

# Differences Between Clinical Trial Efficacy and Real-world Effectiveness

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## Abstract

Aggressive lowering of low-density lipoprotein cholesterol (LDL-C) with statin therapy can reduce the incidence of morbidity and mortality from coronary heart disease (CHD) in primary and secondary prevention settings. Indeed, suboptimal statin treatment has been associated with an increased risk of CHD events. Surveys such as the Lipid Treatment Assessment Project (L-TAP) and National Cholesterol Education Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II have demonstrated that patients in real-world clinical settings often fail to reach the target goals set forth by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III). This failure to reach target LDL-C levels in real-world clinical practice presents a therapeutic treatment gap. There may be multiple reasons for this discrepancy: lack of patient follow-up, absence of well-defined protocols (ie, use of low-potency statins in high-risk patients), adherence controls (eg, pill counts, refill records), cost, and lack of patient motivation are a few possibilities. Several large clinical trials since ATP III have shown that these goals are achievable through aggressive statin therapy. This review sets forth compelling data that starting patients on or switching to high-efficacy LDL-C-lowering therapy enhances achievement of NCEP ATP III guidelines outside of the controlled trial setting.

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Extensive evidence exists that aggressive lowering of low-density lipoprotein cholesterol (LDL-C) can reduce the incidence of morbidity and mortality from coronary heart disease (CHD) in primary and secondary prevention settings. The vast majority of this evidence comes from controlled clinical trials of statins in which drug dosages are carefully titrated and/or sufficient dosages are used initially to achieve target LDL-C levels.

From these clinical data, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) established targets for LDL-C that depend on the individual risk of the patient, with the lowest LDL-C targets (<100 mg/dL) recommended for patients with CHD or other forms of vascular disease.<sup>1</sup>

Suboptimal statin treatment has been associated with an increased risk of CHD events. Among a group of 2045 postmyocardial infarction (post-MI) patients with hypercholesterolemia, 43.4% who suffered a CHD event over the next 30 months were treated with a statin but failed to achieve an LDL-C level less than 115 mg/dL.<sup>2</sup> Suboptimal treatment was found to double the risk of nonfatal MI or CHD death compared with optimal treatment, defined in this study as attainment of an LDL-C less than 115 mg/dL.

Furthermore, landmark clinical studies such as the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)<sup>3</sup> and Treating to New Targets (TNT)<sup>4</sup> trials demonstrated lower rates of CHD events in patients treated to very low levels of LDL-C compared with levels that met the 2001 ATP III goals. Subsequently, the NCEP updated its recommendations to include an option to treat to an LDL-C target <70 mg/dL in certain high-risk patients.<sup>5</sup>

## Undertreatment in the Real World

Evidence exists that supports the effectiveness of statins in real-world practice<sup>6-9</sup>;

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failure to reach target LDL-C levels outside of the clinical trial setting in real-world clinical practice presents an unmet medical need and a therapeutic treatment gap. In 2000, the Lipid Treatment Assessment Project (L-TAP) demonstrated significant undertreatment of patients at risk of CHD events in clinical practice.<sup>10</sup> Among 4888 dyslipidemic patients who had been receiving lipid-modifying therapy for at least 3 months, only 38% achieved their NCEP LDL-C targets.

Three years later, the National Cholesterol Education Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II trial surveyed patients with treated dyslipidemia to assess achievement of treatment goals established by ATP III.<sup>11</sup> Results of the survey showed that, overall, 67% of the 4885 patients achieved their LDL-C treatment goal, suggesting improved lipid management compared with previous surveys. It should be pointed out, however, that among patients in the highest risk category with triglyceride concentrations of at least 200 mg/dL, only 27% achieved their combined LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) targets, indicating that undertreatment is common in patients with hypertriglyceridemia.

In examining 367 hyperlipidemic patients in a preventive cardiology practice, Frolkis et al discovered that the mean observed LDL-C reduction ( $-26\% \pm 20\%$ ) of patients started on statins was significantly less than the expected reduction based on information in the package insert ( $-34\% \pm 7\%$ ;  $P < .001$ ).<sup>12</sup> Therefore, although some improvement in lipid management appears to be occurring, why does the treatment gap continue to persist? Lack of patient adherence, failure to titrate to an effective dose or switching to a more potent statin, inadequate patient follow-up, cost, and lack of patient motivation are some of the considerations for less-than-effective results in the clinical setting.<sup>2,12</sup>

The L-TAP data were collected before the NCEP issued its option to treat LDL-C to  $<70$  mg/dL in the highest risk patients<sup>5</sup>; therefore, one possible assumption is that the levels of LDL-C achieved in the aggressive treatment groups in PROVE IT and TNT are attained even less often in clinical practice than the targets achieved in L-TAP. In

the NEPTUNE II survey, for example, only 18% of patients classified as high risk were at optional goal of less than 70 mg/dL.<sup>11</sup> And in a prospective managed care database analysis by Mosca et al of women at high risk of CHD, initially only 7% had reached optimal lipid levels according to American Heart Association guidelines (eg, LDL-C  $<100$  mg/dL).<sup>13</sup> Only one third received recommended drug therapy, again illustrating substantial undertreatment of at-risk patients.

**Patients at Risk: Identification and Intervention.** An examination of administrative claims data found that in a group of patients receiving a statin other than rosuvastatin patients who required a  $\geq 15\%$  reduction in LDL-C to meet their ATP III goal were less likely to reach their goal than those who needed a  $<15\%$  reduction ( $P < .05$ ).<sup>9</sup> Patients not taking rosuvastatin who were defined as moderate or high risk by NCEP criteria were also less likely to achieve their LDL-C goal than those at low risk of future CHD events.

Clinicians would benefit from guidance in identifying patients at high risk of failure to reach NCEP ATP III LDL-C goals while receiving statins and in selecting therapies and choosing strategies to help these high-risk patients attain their treatment goals.

#### **Lack of Goal Attainment: Comparative Data on Lipid-lowering Efficacy**

Multiple reasons may explain the failure to attain lipid treatment goals in the real-world setting: lack of patient follow-up, absence of well-defined treatment protocols, adherence issues, cost, and lack of patient motivation are all possibilities. More specifically, 3 reasons have a major impact on ability to attain treatment goals: (1) lack of statin dose titration; (2) initiation of low-potency statins inadequate for achieving major reductions in LDL-C; (3) underuse of supplemental (ie, combination or add-on) lipid-lowering therapies.

**Dose Titration.** Lack of dose titration is a cause of failure to reach LDL-C goal in clinical practice. Foley et al found that of the 52% of high-risk (diabetes or CHD) patients who did not reach goal initially, less than half had their dose titrated once; only 14% attained

goal by 6 months, in part due to inadequate titration.<sup>14</sup> The investigators report that true titration and goal attainment rates may be even lower than represented in the study.

**Statin Efficacy: High Potency for High Risk.** The various marketed statins have been compared in their ability to reduce LDL-C levels and achieve NCEP LDL-C targets compared with other statin monotherapies in clinical trials. In these studies, rosuvastatin has proved superior to other commonly used statins.<sup>15</sup>

A 12-week study of 516 hypercholesterolemic patients found that LDL-C reductions were 40% with rosuvastatin 5 mg, 43% with rosuvastatin 10 mg, and 35% with atorvastatin 10 mg ( $P < .01$  and  $P < .05$  for pairwise comparisons with atorvastatin).<sup>16</sup> ATP III treatment goals were achieved more often with rosuvastatin 5 and 10 mg than with atorvastatin 10 mg (84%, 82%, and 72%, respectively). Similarly, in a 52-week study of 412 hypercholesterolemic patients, whose dosages could be titrated at 12 weeks, rosuvastatin 5 or 10 mg was again superior to atorvastatin 10 mg in reducing levels of LDL-C (47% and 53% vs 44%;  $P < .05$  and  $P < .001$ , respectively) and in achieving LDL-C goals (98% for rosuvastatin 10 mg vs 87% for atorvastatin 10 mg).<sup>17</sup>

In the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR), in which 2431 adults with hypercholesterolemia were randomized to 1 of 15 open-label treatment arms for 6 weeks, rosuvastatin 10 to 40 mg/day reduced LDL-C by 46% to 55%, compared with 37% to 51% for atorvastatin 10 to 80 mg/day, 28% to 46% for simvastatin 10 to 80 mg/day, and 20% to 30% for pravastatin 10 to 40 mg/day.<sup>18</sup> The analysis also showed that 89% of the rosuvastatin 20- and 40-mg/day groups reached NCEP LDL-C goals, the highest proportion of the trial groups (Figure).

Emerging data from recent presentations validate the use of rosuvastatin outside of the clinical trial setting as an effective agent to achieve treatment goals in those at greatest risk for treatment failure.<sup>6-9</sup>

**Supplementing Statin Monotherapy.** Not all patients will respond to aggressive statin

dosing or high-potency therapy and will require a combination regimen to attain treatment goals.<sup>19,20</sup> The addition of an intestinal absorption inhibitor to the blunting of endogenous cholesterol production by a statin has proved to be an effective treatment alternative.<sup>21-24</sup> Substantial additional reductions in LDL-C were reported for simvastatin/ezetimibe versus placebo when added to a stable statin regimen.<sup>21</sup> Another study of ezetimibe demonstrated the ability of such add-on therapy to improve goal adherence: 71.5% reached goal with ezetimibe versus 18.9% for placebo ( $P < .001$ ).<sup>22</sup>

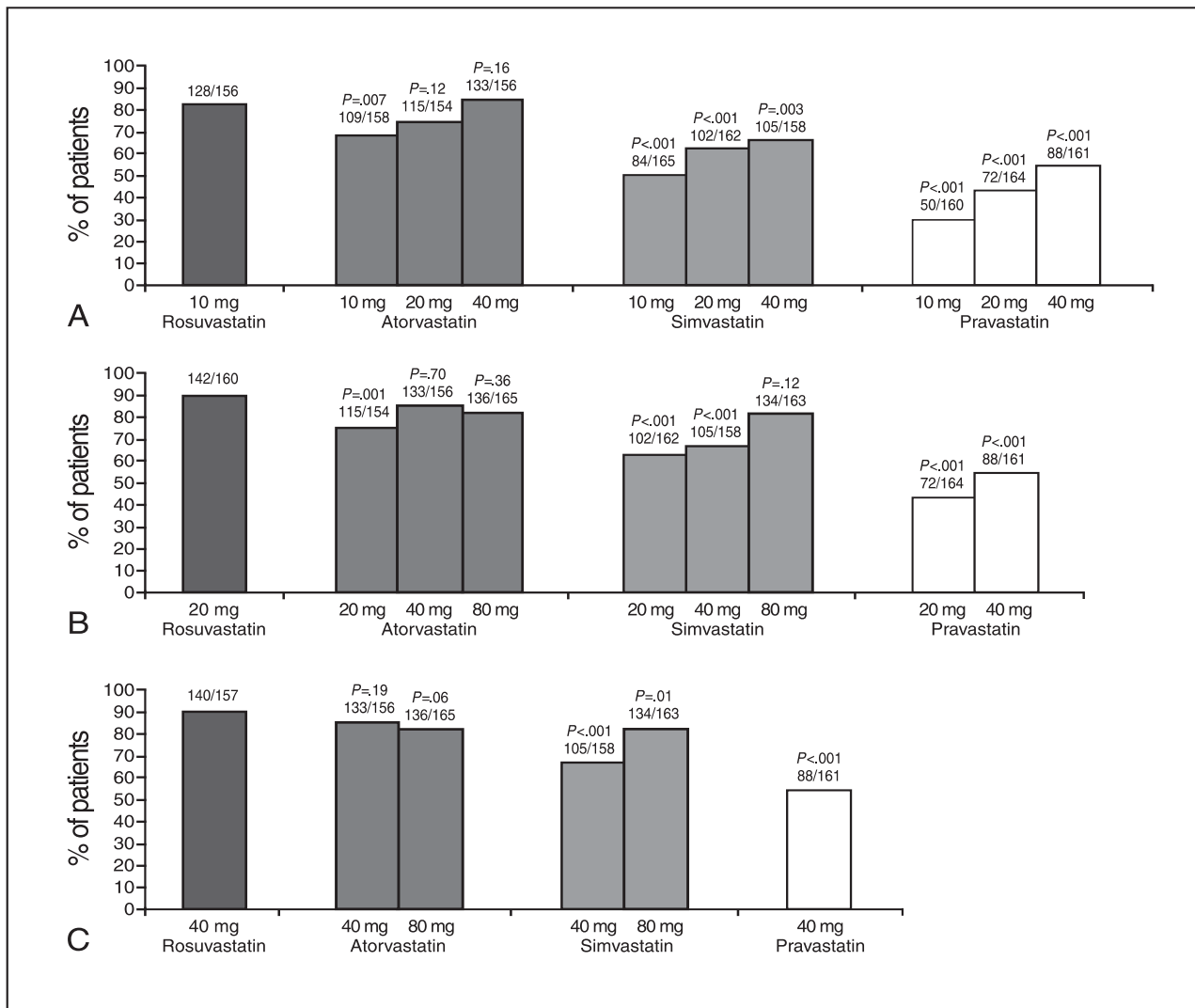
Results from the EXPLORER study, a 6-week, open-label, randomized trial evaluating the results of adding ezetimibe to rosuvastatin was recently reported at the World Congress of Cardiology.<sup>25</sup> High-risk patients (those with a history of CHD, a CHD risk equivalent, or a 10-year CHD risk score  $>20\%$ ) experienced a significant reduction in LDL-C from baseline when ezetimibe 10 mg was added to their current regimen of rosuvastatin (40 mg/day). Before ezetimibe treatment, 79.1% and 35.0% of patients had attained LDL-C levels of  $<100$  mg/dL or  $<70$  mg/dL, respectively; after ezetimibe treatment, those results improved to 94% and 79.6%, respectively.

### Real-world Effectiveness Studies

Given the findings from L-TAP, NEPTUNE II, and other studies conducted in clinical practice settings, in which LDL-C targets were seldom met—especially in the highest risk patients—selection of appropriate statins is important to maximize the clinical benefits of lipid-modifying therapy.

Valuck et al assessed a managed care population of 6247 members with hyperlipidemia, about two thirds of whom were receiving lipid-lowering drugs.<sup>26</sup> Statins defined as high efficacy were used in only 5.4%. Only 160 (2.6%) members had their drug dosages uptitrated during the study period. Patients who were treated with low-efficacy statins were only two thirds as likely to have their LDL-C reduced by 10% or more compared with those treated with high-efficacy statins. An analysis of 352 patients treated outside of a clinical trial provides additional support for the effective-

**Figure.** STELLAR: Percentage of Patients Who Met ATP III Goals at End of Treatment



Results of logistics regression analysis for 22 comparisons versus: (A) rosuvastatin 10 mg, (B) rosuvastatin 20 mg, and (C) rosuvastatin 40 mg (*P* values <.002 are statistically significant).

STELLAR indicates Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin; ATP III, Adult Treatment Panel III. Reprinted with permission from Reference 15.

ness of rosuvastatin over atorvastatin in achieving LDL-C goals (61% vs 48%; odds ratio, 1.96; *P* <.05). Treatment goals in this report were risk based and conformed to NCEP ATP III recommendations; mean dose/duration of treatment was 11 mg and 62 days for rosuvastatin, 15 mg and 79 days for atorvastatin.<sup>8</sup>

In examining medical and pharmacy claims from 8251 hypercholesterolemic patients started on either rosuvastatin, atorvastatin, simvastatin, pravastatin, lovastatin,

or fluvastatin in a managed care setting, Bullano et al found that LDL-C reductions were significantly greater with rosuvastatin than with the other statins.<sup>27</sup> After adjustment for several parameters, including baseline LDL-C, ATP III LDL-C goals were achieved more often in rosuvastatin-treated patients compared with those taking other statins. A presentation by Willey et al confirmed a greater LCL-C lowering effect with rosuvastatin over atorvastatin in clinical practice.<sup>7</sup> Findings were from data retrieved

for 453 patients from a pharmacy claims database retrospectively analyzed to compare percent LDL-C reductions from newly initiated rosuvastatin versus atorvastatin therapy; treatment goals were risk driven and complied with NCEP ATP III guidelines.

Evidence on the effectiveness of statins in real-world clinical practice among the elderly population is limited. Data from a retrospective study of the elderly found the percent reduction in LDL-C to be significantly greater ( $P < .05$ ) in lipid treatment-naïve elderly patients receiving rosuvastatin versus atorvastatin, simvastatin, pravastatin, fluvastatin, or lovastatin (24.3%, 17.5%, 14.8%, 11.3%, 10.7%, or 13.3%, respectively). In addition, older patients receiving rosuvastatin had significantly higher baseline LDL-C levels and lower average statin doses.<sup>6</sup>

### Switching Statin Therapy

In the real world, switching from one statin to another is an option to help achieve the lipid targets for optimal cardiovascular (CV) protection. The Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) was an open-label study in which 3140 patients with CHD or CHD risk equivalents were randomized to 1 of 5 treatment arms for 8 weeks: rosuvastatin 10 mg, atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, or pravastatin 40 mg.<sup>28</sup> At the eighth week, patients initially assigned to treatment with rosuvastatin 10 mg remained on this treatment for another 8 weeks; patients assigned to one of the other arms remained on their original treatments or were switched to rosuvastatin.

Significantly more patients randomized to rosuvastatin 10 mg achieved the NCEP ATP III LDL-C goals (80%) than patients assigned to the other arms (45%-74%;  $P < .0001$  for all comparisons except rosuvastatin 10 mg vs atorvastatin 20 mg,  $P < .01$ ). Switching to rosuvastatin 10 mg permitted significantly more high-risk patients to achieve their ATP III LDL-C goal compared with continuing treatment with atorvastatin 10 mg (79% vs 69%;  $P < .001$ ), simvastatin 20 mg (75% vs 60%;  $P < .0001$ ), or pravastatin 40 mg (80% vs 50%;  $P < .0001$ ). Switching to rosuvastatin 20 mg allowed 86% of patients to achieve their ATP

III LDL-C goal compared with 74% who remained on atorvastatin 20 mg ( $P < .0001$ ).

MERCURY II was an open-label trial in which 1993 high-risk patients with dyslipidemia were randomized to either rosuvastatin 20 mg, atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, or simvastatin 40 mg.<sup>29</sup> After 8 weeks of treatment, all subjects were randomly assigned within each treatment arm to either an additional 8 weeks of treatment on their original study medication or were switched to rosuvastatin. Switching to rosuvastatin significantly increased the percentage of patients who achieved their ATP III LDL-C targets. Switching to rosuvastatin 10 or 20 mg was associated with a significantly greater reduction in LDL-C compared with continued treatment with twice the dose of simvastatin. A significantly higher percentage of those patients classified at very high risk who were switched to rosuvastatin achieved the aggressive optional ATP III goal of less than 70 mg/dL.

### Conclusion

Improvement in the management of hyperlipidemia is required in clinical practice. Despite a significant body of investigative evidence documenting the lipid-modifying effects of statin therapy, patients treated in clinical practice are far less likely to achieve LDL-C targets than those treated in clinical trials. Recent and emerging data from real-world experience are identifying the benefit of high-efficacy statin use, such as rosuvastatin, in those at increased risk for treatment failure. In addition, achievement of reductions below the NCEP ATP III recommended target LDL-C levels have been associated with significant reductions in CHD events compared with less aggressive treatment. Furthermore, patients who are not at goal LDL-C levels with other statins may benefit from switching to more efficacious statins or initiating combination therapy.

When managed care organizations implement strategies to lower the burden of CHD within their membership, they must work closely with providers and their respective pharmacy benefit organizations to ensure formulary access to appropriate treatment alternatives. It is important for medical and pharmacy directors to keep in mind the dis-



crepancy in statin LDL-C reduction efficacy found in clinical trials versus the results observed in real-world settings. Choice of statin should take into consideration the lower reduction found in clinical practice. Educating providers on the most recent clinical findings, such as identifying those at risk for CV events and the use of high-efficacy statins to minimize treatment failure, is a key component to improving CV outcomes.

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