Critical Review of High-Sensitivity C-Reactive Protein and Coronary Artery Calcium for the Guidance of Statin Allocation

Head-to-Head Comparison of the JUPITER and St. Francis Heart Trials

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Statins have been shown to be effective in primary prevention even among patients at low cardiovascular risk. However, statins are associated with moderate medical costs and have potential side effects. As a result, various biomarkers have been proposed for use in a tailored treatment strategy aimed at decreasing the number needed to treat (NNT), increasing the number needed to harm, and maximizing the cost-effectiveness of statin therapy. High-sensitivity C-reactive protein (hsCRP) and coronary artery calcium (CAC) are the leading novel markers of cardiovascular risk and are most commonly suggested for use in a tailored treatment approach.

Despite the theoretical benefits of these 2 biomarkers, there has been a dearth of definitive randomized trials specifically designed to test the efficacy of these, or any, novel biomarker for statin allocation. To date, only 2 randomized control trials have explored the potential use of these tests in improving outcomes with statin therapy: hsCRP in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial and CAC in the St. Francis Heart trial (Table).1b

In this article, we perform a comprehensive review of these trials from several different viewpoints: study rationale, study design, funding source, study population, pharmacological intervention, overall trial result, and overall trial interpretation. Our goal is to critically assess the level of evidence that these 2 randomized control trials provide, to suggest additional secondary analyses of the existing trial data, and to lay out a framework for performing true biomarker randomized control trials in the future.

Study Rationale

JUPITER Trial

hsCRP is an acute phase inflammatory protein shown to predict the likelihood of future cardiovascular events regardless of baseline Framingham risk score, low-density lipoprotein-cholesterol (LDL-C) level, or presence of metabolic syndrome. The large-scale Women’s Health Study demonstrated that the absolute risk of future cardiovascular events was higher in the group with low levels of LDL-C and high levels of hsCRP than those with high levels of LDL-C but low levels of hsCRP. Because statins have anti-inflammatory effects as well as cholesterol-lowering effects, they are known to reduce hsCRP levels in human populations, it was theorized that risk assessment based on hsCRP levels might provide a superior prediction of response to statin therapy. This theory was buoyed by the post hoc analyses of Air Force/Texas Coronary Atherosclerosis Prevention (AFCAPS/TexCAPS) trial and the Cholesterol and Recurrent Events (CARE) trial, which showed that lovastatin allocation significantly lowered primary cardiovascular outcomes among subjects with relatively low LDL-C levels (LDL-C<149 mg/dL) and elevated hsCRP levels (hsCRP>1.6 mg/L).8,9

Thus, the stated rationale of the JUPITER trial was to prove that identification of subclinical inflammation through hsCRP testing is an effective screening method in patients without hyperlipidemia “to detect high-risk individuals for whom the NNT is small enough to make prophylactic statin therapy cost effective.”

St. Francis Heart Trial

Multiple observational studies have verified that the CAC score is a robust, independent predictor of future cardiovascular events. The amount of calcium detected by noncontrast cardiac computed tomography closely correlates with the total atherosclerosis plaque burden of the coronary arteries. Indeed, a finding of zero CAC corresponds to low future event rates, whereas elevated CAC markedly increases risk even among low-risk patients. Studies have demonstrated that medical treatment with statins can delay coronary artery plaque progression, delipidate and stabilize plaque, and cause regression of existing atherosclerosis. Accordingly, it has been hypothesized that treating individuals with higher CAC scores will result in improved outcomes.

Interpretation of Study Rationales

Both of the above study rationales were based on abundant clinical and laboratory evidence that provided the necessary justification to enroll a patient population defined by the...
Elevated hsCRP predicts subjects most likely to benefit from statin treatment\(^1\) is the rationale for the JUPITER trial, whereas the St. Francis Heart Study preceded the contemporary more aggressive lipid guidelines, enrolling subjects with higher LDL (mean LDL, 143 mg/dL). Therefore, the former study was an explicit attempt to expand statin indication by the hsCRP-guided approach, whereas the latter was a proof of the concept of CAC-guided statin therapy.

However, because the biomarkers were measured in an unblinded fashion and enrollment occurred based on the result, neither design was capable of completely assessing the ability of either inflammation (as measured by hsCRP) or subclinical calcified atherosclerosis (as measured by CAC) to guide clinical practice or predict relative statin effect as a preventive therapy. This argument will be discussed further below.

### Funding Source

**JUPITER Trial**
The JUPITER trial was financially supported by Astra-Zeneca. The sponsor performed the trial data collection and study site monitoring but was not involved in data analysis or article drafting.\(^15,16\)

**St. Francis Heart Trial**
The St. Francis Heart trial was mainly supported by the St. Francis Hospital Foundation. Parke-Davis Pharmaceuticals, which is a subsidiary of Pfizer, Inc, supplied the statin and placebo at no cost.\(^4,17\)

### Interpretation of Funding Source

Both of the trials were investigator-initiated, but the JUPITER trial had more involvement by the pharmaceutical company in the study process, from patient enrollment to data accumulation.\(^18\) Although it is well known that industrial-funded trials tend to show more positive findings than trials funded by non-profit organizations, there is no evidence that the involvement of the pharmaceutical company affected the study outcome.\(^19\)

### Study Design

**JUPITER Trial**
The JUPITER trial was a randomized, double-blinded, placebo-controlled, multicenter trial conducted in 26 countries, of which the United States, United Kingdom, Canada, and South Africa were the main sites. After initial screening, a study population with LDL-C <130 mg/dL and hsCRP ≥2 mg/L were randomized to 2 groups. One group received rosuvastatin 20 mg daily and the other group received a placebo.

**St. Francis Heart Trial**
The St. Francis Heart trial was a randomized, double-blinded, placebo-controlled, single center trial that was coordinated at St. Francis Hospital, New York, United States. After the initial computed tomography screening, subjects with CAC scores >80th percentile for age and sex were identified and randomly assigned to either an atorvastatin 20 mg daily (in addition to vitamins C and E) or a placebo.

### Interpretation of Study Designs

The JUPITER trial exclusively enrolled patients with elevated hsCRP >2 mg/L and did not have an arm for subjects with LDL-C <130 mg/dL and hsCRP <2 mg/L. The JUPITER investigators decided not to include this arm based on the results of

### Table. Systematic Comparison of the JUPITER and the St. Francis Heart Trials

<table>
<thead>
<tr>
<th>JUPITER</th>
<th>St. Francis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationale</td>
<td>Elevated hsCRP predicts subjects most likely to benefit from statin treatment(^1)</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomized, double-blinded, placebo-controlled, multicenter trial</td>
</tr>
<tr>
<td>Funding source</td>
<td>Astra-Zeneca</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Men ≥50, Women ≥60 LDL-C &lt;130 mg/dL, hsCRP ≥2 mg/L</td>
</tr>
<tr>
<td>Size</td>
<td>17,802</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>66</td>
</tr>
<tr>
<td>Men, %</td>
<td>62</td>
</tr>
<tr>
<td>Framingham Score</td>
<td>11.6% (mean) 11% (median)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>108 mg/dL (median) 143 mg/dL (mean)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Rosuvastatin 20 mg</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>16%</td>
</tr>
<tr>
<td>Follow-up period, y</td>
<td>1.9</td>
</tr>
<tr>
<td>LDL-C reduction</td>
<td>55 mg/dL (50%) 62 mg/dL (42%)</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>11%</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>44%</td>
</tr>
<tr>
<td>Number needed to treat</td>
<td>25 at 2 y 17 at 4 y in subgroup CAC&gt;400</td>
</tr>
<tr>
<td>Placebo event rate</td>
<td>2.7% at 2 y 9.9% at 4.3 y</td>
</tr>
<tr>
<td>Statin event rate</td>
<td>1.6% at 2 y 6.9% at 4.3 y</td>
</tr>
<tr>
<td>Overall (P) value</td>
<td>&lt;0.00001 0.08</td>
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<tr>
<td>Increased absolute risk reduction with higher biomarker</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect modification with biomarker</td>
<td>No</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium; hsCRP, high-sensitivity C-reactive protein; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; and LDL-C, low-density lipoprotein-cholesterol.

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\(^1\) Investigators decided not to include this arm based on the results of...
post hoc analyses from the AFCAPS/TexCAPS study and the CARE trial, which demonstrated that people with low hsCRP levels had no cardiovascular benefit with statin treatment.9

However, it is still debatable whether statin therapy truly has no or little benefit in subjects with low hsCRP. A post hoc analysis from the Heart Protection Study demonstrated that there was a similar 29% relative risk reduction in major cardiovascular events even in people with low hsCRP levels (<1.25 mg/L) when they were treated with simvastatin 40 mg daily.20 Furthermore, reanalysis of the AFCAPS/TexCAPS trial for a true treatment–subgroup interaction did not show true effect modification by hsCRP status (interaction \( P \) value=0.305).21

Evaluation of a negative biomarker arm is essential to assess the effectiveness of a biomarker-guided statin allocation strategy, because otherwise it is impossible to disprove that statin treatment is effective for all subjects, irrespective of the level of hsCRP.22 Therefore, the JUPITER trial is best considered a well-conducted cholesterol-lowering trial rather than a biomarker trial because the efficacy of hsCRP as a biomarker was not fully assessed (Figure 1).

Like the JUPITER trial, the St. Francis Heart trial does not qualify as a biomarker trial. The St. Francis Heart trial lacks an arm with CAC scores <80th percentile for age and sex, which makes it difficult to exclude the possibility that statins provide equivalent benefit in patients with low CAC scores.

**Study Population**

### JUPITER Trial

A total of 89,890 people were screened for enrollment and 17,802 were included and ultimately randomly assigned to a study group. The main excluding factors were LDL-C levels ≥130 mg/dL (52.2%) and hsCRP levels <2.0 mg/L (36.1%). The final study population comprised men age ≥50 years and women age ≥60 years, with hsCRP levels ≥2 mg/L and LDL-C levels <130 mg/dL, who had no history of cardiovascular disease or stroke.

### St. Francis Heart Trial

Approximately 20,000 people were screened for inclusion and exclusion and 5,582 people were scanned with computed tomography. A total of 1,007 subjects with CAC scores >80th percentile for age and sex were identified and randomly assigned to a study group. The final study population consisted of men and women aged 50 to 70 years, with CAC scores >80th percentile for age and sex, who did not have pre-existing history of cardiovascular disease. Subjects with LDL-C <90 mg/dL were excluded from the trial after initial screening. This was because of the concern that LDL-C <60 mg/dL might alarm primary care physicians, affecting compliance with statin and the study outcome.

### Interpretation of Study Populations

The 2 studies had similar patient characteristics: mean age (66 years JUPITER versus 59 years St. Francis Heart Trial), sex distribution (62% men versus 74% men), and Framingham Risk Score (mean 11.6% versus median 11%). By design, the St. Francis Heart trial population had a higher mean LDL-C compared with that of the JUPITER trial (143 versus 104 mg/dL).23,24 Although the Framingham Risk Score was similar, 77% of the JUPITER trial subjects were non-US populations and Framingham Risk Score may not calibrate as well to non-US populations including Europeans.25 The placebo event rate was significantly higher in the St. Francis Heart trial (9.9% at 4.3 years versus 2.7% at 2 years), suggesting that a high CAC may select a higher cardiovascular risk population as compared with high hsCRP.

It is also noteworthy that the study population is much larger in the JUPITER trial compared with the St. Francis Heart trial (17,802 versus 1,005). The authors of the St. Francis trial calculated that with an annual cardiovascular event rate of 3%, 472 patients per group will give an 80% power to identify a hazard ratio of 0.85.4 It turned out, however, that the annual major cardiovascular event rate was <1% per year.

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**Figure 1.** Study designs for assessing the efficacy of statins, eg, the JUPITER trial (A), and a true biomarker trial (B).
Both trials had a relatively arbitrary cutoff value of the biomarker. The JUPITER trial defined people with hsCRP ≥2 mg/L as a high cardiovascular risk group. A study from the Multi-Ethnic Study of Atherosclerosis (MESA) population illustrated that hsCRP ≥2 mg/L is not an independent predictor of cardiovascular events. Numerous studies have suggested a better risk prediction with the hsCRP cutoff at ≥2 mg/L,

The St. Francis Heart trial defined the high CAC score group as subjects with CAC scores >80th percentile for age and sex. This strategy resulted in setting a lower calcium score threshold for younger subjects, particularly women, and therefore a significant number of traditionally low-risk patients were included in the study population. As of yet, there is no definite agreement on the CAC cutoff value to identify higher cardiovascular risk populations.

Recent data from the MESA sheds light on the expected CAC profile of JUPITER-eligible patients. It has been projected that 47% of the JUPITER-eligible population would have no CAC, 28% would have CAC 1 to 100, and 25% would have CAC >100. Approximately 50% of St. Francis participants had hsCRP ≥2 mg/L.

Study Intervention

JUPITER Trial

Eligible subjects underwent a 4-week run-in period before randomization to ensure the capacity of long-term protocol compliance. After the run-in period, participants were randomized to either a rosvuastatin 20 mg daily group or a placebo group. Participants were evaluated at 3 and 6 months initially and then every 6 months for follow-up.

St. Francis Heart Trial

Eligible subjects went through a 2-week wash-in period before randomization. After that, participants were randomized to either an atorvastatin 20 mg daily group or aspirin, vitamin C (1 g/d), and vitamin E (1000 IU/d) group or placebo with aspirin (81 mg/d). Participants were followed up every 6 weeks for 3 months and thereafter at 3-month intervals.

Interpretation of Study Interventions

Rosuvastatin offers the greatest LDL-C lowering and high-density lipoprotein increasing efficacy compared with other statins. The Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial showed that 20 mg of rosuvastatin reduced LDL-C by a mean of 52.4%, whereas 20 mg of atorvastatin reduced LDL-C by 42.6%. This result is in line with the results of the JUPITER trial and the St. Francis Heart trial, which showed LDL-C reductions by a mean of 50% and 43%, respectively. Therefore, the differential statin potency must be accounted for in the interpretation of the overall study results. Furthermore, the atorvastatin dose in the St. Francis Heart trial was reduced to 10 mg daily when the LDL-C level fell <50 mg/dL. The less aggressive LDL-C reduction with statin may have attenuated event rate reduction in the St. Francis study.

In the St. Francis Heart trial, the atorvastatin treatment arm received high doses of vitamins C (1 g/d) and E (1000 IU/d) along with atorvastatin based on the theoretical benefit of antioxidant treatment. However, some studies have demonstrated that coadministration of antioxidant vitamins C and E with statin may attenuate the effect of the statin in cardiovascular outcomes. These studies suggest that antioxidant use in the St. Francis Heart trial may have diminished the effects of statin therapy.

It is also noted that both the statin treatment arm and placebo arm in the St. Francis Heart trial received aspirin 81 mg daily. It was deemed unethical not to give aspirin to subjects with elevated CAC scores who may be at increased risk of cardiovascular disease. Given that the annualized cardiovascular event rate in the placebo arm was lower than expected (2% for the composite end point and <1% for major cardiovascular events), it is likely that aspirin therapy might have reduced the power of the St. Francis study.

Study Results

JUPITER Trial

The JUPITER trial was terminated early after a median follow-up of 1.9 years because of significantly favorable primary outcomes in the rosvuastatin treatment group (1.6% event rate in statin group versus 2.7% in placebo group, 1.1% absolute risk reduction, and 44% relative risk reduction; P<0.00001). The hazard ratio and NNT for rosvuastatin in 2 years were 0.56 and 95, respectively. Extrapolation of the study results outside of the follow-up enabled calculation of an NNT at 5 years of 25 using the method of Altman and Andersen.

St. Francis Heart Trial

At a mean of 4.3 years of follow-up, treatment reduced total cholesterol by 6.5% to 30.4% (P<0.0001) and LDL-C by 39.1% to 43.4% (P<0.0001). However, the St. Francis Heart trial researchers failed to show a statistically significant difference in the incidence of major cardiovascular events (6.9% versus 9.9%; P=0.08), despite a large absolute risk reduction (3%). Importantly, in a post hoc subgroup analysis, participants with the highest CAC scores (>400) had the greatest benefit from statin treatment (8.7% versus 15.0% event rate, 6.3% absolute risk reduction, 42% relative risk reduction; P=0.046) with associated NNT of 17 at 4 years (14 at 5 years).

Interpretation of Study Results

It is now firmly established that statins benefit a wide variety of patients. Indeed, both study results are in agreement with a recent meta-analysis of previous randomized control trials that showed a linear relationship between LDL-C reduction and cardiovascular events reduction. (Figure 2) Given the fact that statin therapy has benefits even in people with LDL-C as low as 80 mg/dL, the cardiovascular risk reduction shown in both the JUPITER trial and the St. Francis Heart trial (with median LDL-C 108 mg/dL and mean 143 mg/dL, respectively) were predictable without the use of hsCRP and CAC.
The JUPITER trial did not demonstrate effect modification by baseline hsCRP levels. A Food and Drug Administration (FDA)-mandated subgroup analysis of the JUPITER trial revealed that subjects with hsCRP >4.2 mg/L had lower relative risk reduction with statin therapy than those with hsCRP ≤4.2 mg/L (relative risk reduction, 29% versus 58%; P = 0.015). Moreover, a post hoc analysis of the trial demonstrated that the treatment benefit was confined to people with ≥1 additional risk factor. The Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) also showed that while hsCRP is a mild predictor of baseline risk, there is no improvement in predicting response to statins when adding hsCRP to LDL-C. Thus, none of the JUPITER, ASCOT, or the above-mentioned Heart Protection Study showed evidence of effect modification with elevated hsCRP.

In contrast to the JUPITER trial, the St. Francis Heart trial raises the possibility of effect modification despite being a negative study. In subjects with a baseline CAC score >400, who comprised 47% of the study population in the St. Francis Heart trial, the reduction in incidence of major cardiovascular events was higher than that in subjects with a CAC score ≤400 (8.7% versus 15%; P = 0.046; NNT = 17 at 4 years). However, the possible effect modification with CAC cannot be viewed as definitive in the setting of an overall nonsignificant trial result.

As mentioned, the sample size of the JUPITER trial was much larger than that of the St. Francis Heart trial (17,802 versus 1,007). Given that the St. Francis Heart trial had a higher absolute risk reduction (3% versus 1.1%), the sample size is likely to be the main explanation for the nonsignificant P value in the St. Francis heart trial. In exploratory analysis, calculation of the estimated P value in a theoretical St. Francis Heart trial with a similar sample size would be cumbersome if trying to compare multiple biomarkers, and randomize them to 2 groups based on the biomarker level. This study design would allow for testing the efficacy of the biomarker-guided statin therapy, allowing for true effect modification by biomarker status and would provide an additional post hoc analysis of 4 subgroups based on hsCRP (hsCRP >2 mg/L, hsCRP ≤2 mg/L) and CAC levels (CAC score >400, CAC score ≤400) to identify the group that best predicts statin benefit.

As described earlier, neither of the studies succeeded in assessing the efficacy of the biomarker-guided statin therapy, because of the lack of the negative biomarker arm. Therefore, a true biomarker trial is eventually needed to definitively answer the uncertainty of a biomarker-guided statin allocation strategy. An ideal biomarker trial would enroll subjects and randomize them to 2 groups based on the biomarker level. As seen in Figure 1B, each arm (positive versus negative biomarker) of the population would be randomized to either statin treatment or placebo. This study design would allow for testing for true effect modification by biomarker status and would also allow a comparative effectiveness analysis of absolute risk reduction between the 2 strategies. This approach, however, requires 2 separate randomizations for each biomarker and would be cumbersome if trying to compare multiple biomarkers, such as hsCRP and CAC.

**Discussion**

The JUPITER trial and St. Francis Heart trial were designed to evaluate the value of hsCRP and CAC as biomarkers. Although not exactly parallel studies, in large part because of differences inherent in =15 years of separation in time, the trials are clearly analogous. The JUPITER trial was notable in terms of statistical significance and sample size. The St. Francis Heart trial had a nonsignificant P value, but the trial is in keeping with what we know about statins (Figure 2), and the results strongly suggested that subjects with CAC scores >400 receive a large absolute benefit from statin therapy. The studies were more similar than different in that they both lacked a negative biomarker arm, and neither showed definite effect modification by baseline biomarker status. Therefore, we conclude that both trials provide a modest level of evidence, which by themselves are insufficient to reclassify the level of evidence and recommendations of professional societies for biomarker-guided statin therapy at this time (American College of Cardiology/American Heart Association: IIb both, European: IIb for hsCRP, IIA for CAC [all level of evidence B]).

The St. Francis Heart trial is the only study that measured both hsCRP and CAC at baseline. Perhaps, because of the P value and the lack of industry funding, the study has been infrequently referenced in the past several years. However, its value still remains critical. Reanalysis of the data from the St. Francis Heart trial could give further insight about which biomarker better predicts absolute and relative risk reduction with statins. True effect modification should be tested for in this study and placed in context with the preceding data. We propose an additional post hoc analysis of 4 subgroups based on hsCRP (hsCRP >2 mg/L, hsCRP ≤2 mg/L) and CAC levels (CAC score >400, CAC score ≤400) to identify the group that best predicts statin benefit (Figure 3B).

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![Figure 2](image-url)
Another framework for a true biomarker trial allowing comparative effectiveness analysis is shown in Figure 3 (once again using hsCRP and CAC as the example). Subjects with low-to-intermediate cardiovascular risk (ie, 5%–7.5% risk based on the Pooled Cohort Equations) who are not eligible for statin treatment under the current guidelines would be enrolled. After the initial cardiovascular risk assessment, both hsCRP and CAC would be measured blindly at baseline, and then the study population would be randomized to either a statin treatment arm or placebo arm (Figure 3A). The groups would then be followed up for a sufficient period of time to accrue outcomes and presumably observe a difference between the treated and placebo groups. Prespecified group analysis of the 4 subgroups based on hsCRP and CAC levels will be performed (Figure 3B). This study design will give answers for (1) risk prediction, by defining the group in which the majority of events happen; (2) effect modification, by defining if high levels of a biomarker selectively identify greater benefit; and (3) cost-effectiveness, comparing a treat all approach versus targeting therapy using hsCRP or CAC. However, several issues have been raised with regards to the feasibility of a true, ideal biomarker trial in the current...
era. Although an ideal biomarker trial with a placebo arm was feasible at the time the JUPITER and St. Francis Heart trials were conceived, withholding treatments to subjects with elevated hsCRP and CAC would likely be considered unethical at the present. Multiple population studies have already shown that subjects with CAC score >100 have an increased risk equivalent to those with pre-existing coronary heart disease (a coronary heart disease risk equivalent).\textsuperscript{17,26} For example, using data from MESA predicted a 5-year NNT of just 24 in JUPITER-like patients with CAC>100.\textsuperscript{26}

It is debatable whether we have missed the opportunity to run conventional trials investigating biomarker-driven statin allocation in primary prevention. A more pragmatic approach of performing a biomarker study in the current era is a strategic trial that allows statin treatment in the biomarker-negative arm based on the physician’s decision, rather than withholding statin treatment. For instance, after initial enrollment and biomarker (hsCRP and CAC) screening, the study population could be randomized to 3 groups and receive (1) hsCRP-guided treatment; (2) CAC-guided treatment; and (3) current strategy—guided treatment (Figure 4). Instead of having a placebo group, this strategy will allow the physician to give statin if it is deemed appropriate to avoid harm to the study population. This approach, while needing a larger study population in proportion to the degree of statin therapy in the current strategy group, is more ethical to perform in the current era and could potentially be performed using a collaborative research trial network.

Statins have proven efficacy in cardiovascular disease prevention. Despite this, the best way to safely and cost-effectively deliver statin to a worldwide population remains in question. A targeted approach may lower the NNT, raise the number needed to harm, save money, and avoid unnecessary medicalization. It is time to move into an era of true biomarker studies to investigate the clinical effectiveness of a biomarker-guided strategy.

Disclosures
Dr Arad is employed by Tiara Pharmaceuticals. There is no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could seem to have influenced the submitted work. The other authors report no conflicts.

References


**Key Words:** atherosclerosis ◦ biomarkers ◦ C-reactive protein ◦ cardiovascular diseases ◦ coronary disease ◦ stents, HMG-CoA
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