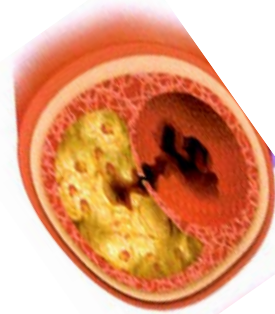


Statins for Cardiovascular Disease Prevention in Women: Review of the Evidence

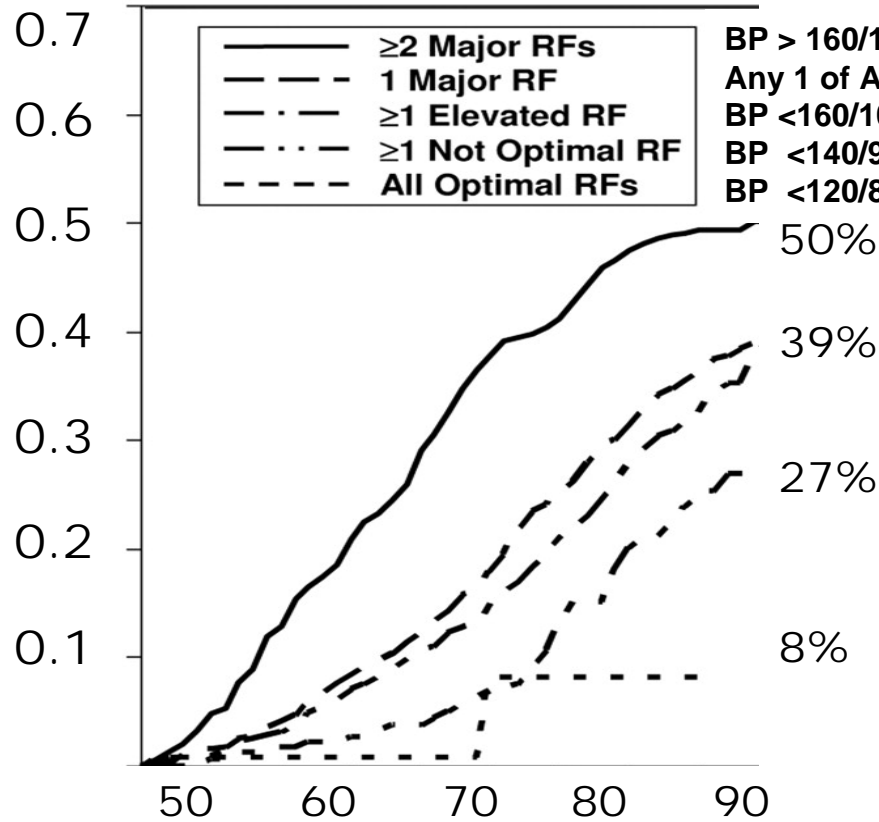


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Risk Factor Burden at Age 50 Predicts Lifetime Incidence of Cardiovascular Disease in Women

Framingham Study
(N = 4,362 Women—30 Yr F/U)

Cumulative
Incidence
of a First
CV Event



BP > 160/100	TC > 240	Smoking	DM
Any 1 of Above			
BP < 160/100	TC < 240	No Smoking or DM	
BP < 140/90	TC < 200	No Smoking or DM	
BP < 120/80	TC < 180	No Smoking or DM	

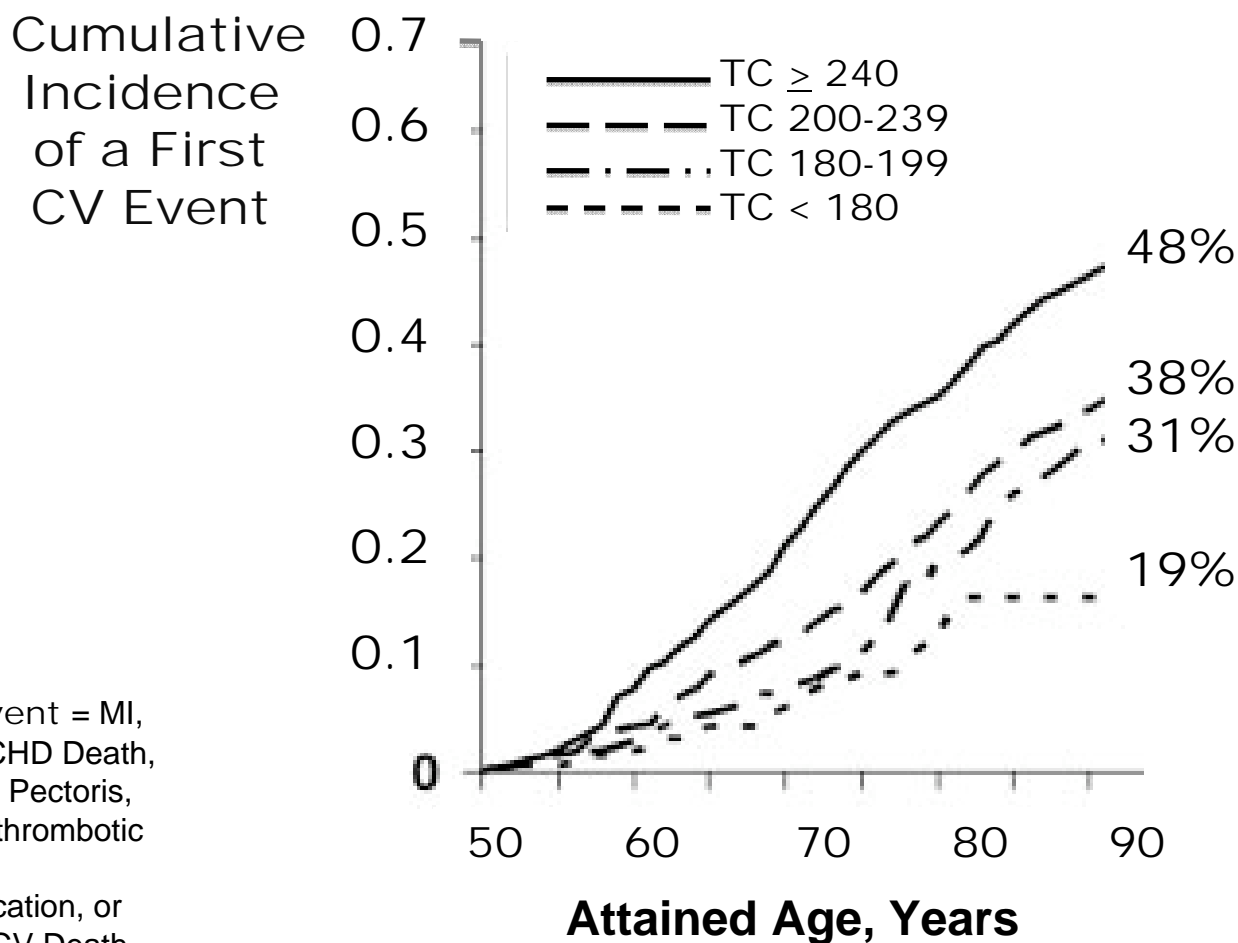
CV Event = MI,
USA, CHD Death,
Angina Pectoris,
Atherothrombotic
Stroke,
Claudication, or
Other CV Death

Attained Age, Years

Modified from: Lloyd-Jones D M et al.
Prediction of Lifetime Risk of CVD
by Risk Factor Burden at Age 50.
Circulation 2006;113:791-798.

Serum Total Cholesterol at Age 50 Predicts Lifetime Incidence of Cardiovascular Disease in Women

Framingham Study
(N = 4,362 Women—30 Yr F/U)



CV Event = MI, USA, CHD Death, Angina Pectoris, Atherothrombotic Stroke, Claudication, or Other CV Death

Modified from: Lloyd-Jones D M et al. Prediction of Lifetime Risk of CVD by Risk Factor Burden at Age 50. *Circulation* 2006;113:791-798.

Statin Therapy for Secondary Prevention of Cardiovascular Disease in Women & Men

A Sex-Based Meta-Analysis -- 2012

Secondary Prevention Trials	4S SPARCL PLAC-1	CARE PROSPER § CCAIT	LIPID FLORIDA REIGGER	MIRACL ASCOT §
Subjects	11,243 Women + 31,950 Men + CVD			
Designs	Statin vs. Placebo, F/U 16 wk - 6.1 Yrs			
Outcomes on Statins	<p>Any CV Event* Both women and men showed significant ~20% relative risk reductions [RR's 0.81 - 0.82 p < 0.05]</p> <p>Any Death Men showed a significant 21% relative decrease--women had a favorable risk estimate only [RR 0.92 p > 0.05]</p>			

*= MI, CHD Death, CV Death, CVA, STENT, or CABG

Gutierrez, J et al. *Arch Int Med* 2012;172: 909-19.

§ Classified as a primary prevention trial in some analyses

Primary Prevention Statin Trials Enrolling Women

Trial	# Women (%)	Mean Age, Yrs	% With CVD	% With DM	Baseline LDL-C (mg/dL)	Active Drug (mg/day)	% LDL Change At 1 Yr	F/U, Yrs	Sex-Specific Results
AF/TEXCAPS	997 15%	58	< 1%	< 5 %	150	Lova 20-40	- 36 %	5.2	Yes
MEGA	5,356 68%	58	< 1%	21 %	155	Prava 10-20	- 25 %	5.0	Yes
JUPITER	6,801 38%	66	0 %	0 %	104 + hsCRP >2	Rosuva 20	- 42 %	2.0	Yes
ASCOT	1,942 19%	63	14 %	24 %	131	Atorva 10	- 41 %	3.3	Yes
ALLHAT	5,051 49%	66	22 %	34 %	145	Prava 40	~ 10 %	4.9	Yes
PROSPER	3,000 52%	75	44%	12 %	147	Prava 40	- 40 %	3.3	No
HPS	5,082 25%	NR	85%	29 %	131	Simva 40	- 49 %	5.4	No
CARDS	909 32%	62	31%	100%	117	Atorva 10	- 44 %	4.1	No
ASPEN	811 34%	61	31%	100%	113	Atorva 10	-38 %	4.0	No

Limitations of Primary Prevention Statin Trials Enrolling Women

- **Inability to classify many trials**
- **Low numbers of women in early trials**
- **Low numbers of older women**
- **Methodologic problems in large early trial**
- **Lack of sex-specific analyses**
- **Lack of reporting of individual events**
- **Short durations of follow up**

Lipid Drug Therapy for Primary Prevention of Coronary Disease in Women

A Systematic Review – 2004

Primary Prevention Trials to 2004	AF/TEXCAPS COLESTIPOL	ALLHAT ACAPS	ASCOT HPS
Subjects	11,435 Women “No” CHD		
Designs	Lipid Drug vs. Placebo, F/U 2.8 – 5.2 Yrs		
Outcomes on Drug (Statins in all except 1 Trial)	<p>Any CHD Event*</p> <p>Non-significant but favorable risk estimate [RR 0.87 p >.05]</p> <p>Excluding ALLHAT yielded significant 23% risk reduction [RR 0.77 p < .05]</p> <p>Any Death</p> <p>Non-significant but favorable estimate [RR 0.95 p=NS]</p>		

* = MI, USA, CHD Death, PCI or CABG

Walsh, J and Pignone, M JAMA 2004; 291: 2243-53.

Statin Therapy for Primary Prevention of Coronary Disease in Women vs. Men

A Sex-Based Meta-Analysis – 2010

Primary Prevention Trials to 2008	AF/TEXCAPS WOSCAPS	ALLHAT PROSPER	ASCOT MEGA	HPS ACAPS
Subjects	19,052 Women + 30,194 Men “No” CVD			
Designs	Statin vs. Placebo, Mean F/U 3.9 Yrs			
Outcomes on Statins	<p>Any CHD Event*</p> <p>Women had borderline 11% risk reduction [RR 0.89 p = 0.05]</p> <p>Men had a significant 41% risk reduction [RR 0.59 p < 0.05]</p> <p>Any Death Both women and men had non-significant favorable risk estimates [RR 0.96 - 0.93 p > 0.05 for both]</p>			

= MI, USA, CHD Death, PCI or CABG.

Does The Argument To Withhold Statins in Women At Risk “Stretch the Limits” of Evidence Based Medicine?

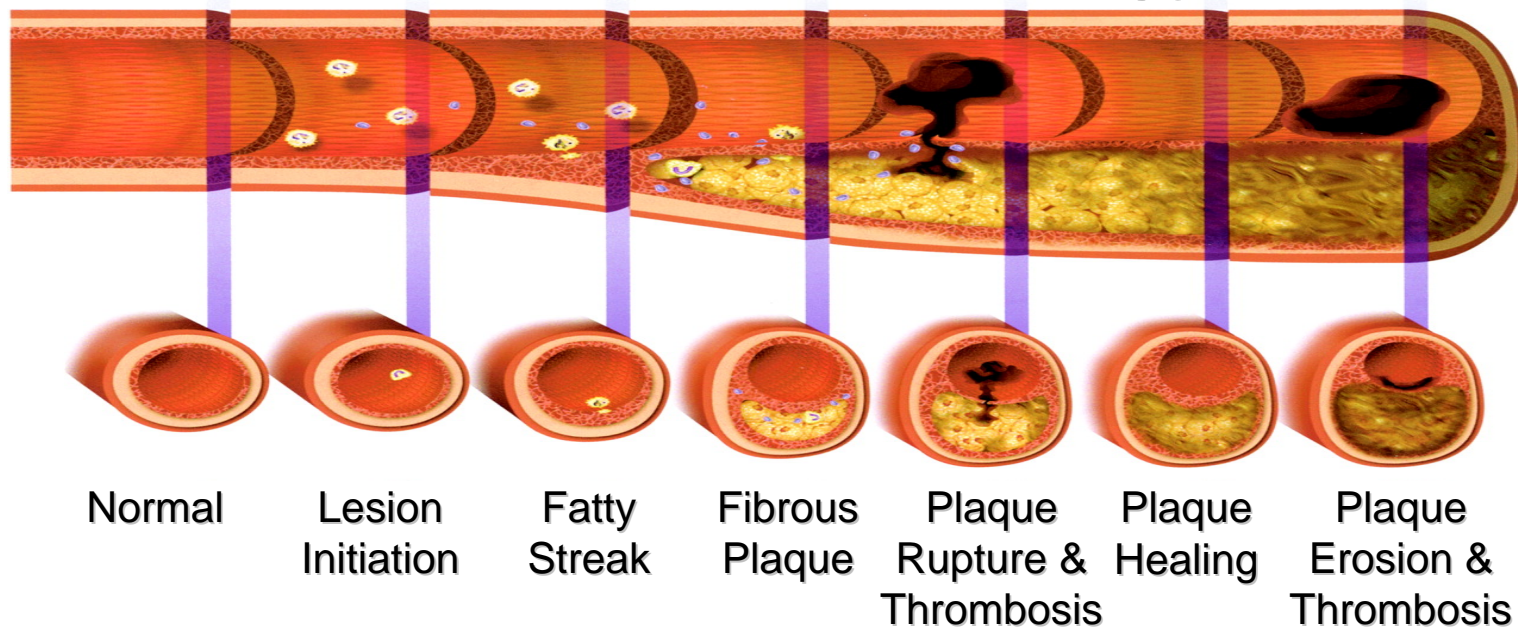
No

- **P values >0.05 indicate insufficient evidence to support treatment**

Ye

- **‘P < 0.05 ’ is an arbitrary cutoff**
- **P values reflect only the strength of evidence against the ‘null’ hypothesis**
- **P-values must be interpreted within the context of other trial data and human physiology**

Evidence Suggests Few Sex-Based Differences in Atherosclerotic Plaque Histology or Biology



Raised plaques exist in a large proportion of women and men by middle age

Plaques in women are histologically identical to those in men

There is no evidence that plaques in women are less vulnerable to rupture

There is no evidence that statins stabilize vulnerable plaques after rupture, but not before

Statin Therapy for Primary Prevention of Cardiovascular Disease in Women with Elevated hsCRP

JUPITER Trial -- 2010

Females	N=6,801 ≥ 60 Yr 0 CVD LDL-C <130 hsCRP ≥2
Design	Rosuvastatin 20 mg vs. Placebo F/U 2 Yr
Endpoint	MI CVA USA STENTS CABG or CV Death
Outcomes in Women on Statins	<p>Primary Endpoint - Any CV Event Women had a significant 46% decrease in relative risk [HR 0.54 p = 0.002]. Those with FHx CAD had an 80% decrease [HR 0.20, p <.05]</p> <p>Unstable Angina or Revascularization Women had a significant 76% decrease in relative risk [HR 0.24 p=.0001]</p> <p>Any MI, CVA or CV Death [HR 0.73 p=0.16] Any Death [HR 0.77 p = 0.12]</p>

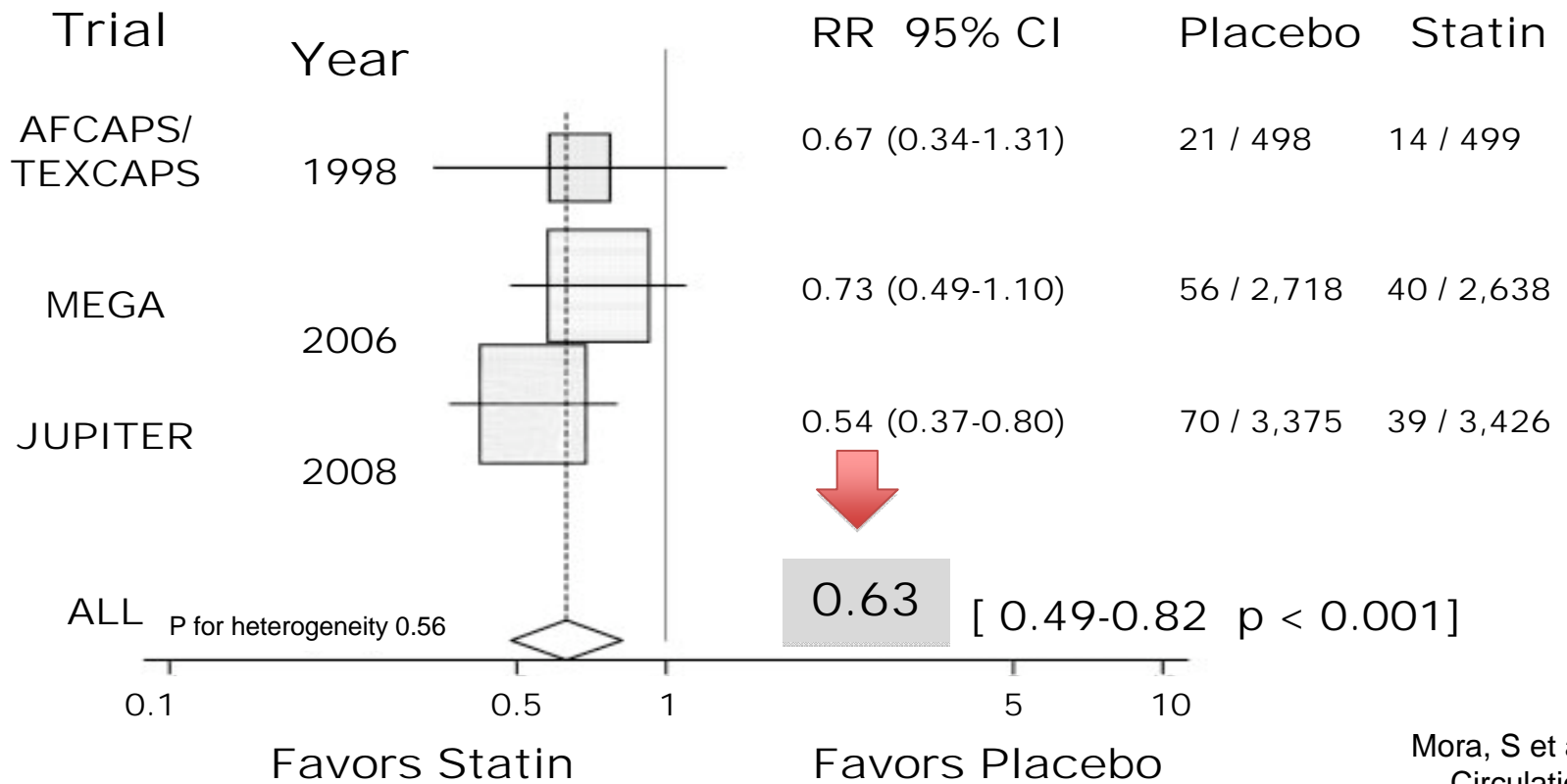
Absolute CVD Rate

Statin
0.56% / Yr
 Placebo
1.04% / Yr

Statin Therapy for Primary Prevention of Cardiovascular Disease In Women With Elevated hsCRP or Dyslipidemia

An Updated Sex-Based Meta-Analysis—Post JUPITER - 2010

RR for Total CVD* in Statin vs. Placebo Treated Women
In the 3 *Exclusively Primary Prevention* Trials (N=13,154)



*= MI,
CHD
Death,
CV Death,
CVA,
STENT,
or CABG

Statin Effects in Women vs. Men

Most Recent Sex-Based Meta-Analysis -- 2012

18 Trials	A to Z CORONA SEARCH	AFTEXCAPS GREASE JUPITER	ALLHAT GISSI-P HPS	ASCOT LIPID PROSPER	AURORA MEGA PROVEIT	CARE 4S TNT
Subjects	40,275 Women + 100,960 Men ± CVD					
Designs	Statin vs. Placebo or More vs. Less Statin					
Outcomes on Statins	<p>CV Events were significantly reduced 17% in women and 23% in men in primary and secondary prevention trials, regardless of baseline risk [OR-Women 0.83, OR-Men 0.77 p < .001]</p> <p>Total Deaths were reduced significantly by 13% in women in primary prevention trials [OR 0.87 p ~ 0.01]</p>					

Remaining Questions About Statins for Primary Prevention in Women

How Do We Assess Global Risk, and At What Level of Risk Do We Treat ?

- Which Risk Score is Best For Women?
 - ATP III Score **predicts MI or CHD death only**
 - Updated Framingham Score **includes all CVD**
 - Reynolds Score **adds hsCRP, family history**
- Do We Treat at >5%, >10% or >20% Risk?
 - **Cost efficacy is greater in high risk women, but majority of events will occur in women with low and intermediate 10-year risk**

Remaining Questions About Statins for Primary Prevention in Women

What Costs Are We Willing to Pay?

- Drug Costs Are Low and Gender Neutral
 - **A generic statin = \$ 0.06 tab/day x 1 yr = \$ 22**
- Cost Efficacy is Lower in Women
 - **Absolute risk reduction (ARR) is low in primary prevention [$\sim 0.5\%$ / year in women in JUPITER]**
 - **Since the NNT to prevent 1 event = $1 / \text{ARR}$, an ARR of $\sim 0.5\%$ / year (or 2.5% in 5 years) translates to needing to treat ~ 40 women for 5 years to prevent 1 event [at a cost of \$4,500 to \$255,000]**

*NNT = Number Needed To Treat

Remaining Questions About Statins for Primary Prevention in Women

What Side Effect Risks Are Acceptable ?

- Diabetes Mellitus
 - **Risk: ~ 9% - 13% from meta-analyses**
 - **Risk Factor: Pre-Diabetes**
- Neuro-Cognitive Dysfunction
 - **Risk: Unknown—reports based only on FDA AERS**
- Liver Injury
 - **Risk: “Transaminitis” 1 / 100; Liver Failure 1/1,000,000**
- Myopathy
 - **Risks: Myositis 5/100,000; Rhabdomyolysis 1.5/100,000**
 - **Risk Factors: Age, Small BMI, CKD, Drug interactions**

1 out of ~250
affected, but 5
CV Events will
be avoided

Summary: What To Tell Patients

- **The lifetime risk of CV disease in women is closely tied to the risk factor burden at age 50**
- **In women *with* CV disease, statins significantly reduce the risk of CV events**
- **In those *at risk of* CV disease, early statin trials showed benefits for men, but non-significant results in women were due to trial limitations**
- **Recent meta-analyses show statins reduce CV events in at-risk women with elevated lipids or hsCRP, especially those with a family history of early CHD—and may reduce the risk of death**
- **Specific clinical benefits, cost efficacy, and the risk-to-benefit ratio may be different in women and must be considered when treating**