Title

Impact of C-Reactive Protein and Coronary Artery Calcium on Benefit Observed With Atorvastatin

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Letters

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Controversy persists regarding the optimal strategy for allocating statins in primary prevention, with continued interest in a biomarker-guided approach. An effective biomarker in this setting might signal either improved relative risk reduction (effect modification) or greater absolute risk reduction (via improved risk prediction) with statin therapy.

High-sensitivity C-reactive protein (hsCRP), a marker of inflammation, and coronary artery calcium (CAC), a marker of coronary plaque burden, have emerged as leading candidates. For example, the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial showed that patients with hsCRP ≥2 clearly benefit from rosuvastatin, although subsequent studies have suggested similar benefit with hsCRP <2 (1). Prior studies have confirmed statin benefit in coronary disease, although doubt has been cast because certain patients likely to have high CAC—such as those with end-stage renal disease—do not benefit from statins (1).

We sought to compare the impact of hsCRP and CAC on statin benefit in the only large randomized controlled trial with each biomarker measured at baseline. The single-center St. Francis Heart Study, with an overall biomarker-driven design similar to that of the JUPITER trial (1), randomized asymptomatic patients with elevated CAC (>80th percentile for age and sex) to atorvastatin 20 mg and vitamin C+E versus placebo (1,2). A total of 1,003 patients were followed for mean 4.3 years for the primary major adverse cardiovascular events (MACE) outcome, inclusive of myocardial infraction, stroke, cardiovascular death, coronary revascularization, or peripheral arterial surgery. The study launched in 1996, was first reported in 2005 (2), with a study population of mean age 59 ± 6 years, with 74% men and median Framingham Risk Score of 11%. Median baseline hsCRP

(n = 960) and CAC were 2.07 mg/l and 371 Agatston units, respectively, with biomarker values balanced across treatment groups (p = 0.68 and p = 0.80, respectively). There were 85 MACE events in follow-up, 34 (6.9%) in the treatment group and 51 (9.9%) in the placebo group, consistent with a non-statistically significant benefit in the atorvastatin-containing arm (hazard ratio: 0.67; p = 0.08).
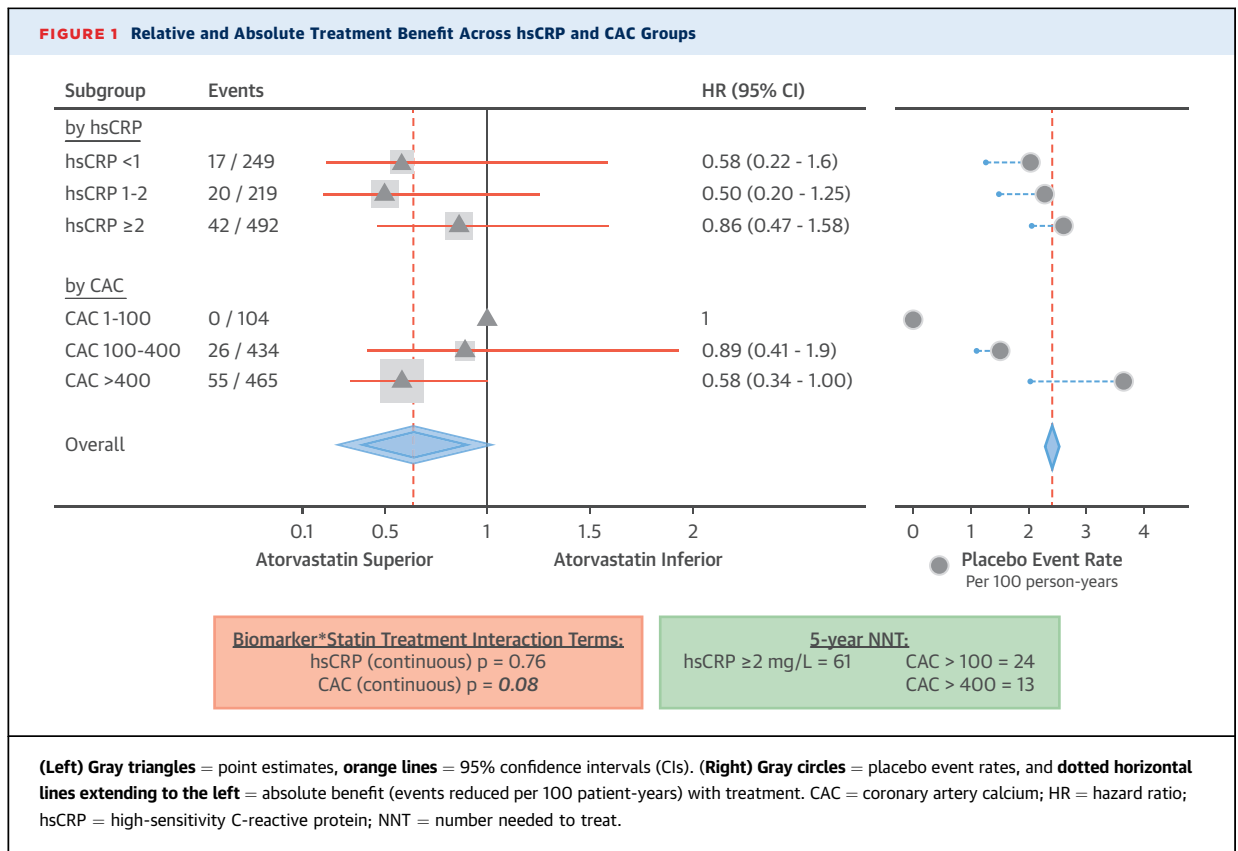
Our goal was to compare the benefit of therapy across a priori defined baseline hsCRP (<1, 1 to 2, ≥2 mg/l) and CAC (1 to 100, 101 to 400, >400) groups. We conducted additional analyses using hsCRP ≥2 mg/l and CAC >100 as binary cutpoints. Both the relative risk reduction and the absolute risk reduction per 100 patient-years were computed for each marker. In addition, an interaction term was tested, calculated as the log-transformed biomarker (continuous) × treatment assignment.

The complete results are shown in **Figure 1**. The hazard ratios for treatment benefit across hsCRP groups trended higher with increasing hsCRP, pointing toward less benefit with higher hsCRP, although the interaction term was nonsignificant (p = 0.76). The absolute risk reduction was similar across hsCRP groups, consistent with poor to fair discrimination of risk.

In contrast, the hazard ratio for treatment benefit across CAC groups trended lower with higher CAC, suggesting possible greater benefit with higher CAC, with a borderline but nonstatistically significant interaction term (p = 0.08). Absolute risk reduction was markedly larger with higher CAC, consistent with strong predictive value of CAC.

Direct comparison of annualized absolute benefit in patients with hsCRP ≥2 mg/l versus CAC >400 was 0.33 versus 1.54 events reduced per 100 patient-years, translating to an estimated 5-year number needed to treat of 61 versus 13. The 5-year number needed to treat of CAC >100 was 24. Results were unchanged after excluding 10 (12%) events occurring within 90 days of randomization.

These results, although limited by statistical power, do not support the previous hypotheses that: 1) hsCRP signals selective benefit from statins; or 2) CAC signals selective failure to benefit from statins. The signal that patients with higher CAC may obtain a greater relative benefit from treatment (weak evidence for positive effect modification [p = 0.08])

FIGURE 1 Relative and Absolute Treatment Benefit Across hsCRP and CAC Groups

Subgroup	Events		HR (95% CI)
by hsCRP			
hsCRP <1	17 / 249		0.58 (0.22 - 1.6)
hsCRP 1-2	20 / 219		0.50 (0.20 - 1.25)
hsCRP ≥2	42 / 492		0.86 (0.47 - 1.58)
by CAC			
CAC 1-100	0 / 104		1
CAC 100-400	26 / 434		0.89 (0.41 - 1.9)
CAC >400	55 / 465		0.58 (0.34 - 1.00)
Overall			

0.1   0.5   1   1.5   2
Atorvastatin Superior   Atorvastatin Inferior

0   1   2   3   4
● **Placebo Event Rate**
Per 100 person-years

Biomarker*Statin Treatment Interaction Terms:
hsCRP (continuous) p = 0.76
CAC (continuous) p = *0.08*

5-year NNT:
hsCRP ≥2 mg/L = 61   CAC > 100 = 24
                        CAC > 400 = 13

(Left) Gray triangles = point estimates, **orange lines** = 95% confidence intervals (CIs). (Right) Gray circles = placebo event rates, and **dotted horizontal lines extending to the left** = absolute benefit (events reduced per 100 patient-years) with treatment. CAC = coronary artery calcium; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; NNT = number needed to treat.

is intriguing, yet should be considered purely hypothesis generating. Unfortunately, baseline CAC has not been measured in any other statin randomized controlled trials, so confirmation would require a de novo clinical trial.

Limitations of this analysis include: 1) the hypothesis-generating nature of this secondary analysis; inclusion of revascularization endpoints in the primary MACE endpoint (although median time from CAC to randomization was already 63 days, limiting impact of CAC knowledge on outcomes); 2) the insufficient power for hard event-only analysis and for drawing strong conclusions of effect modification; and 3) the complicated intervention of the St. Francis Heart Study, which included a protocol for statin de-escalation, concomitant use of vitamin antioxidants, and aspirin therapy for all patients.

In the absence of any available strong evidence for effect modification, statins are perhaps best allocated by baseline risk (and therefore expected absolute benefit), consistent with 2013 American College of Cardiology/American Heart Association guidelines. In this regard, evidence from multiple prior studies, as well as the present study, point to potential superiority of using CAC for allocating statins (1,2).

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