

Primary Prevention with Statins

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Background: What we know

1. Half of all MI's occur without elevated LDL
2. Increased CRP predicts CV events
3. Statins lower cholesterol and CRP

Research Question: Will people with elevated CRP without hyperlipidemia benefit from statin Rx?

Methods: RCT of ~18,000 healthy men and women from 26 countries, 1,315 sites.

Inclusion Criteria:

1. LDL < 130
2. CRP > 2.0
3. Men > 50 yr and Women > 60 yr
4. Triglycerides < 500

Exclusion Criteria: Previous lipid lowering Rx, DM, HRT, any inflammatory condition, on immunosuppressants, increased Cr, poorly controlled HTN (SBP>190 or DBP>100)

Results:

1. Trial was so successful that monitoring and safety board stopped the 4 yr trial at 1.9 years.
2. LDL decreased by 50% in treatment group.
3. CRP decreased by 37%.
4. ~50% reduction in MI, stroke, and death from CV cause in the treatment group (83 events in treatment group vs. 157 events in placebo group, hazard ratio of 0.53, 95% CI, 0.40 to 0.69).
5. NNT for 5 years of treatment is 25.

Critiques of the Study:

1. Early termination of the study (at 1.9 of 4 yrs) may exaggerate results.
2. CRP is not the only way, or necessarily the best way to identify people who'll benefit from Rx.
3. Long-term safety of lowering LDL so significantly (to 55) must be established. Should we put low-risk subjects with no clinical disease on years of prophylactic treatment?
4. Adverse Effects: study showed increase incidence of DM in treatment group (3% vs. 2.4% p=0.1) and increased HgBA1C (5.9 vs. 5.8).
5. Cost of Rosuvastatin is \$3.45 per day, much more than generics. Studies are needed for other statins. Rosuvastatin is not cost effective with mildly elevated CRP (e.g. 2.5) but probably for higher CRP's (e.g. > 4.0).
6. Conflict of Interest: The study was funded by Astra Zeneca (maker of Rosuvastatin) who collected data and monitored sites. Additionally, Ridker (lead author) co-owns the patent on CRP screening.

A Summary of the JUPITER Trial:

Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin

Limitations of the Study

1. The data didn't compare the benefit of Rosuvastatin in averting CV events in patients with very high vs. minimally high CRP. Is there a linear relationship? Is there a CRP threshold for justifying intervention?
2. Data didn't compare CRP vs. other markers of CV risk.
3. We don't know if patients with CRP < 2.0 would benefit from a prophylactic statin.
4. 80% of initial subjects screened were excluded (previous lipid lowering Rx, DM, increased Cr, poorly controlled HTN). What role, if any, does CRP play in risk stratifying them for statin Rx?

Questions that the study brings up:

1. Should statin treatment be expanded for primary prevention?

-what issues come up for long-term prophylaxis in healthy patients with no clinical disease?
risks vs. benefits of statin treatment?

-should we use CRP as a screening tool to determine risk reduction from statin Rx?

-what's the CRP threshold warranting prophylactic statin Rx?

-should we instead change guidelines and lower LDL thresholds for starting statin Rx?

2. How should measurements of CRP be used?
-what risk factors, biomarkers, should a patient have to warrant getting a CRP screen?

Sources:

Original Article: "Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (NEJM Nov 20, 2008. 359;2195-2207 Ridker et al).

Editorial by Hlatky: "Expanding the Orbit of Primary Prevention-Moving Beyond JUPITER." NEJM Nov 20, 2008. 359;2280-2282.