Should statin therapy be considered for patients with elevated C-reactive protein? The need for a definitive clinical trial

Clinical trials demonstrate that HMGCoA reductase inhibitors reduce the risk of first cardiovascular events[1,2]. However, better screening methods are needed in primary prevention to detect high risk individuals for whom the number needed to treat is small enough to make prophylactic statin therapy cost-effective. Although LDL screening improves cost-effectiveness of statins in some primary prevention settings, this approach is incomplete as nearly half of all coronary events occur among persons without overt hyperlipidaemia[3,4].

In an effort to improve vascular risk detection, many physicians have considered screening for C-reactive protein (CRP), an inflammatory biomarker associated with increased risk of myocardial infarction, stroke and peripheral arterial disease[5–9]. Such a combined lipid plus CRP screening approach has intuitive appeal, in part because CRP predicts future vascular risk even among those with low to normal lipid levels. Further, as statin therapy lowers CRP in an LDL independent fashion[10,11], it has been hypothesized that CRP screening might provide a novel method to improve the targeting of statin therapy, particularly among those with low to normal levels of LDL cholesterol.

This important hypothesis was addressed in a recent analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[12]. In brief, AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled trial of lovastatin in the primary prevention of cardiovascular events conducted among 6605 American men and women with average cholesterol levels and below average HDL levels. Individuals with uncontrolled hypertension, secondary hyperlipidaemia, diabetes requiring insulin, or morbid obesity were excluded. Following randomization to either lovastatin or matching placebo, participants were followed over an average period of 5.2 years for the occurrence of first acute coronary events, prospectively defined as fatal or non-fatal myocardial infarction, unstable angina, or sudden cardiac death.

As had previously been reported, allocation to lovastatin in the AFCAPS/TexCAPS trial was associated with a 37% reduction in this primary clinical end-point (RR=0.63, 95% CI 0.50–0.79, \(P<0.001\))[2]. However, after measuring baseline CRP as well as lipid levels in the AFCAPS/TexCAPS population, several important observations regarding clinical efficacy of lovastatin were observed.

First, consistent with prior reports in primary prevention, coronary event rates increased with baseline CRP levels such that the relative risks from lowest (referent) to highest quartiles of baseline CRP among those allocated to placebo were 1.0, 1.2, 1.3 and 1.7 (\(P=0.01\)). This effect was independent of all other factors known to predict risk in AFCAPS/TexCAPS, including basal lipid values[13].

Second, and consistent with prior reports for pravastatin[10] and cerivastatin[14], random allocation to lovastatin resulted in a statistically significant 14.8% reduction in median CRP levels at the end of the first year of treatment (95% CI of the median \(-17.4\) to \(-12.5\), \(P<0.001\)). Moreover, this reduction in CRP was not related to the effect of lovastatin on lipid levels; in AFCAPS/TexCAPS, less than 2% of the variance in the change in CRP over time could be explained by lovastatin-induced changes in lipid fractions.

Third, and most importantly, there were major differences in observed statin efficacy when the AFCAPS/TexCAPS data were stratified into four groups of equal size based upon the median baseline level of LDLC and upon the median baseline level of CRP (Table 1). As would be expected, lovastatin was clinically effective among participants with above median LDLC levels regardless of CRP (RR=0.53, 95% CI 0.37–0.77, number needed to treat=42, \(P=0.001\)). However, lovastatin was equally effective among those with below median LDLC levels and above median CRP levels (RR=0.58, 95% CI 0.34–0.98, number needed to treat=48, \(P=0.04\)). In fact, this subgroup with low LDLC and high CRP had a risk of future vascular events just as high as
that observed in the subgroups with overt hyperlipidaemia. In marked contrast, event rates were low among AFCAPS/TexCAPS participants with below median LDLC and below median CRP levels, a subgroup in which there was no evidence that lovastatin reduced the risk of future cardiovascular events (RR=1.08, 95% CI 0.56–2.08, P=0.7). These results were virtually identical when the TC:HDLC ratio was used rather than LDLC.

Publication of the AFCAPS/TexCAPS CRP data has been seen in some quarters as a widespread call for an immediate increase in the utilization of statin therapy in primary prevention. For example, within the United States managed care community, the AFCAPS/TexCAPS CRP analysis has been interpreted as a ‘win/win’ situation in which more aggressive use of statins is being advocated among those with low to normal LDLC but elevated CRP. At the same time, the AFCAPS/TexCAPS data also provide managed care providers with evidence that statins can be withheld among those where the global risk is low and where there is minimal evidence of efficacy (i.e. those with low to normal LDLC but below average CRP).

Despite the intuitive appeal of this interpretation, it is important to point out that this is not the consensus opinion of the AFCAPS/TexCAPS investigators themselves. Indeed, despite the striking nature of these findings, the investigators correctly note that the AFCAPS/TexCAPS CRP observations were made on a post hoc basis and thus require direct confirmation or refutation in a large-scale prospective trial.

The general design of such a trial is shown in Fig. 1. In brief, primary prevention patients with low to normal LDLC but with above average CRP values would be randomly allocated to either statin or placebo therapy and then followed for the occurrence of first cardiovascular events (hospitalization for unstable angina, non-fatal MI, non-fatal stroke, or cardiovascular death). To enrich end-points, enrolment might be limited to men and women over the age of 60. Annual follow-up blood sampling would be used to address participant compliance and

Table 1  Crude event rates, relative risks (RR) and the number needed to treat (NNT) associated with lovastatin allocation among AFCAPS/TexCAPS participants, according to baseline levels of LDLC and CRP. Adapted from[12]

<table>
<thead>
<tr>
<th>Study group</th>
<th>Lovastatin n</th>
<th>Placebo n</th>
<th>RR</th>
<th>95% CI</th>
<th>NNT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below median LDLC/below median CRP</td>
<td>19/726</td>
<td>17/722</td>
<td>0.98</td>
<td>0.56–2.08</td>
<td>—</td>
</tr>
<tr>
<td>Below median LDLC/above median CRP</td>
<td>22/718</td>
<td>37/710</td>
<td>0.58</td>
<td>0.34–0.98</td>
<td>48</td>
</tr>
<tr>
<td>Above median LDLC/below median CRP</td>
<td>15/709</td>
<td>37/711</td>
<td>0.38</td>
<td>0.21–0.70</td>
<td>33</td>
</tr>
<tr>
<td>Above median LDLC/above median CRP</td>
<td>29/741</td>
<td>40/705</td>
<td>0.68</td>
<td>0.42–1.10</td>
<td>58</td>
</tr>
</tbody>
</table>

*Event rates and number needed to treat (NNT) calculated based on 5 patient years at risk.

Figure 1  Proposed randomized trial of statin therapy among individuals with low levels of LDL-C and elevated levels of hs-CRP.

to evaluate changes in both lipid and inflammatory parameters over time. A study registry would be formed for those individuals screened but not eligible for randomization.

The need for such a trial is underscored by the very large number of individuals who might well benefit from statin therapy, yet fall below current American and European guidelines on the basis of LDL levels. In the United States alone, it has been estimated that 20 to 25 million Americans outside treatment guidelines would have a cost-effective benefit from statin therapy if the low LDL/high CRP hypothesis is confirmed. The likelihood of success for such a trial is high; in the setting of patients with a history of myocardial infarction, two studies have already shown that statins reduce the risk of recurrent coronary events associated with elevated levels of CRP.[15,16]. In the AFCAPS/TexCAPS study of primary prevention, statin therapy was found to reduce vascular risk associated with CRP, even in the absence of hyperlipidemia. Nonetheless, the absolute number of events within the low LDL/high CRP subgroup of AFCAPS/TexCAPS is modest and testing for a multiplicative interaction in the trial between lovastatin, lipids and CRP was of borderline significance. A prospective, placebo-controlled trial of statin therapy among individuals without overt hyperlipidemia but with evidence of systemic inflammation is thus needed to directly test this hypothesis. If positive, such a trial would provide a clear rationale for far wider use of statins than is typically achieved in current practice.

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References