Relative Efficacy of Atorvastatin 80 mg and Pravastatin 40 mg in Achieving the Dual Goals of Low-Density Lipoprotein Cholesterol <70 mg/dl and C-Reactive Protein <2 mg/l

An Analysis of the PROVE-IT TIMI-22 Trial

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OBJECTIVES
The aim of this research was to compare relative efficacy of different statin regimens in achieving the dual goals of low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP) reduction.

BACKGROUND
While secondary prevention guidelines for statin therapy suggest lowering LDL-C levels <70 mg/dl, we have recently shown that clinical outcomes are improved when CRP levels are also lowered <2 mg/l.

METHODS
We addressed the relative efficacy of pravastatin 40 mg and atorvastatin 80 mg daily to reduce LDL-C and CRP among 3,745 acute coronary syndrome patients.

RESULTS
A total of 1,018 participants (27.1%) achieved the dual goals of LDL-C <70 mg/dl and CRP <2 mg/l. After adjustment for age, gender, smoking, diabetes, hypertension, obesity, and HDL-C, these individuals had a 28% lower risk of recurrent myocardial infarction or vascular death (relative risk = 0.72; 95% confidence interval 0.52 to 0.99). Of those who achieved dual goals, 80.6% received atorvastatin 80 mg, while 19.4% received pravastatin 40 mg (p < 0.001). Only 11% allocated pravastatin and 44% allocated atorvastatin achieved the goals of LDL-C <70 mg/dl and CRP <2 mg/l, and only 5.8% allocated pravastatin 40 mg and 26.1% allocated atorvastatin 80 mg reached the even lower goals of LDL-C <70 mg/dl and CRP <1 mg/l. The correlation coefficient for CRP measured at 30 days and at end of study was 0.61 (p < 0.001), a value almost identical to that for LDL-C over the same follow-up period (r = 0.62, p < 0.001).

CONCLUSIONS
While atorvastatin 80 mg was superior to pravastatin 40 mg in terms of achieving the dual goals of aggressive LDL-C and CRP reduction, neither agent brought the majority of patients below thresholds needed to maximize patient benefit.

Current guidelines for statin therapy provide the option to reduce low-density lipoprotein cholesterol (LDL-C) <70 mg/dl among very high-risk patients with a history of myocardial infarction or acute coronary syndrome (1). However, in addition to lowering LDL-C, statin therapy also lowers high-sensitivity C-reactive protein (hsCRP) in a largely lipid-independent manner (2–5), and it has been demonstrated that the relative efficacy of statins appears greater among those with elevated hsCRP levels (4,6).

We recently showed in the Pravastatin or Atorvastatin Evaluation and Infection (PROVE-IT) Thrombolysis In Myocardial Infarction (TIMI)-22 trial that the lowest rates of recurrent myocardial infarction or cardiovascular death among statin-treated patients occur among those who not only achieve LDL-C goals <70 mg/dl, but also achieve hsCRP goals <2 mg/l (7). On this basis, physicians providing optimized statin care may elect to measure and monitor hsCRP levels in a manner analogous to that of LDL-C. To date, however, there are no comparative data describing the relative ability of different statin regimens to achieve the “dual goals” of aggressive LDL-C and hsCRP reduction.

METHODS
The PROVE-IT TIMI-22 study was a randomized 2 by 2 factorial design trial evaluating the effects of intensive (atorvastatin 80 mg oral daily) versus moderate (pravastatin 40 mg oral daily) statin therapy and of gatifloxacin versus...
placebo in the prevention of recurrent coronary events among 4,162 patients with acute coronary syndrome (8).

Details of the overall PROVE-IT TIMI-22 study design and of the prespecified C-reactive protein (CRP) protocol (7,8) have been presented previously. In brief, as part of the study design, plasma samples were sought at randomization and at day 30, 4 months, and the end of study. The level of LDL-C and hsCRP achieved after initiation of statin therapy was defined as the level at 30 days, a period of time adequate for the effect of statin therapy to be observed for both LDL-C and hsCRP, and when the residual effects of ischemia on both of these parameters would be overcome. A total of 3,745 participants (90%) were alive and free of recurrent events at day 30 and underwent evaluation for both LDL-C and hsCRP. All laboratory measures were made in a core facility, and a validated assay was used for hsCRP.

The relative efficacy of pravastatin 40 mg and atorvastatin 80 mg in lowering LDL-C and hsCRP was evaluated in several stages. First, Spearman correlation coefficients were used to evaluate the relationship between achieved LDL-C at 30 days and achieved hsCRP at 30 days for each statin. Second, we calculated the number of study participants who did and did not achieve the dual goals of LDL-C <70 mg/dl and hsCRP <2 mg/l, both for the total study cohort, and in separate strata according to randomized drug assignment. The relative proportions of study participants on each agent were then calculated and compared using chi-square analysis. Age-adjusted incidence rates for recurrent myocardial infarction or cardiovascular death were computed for those who did and did not achieve the dual goals cited above, and Cox proportional hazards models were used to determine relative risks of these recurrent events in age-adjusted analyses, fully adjusted analyses, and according to pravastatin or atorvastatin allocation. Incidence rates were age-adjusted by the method of direct standardization using 10-year age categories. Similar analyses were performed addressing the proportion of participants on each randomized agent who not only achieved LDL-C <70 mg/dl, but who also achieved hsCRP levels <1.5, <1.0, and <0.5 mg/l. Comparisons were also made between hsCRP and LDL values obtained at 30 days to those obtained at 4 months and at end of study. All p values are two-tailed; all confidence intervals computed at the 95% level, and all outcomes adjusted for statin therapy, an agent that had no significant effects on hsCRP levels in this population.

### RESULTS

Both pravastatin 40 mg and atorvastatin 80 mg reduced LDL-C and hsCRP levels after 30 days of therapy. However, for both agents, the correlation between achieved LDL-C and achieved hsCRP at 30 days was minimal such that the magnitude of LDL-C reduction could not be used to gauge hsCRP reduction for individual patients (r = 0.04 for pravastatin, r = 0.15 for atorvastatin).

Of the 3,745 acute coronary syndrome patients randomized in the PROVE-IT TIMI-22 trial who were alive and free of recurrent events at 30 days, 1,018 (27%) achieved the dual goals of LDL-C <70 mg/dl and hsCRP <2 mg/l after initiation of statin therapy (Table 1). Compared to those who did not achieve both target goals, those who did had significantly improved event-free survival in terms of recurrent myocardial infarction or coronary death during the subsequent 2.5 years of follow-up (2.4 vs. 3.7 per 100 person years, p = 0.007) (Fig. 1). Overall, those who achieved the dual goals had a 35% lower risk of recurrent events (age-adjusted relative risk = 0.65, 95% confidence interval 0.47 to 0.89, p = 0.007). After full adjustment of age, gender, smoking status, diabetes, hypertension, and body mass index, those who achieved dual goals had a 29% lower risk of recurrent cardiovascular events (fully adjusted relative risk = 0.71, 95% confidence interval 0.52 to 0.98, p = 0.04). As also shown in Table 1, the magnitude of relative risk reduction comparing those who did and did not achieve dual goals was virtually identical in analyses stratified by

### Table 1. Proportion of Patients in the PROVE-IT TIMI-22 Trial Reaching Dual Goals of Low-Density Lipoprotein Cholesterol <70 mg/dl and C-Reactive Protein <2 mg/l in the Total Cohort and According to Statin Allocation

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Total Cohort</th>
<th>Atorvastatin</th>
<th>Pravastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) Event Rate*</td>
<td>RR&lt;sub&gt;adj&lt;/sub&gt; (95% CI)</td>
<td>RR&lt;sub&gt;adj&lt;/sub&gt; (95% CI)</td>
</tr>
<tr>
<td>Dual goals not achieved</td>
<td>2,727</td>
<td>3.7</td>
<td>ref</td>
</tr>
<tr>
<td>(72.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,018</td>
<td>2.4</td>
<td>0.65 (0.47-0.89)</td>
</tr>
<tr>
<td>(27.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,676</td>
<td>3.9</td>
<td>ref</td>
</tr>
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</tbody>
</table>

This table also shows incidence rates and relative risks of recurrent myocardial infarction or cardiovascular death comparing those who achieved dual goals to those who did not (referent group). *Rate is age-adjusted per 100 person years. RR<sub>adj</sub> is the age-adjusted relative risk while RR<sub>adj</sub> is the relative risk fully adjusted for age, gender, smoking status, diabetes, hypertension, and body mass index.

CI = confidence interval; ref = referent group.
statin allocation (fully adjusted relative risk = 0.73 in the atorvastatin group, 0.71 in the pravastatin group, p value between groups = NS). In post-hoc analyses limited to the end point of cardiovascular death (n = 38), those who achieved the dual goals had, if anything, an even larger reduction in risk (incidence rates 0.3 vs. 0.6 cardiovascular deaths per 100 person-years for those who did and did not achieve dual goals, relative risk = 0.50, 95% confidence interval 0.21 to 1.19).

The relative efficacy of pravastatin 40 mg and atorvastatin 80 mg in achieving LDL-C levels \(<70\) mg/dl and hsCRP levels \(\leq 2\) mg/l are presented in Table 2. Of the 1,018 participants who achieved these dual goals, 821 (43.9%) had been randomly allocated to atorvastatin 80 mg while 197 (19.4%) had been randomly allocated to pravastatin 40 mg, a highly significant difference (p \(<0.001\)). However, as also shown in Table 2, neither agent brought the majority of patients treated below thresholds needed to maximize patient benefit. Specifically, only 11% of those allocated pravastatin 40 mg and 44% of those allocated atorvastatin 80 mg achieved the dual goals of LDL-C \(<70\) mg/dl and hsCRP \(\leq 2\) mg/l.

As would be anticipated given known differential effects on high-density lipoprotein cholesterol (HDL-C), those allocated to pravastatin 40 mg had higher HDL-C levels after 30 days of therapy than those allocated to atorvastatin (41.0 vs. 38.2 mg/dl, p \(<0.01\)). Because those allocated to atorvastatin were, on average, more likely to achieve dual goals, it follows that those who achieved dual goals also had lower HDL-C levels (39.4 vs. 41.4 mg/dl, p \(<0.001\)). However, even after further additional adjustment for HDL-C, those who achieved dual goals still had a 28% lower risk of recurrent cardiovascular events (fully adjusted relative risk with additional HDL-C control = 0.72, 95% confidence interval 0.52 to 0.99, p \(<0.04\)).

Figure 2 presents the proportion of patients allocated to either atorvastatin 80 mg or pravastatin 40 mg who not only achieved an LDL-C \(<70\) mg/dl, but who also achieved the hsCRP goals of \(\leq 2.0, \leq 1.5, \leq 1.0, \text{ and } \leq 0.5\) mg/l; data are shown after 30 days of therapy (Fig. 2, top panel), 4 months after randomization.

### Table 2. Relative Efficacy of Pravastatin 40 mg and Atorvastatin 80 mg in Achieving LDL-C Levels \(<70\) mg/dl and CRP Levels \(\leq 2\) mg/l in the PROVE-IT TIMI-22 Trial

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Total Cohort (%Pravastatin/Atorvastatin)</th>
<th>Pravastatin 40 mg N (%)</th>
<th>Atorvastatin 80 mg N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (\geq 70) mg/dl, CRP (\geq 2) mg/l</td>
<td>75.8/24.2</td>
<td>823 (43.9)</td>
<td>263 (14.0)</td>
</tr>
<tr>
<td>LDL-C (\geq 70) mg/dl, CRP (\leq 2) mg/l</td>
<td>71.6/28.4</td>
<td>644 (34.4)</td>
<td>255 (13.6)</td>
</tr>
<tr>
<td>LDL-C (&lt; 70) mg/dl, CRP (\geq 2) mg/l</td>
<td>28.2/71.8</td>
<td>209 (11.2)</td>
<td>533 (28.5)</td>
</tr>
<tr>
<td>LDL-C (&lt; 70) mg/dl, CRP (&lt; 2) mg/l</td>
<td>19.4/80.6</td>
<td>197 (10.5)</td>
<td>821 (43.9)</td>
</tr>
</tbody>
</table>

Data are shown as the proportion of patients on pravastatin or atorvastatin within each LDL-C/CRP category (total cohort) and as the number (N) and percent on each agent achieving respective LDL-C and CRP goals.

CRP = C-reactive protein; LDL-C = low-density lipoprotein cholesterol.
Figure 2. Proportion of patients treated with atorvastatin 80 mg (black bars) and pravastatin 40 mg (white bars) who achieved low-density lipoprotein cholesterol (LDL-C) levels <70 mg/dl and high-sensitivity C-reactive protein (hsCRP) levels <2, <1.5, <1, and <0.5 mg/l. Data are shown for measures taken after 30 days of therapy, after 4 months of therapy, and at the end of study.

The proportion of patients who achieved the dual goals of LDL-C <70 mg/dl and hsCRP levels <2, <1.5, <1, and <0.5 mg/l is shown in Figure 2. As shown in the initial 30-day data, only 5.8% of those allocated pravastatin 40 mg achieved LDL-C levels <70 mg/dl and hsCRP levels <1 mg/l, whereas these even lower goals were achieved by 26.1% of those allocated atorvastatin 80 mg. This subgroup with achieved hsCRP levels <1 mg/l also had lower recurrent event rates compared even to those who achieved the dual goals of LDL-C <70 mg/dl and hsCRP <2 mg/l (Fig. 1, dotted line). Only 2.2% of those on pravastatin 40 mg and 11.5% on atorvastatin 80 mg achieved the very lowest goals of LDL-C <70 mg/dl and hsCRP <0.5 mg/l (all p values <0.001). Consistent with prior data, the stability of hsCRP levels over long periods of follow-up were comparable to that of LDL-C. In these data, the correlation between hsCRP levels measured at 30 days for the total study group and hsCRP levels measured at the end of study was 0.61 (p < 0.001), a magnitude of correlation almost identical to that of LDL-C levels measured at both time points for the same population (r = 0.62, p < 0.001).

**DISCUSSION**

In this analysis of the PROVE-IT TIMI-22 trial, acute coronary syndrome patients treated with statin therapy who achieved the dual goals of LDL-C <70 mg/dl and hsCRP <2 mg/l had a 28% lower risk of recurrent myocardial...
infarction or cardiovascular death after adjustment for age, gender, smoking, diabetes, hypertension, body mass index, and HDL-C. Moreover, we demonstrate here that an aggressive lipid-lowering regimen of atorvastatin 80 mg daily is superior to a moderate regimen of pravastatin 40 mg daily in terms of the proportion of individuals treated who ultimately will achieve LDL-C <70 mg/dl and hsCRP <2 mg/l. Importantly, we also demonstrate that neither regimen brought the majority of treated individuals into the range needed for the best long-term event-free survival. For example, while achieving the even lower hsCRP goal of <1 mg/l along with an LDL-C <70 mg/dl appears to provide further survival benefit, this very low level of hsCRP was achieved by only 5.8% of those allocated pravastatin 40 mg and only 26.1% of those allocated atorvastatin 80 mg. Finally, our data demonstrate that the long-term stability of hsCRP levels after reduction with statin therapy is of almost identical magnitude to that of LDL-C.

We believe these data on the relative efficacy of different statin regimens in achieving both hsCRP and LDL-C goals are clinically relevant for several reasons. First, these data emphasize the importance of continued aggressive programs of weight loss, dietary control, exercise, and smoking cessation among post-acute coronary syndrome patients, in addition to aggressive statin therapy. Weight loss, exercise, and smoking cessation consistently lead to reductions in CRP that are at least as large in magnitude as those achieved with pharmacologic intervention, and it is these core lifestyle issues that must be emphasized as being of crucial importance to long-term secondary prevention (9).

Second, while atorvastatin 80 mg was more effective than pravastatin 40 mg in achieving the “dual goals” of LDL-C and hsCRP reduction, the fact that the majority of those taking the more aggressive treatment still did not meet these goals emphasizes the need to continue evaluating agents that might further lower hsCRP levels. From this perspective, our observations may help to explain results from the A to Z trial in which no significant difference in outcome was observed early in the trial despite large differences in achieved LDL-C, yet evidence of a benefit was observed later when differences in achieved hsCRP emerged between study groups (10). Our data also raise important clinical questions about alternative lipid reduction approaches such as ezetimibe, an agent that on its own does not lower hsCRP, but that in combination with statin therapy appears to augment reduction of both LDL-C and hsCRP (11). Similarly, these data raise intriguing hypotheses regarding the potential additive benefits of fibrates, gemfibrozil, and TZD therapy, all of which lower hsCRP levels (12,13). Our observations also support trials of agents that specifically block CRP itself, either using antisense drug technologies, enzyme blockade strategies, or anti-CRP antibody approaches. Such trials will be critical in evaluating the mechanistic possibility that CRP is more than a marker of disease, but also potentially is a direct participant in the atherogenic process.

The PROVE-IT TIMI-22 trial was limited to those with acute coronary syndromes and, thus, represents a secondary prevention population in which all participants had a clear indication for statin therapy. As such, these data additionally support continued enrollment into the JUPITER trial, an ongoing randomized, placebo-controlled study of rosuvastatin 20 mg versus placebo in the primary prevention of cardiovascular disease among apparently healthy individuals who do not qualify for statin therapy because their LDL-C levels are <130 mg/dl, yet who are at increased risk due to elevated CRP levels (14).

**REFERENCES**