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**International Task Force for Prevention  
Of Coronary Heart Disease**

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*Coronary heart disease and stroke:  
Risk factors and global risk*

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**Cardiovascular risk factors in women**

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Slide 1:

**Effect of menopause as opposed to age on lipid risk factors in the PROCAM study.**



**PROCAM (Münster Heart Study):  
Menopause and Lipid Risk Factors  
in 45 to 55 Years Old Women**



	Pre- Menopause (n = 1537)	Menopause (n = 2456)	P
age (years)	48.3 ± 2.8	51.0 ± 3.0	< 0.001
BMI (kg/m <sup>2</sup> )	25.8 ± 4.3	26.4 ± 4.5	< 0.001
cholesterol (mg/dl)	221 ± 39	239 ± 41	< 0.001
triglycerides (mg/dl)*	88	99	< 0.001
LDL-C (mg/dl)	143 ± 36	158 ± 38	< 0.001
HDL-C (mg/dl)	59 ± 15	59 ± 16	n.s.
chol./HDL-C ratio	4.02 ± 1.25	4.31 ± 1.32	< 0.001

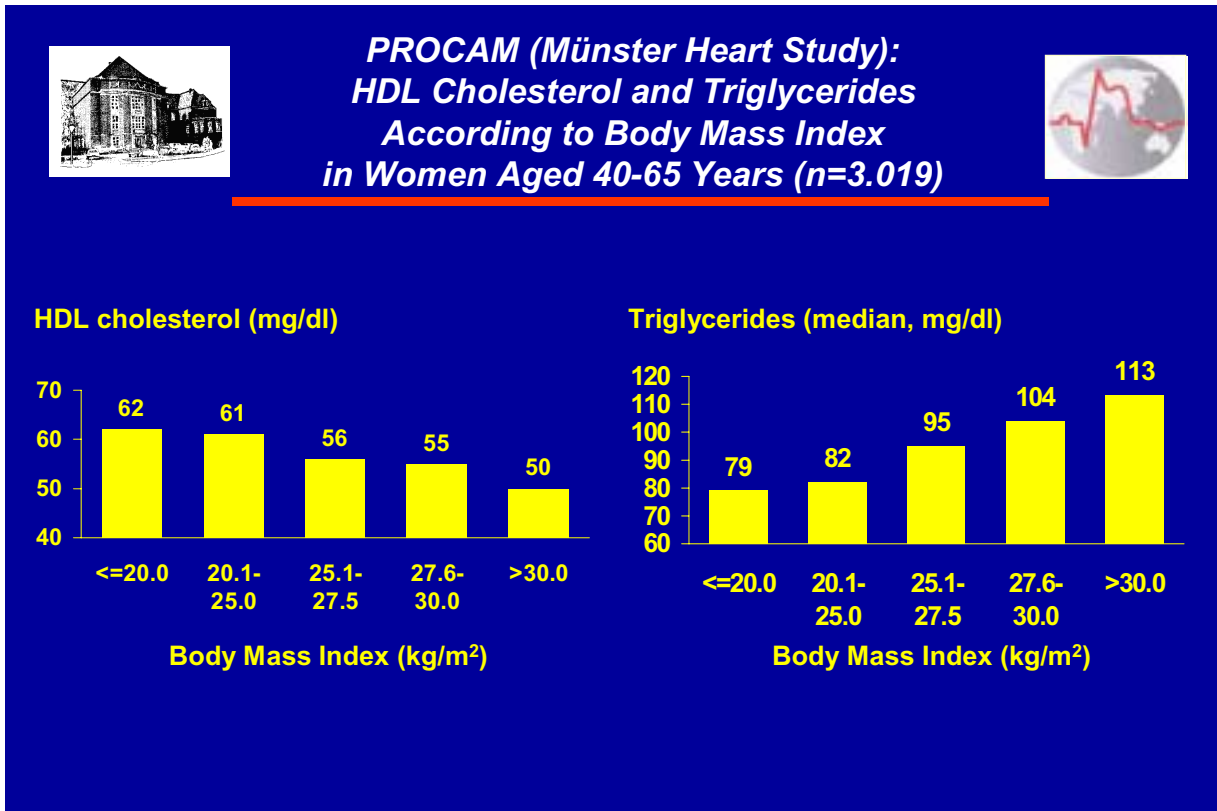
\*: geometric mean, n.s.: not significant

**Effect of menopause as opposed to age on lipid risk factors in the PROCAM study.**

An important question is if the age-related changes in lipid risk factors in women are due to increasing age alone or due to the effects of the menopause. In order to investigate this, the levels of a variety of lipid risk factors were investigated in women in the PROCAM study aged 45 to 55 years. These women were then divided into two groups, a premenopausal group and a group in whom the menopause had occurred. Levels of risk factors in the premenopausal and postmenopausal groups are shown on this slide. Not surprisingly, the age of the premenopausal women was significantly less than that of the postmenopausal women. Nevertheless, the difference in many risk factors between premenopausal and postmenopausal women was greater than can be explained on the basis of age alone. This particularly applied to LDL cholesterol, triglycerides and BMI. The HDL cholesterol level did not differ between premenopausal and postmenopausal women.

Slide 2:

## Lipids and body weight in women

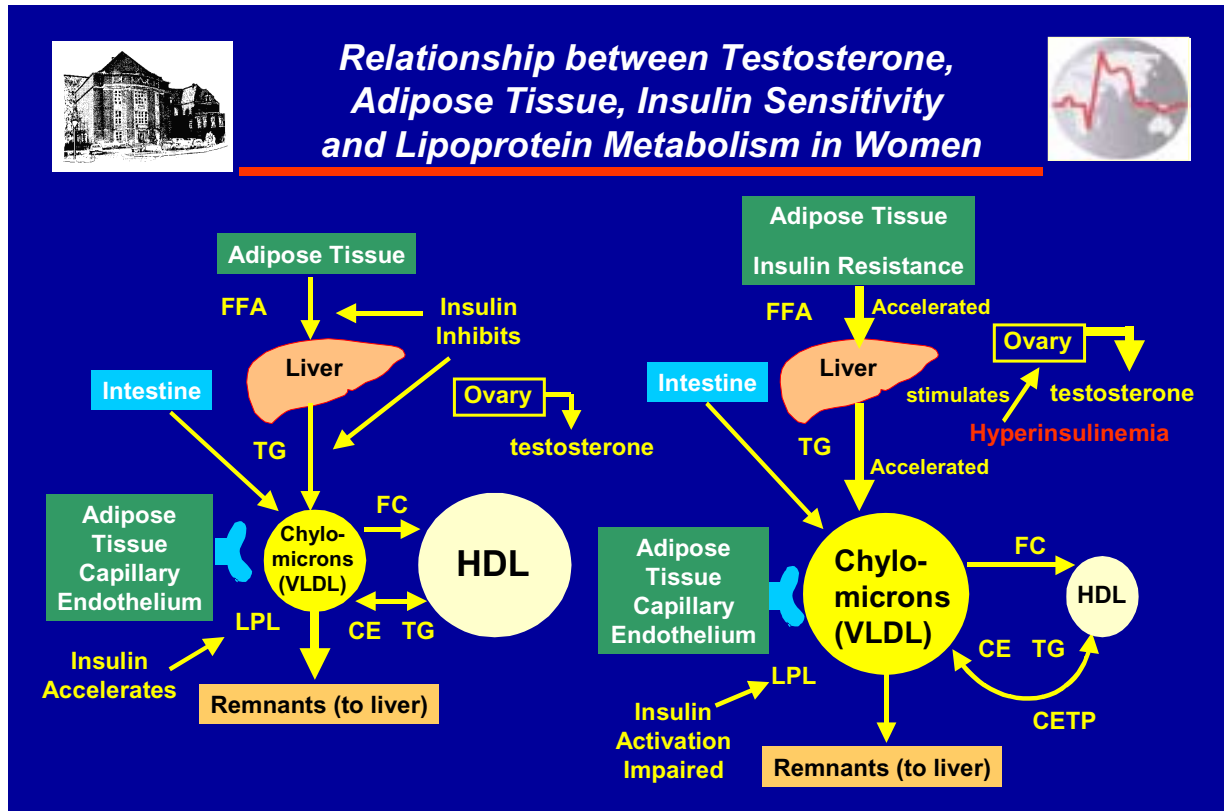


### Lipids and body weight in women:

This slide shows the relationship between HDL-cholesterol, triglyceride, and body weight in women aged 40-65 years in the PROCAM study. With increasing body mass index, there is an increase in fasting triglyceride levels and a decrease in HDL cholesterol levels.

Slide 3:

## Metabolic syndrome in women

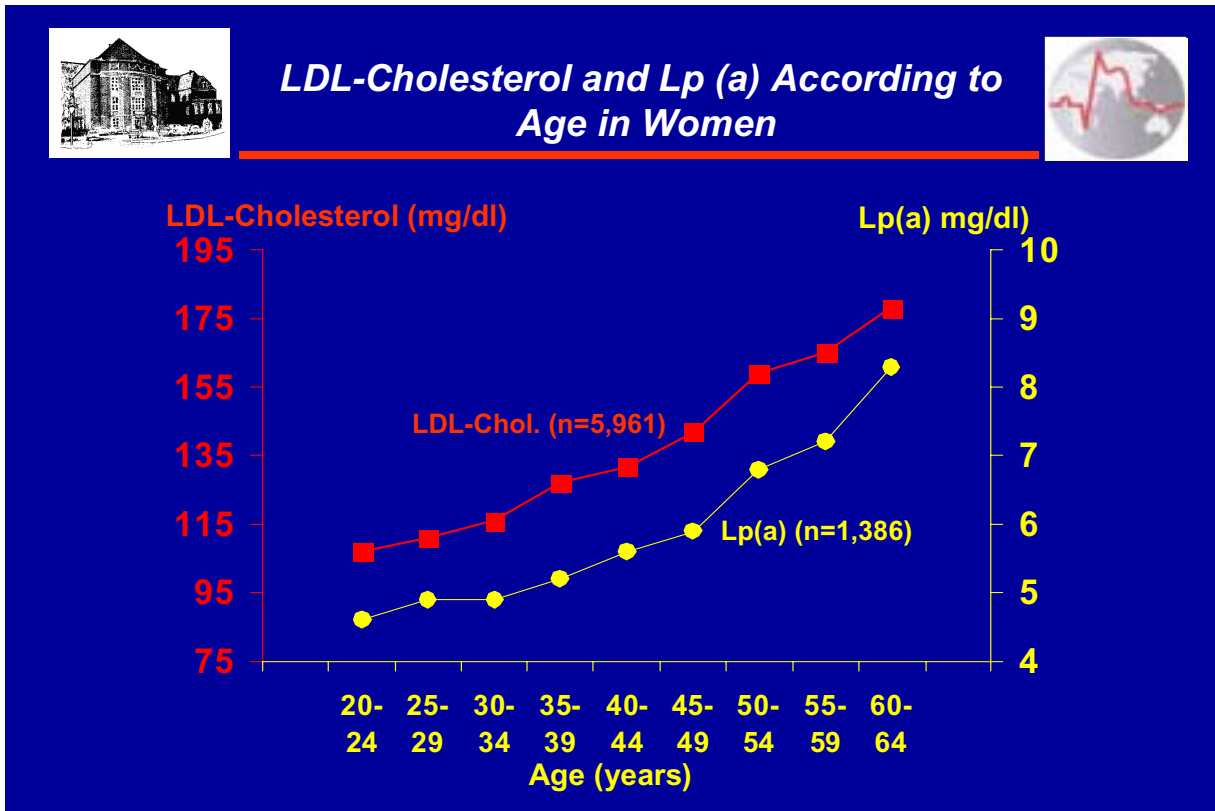


### Metabolic syndrome in women

One of the major clinical features of the metabolic syndrome is obesity. Obesity is frequently associated with insulin resistance and, hence, with hyperinsulinemia. Hyperinsulinemia in women has been shown to stimulate the release of testosterone from the ovaries. The low circulating level of testosterone in turn promotes an increase in adipose tissue bulk. This leads to increased release of free fatty acids which are transported to the liver where they stimulate the production of triglyceride-rich, Apo-B containing very low density lipoproteins. Both this release of free fatty acids and the secretion of triglyceride-rich lipoproteins are inhibited by insulin, so that insulin resistance leads to overproduction of triglyceride-rich lipoproteins. In insulin resistance, there is also a reduced activity of peripheral lipoprotein lipase which in turn leads of accumulation of triglyceride-rich lipoproteins within the circulation. Via the action of cholesterol ester transfer protein, triglycerides are transferred from these lipoproteins to high density lipoproteins in exchange for cholesterol esters. The enrichment of the triglyceride-rich remnant particles with cholesterol ester leads to formation of small dense LDL. Moreover, because of this exchange, the level of high density lipoprotein cholesterol falls.

Slide 4:

## LDL cholesterol and Lp(a) in women



### LDL cholesterol and Lp(a) in women

In contrast to men (see slide 3, kit 3), both LDL cholesterol and Lp(a) show a steady increase with age in women.

Slide 5:

## Menopause and hemostatic risk factors in 45 to 55 year old women



### *PROCAM (Münster Heart Study): Menopause and Hemostatic Risk Factors in 45 to 55 Years Old Women*



	Pre- Menopause (n = 229)	Menopause (n = 307)	P
fibrinogen (mg/dl)	265 ± 50	276 ± 56	< 0.001
D-dimer (µg/l)*	321	345	n.s.
factor VIIc (mg/dl)	108 ± 26	120 ± 34	< 0.001
protein C (%)	111 ± 19	120 ± 24	< 0.001
plasminogen (%)	104 ± 14	106 ± 14	< 0.05
PAI-1 (U/l) *	2.22	2.48	< 0.05
vWF (%)	103 ± 35	96 ± 31	n.s.
CRP (mg/dl)*	0.32	0.28	< 0.05

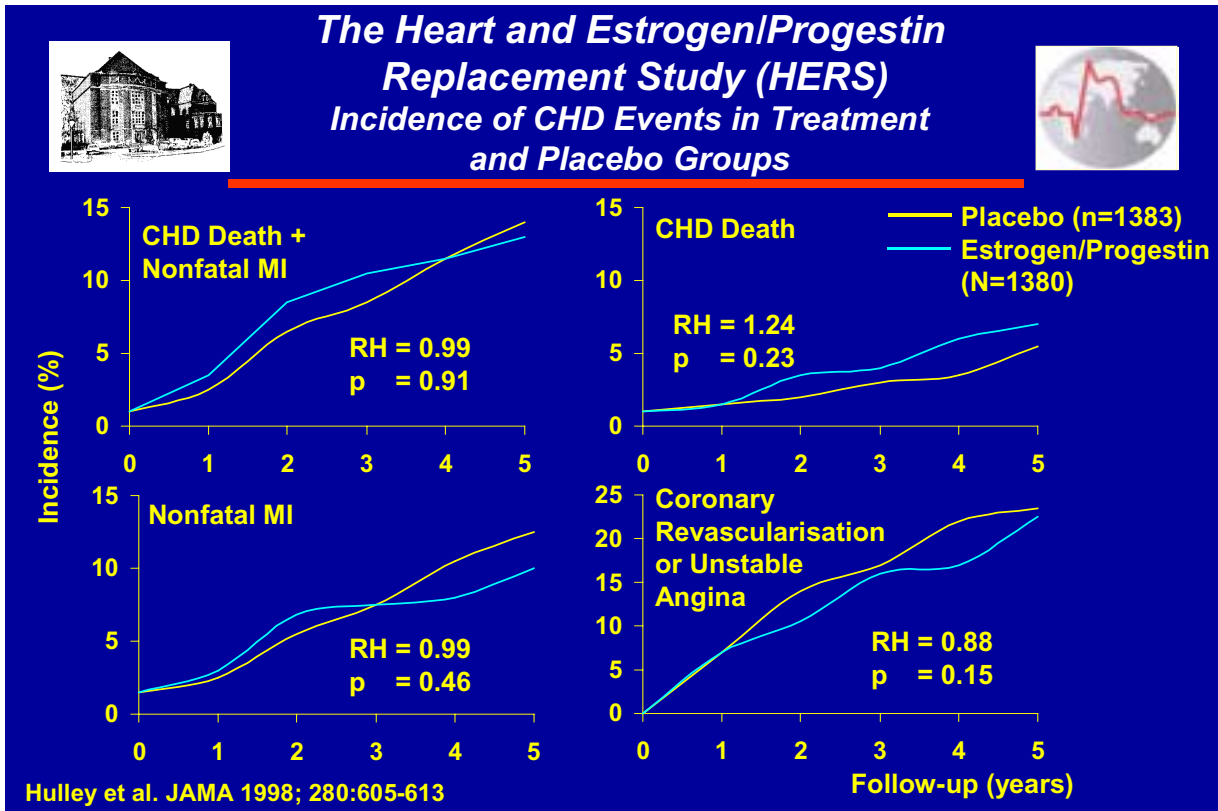
\*: geometric mean

#### Menopause and hemostatic risk factors in 45 to 55 year old women

It is unclear if changes in hemostatic risk factors in women around the time of menopause are due to aging or to the effect of the menopause itself. In order to investigate this question we divided the cohort of 45-55 year old women in the PROCAM study into those who were pre-menopausal and those in whom the menopause had occurred. As can be seen from this slide, the menopause was associated with significant increases in fibrinogen, factor VIIc, protein C, plasminogen, PAI-1, and CRP. There was no significant difference in the level of d-dimers and von Willebrand factor between pre- and post-menopausal women. This data indicates that there is a clear worsening in hemostatic risk factors in women due to the menopause.

Slide 6:

## Results of the Heart and Estrogen/Progestin Replacement Study (HERS)





### Results of the Heart and Estrogen/Progestin Replacement Study (HERS)

This slide summarizes the major results of HERS, a randomized, double-blind, placebo-controlled trial, where 2763 women aged 44-79 years with coronary heart disease received 0.0625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone or placebo. The patients were followed up for 5 years. For all major end-points (CHD death + nonfatal MI, CHD death, nonfatal MI, coronary revascularization or unstable angina), there was no significant difference between the intervention groups treated with hormone replacement therapy and the controls.

Slide 7:

## Side effects of Heart and Estrogen/Progestin Replacement Study (HERS)

		<b>Side-Effects in HERS Study</b>			
Side-effects	oestrogen/ progestin (n=1380)	placebo (n=1383)	relative risk	P value	
<b>confirmed venous thrombosis</b>	<b>34</b>	<b>12</b>	<b>2.3</b>	<b>0.002</b>	
<b>deep vein thrombosis</b>	<b>25</b>	<b>8</b>	<b>3.1</b>	<b>0.004</b>	
<b>pulmonary embolus</b>	<b>11</b>	<b>4</b>	<b>2.8</b>	<b>0.08</b>	
<b>fatal pulmonary embolus</b>	<b>2</b>	<b>0</b>	<b>-</b>	<b>-</b>	
<b>gallbladder disease</b>	<b>84</b>	<b>62</b>	<b>1.4</b>	<b>0.05</b>	



Hulley et al. JAMA 1998; 280:605-613

### Side effects of Heart and Estrogen/Progestin Replacement Study (HERS)

In HERS, not only did hormone replacement have no effect on major endpoints (see slide 6), but was also associated with an increased rate of side-effects. Most prominent was an increased tendency to venous thrombosis, including pulmonary thromboembolism (trend), in the treated group.

Slide 8:

**Lp(a) as a coronary risk factor in postmenopausal women**

**HERS: Multivariate Hazard Ratios\*  
 of Recurrent Coronary Heart Disease Events  
 by Baseline Lipoprotein (a) Level  
 Among Women Assigned to Placebo**

	1 <sup>st</sup> Quartile (0-7.0 mg/dl) (n=364)	2 <sup>nd</sup> Quartile (7.1-25.3 mg/dl) (n=337)	3 <sup>rd</sup> Quartile (25.4-54.9 mg/dl) (n=333)	4 <sup>th</sup> Quartile (55-236 mg/dl) (n=348)	p value
Primary CHD events (n=182)	1.0	1.01 (0.6-1.6)	1.31 (0.9-2.0)	1.54 (1.0-2.4)	<0.001
Myocardial Infarction (n=134)	1.0	0.88 (0.5-1.5)	1.06 (0.6-1.8)	1.51 (0.9-2.5)	0.005
CHD death (n=59)	1.0	1.13 (0.5-2.7)	2.02 (0.9-4.4)	1.39 (0.6-3.2)	0.03
CABG/PTCA (n=259)	1.0	0.93 (0.7-1.3)	1.06 (0.7-1.5)	1.61 (1.1-2.3)	<0.001
Unstable angina (n=120)	1.0	1.21 (0.7-2.0)	1.07 (0.6-1.8)	1.54 (0.9-2.6)	0.01

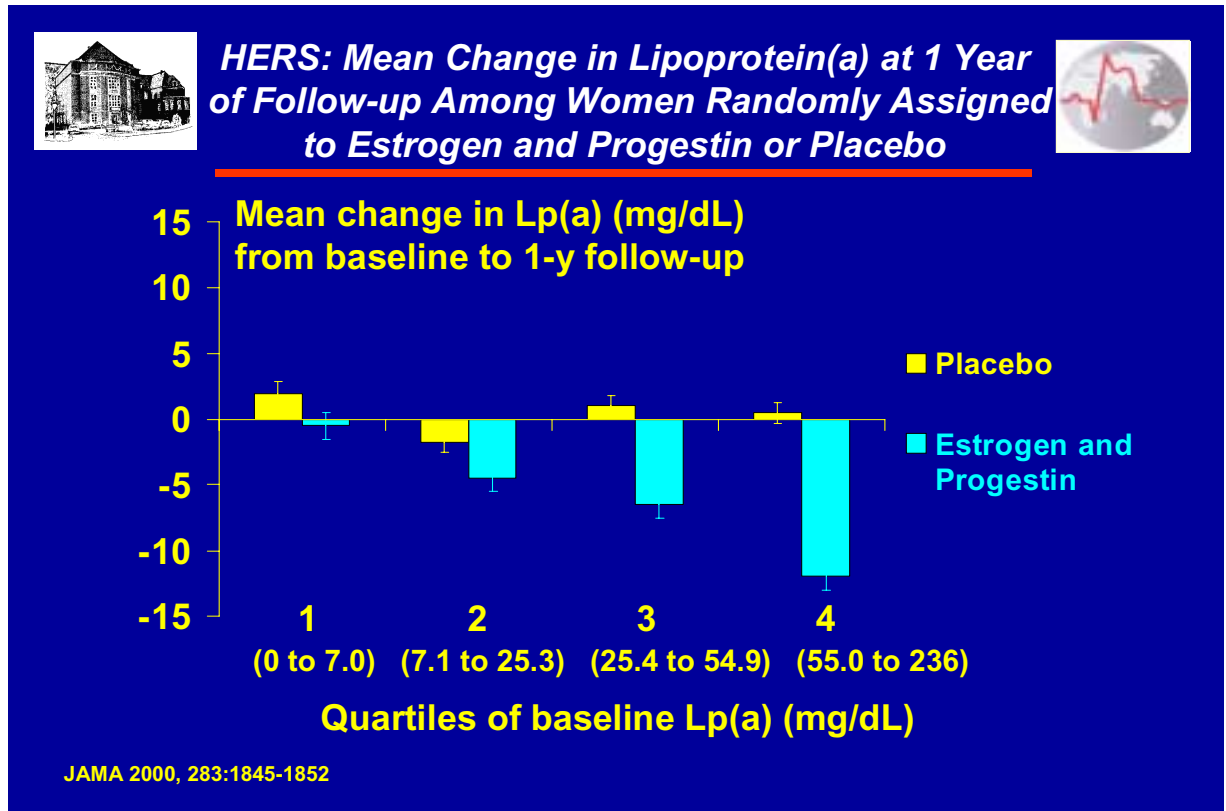
\* (95 % confidence intervals), n=1383  
 Models are adjusted for other predictors (p<0.10) including race/ethnicity, diabetes mellitus, waist-to-hip ratio, tobacco use, high- and low-density lipoprotein cholesterol levels, triglyceride level, and use of lipid-lowering agents, aspirin, and calcium channel blockers.  
 JAMA 2000, 283:1845-1852

**Lp(a) as a coronary risk factor in postmenopausal women**

These data from the placebo group of the HERS study suggest that in postmenopausal women with heart disease Lp (a) is a risk factor for future cardiovascular events.

Slide 9:

## Mean change in Lp(a) at 1 year of follow-up among women randomly assigned to estrogen and progestin or placebo (HERS)



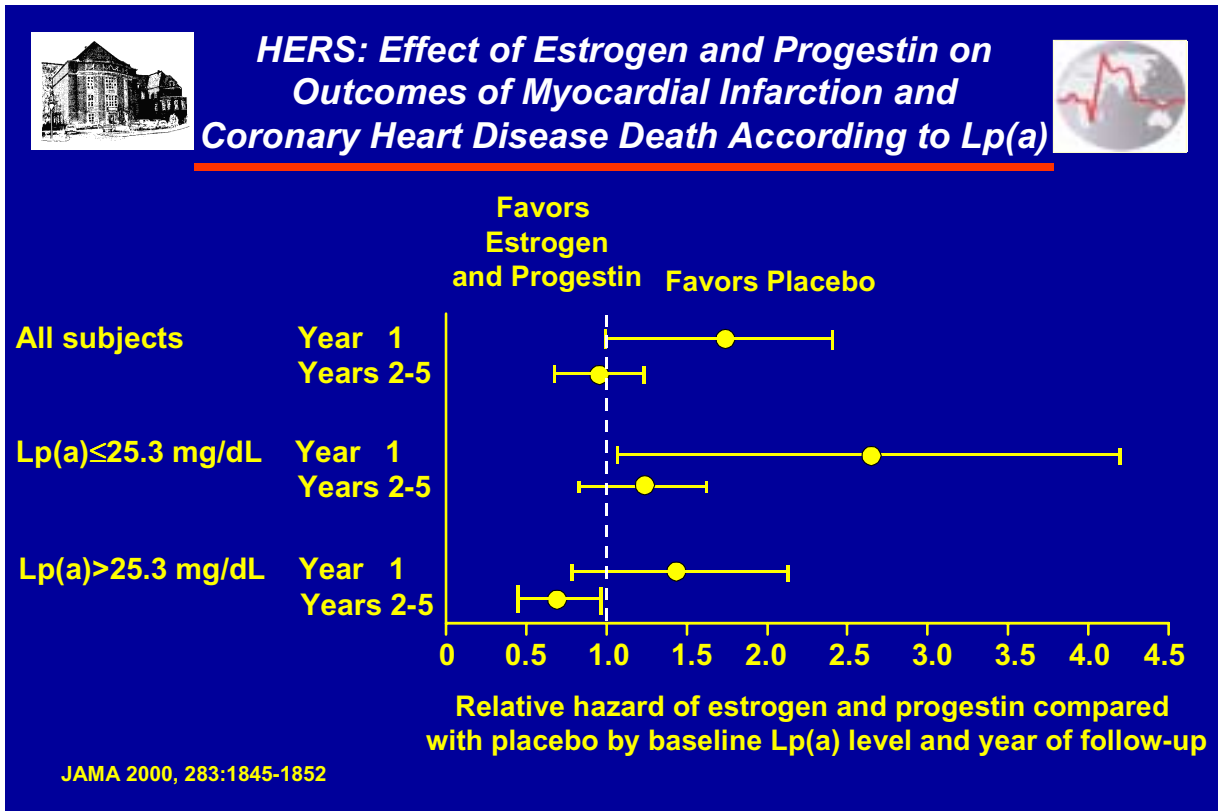
### Mean change in Lp(a) at 1 year of follow-up among women randomly assigned to estrogen and progestin or placebo (HERS)

In the HERS study women assigned to estrogen and progestin had a significantly greater reduction in Lp(a) level than women assigned to placebo ( $p < 0.001$ ). A trend of greater reduction in the estrogen/progestin treatment group with increasing quartiles of baseline Lp(a) was observed ( $p < 0.001$ ). Error bars indicate SD.

These data suggest that high Lp(a) levels in postmenopausal women may effect treatment decisions.

Slide 10:

**Effect of estrogen and progestin on outcomes of myocardial infarction and coronary heart disease death according to Lp (a) (HERS)**



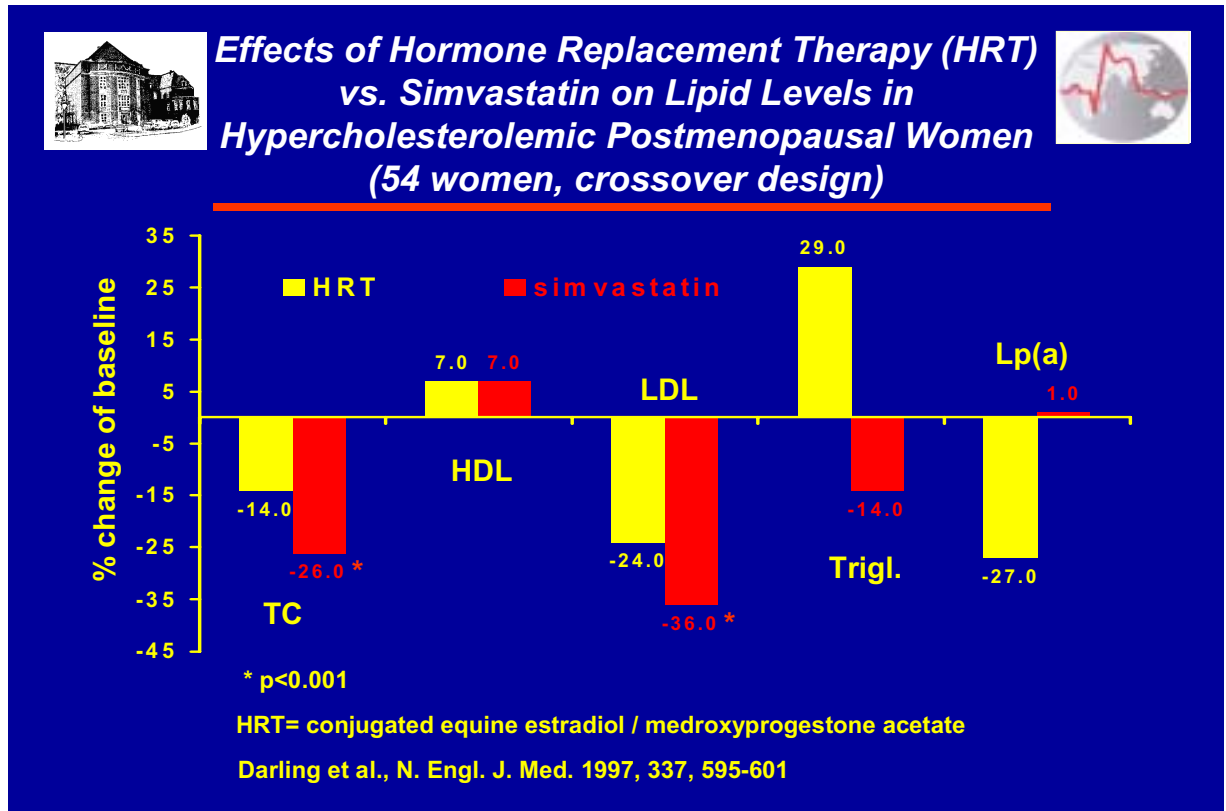
**Effect of estrogen and progestin on outcomes of myocardial infarction and coronary heart disease death according to Lp (a) (HERS)**

Women with baseline lipoprotein(a) levels below or equal to 25.3 mg/dl (the median) who were assigned to estrogen and progestin had an increased risk of coronary heart disease events in year 1, but not in later years. Women assigned to estrogen and progestin with baseline Lp(a) levels above the median had no significant difference in year 1 coronary heart disease events, but had significant reduction in events during years 2 through 5 of follow-up. Data were stratified by year of follow-up and baseline Lp(a) level. To convert mg/dl to  $\mu\text{mol/L}$ , multiply by 0.0357.

These data suggest that postmenopausal women with heart disease and high Lp(a) levels profit from estrogen/progestin treatment.  
 JAMA 2000; 283:1845-1852.

Slide 11:

## Effects of Hormone Replacement Therapy (HRT) vs. Simvastatin on Lipid Levels in Hypercholesterolemic Postmenopausal Women





### Effects of Hormone Replacement Therapy (HRT) vs. Simvastatin on Lipid Levels in Hypercholesterolemic Postmenopausal Women

The choice of hypolipidemic therapy in postmenopausal women depends on the predominant lipid disturbance. If the main abnormality is a rise in LDL-cholesterol or triglycerides, then statins are indicated. Statins, however, have no effect on Lp(a) levels, which are lowered by hormone replacement therapy. See also slide 9 in kit 10 for further details of LDL lowering in women.

Slide 12:

**Intervention studies aimed at the prevention of coronary heart disease (subgroups of women)**

**Intervention Studies Aimed at the Prevention of Coronary Heart Disease (subgroups of women)**

	<b>4S (simvastatin)</b>	<b>CARE (pravastatin)</b>	<b>AFCAPS/ TexCAPS (lovastatin)</b>
<b>CHD</b>	<b>Yes</b>	<b>Yes</b>	<b>No</b>
<b>Number of women</b>	<b>827</b>	<b>576</b>	<b>997</b>
<b>Age (years)</b>	<b>35-69</b>	<b>21-75</b>	<b>55 – 73</b>
<b>Average follow-up (years)</b>	<b>5.4</b>	<b>5.0</b>	<b>5.2</b>
<b>Mean LDL-C (mg/dl) at baseline</b>	<b>188</b>	<b>139</b>	<b>150</b>
<b>Mean lowering of LDL-C in the verum group</b>	<b>38%</b>	<b>32%</b>	<b>25%</b>
<b>Mean CHD risk reduction (95% confidence interval)</b>	<b>35 (9-53)%</b>	<b>46 (22-62)%</b>	<b>46%</b>

**4S:** The Lancet 1994;344:1383-1389  
**Care:** Sacks FM et al. N Engl J Med 1996;335:1001-1009  
**AFCAPS/TexCAPS:** Downs JR et al. JAMA 1998;279:1615-1622

**Intervention studies aimed at the prevention of coronary heart disease (subgroups of women)**

This slide shows the results of lipid lowering therapy among the subgroups of women in three of the major recent intervention studies. The Scandinavian Simvastatin Survival Study (4S) was a secondary prevention study, reported in November 1994, and the Cholesterol and Recurrent Events Study (CARE) was a secondary prevention study reported in October 1996. The Airforce/Texas Armed Forces Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) Study was a primary prevention study which was reported in May 1998. Each of these three studies contained a substantial subgroup of women. As can be seen, statins produced an approximate 30% lowering LDL cholesterol across the range of baseline LDL cholesterol levels. This lowering was associated in all three studies with an approximate 40% reduction in coronary events. Thus it is clear that women benefit from statin therapy to an extent equal to that of men.