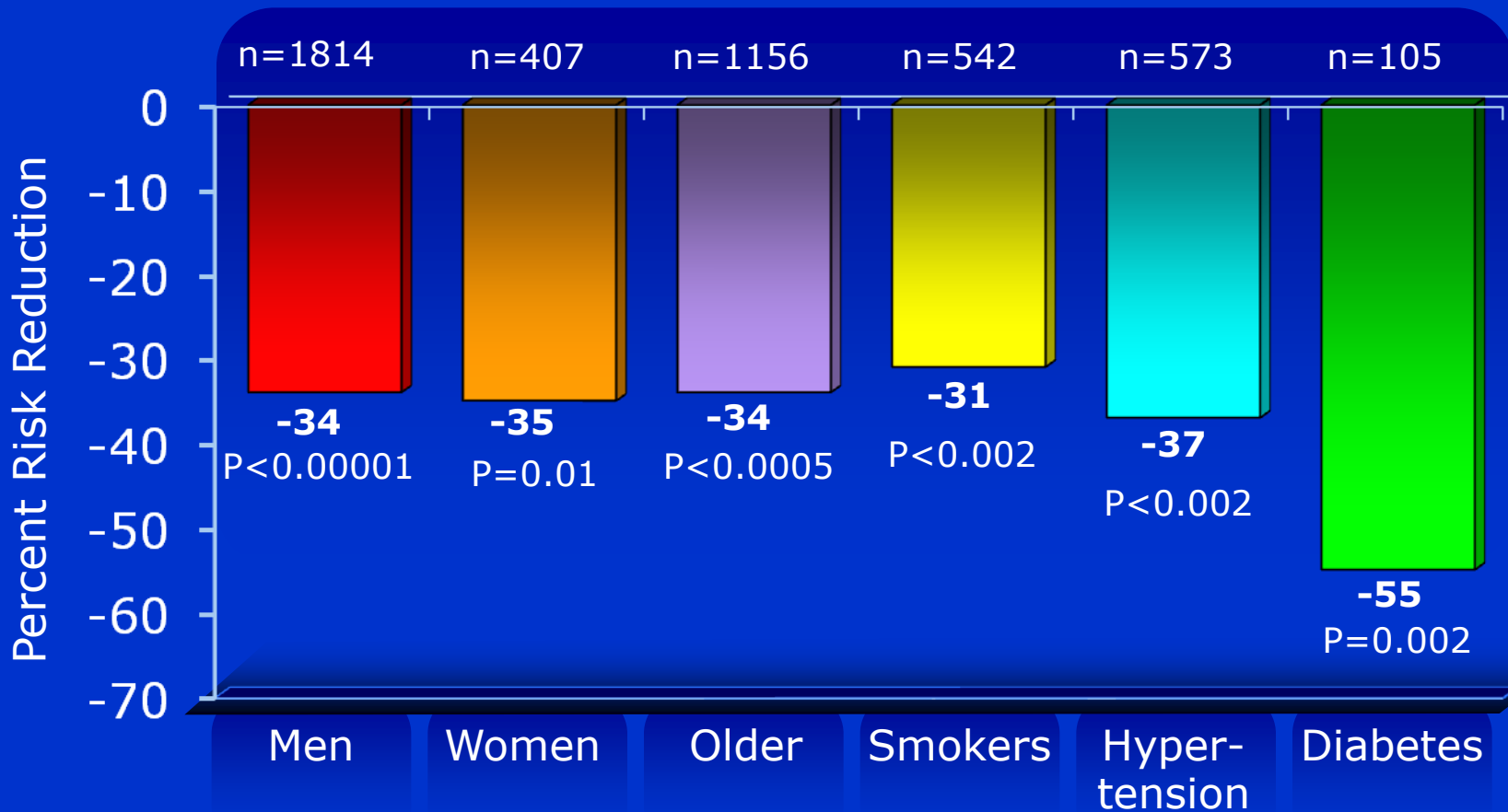


# CTT: Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol



# Secondary Prevention:

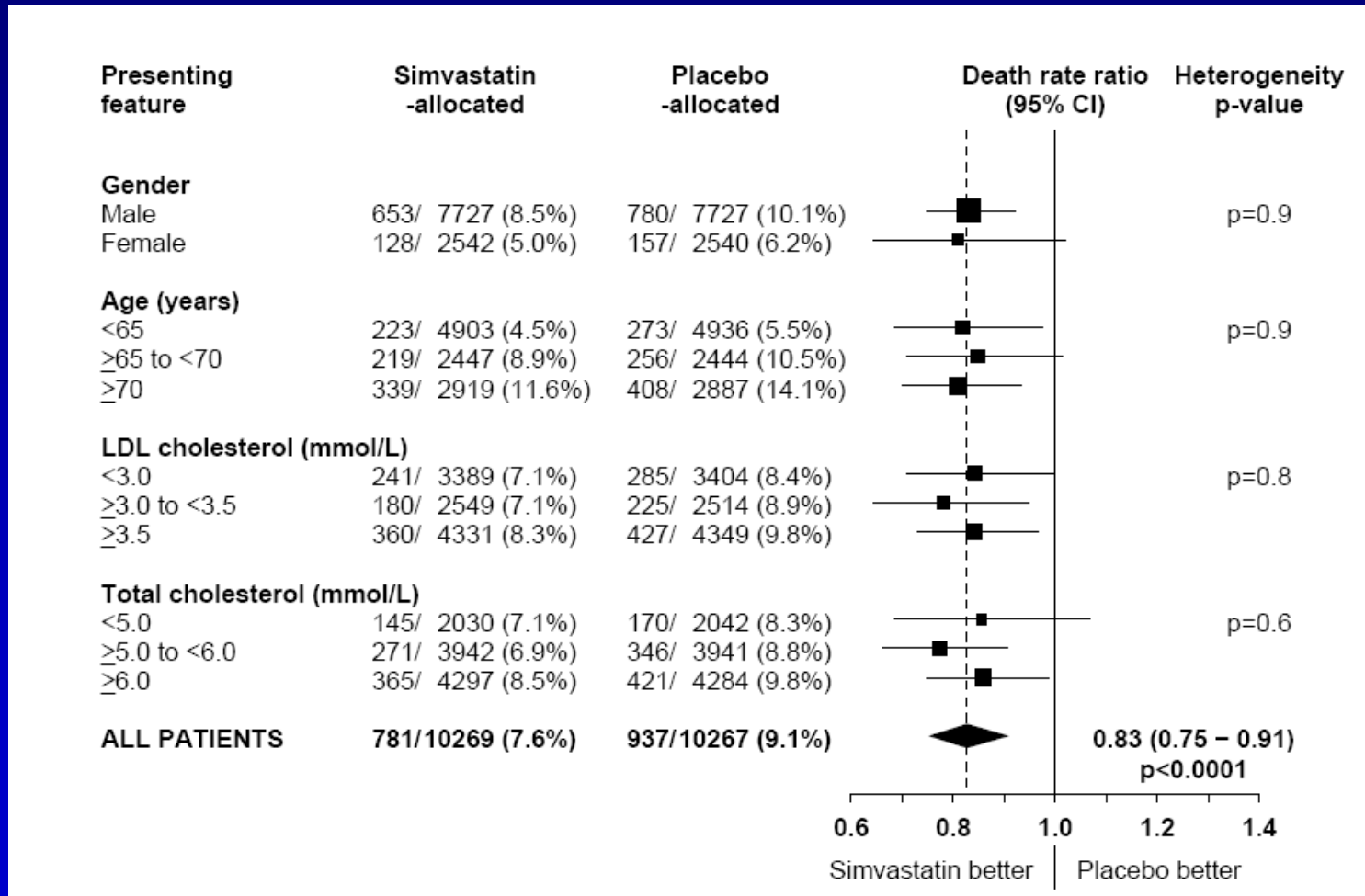
Coronary Events were reduced to same extent in both genders in 4S





# HPS:

## Statin reduces vascular deaths 17 % in men, 19 % in women with DM or CVD

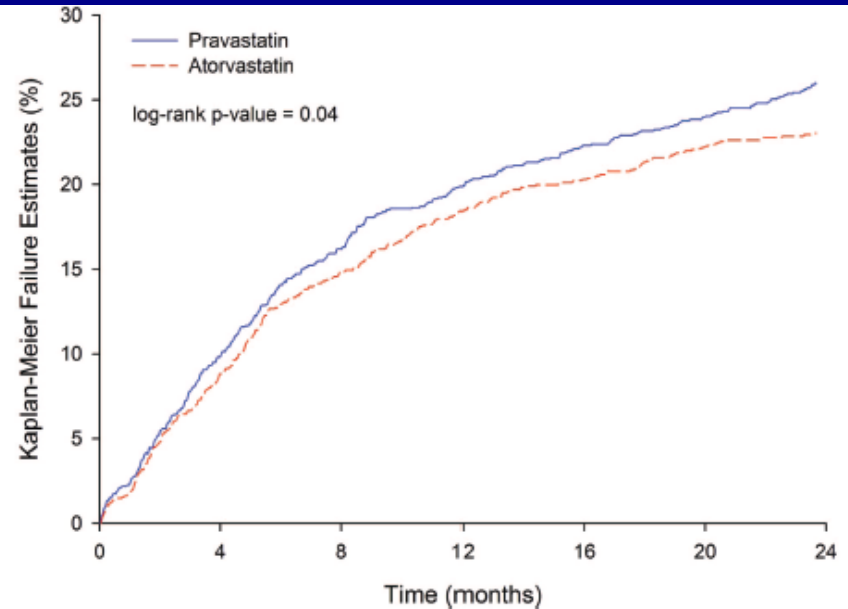
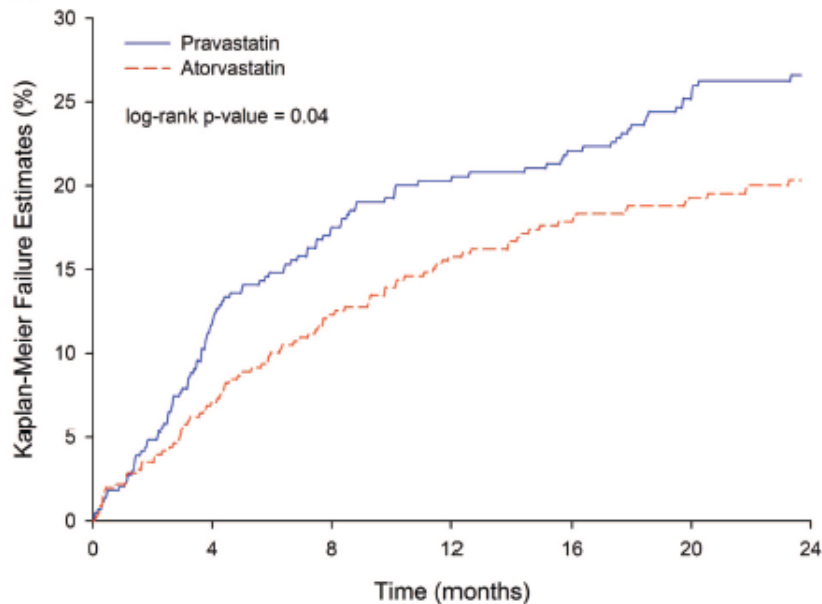


# How about statin use in ACS ?

## Benefit of Intensive Statin Therapy in Women Results From PROVE IT-TIMI 22

Women

Men



**Should statins be used  
for primary prevention in  
women ?**

# Meta-analysis of Drug Treatment Studies in Primary Prevention in Women: No change in total and CV mortality

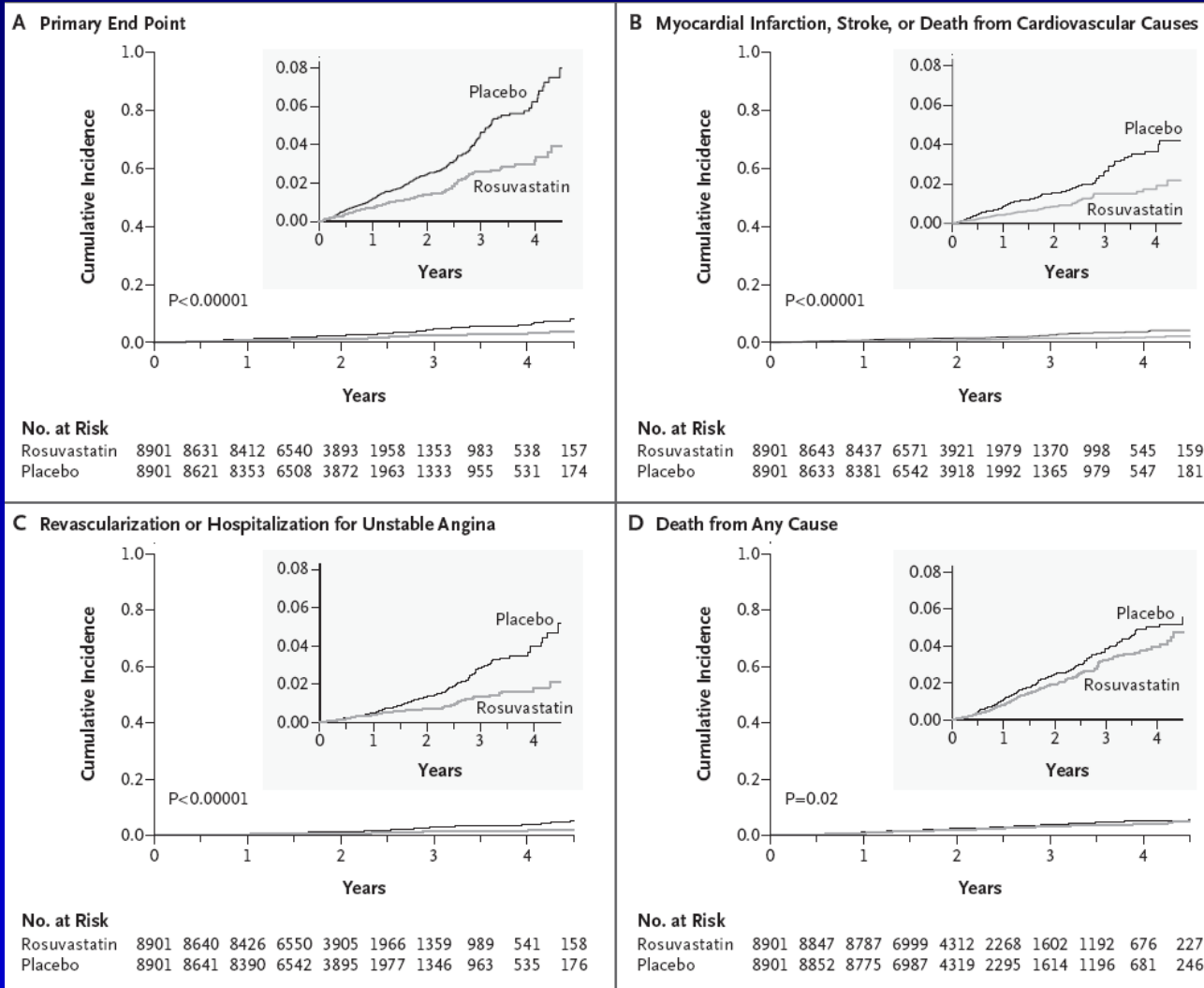
	Placebo, No.		Intervention, No.		RR (95% CI)	P Value for Heterogeneity
	Events	At Risk	Events	At Risk		
<b>Total Mortality</b>						
Colestipol	21	583	20	601	0.92 (0.51-1.69)	
ACAPS	5	227	0	218	0.09 (0.01-1.70)	
AFCAPS/TEXCAPS	7	498	11	499	1.53 (0.62-3.81)	
ALLHAT	NR†	2540	NR†	2511	0.98 (0.83-1.17)	
Total and summary	UC	3848	UC	3829	0.95 (0.62-1.46)	.98
<b>CHD Mortality</b>						
Colestipol	9	583	10	601	1.08 (0.44-2.63)	
ACAPS	1	227	0	218	0.35 (0.01-8.47)	
AFCAPS/TEXCAPS	0	498	1	499	2.99 (0.12-73.3)	
Total and summary	10	1308	11	1318	1.07 (0.47-2.40)	.87
<b>Nonfatal MI</b>						
ACAPS	3	227	1	218	0.35 (0.04-3.31)	
AFCAPS/TEXCAPS	6	498	4	499	0.69 (0.21-2.28)	
Total and summary	9	725	5	717	0.61 (0.22-1.68)	.70
<b>Revascularization</b>						
AFCAPS/TEXCAPS	8	498	7	499	0.87 (0.33-2.31)	
<b>CHD Events</b>						
AFCAPS/TEXCAPS	13	498	7	499	0.55 (0.22-1.34)	
ALLHAT	NR†	2540	NR†	2511	1.02 (0.81-1.28)	
ASCOT-LLA	17	963	19	979	1.10 (0.57-2.12)	
HPS	168	902	130	914	0.76 (0.62-0.94)	
Total and summary	UC	4903	UC	4903	0.87 (0.69-1.09)	.17

# Why was no benefit shown for women ?

- Underrepresentation of women in trials
- NNT to prevent one event high since risk is lower in women
- Small number of events
- Relatively young women included
- Follow up times 2.6 years
- Focusing on a lack of statistical significance is misleading

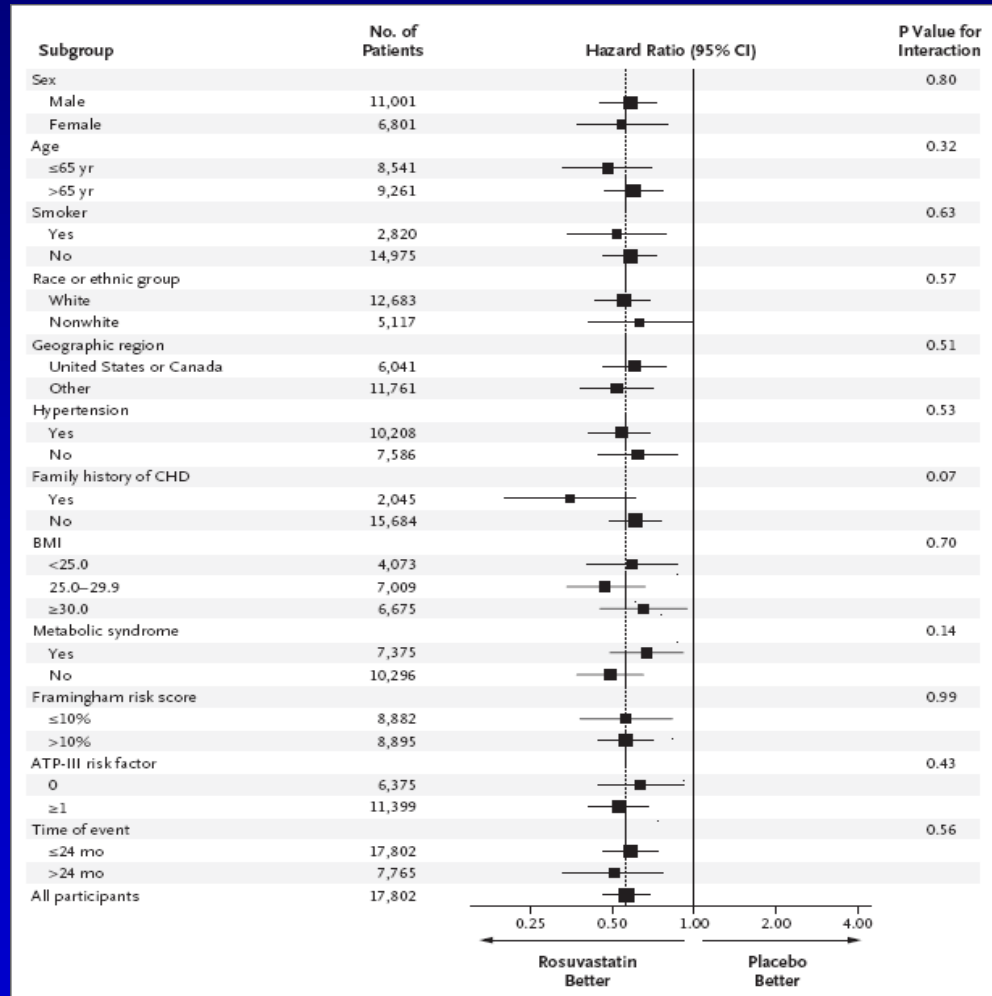
# JUPITER:

## Statins in Primary Prevention reduce CV events significantly



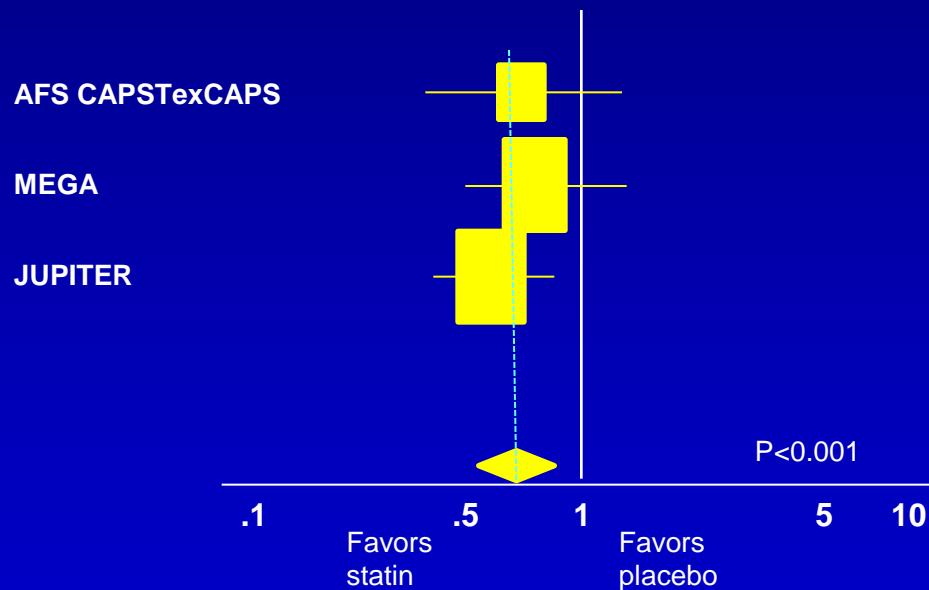
# JUPITER:

## Effects on CV outcome in subgroups show similar risk reduction in both genders

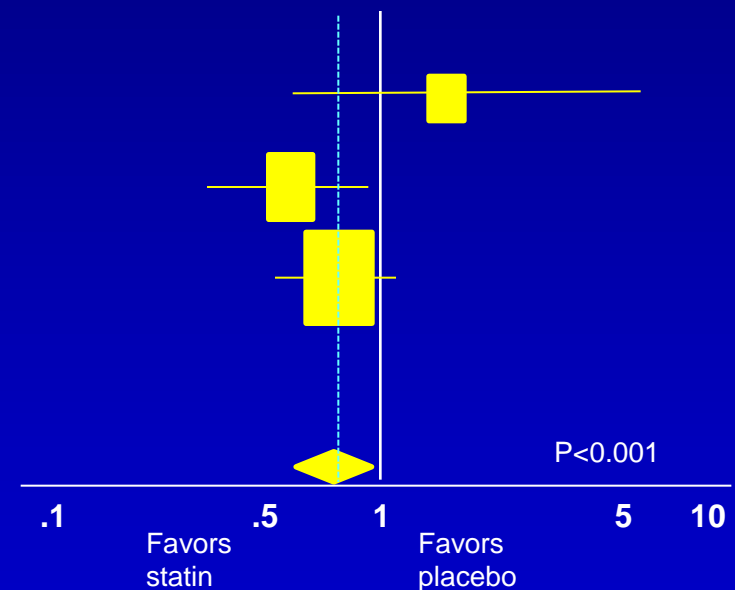


# Meta-analysis of Primary Prevention Trials in Women: 1/3 reduction in CV events

## TOTAL CVD

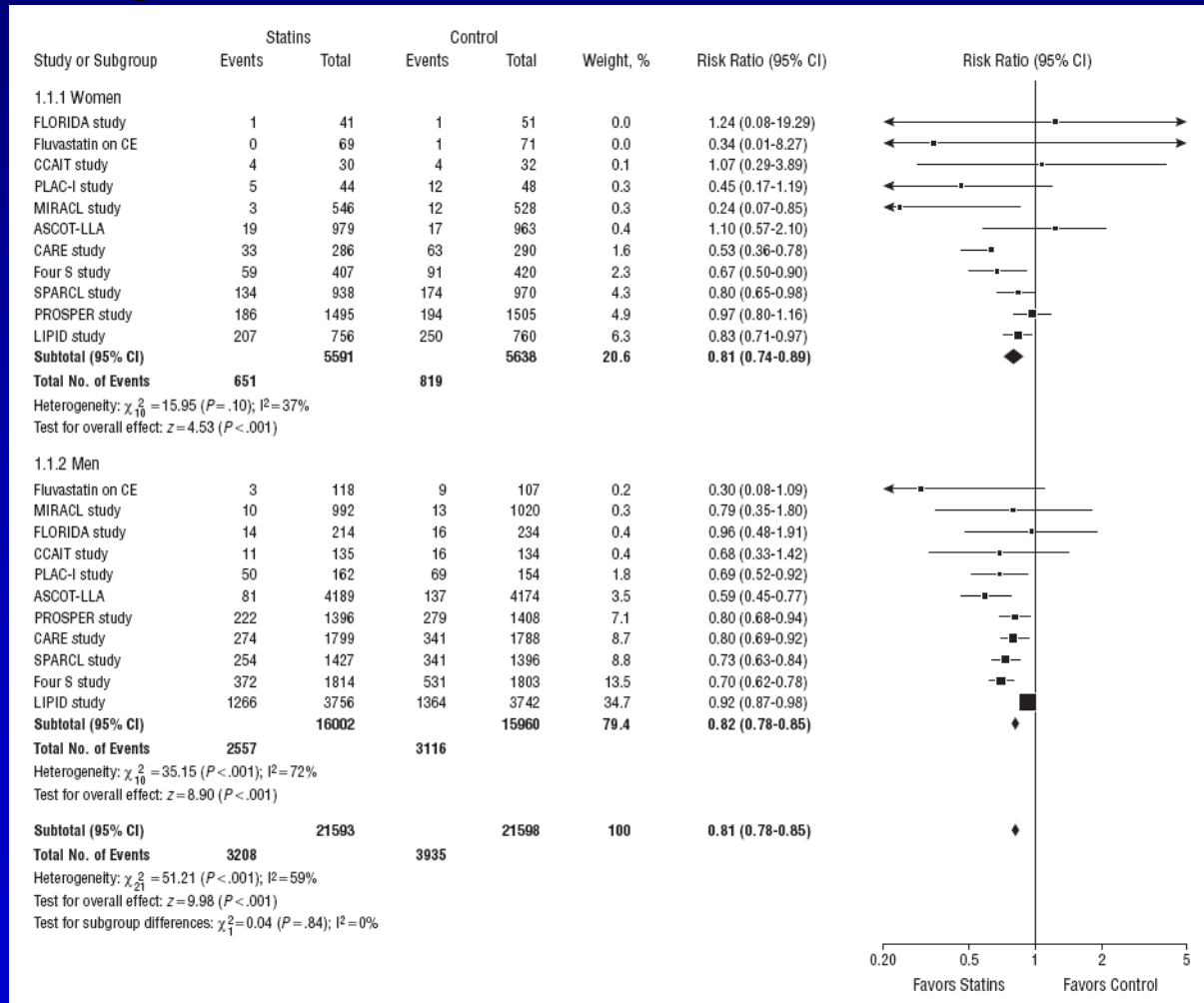


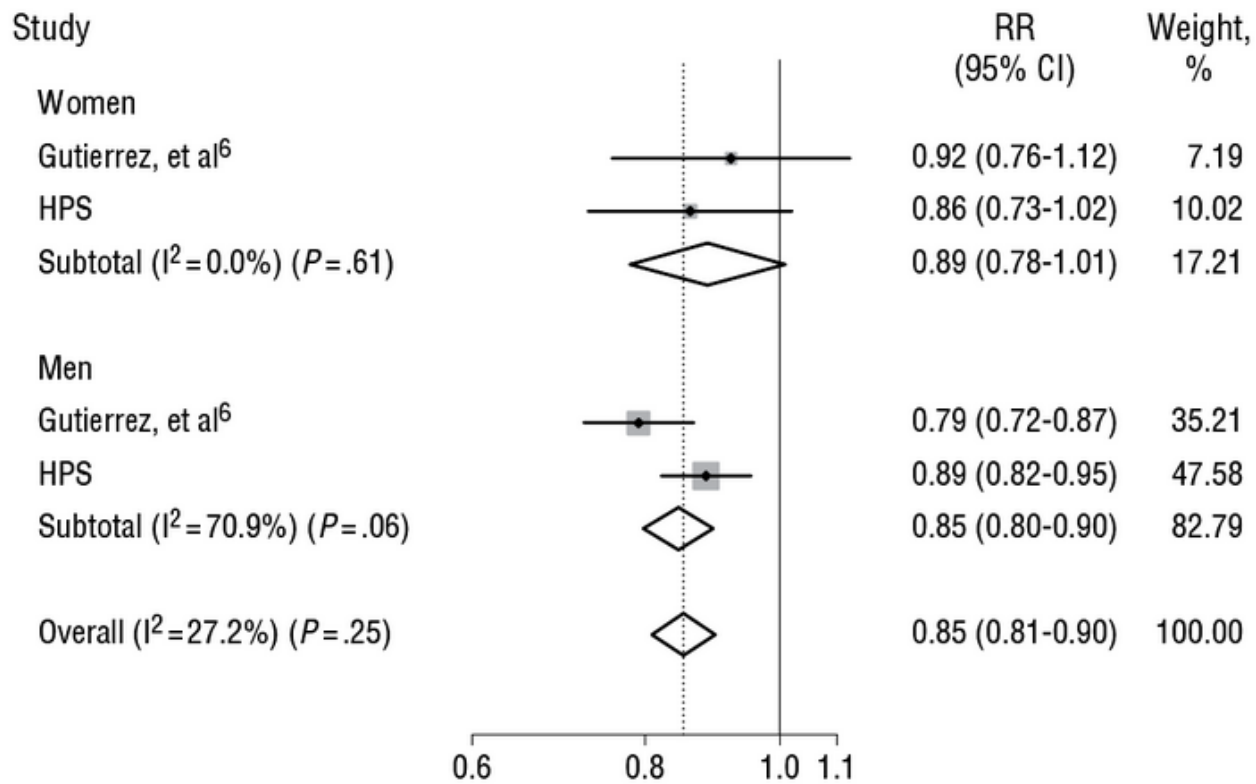
## TOTAL MORTALITY



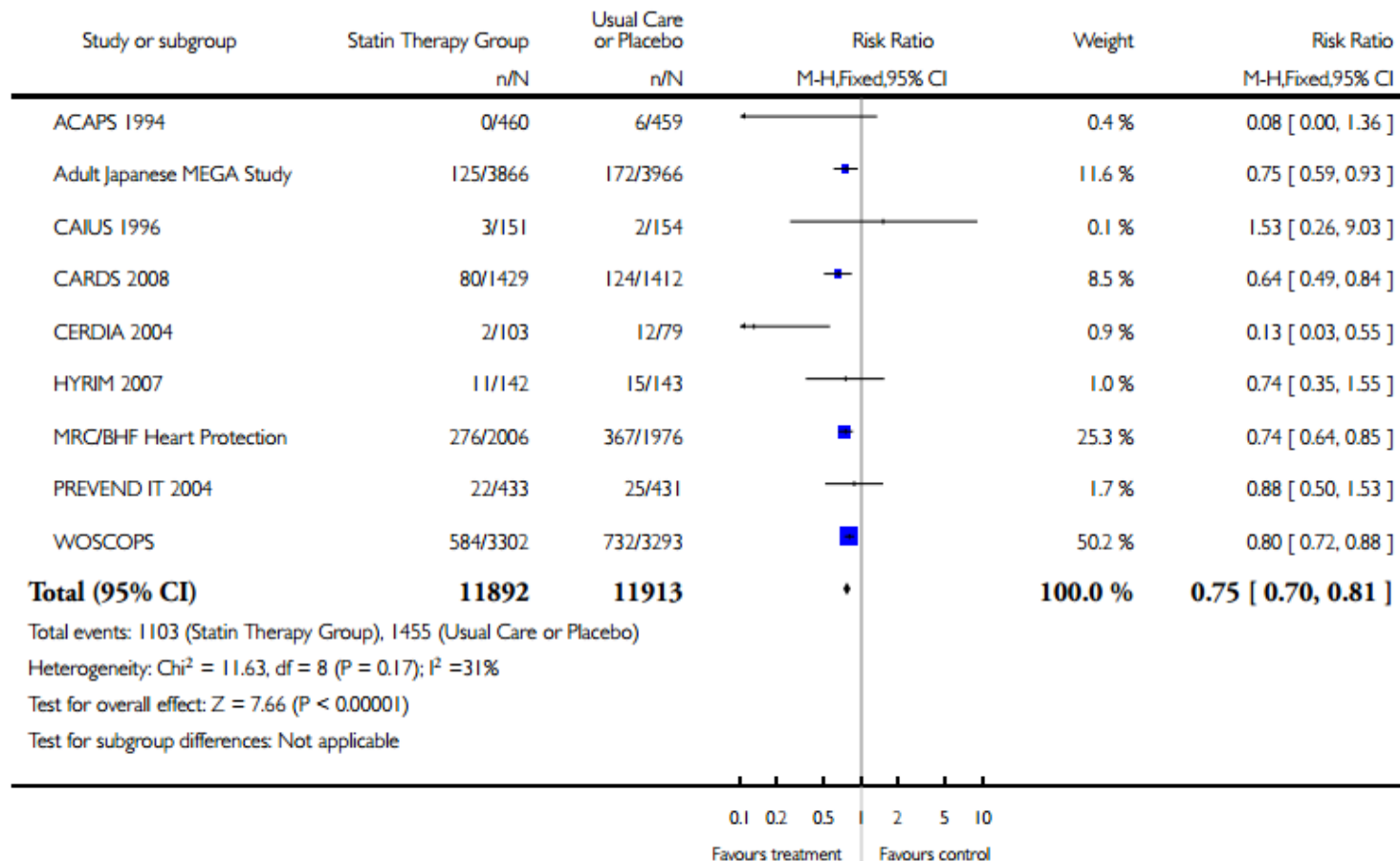


# All cause mortality and stroke not decreased for women on statin: A sex based meta-analysis

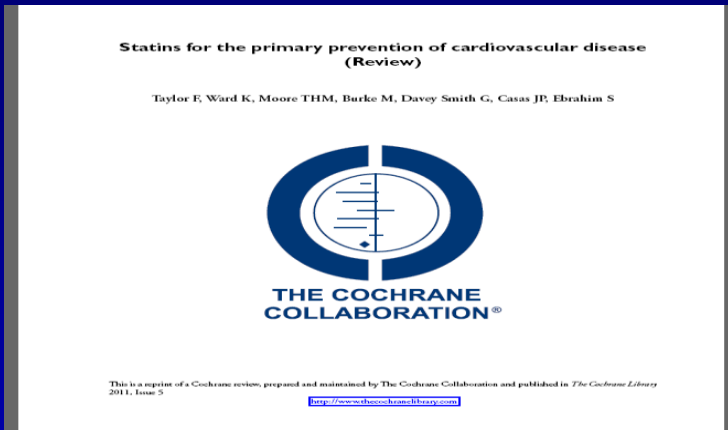




# Cochrane 2013 Analysis: Mortality and morbidity with statins in primary prevention: All cause mortality and CV events reduced



# Are statins effective in primary prevention in both genders ?

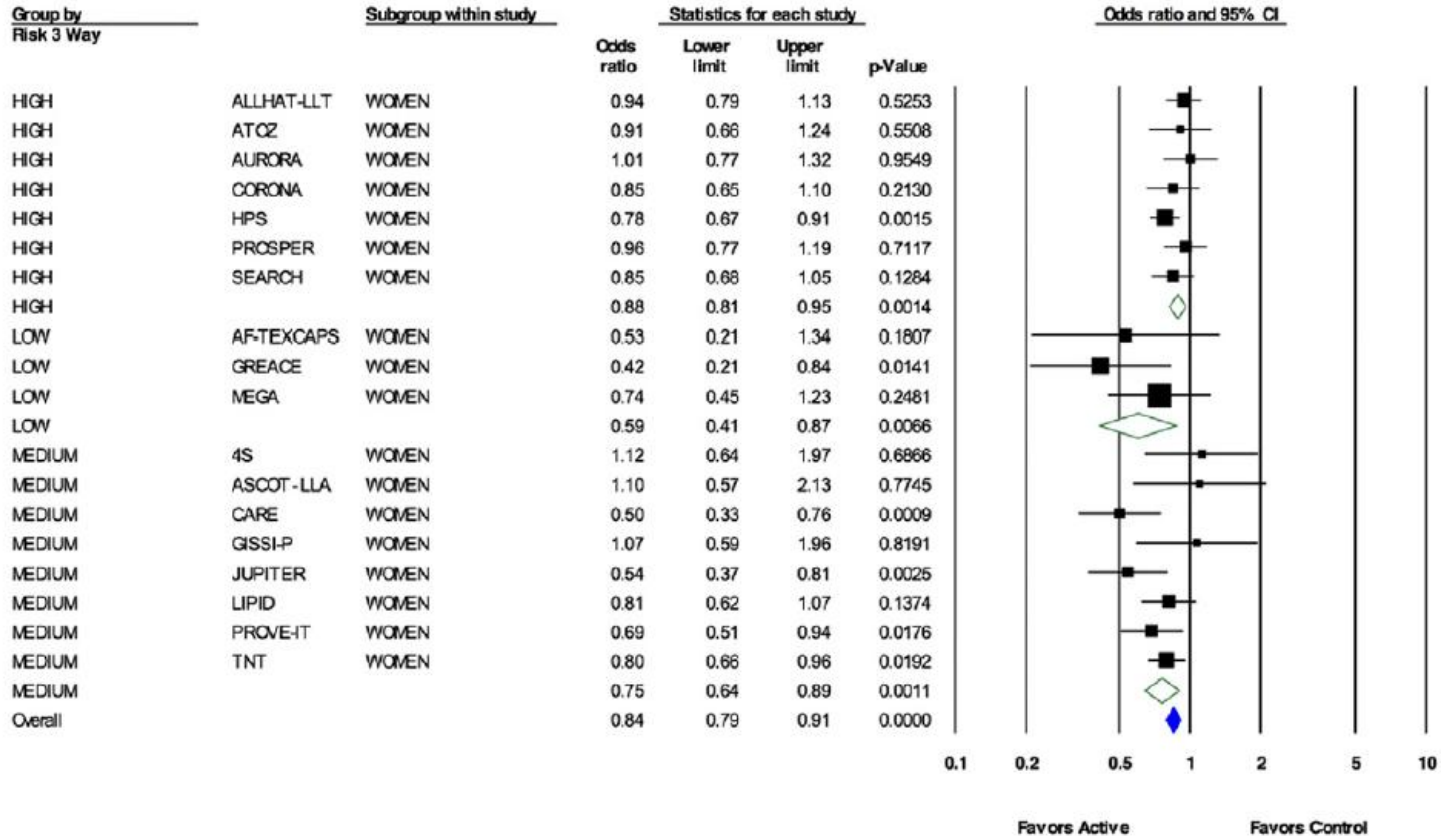


Overall the populations sampled within this review were white, male and middle aged. Therefore, caution needs to be taken regarding generalisability to women who are at lower risk of CVD events.

**Widespread use of statins in people at below a 1% annual all-cause mortality risk is not supported by the existing evidence**

- **Fourteen randomised control trials (16 trial arms; 34,272 participants) were included.**
- **All-cause mortality was reduced by statins (RR 0.83, 95% CI 0.73 to 0.95) as was combined fatal and non-fatal CVD endpoints (RR 0.70, 95% CI 0.61 to 0.79). Benefits were also seen in the reduction of revascularisation rates (RR 0.66, 95% CI 0.53 to 0.83).**

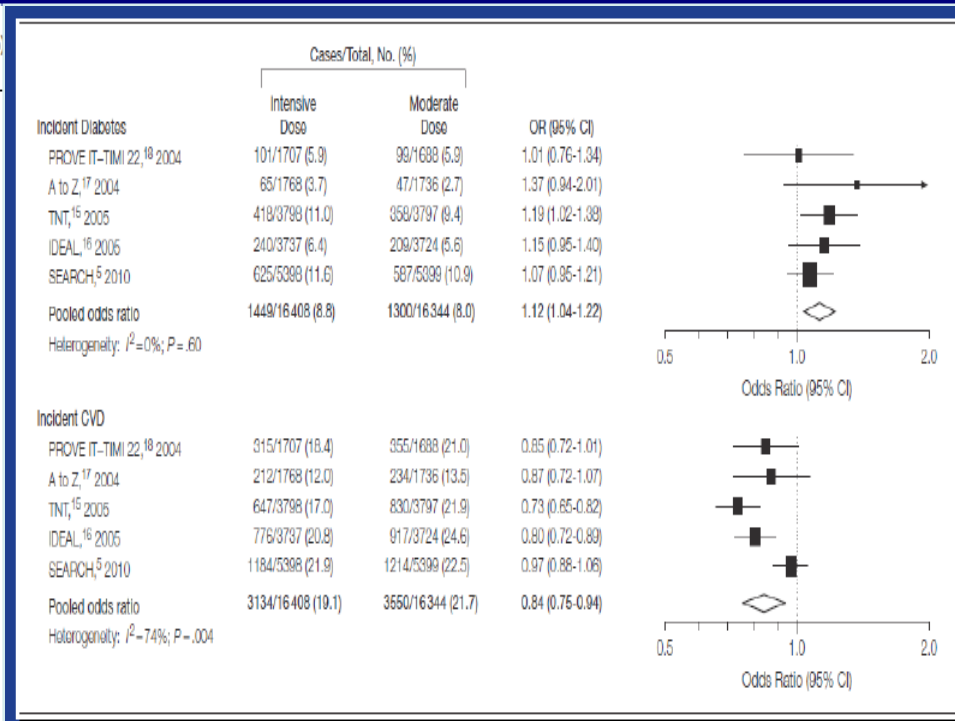
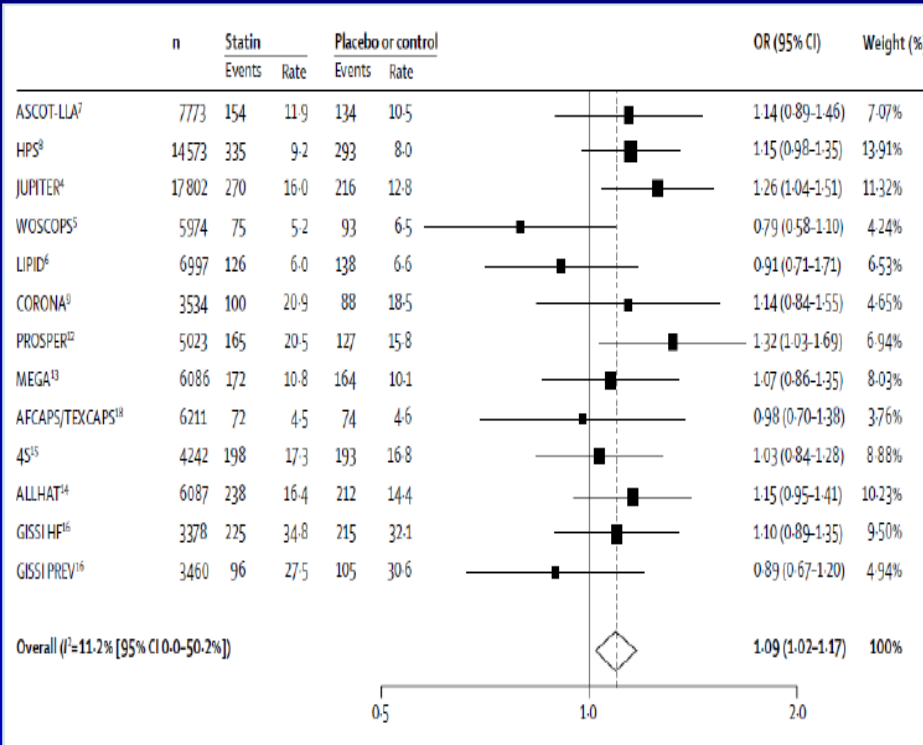
# Meta-Analysis of Statin Effects in Women Versus Men in Primary Prevention: Mortality and events reduced in all risk levels



All studies

**Other issues to be  
considered in primary  
prevention:  
Diabetes risk  
Cost**

# Statins diabetes and CV risk



*Lancet* 2010;375:735  
*JAMA* 2011;305:2556

# Statins and diabetes

- **The risk of developing diabetes is 1 in every 255 patients treated**
- **Higher dose of statins, elderly, patients with hypertension, multiple risk factors and metabolic syndrome**
- **HbA1c over 6 %**

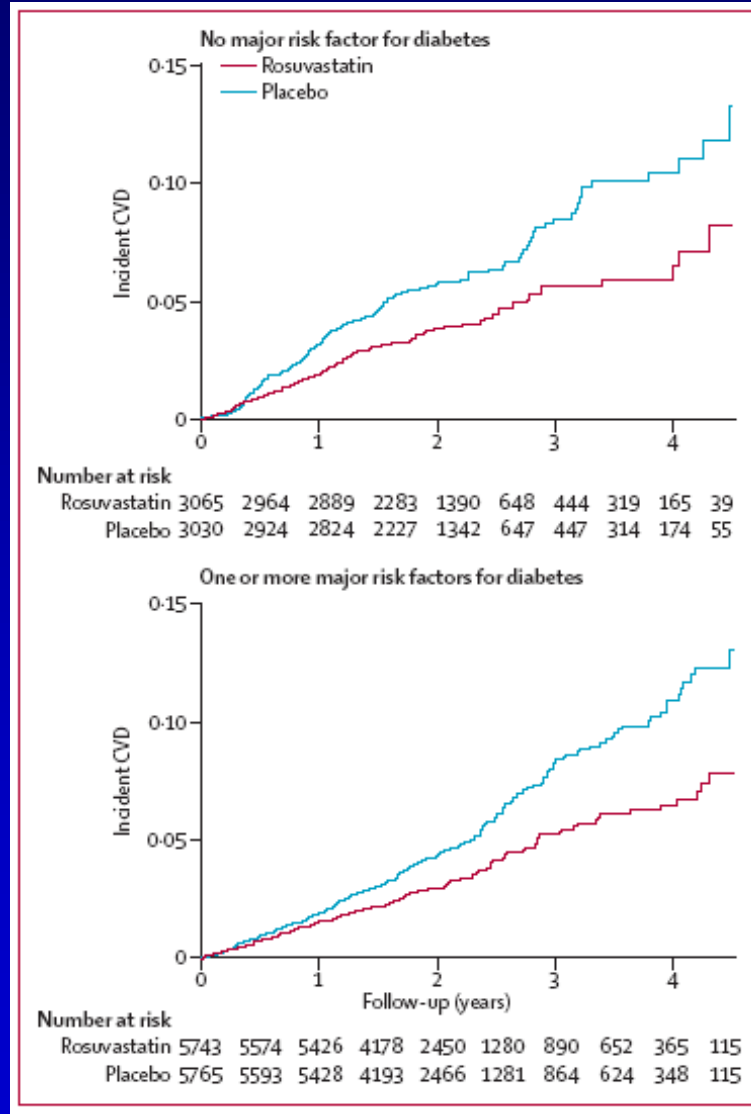


# Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the WHI Study

Table 5. Risk of Diabetes Mellitus (DM) by Statin Use at Baseline and 3-Year Follow-up in 125 575 Participants

Description	Statin Use Only at Baseline	Statin Use Only at 3-y Follow-up	Statin Use at Baseline and 3-y Follow-up	Never Use
Participants, No.	1531	9571	7076	107 397
Incident DM cases, No.	98	644	442	4294
Cumulative incidence rate, %	6.40	6.73	6.25	4.00
Unadjusted HR (95% CI) <sup>a</sup>	1.75 (1.43-2.14)	1.81 (1.67-1.97)	1.82 (1.65-2.00)	1 [Reference]
Adjusted HR (95% CI)				
Age and race/ethnicity <sup>b</sup>	1.65 (1.35-2.01)	1.79 (1.65-1.95)	1.81 (1.64-2.00)	1 [Reference]
Multivariate <sup>c</sup>	1.49 (1.19-1.86)	1.65 (1.51-1.81)	1.56 (1.41-1.74)	1 [Reference]
Propensity score <sup>d</sup>	1.49 (1.20-1.85)	1.63 (1.49-1.78)	1.43 (1.28-1.58)	1 [Reference]
Multivariate, including propensity score <sup>e</sup>	1.44 (1.15-1.80)	1.60 (1.47-1.75)	1.47 (1.32-1.64)	1 [Reference]

# Cardiovascular benefits exceeded the diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial



DM risk limited to subjects with high BMI, HbA1C, MS or obesity

# Statins in primary prevention: Cost effectiveness analysis

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Cite this as: *BMJ* 2011;342:d1672  
doi:10.1136/bmj.d1672

## ABSTRACT

**Objective** To assess the cost-effectiveness of low dose statins for primary prevention of vascular disease, incorporating current prices, non-adherence (reduced clinical efficacy while maintaining healthcare costs), and the results of the recently published JUPITER trial.

**Design** Cost-effectiveness analysis using a Markov model. Sensitivity analyses and Monte Carlo simulation evaluated the robustness of the results.

**Setting** Primary care in The Netherlands.

**Participants** Hypothetical populations of men and women aged 45 to 75 years without a history of vascular disease at different levels of risk for vascular disease (myocardial infarction and stroke) over 10 years.

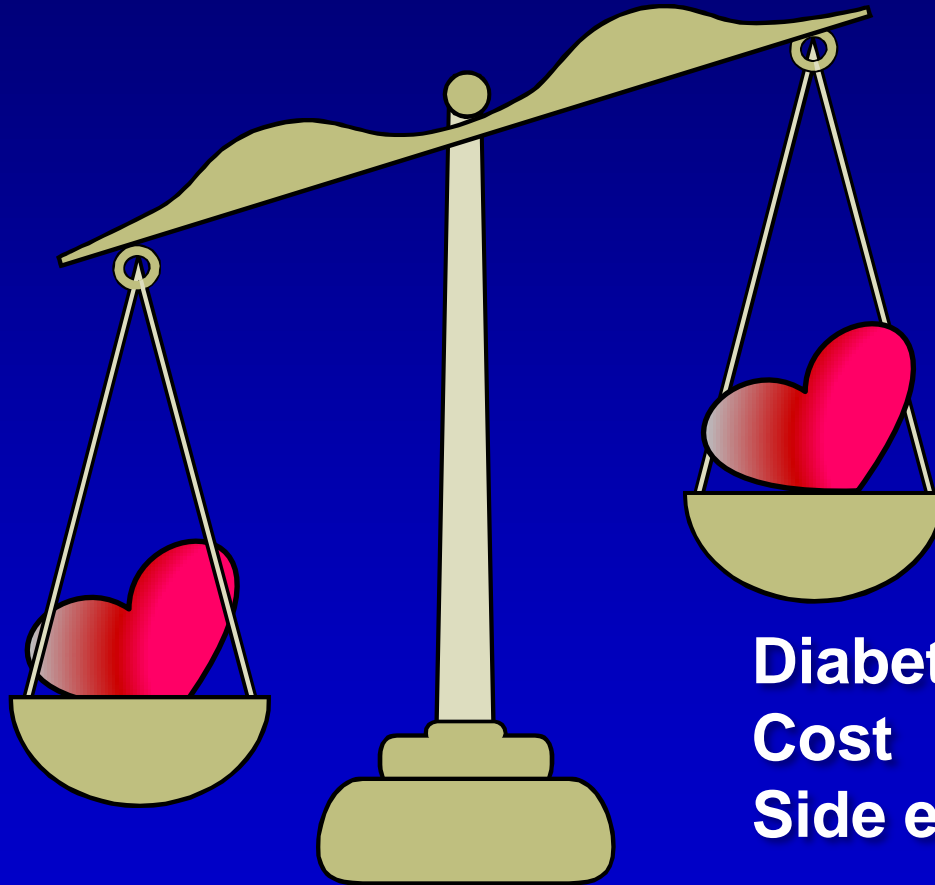
**Interventions** Low dose statin treatment daily versus no treatment for 10 years.

**Main outcome measures** Number of fatal and nonfatal vascular events prevented, quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios over 10 years.

**Results** Over a 10-year period, statin treatment cost €35 000 (£30 000, \$49 000) per QALY gained for men aged 55 years with a 10-year vascular risk of 10%. The incremental cost-effectiveness ratio improved as risk for vascular disease increased. The cost per QALY ranged from approximately €50 000 to €1 25 000 when the 10-year vascular risk for men aged 55 years was varied from 25% to 5%. The incremental cost-effectiveness ratio slightly decreased with age after the level of vascular risk was specified. Results were sensitive to the costs of statin treatment, statin effectiveness, non-adherence, disutility of taking medication daily, and the time horizon of the model.

**Conclusions** In daily practice, statin treatment seemed not to be cost-effective for primary prevention in populations at low risk of vascular disease, despite low costs of generic drug pills. Adherence to statin treatment needs to be improved to enhance the cost-effectiveness of the use of statins for primary prevention.

# Use of statins in low risk women



**CV benefits**

**Diabetes risk  
Cost  
Side effects**

# What other parameter can help us decide ?

- **Family history**
- **CRP levels, biomarkers**
- **Imaging**

**Problems in real life:**

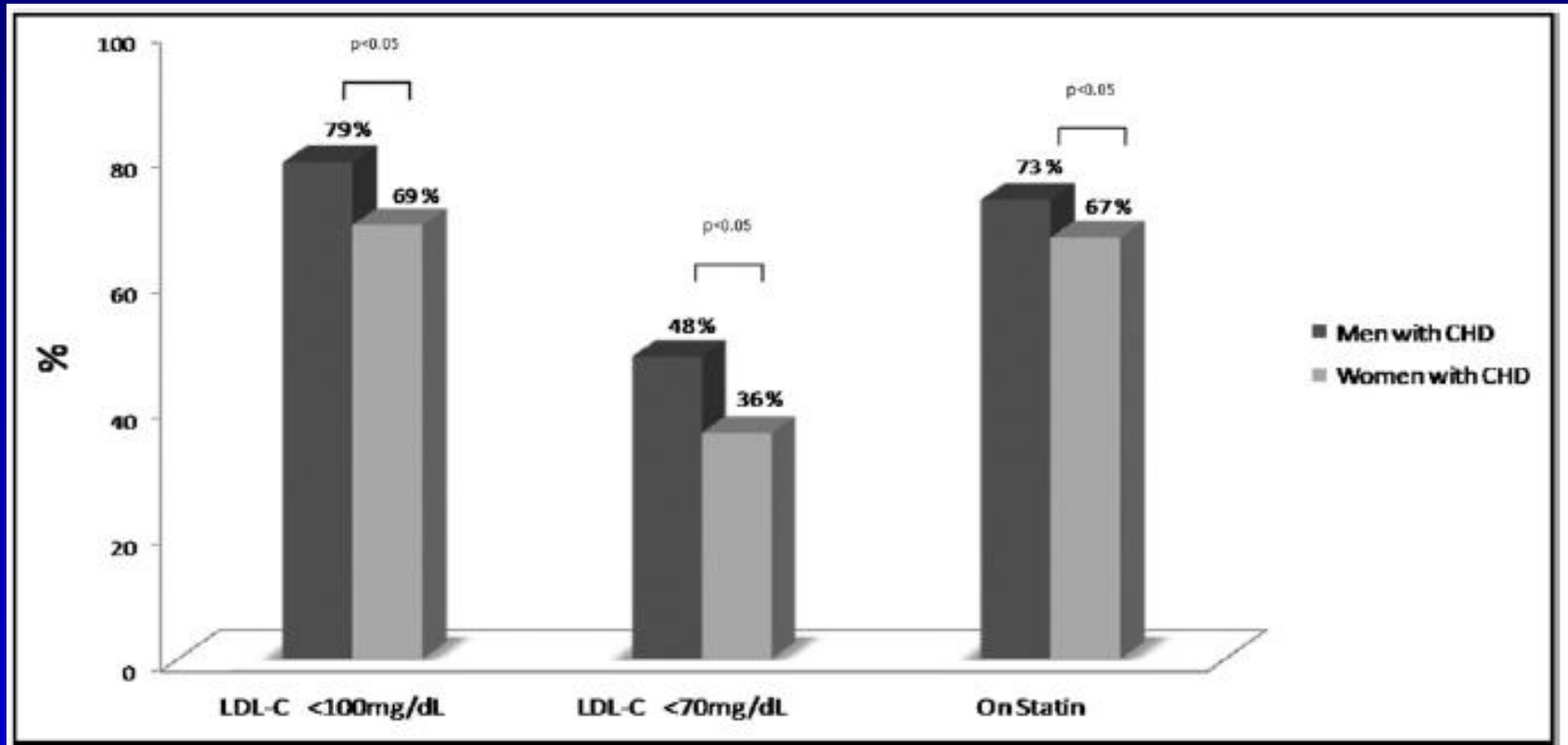
**Lack of recognition**

**Less aggressive treatment**

# Gender disparities in the assessment and management of cardiovascular risk in primary care: the AUSHEART Study

	Men (N = 2325) n (%)	Women (N = 2968) n (%)	Age-adjusted relative risk	P-value
Blood pressure-lowering therapy				
Low (<10%)	76 (38)	356 (45)	1.13 (0.93–1.36)	0.22
Moderate (10–15%)	112 (51)	132 (60)	1.15 (0.97–1.37)	0.11
High (>15%)	665 (69)	793 (67)	0.96 (0.90–1.02)	0.19
Established CVD	681 (80)	506 (77)	0.95 (0.90–1.00)	0.05
Statin therapy				
Low (<10%)	51 (25)	234 (29)	1.09 (0.84–1.41)	0.51
Moderate (10–15%)	67 (30)	67 (31)	0.99 (0.74–1.31)	0.92
High (>15%)	430 (44)	532 (45)	1.02 (0.92–1.13)	0.66
Established CVD	648 (76)	437 (67)	0.87 (0.81–0.93)	<0.001
Antiplatelet therapy				
Low (<10%)	34 (17)	135 (17)	0.92 (0.65–1.31)	0.65
Moderate (10–15%)	43 (20)	54 (25)	1.12 (0.78–1.63)	0.53
High (>15%)	353 (37)	407 (35)	0.91 (0.81–1.02)	0.09
Established CVD	637 (75)	436 (67)	0.88 (0.82–0.94)	<0.001
Combination therapy <sup>a</sup>				
Low (<10%)	12 (6)	47 (6)	0.86 (0.46–1.59)	0.63
Moderate (10–15%)	20 (9)	21 (9)	0.95 (0.52–1.73)	0.86
High (>15%)	191 (19)	218 (18)	0.92 (0.77–1.10)	0.36
Established CVD	483 (56)	297 (44)	0.78 (0.70–0.87)	<0.001

# Effect of Gender on Cholesterol Control and Statin Use for Secondary Prevention Among Hospitalized Patients With Coronary Heart Disease



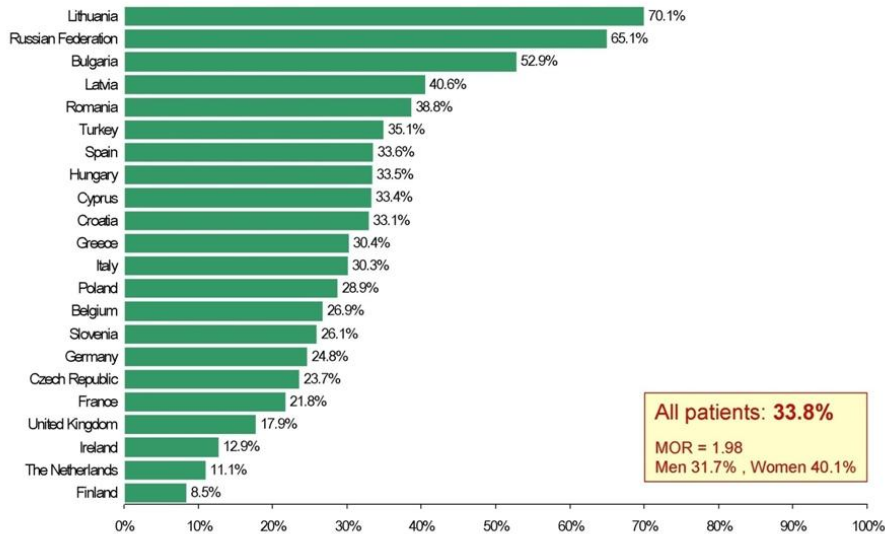


# LDL Control and Statin Use: EUROASPIRE III



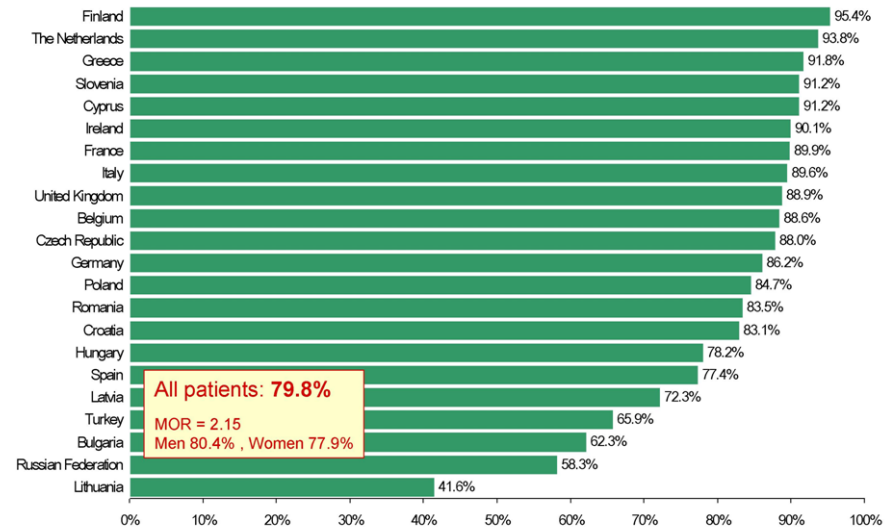
EuroASPIRE III

Prevalence of raised LDL cholesterol ( $\geq 3$  mmol/L)



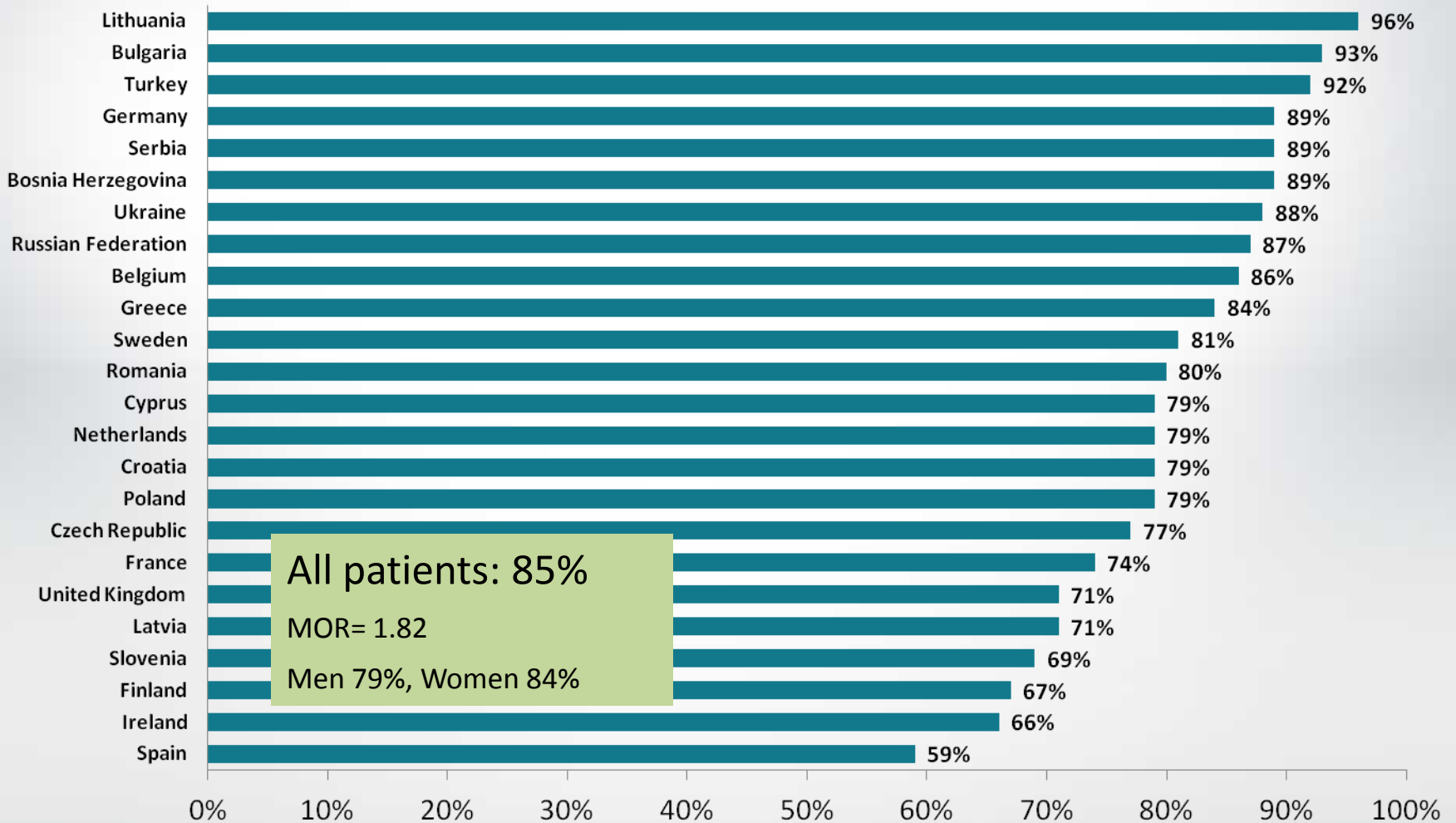
EuroASPIRE III

Use of lipid-lowering drugs



# Euroaspire IV

## LDL cholesterol $\geq 1.8$ mmol/L



# How do we treat dyslipidemia in women today ?

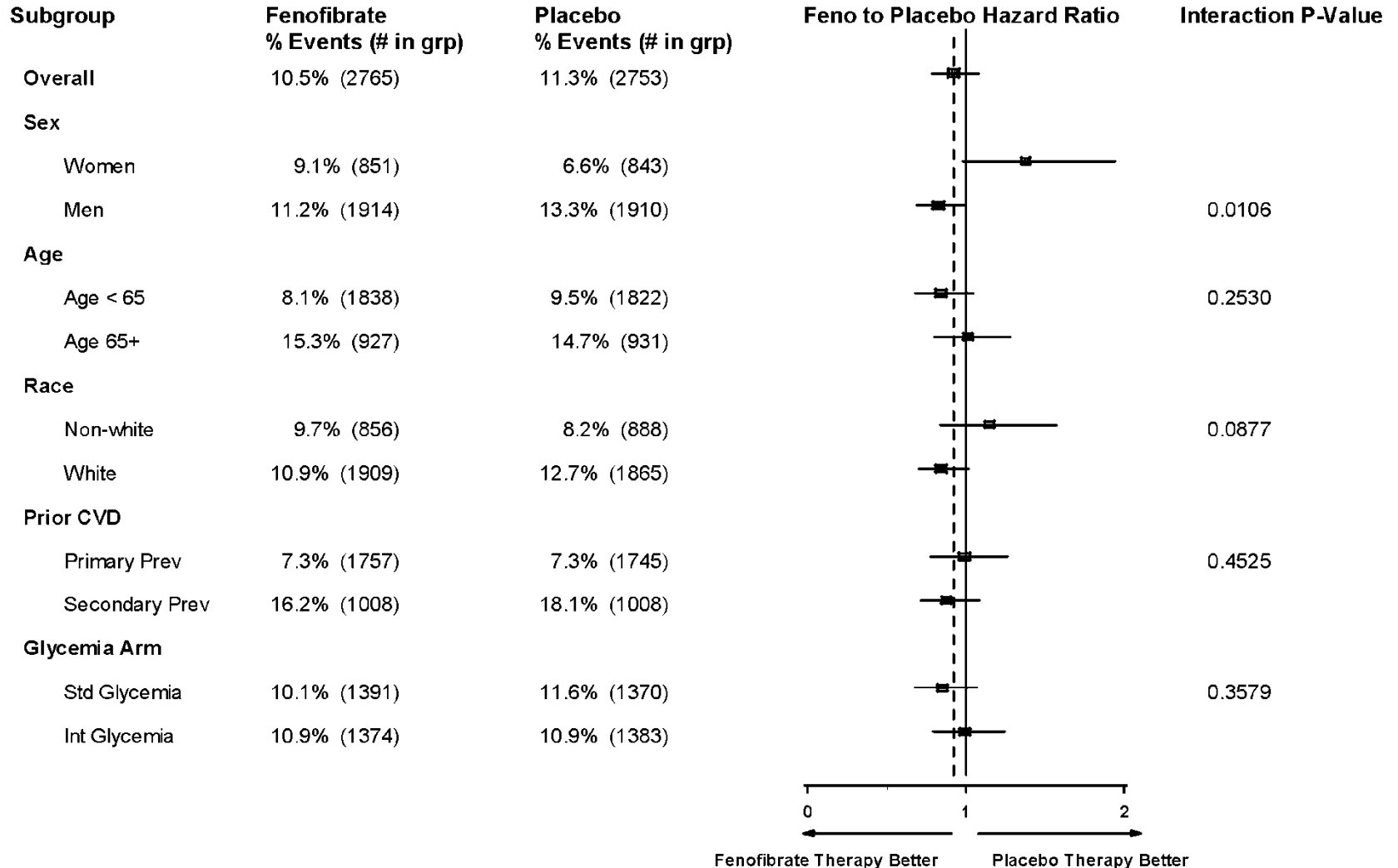
- Lifestyle modification is extremely important
- For secondary prevention, statins are recommended as same indications and targets in men
- Statins are recommended for high risk primary prevention
- LLT should not be given before, during pregnancy and at breastfeeding
- For low risk primary prevention each patient should be evaluated individually



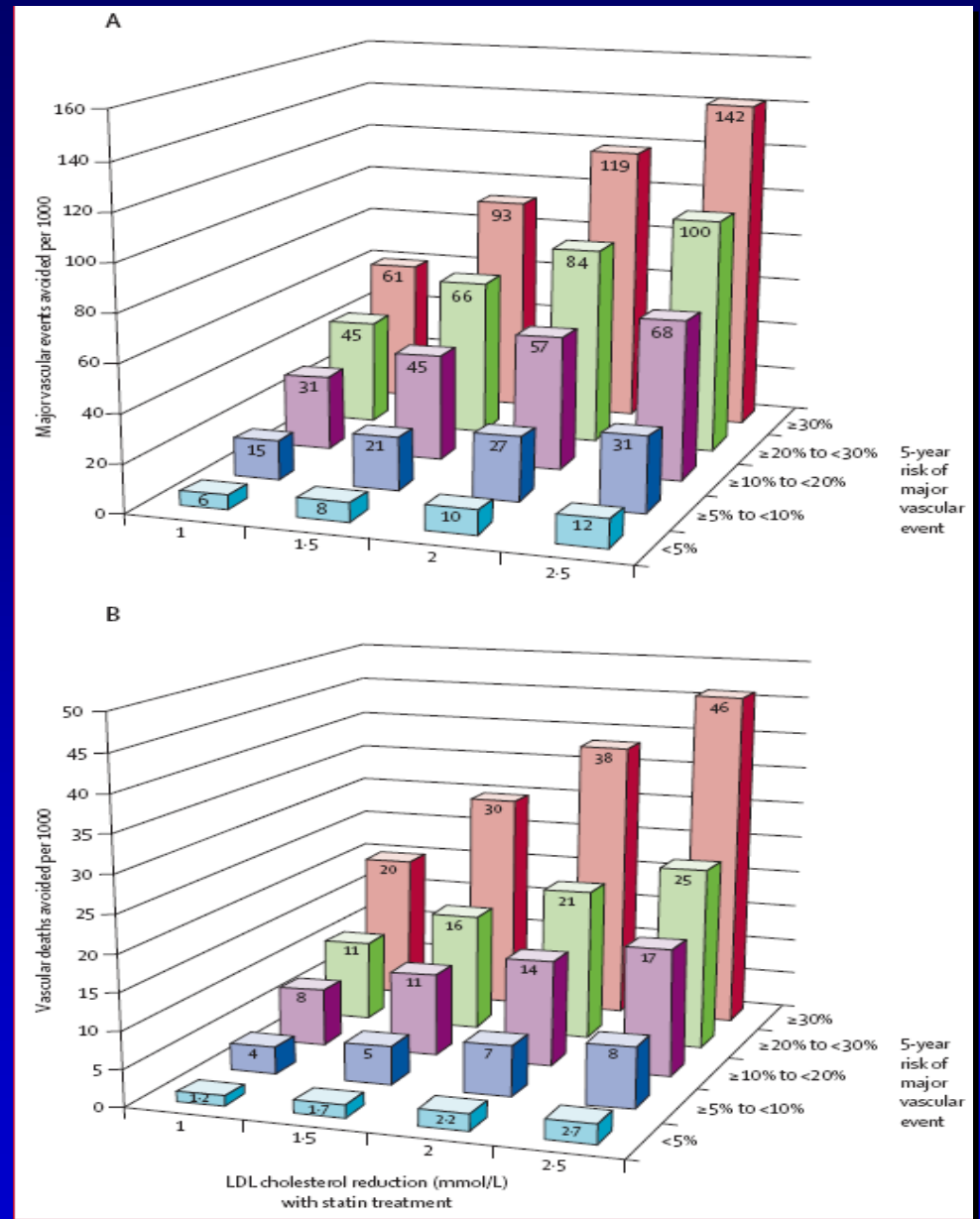
# ESC/EAS Dyslipidemia Guidelines 2011: Recommendations for diabetics

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (at least 30%) with statins as the first choice (eventually drug combination) is recommended irrespective of the basal LDL-C concentration.	<b>I</b>	<b>C</b>	
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (less than ~70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (100 mg/dL) and for apo B is <80 mg/dL.	<b>I</b>	<b>B</b>	15, 16
In all people with type 2 diabetes LDL-C <2.5 mmol/L (less than ~100 mg/dL) is the primary target. Non-HDL-C <3.3 mmol/L (130 mg/dL) and apo B <100 mg/dL are the secondary targets.	<b>I</b>	<b>B</b>	15, 16

# Accord Lipid Trial Primary Outcomes



# CTT Analysis shows LDL reduction beneficial even in low risk



# JUPITER Analysis Shows Intermediate Risk Patients Benefit From Statin

Risk category	Event rate per 100-person years, rosuvastatin 20 mg	Event rate per 100-person years, placebo	Hazard ratio (95% CI)
Framingham 10-year risk			
<5% (n=2791)	0.22	0.34	0.64 (0.23-1.81)
5%-10% (n=6091)	0.50	0.92	0.55 (0.36-0.84)
11%-20% (n=7340)	0.95	1.84	0.51 (0.39-0.68)
>20% (n=1555)	1.72)	2.41	0.70 (0.45-0.90)

*Circulation, 2010;Aug 24; epub.*