On the basis of the evidence obtained from observational studies, randomized controlled trials and their meta-analyses, current guidelines recommend initiating high-dose statin therapy pre-discharge regardless of the baseline low-density lipoprotein (LDL) level in patients with acute coronary syndromes (ACS). Careful review of the evidence indicates that early initiation of high-dose statin therapy reduces recurrent ischemia and may reduce revascularization, but does not confer benefit in terms of hard clinical outcomes such as death or myocardial infarction in any of the randomized controlled trials, and may be associated with increased liver and muscle-related adverse outcomes leading to increased withdrawal and suboptimal long-term adherence. A mortality benefit is apparent in pooled analyses of randomized controlled trials only at long-term (24-month) but not short-term (4-month) follow-up. The critical role of the timing of initiation of therapy (early vs. late) on the benefit-risk profile of statin treatment has not been systematically assessed. It is unclear whether the clinical benefits are attributable to lipid-lowering or lipid-lowering-independent effects. Finally, an optimal LDL threshold for initiating treatment or target LDL level for treatment in ACS remains yet to be defined. On the basis of these observations, and despite a compelling pathophysiologic rationale, the justification for current Class I, Level of Evidence: A recommendation for statin therapy in patients with ACS remains open to question. (J Am Coll Cardiol 2009;54:1425–33) © 2009 by the American College of Cardiology Foundation

“There are no facts, only interpretations.”
—Friedrich Nietzsche (1)

Each year, nearly 1.5 million people living in the U.S. suffer an acute coronary syndrome (ACS) (2). The administration of aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors in patients during ACS has been shown to be beneficial (3–5). The evidence supporting the use of statins, however, is less clear (6).

Statins clearly reduce cardiovascular mortality and morbidity in primary and secondary prevention of coronary heart disease (CHD) (7). A majority of the secondary prevention trials have been limited to the timeframe immediately (3 to 6 months) following an index acute coronary event (7). Consequently, over the past decade, a number of investigations have specifically evaluated the role of statins during the course of ACS. Based on the results of these investigations, early intensive statin therapy has become formally endorsed as a treatment guideline (3,4) and a performance measure (5) in patients with ACS. We herein review the evidence base in support of these policy recommendations.

Efficacy of Statin Therapy

Statins exhibit a number of biologic effects that may be relevant in the setting of acute ischemic events (8). They act rapidly to improve vascular endothelial function (8–10), attenuate vascular inflammation (8,11), stabilize plaques (12), correct prothrombotic tendencies (8,12), and influence myocardial protection and remodeling (13). These effects may be related to low-density lipoprotein (LDL) reduction or to a variety of LDL-independent mechanisms—the so-called pleiotropic effects. The relative importance of these 2 mechanisms continues to be hotly debated.

A meta-regression analysis found that the nonstatin (diet, bile acid sequestrants, and ileal bypass surgery) and statin interventions in stable patients appear to reduce CHD risk in a similar manner, consistent with the 1-to-1 relationship with the degree of LDL cholesterol lowering (14). This is true for the ACS trials as well. For example, despite significant reductions in inflammatory markers, a 31% greater reduction in LDL with atorvastatin 80 mg over pravastatin 40 mg was associated with an additional 18% reduction in CHD events in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial (15). Similarly, a 14% greater reduction in LDL was associated with a 12% better outcome in the aggressive statin treatment arm in the A to Z (Aggrastat to Zocor) trial (16). A meta-analysis of placebo-controlled trials found that statin
therapy had no significant effect on C-reactive protein, an inflammatory biomarker, after adjustment for change in LDL (17). Multivariate modeling revealed that only 2% to 11% of the C-reactive protein change (28% reduction) could not be accounted by LDL lowering. Thus, these results provide insufficient evidence in support of the pleiotropic effects of statins.

Nevertheless, the role of statin therapy in patients with ACS relies more on empirical observation than on mechanism of action. The efficacy of statin therapy in ACS has been evaluated in observational studies, post-hoc analyses of ACS clinical trials performed for other purposes, placebo- or active-controlled randomized controlled trials and their meta-analyses. The results of key trials and meta-analyses are summarized in Table 1.

**Observational studies.** A number of observational studies indicate that statins decrease major cardiovascular outcomes including mortality by approximately 30% to 40% in treatment subjects compared with control subjects when initiated before or at discharge after ACS (18–24). In a large Swedish registry, RIKS-HIA (Register of Information and Knowledge about Swedish Heart Intensive Care Admissions), of nearly 20,000 cardiac intensive care patients, treatment with a statin was associated with significantly lower 1-year mortality (adjusted relative risk: 0.75, 95% confidence interval [CI]: 0.63 to 0.89) (19). These observations were confirmed in a pooled analysis of the GUSTO-IIb (Global Utilization of Streptokinase and TPA for Occluded Arteries IIb) plus PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trials enrolling about 20,000 patients (adjusted mortality hazard ratio [HR]: 0.67, 95% CI: 0.48 to 0.95) (25), the NMRI (National Registry of Myocardial Infarction) 4 database (adjusted in-hospital mortality odds ratio [OR]: 0.58, 95% CI: 0.54 to 0.63) (22), and Nagashima et al. (24) that demonstrated sustained mortality benefit at 5-year follow-up. The benefit associated with early initiation of statin therapy documented in the NMRI-4 registry coupled with the harm associated with suddenly stopping statins after an ACS documented in the NMRI-4 registry (22) and the PRISM (Platelet-Receptor Inhibition for Ischemic Syndrome Management) study (26) further highlight the efficacy of statin treatment. In contrast, pooled analysis of the first and the second SYMPHONY (Sibrafiban Versus Aspirin To Yield Maximum Protection From Ischemic Heart Events Post-Acute Coronary Syndromes) trials found no improvement in outcomes (adjusted mortality HR: 0.99, 95% CI: 0.73 to 1.33) (27). The inconsistency among these observational studies is likely related to confounding arising from nonrandomized comparisons and heterogeneity in the timing of statin therapy.

**Randomized trials.** Several placebo-controlled (28–35) and 2 active-control randomized trials (15,16) have evaluated the efficacy and safety of statins in ACS. With the exception of the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial (32), none of the placebo-controlled trials showed a significant reduction in the primary end point. These studies were, however, limited by insufficient statistical power to detect differences over placebo due to premature study termination as a consequence of slow enrollment in the PACT (Plasminogen Activator-Angioplasty Compatibility Trial) (33), statin withdrawal in the PRINCESS (Prevention of Ischaemic Events by Early Treatment of Cerivastatin after Acute Myocardial Infarction) trial (34), or low event rates in the FLORIDA (Fluvastatin on Risk Diminishing After Acute Myocardial Infarction) trial (35). In the MIRACL study, the reduction in the primary composite end point was driven by recurrent angina requiring hospitalization without significant effects on death, cardiac arrest, myocardial infarction (MI), or revascularization (32). Furthermore, an unplanned interim analysis was performed in the MIRACL trial without adjustment of p value in the reported results (p = 0.048). Whether the primary end point would have reached statistical significance had such an adjustment been made remains unclear.

**Meta-analyses.** A meta-analysis of 12 trials comparing early statin therapy with placebo or usual care demonstrated that initiation of statin therapy within 14 days following onset of ACS did not reduce death, MI, or stroke at 4 months of follow-up (6). Additional meta-analyses of randomized controlled trials demonstrate that early initiation of statins after ACS improves cardiovascular outcomes, although these benefits take 6 months for morbid events (36) and 24 months for fatal events (36,37) to become evident.

**Safety of Statin Therapy**

Moderate doses of statins are generally safe and well tolerated (Table 1). Regarding the safety of high-dose statins used in ACS trials, higher doses of simvastatin were associated with a greater incidence of myopathy compared with lower doses in the A to Z trial (Table 1), a finding also observed in the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) study, a recent trial of aggressive versus moderate LDL lowering in more than 12,000 heart attack survivors (38). There were 53 cases of myopathy reported with 80-mg simvastatin compared with only 3 cases with 20-mg simvastatin. Similarly, a greater incidence of liver enzyme elevation was seen with 80 mg/day of atorvastatin compared with 40 mg/day of pravastatin in the PROVE-IT study (15). In the MIRACL study, there was a statistically significant 4-fold increase in liver enzyme elevations with 3 cases of hepatitis (2 of them resolving upon discontinuation) (32). Meta-analyses of intensive- versus moderate-dose statin trials reveal a 2- to 4-fold increase in adverse hepatic and
<table>
<thead>
<tr>
<th>Trial (Ref. #)</th>
<th>Treatment</th>
<th>Initiation, Days (Mean)</th>
<th>Primary End Point</th>
<th>Follow-Up, Months</th>
<th>On-Treatment LDL (mg/dl)</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACL (32)</td>
<td>Atorvastatin 80 mg vs. placebo</td>
<td>1–4 (2.6)</td>
<td>Death, MI, cardiac arrest, RI</td>
<td>4</td>
<td>135 72 17.4 14.8 0.84 (0.71–1.00)</td>
<td>0.6 2.5 4.33 (2.09–8.99)</td>
<td>0 0 Not estimable</td>
</tr>
<tr>
<td>A to Z (16)</td>
<td>Simvastatin 40/80 mg vs. placebo/simvastatin 20 mg</td>
<td>&lt;5 (3.7)</td>
<td>CV death, MI, stroke, ACS</td>
<td>24</td>
<td>81 66 16.7 14.4 0.89 (0.76–1.04)</td>
<td>0.36 0.84 2.35 (1.03–5.38)</td>
<td>0.04 0.40 8.90 (1.13–70.28)</td>
</tr>
<tr>
<td>PROVE-IT (15)</td>
<td>Atorvastatin 80 mg vs. pravastatin 40 mg</td>
<td>&lt;10 (5.7)</td>
<td>Death, MI, RI, revasc, stroke</td>
<td>24</td>
<td>95 62 26.3 22.4 0.84 (0.74–0.95)</td>
<td>1.1 3.3 3.01 (1.87–4.85)</td>
<td>0.15 0.10 0.65 (0.11–3.92)</td>
</tr>
<tr>
<td>Briel et al. (6) (12 RCTs)</td>
<td>Statin vs. placebo</td>
<td>&lt;14 (4.3)</td>
<td>Death, MI, stroke</td>
<td>4</td>
<td>137 110 7.5 8.1 0.93 (0.81–1.07)</td>
<td>0.4 1.1 NA</td>
<td>0.06 0.1 NA</td>
</tr>
<tr>
<td>Bavry et al. (37) (7 RCTs)</td>
<td>Early intensive statin vs. control</td>
<td>&lt;12 (5.3)</td>
<td>Death</td>
<td>24</td>
<td>121 96 4.6 3.3 0.75 (0.61–0.93)</td>
<td>0.56 1.6 2.93 (2.09–4.09)</td>
<td>0.71* 0.97* 1.35 (0.96–1.89)</td>
</tr>
<tr>
<td>Stroke†</td>
<td>24</td>
<td>12.2 1.1 0.90 (0.62–1.30)</td>
<td></td>
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<tr>
<td>RI†</td>
<td>24</td>
<td>5.0 4.1 0.81 (0.68–0.98)</td>
<td></td>
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<tr>
<td>Revasc†</td>
<td>24</td>
<td>12.9 11.2 0.86 (0.78–0.96)</td>
<td></td>
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<tr>
<td>Afiallo et al. (40) (PROVE-IT + A to Z)</td>
<td>Intensive vs. moderate statin</td>
<td>&lt;10 (4.7)</td>
<td>CV death, ACS, stroke</td>
<td>24</td>
<td>89 64 24.8 22.0 0.86 (0.73–1.01)</td>
<td>0.72 2.0 2.83 (1.88–4.27)</td>
<td>0.02 0.21 8.87 (1.12–70.07)</td>
</tr>
<tr>
<td>Death†</td>
<td>24</td>
<td>4.6 3.5 0.75 (0.61–0.93)</td>
<td></td>
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*Reported as myositis; †secondary end point; ‡pooled analysis. Efficacy refers to the primary end point.

ACS = acute coronary syndrome; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; NA = not available; RCT = randomized control trial; Revasc = coronary artery bypass graft surgery or percutaneous coronary intervention; RI = recurrent ischemia requiring hospitalization; Rx = prescription; ULN = upper limit of normal.
Guidelines for Statin Therapy in ACS

Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines provide a Class I, Level of Evidence: A (strong and compelling evidence in favor of benefit outweighing the risk) recommendation for initiating statin therapy pre-discharge regardless of the baseline LDL level (3,4). Furthermore, the guidelines also provide a Class I, Level of Evidence: A recommendation for LDL target of <100 mg/dl and Class IIa, Level of Evidence: A (reasonable but high-quality evidence) for LDL target of <70 mg/dl in ACS (3,4). Let us examine whether these guideline recommendations are supported by evidence.

Timing of statin therapy. The critical role of the timing of initiation of statin therapy (i.e., early vs. late during hospitalization or pre- vs. post-discharge) has been formally evaluated in only 2 observational studies and 1 randomized controlled trial.

Li et al. (43) compared patients started on statin therapy <2 days versus >2 days after admission for first episode of ACS. After multivariate analysis, there was no significant influence on the primary end point at 4 months or at 12 months. Similarly, Saab et al. (44) observed no significant differences in cardiovascular outcomes at 6 months in patients receiving statin therapy <24 h versus >24 h after admission. These observational data do not suggest a treatment advantage for initiating statin treatment within 24 to 48 h of admission for ACS.

The randomized clinical trial A to Z (16) compared early intensive to delayed conservative statin therapy in patients with ACS. Patients were randomized within 5 days of admission to simvastatin 40 mg/day for 1 month followed by simvastatin 80 mg/day versus placebo for 4 months (acute phase) followed by simvastatin 20 mg/day thereafter (chronic phase). No significant differences in outcomes were observed either during the acute phase (primary end point HR: 1.01, 95% CI: 0.83 to 1.25) or at 24 months (HR: 0.89, 95% CI: 0.76 to 1.04). However, the trial was limited by insufficient power as fewer than expected events were accrued in the trial (652 instead of the planned 970) (16).

Treatment threshold. The influence of baseline pre-treatment LDL on the clinical benefit of lipid-lowering therapy remains controversial. Two observational studies reported favorable outcomes in patients prescribed statin treatment at discharge even in those with LDL levels <100 mg/dl (45) or <60 mg/dl (46). In contrast, randomized controlled trials have shown inconsistent results. A post hoc analysis of the CARE (Cholesterol And Recurring Events) trial found no significant benefit of LDL lowering with 40-mg pravastatin in individuals whose baseline LDL levels were <125 mg/dl (47). However, in a post hoc analysis of the HPS (Heart Protection Study) trial, significant benefits were seen in high-risk individuals even when their baseline LDL levels were low, that is, <100 mg/dl (48). Data from intensive-versus moderate-LDL lowering trials provide inconsistent information in this regard. A threshold relationship was seen in the TNT (Treatement to New Targets) study (34% reduction in those with baseline LDL ≥125 mg/dl compared with 7% reduction in those with LDL <125 mg/dl) (49) and the PROVE-IT trial (37% reduction in those with baseline LDL >132 mg/dl compared with 7% reduction in those with LDL <92 mg/dl) (50), but not in the IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) study (51). In the PROVE-IT (50) and MUSASHI-AMI (Multicenter Study for Aggressive Lipid-lowering Strategy by HMG-CoA Reductase Inhibitors in Patients with Acute Myocardial Infarction) (31) trials, the benefit of intensive therapy progressively declined as baseline LDL cholesterol decreased. A post hoc multivariable analysis of the PROVE-IT trial revealed no evidence of benefit in patients with baseline LDL <66 mg/dl (50).

A meta-analysis of data from 90,056 patients in 14 trials indicated that the treatment benefit associated with statin was not shown to be related to baseline pre-treatment LDL level but to the reduction in LDL levels—a 40-mg/dl reduction in LDL translating into a 20% improvement in outcomes (7). A key limitation is that in none of these trials were patients randomized to statin therapy according to low and high pre-treatment LDL levels. Thus, the guideline recommendation for initiating statin therapy in ACS regardless of the baseline LDL level reflects the current emphasis on risk stratification-based rather than an LDL level-driven approach to treating dyslipidemias. The justification for this approach, however, is based on extrapolation from epidemiologic observations, post hoc review of trial data, expert opinion, and a belief in pleiotropic effects of statins rather than an evidence-based conclusion derived from prospective randomized controlled trials.

Treatment target. The current ACC/AHA guideline recommendations for statin treatment target were adapted from LDL targets proposed by National Cholesterol Education Program guidelines that offer an “optional” LDL goal of <70 mg/dl for patients believed to be at very high risk of atherosclerotic heart disease such as ACS and a “mandatory” less ambitious target LDL goal of <100 mg/dl for standard high-risk patients (52). The scientific validity of these targets, particularly the ultralow LDL target of <70 mg/dl, has been challenged recently by Hayward et al. (53) as not being based on compelling evidence. Further, they also
remain unconvinced about the evidence previously cited to support an LDL goal of <100 mg/dl for high-risk patients, pointing out several methodological limitations such as failure to account for known confounders such as a “healthy volunteer” effect, post-randomization analysis based on observational cohort data, lack of randomization to achieved LDL targets, failure to consider pleiotropic effects of statins, and flaws intrinsic to ecological analyses that drive the guideline recommendations (53). The supporters of the guideline recommendations counter these criticisms by citing a vast body of favorable evidence derived from clinical trials, epidemiological data, anthropological data (54) and experimental laboratory data that cannot be ignored.

A critical examination of the data indicates that although angiographic (55), intracoronary ultrasound (56) and carotid intima-media thickness (57) studies have generally shown that lowering LDL to very low levels arrests or even reverses the development of atherosclerosis (a surrogate outcome), there is very little clinical outcome data to support the “lower is-better” hypothesis.

The results of trials of intensive lipid lowering with high-dose statin therapy versus moderate lipid lowering with standard-dose statin therapy—the subject of 5 randomized controlled trials, 2 in patients with ACS (PROVE-IT [15], A to Z [16]) and 3 in patients with stable CHD (TNT [49], IDEAL [51], SEARCH [38])—provide important insights. None of these trials was designed to address the “treat to target” hypothesis but they used a fixed dose of statin (high- vs. standard-dose) throughout. Two of the five trials compared nonequipotent doses of different statins (PROVE-IT and IDEAL). Pooled pre-treatment LDL averaged 130 mg/dl and post-treatment LDL averaged 101 and 75 mg/dl with moderate- and intensive-dose treatment, respectively (39). The guideline-recommended LDL target of <70 mg/dl was achieved in the 2 ACS trials—median LDL of 62 mg/dl in the PROVE-IT trial on atorvastatin 80 mg/day (15), 66 mg/dl in the A to Z trial on simvastatin 80 mg/day (16) (Table 1). The primary end point was significantly reduced in favor of intensive therapy in 2 out of the 5 trials (PROVE-IT and TNT), mostly driven by reductions in revascularization or unstable angina requiring hospitalization in the PROVE-IT trial (which constituted >75% of the composite end point) (15) and nonfatal MI or stroke in the TNT study (49). Pooled analyses of randomized controlled trials of intensive versus moderate LDL lowering failed to reveal a benefit in all-cause or cardiovascular mortality (39–41). Although intensive-dose statin therapy was associated with a reduced risk for important cardiovascular events, it was also associated with an increased risk for statin-induced adverse events. Pooling the results of only ACS trials (A to Z and PROVE-IT), Afilalo et al. (40) reported a reduction in all-cause mortality from 4.6% to 3.5% over 2 years (OR: 0.75, 95% CI: 0.61 to 0.93) with intensive statin therapy. Similar observations were also reported by Josan et al. (58). Despite lack of statistical heterogeneity, there is substantial clinical heterogeneity between the 2 trials with respect to trial design, patient characteristics, treatment protocols, and outcome event rates (Table 2) that argue against pooling, thereby challenging the interpretability of the pooled data.

The results from the PROVE-IT trial have been interpreted as providing strong support for aggressive LDL lowering. There are, however, several issues with the design and analysis of the PROVE-IT trial that merit careful consideration. First, the PROVE-IT trial was not designed to prospectively address the “lower-is-better” hypothesis,

| Table 2 Comparison of PROVE-IT and A to Z Trials of Early Intensive Statin Therapy in ACS |
|---------------------------------|---------------------------------|---------------------------------|
| Variable                        | PROVE-IT (n = 4,162)            | A to Z (n = 4,497)              |
| Placebo-controlled phase        | No                              | Yes                             |
| Trial design                    | Active-control noninferiority   | Active-control superiority, factorial design |
| Time of statin initiation, mean (days) | 5.7                           | 3.7                             |
| Follow-up, yrs                  | 2                               | 2                               |
| Primary end point               | Death, MI, hospitalization for recurrent ischemia, revascularization, and stroke | CV death, MI, stroke, readmission for ACS |
| U.S. enrollment                 | 71%                             | 21%                             |
| Age, mean (yrs)                 | 58                              | 61                              |
| Females                         | 22%                             | 24%                             |
| History of diabetes             | 18%                             | 24%                             |
| Hypertension                    | 50%                             | 50%                             |
| Smoker                          | 36%                             | 41%                             |
| Prior history of CHD            | 18% MI, 38% CHD, 15% PCI, 11% CABG | 17% MI, 45% PCI, 4% CABG        |
| Previous statin use             | 25%                             | 0%                              |
| Index event                     | 29% UA, 36% NSTEMI, 35% STEMI   | 40% STEMI, 60% NSTEMI           |
| PCI for index event             | 69%                             | 44%                             |
| Death rate                      | 2.2% vs. 3.2%                   | 5.5% vs. 6.7%                   |
| Death or MI rate                | 8.3% vs. 10.0%                  | 11.1% vs. 12.4%                 |

CABG = coronary artery bypass graft surgery; CHD = coronary heart disease; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; other abbreviations as in Table 1.
that is, an LDL reduction of 50% would be more beneficial than an LDL reduction of 25%. To the contrary, the primary hypothesis of the trial was to show that moderate lipid lowering with standard-dose pravastatin would be “not much worse” (noninferior) than aggressive lipid lowering with high-dose atorvastatin. In science, hypothesis should be fixed a priori and tested rather than assumed (hypothesis should drive the data and not vice versa). Second, the difference in favor of aggressive LDL lowering with atorvastatin was largely driven by reduction in soft end points of recurrent angina and revascularization (the most prevalent components of the composite end point) with a nonsignificant impact on the hard end points of death, MI, or stroke. Third, the fact that 2 different statins (atorvastatin 80 mg vs. pravastatin 40 mg) with slightly different effects on the lipid profile and possibly different pleiotropic properties were used makes it difficult to ascertain whether all differences between the 2 regimens can be explained by the intensity of lipid lowering. Finally, post-hoc analysis of the 4-month data in the PROVE-IT trial has been argued to indicate that further benefit is conferred without additional risk for adverse events when LDL is reduced to 40 to 60 mg/dl compared with 61 to 80 mg/dl (59). However, 30% of the patients discontinued drug therapy prematurely, which might have contributed to the reported low rate of side effects. In addition, lack of adequate power to detect adverse events and residual confounding challenge the interpretation of the results. A post-hoc analysis of 2-year data in the PROVE-IT trial failed to reveal significant differences in the primary end points in patients with median follow-up LDL concentrations of 53 mg/dl versus 82 mg/dl (50). Therefore, the intensity of statin therapy and the associated target threshold of LDL reduction at which the benefits still outweigh potential adverse effects remain open to question. Thus, it can be argued that the results from the PROVE-IT trial do not provide unequivocal evidence in support of the “lower-is-better” hypothesis.

Based on these observations, there is insufficient evidence to recommend treating to particular LDL targets as advocated by the guidelines. It is interesting to note that the European Society of Cardiology guideline recommendations for statin treatment in ACS are less sanguine than the ACC/AHA guidelines. They recommend early initiation (within 1 to 4 days) of statin treatment with the aim of achieving LDL levels <100 mg/dl (Class I, Level of Evidence: B), and intensive lipid-lowering therapy with target LDL levels <70 mg/dl initiated within 10 days after admission (Class IIa, Level of Evidence: B) (60). Implicit in the Level of Evidence: B recommendations (compared with Level of Evidence: A recommendations endorsed by the ACC/AHA guidelines) is the acknowledgment of lack of “high-quality” evidence in support of LDL treatment targets.

Finally, an analysis of existing data from primary and secondary prevention trials, including the ACS trials, could provide useful insights into the threshold and target issues by documenting the multivariate relationship (or lack thereof) of clinical outcome to baseline LDL and magnitude of LDL reduction. One such hypothetical analysis, demonstrating a graded relationship of treatment benefit according to tertiles of baseline LDL (from <70 to >100 mg/dl) and quartiles of percent LDL lowering (from <10% to >30%), is illustrated in Figure 1. We urge those with access to these data to conduct such analyses. However, given the lack of randomization according to LDL treatment thresholds or to achieved LDL targets in these trials, it is important to keep in mind the exploratory nature of such analyses and the limited ability to draw inferences from them. Only randomized controlled trials that are properly designed to prospectively evaluate LDL threshold and LDL target can provide more valid and persuasive evidence in support of guideline recommendations to inform clinical practice.

**Statin Adherence After ACS**

It has been argued that perhaps the most important reason to initiate statin therapy during the hospital phase of the ACS is to ensure that patients receive this critical component of secondary prevention and to improve long-term adherence by taking advantage of a “teachable moment” when patients are most motivated. Recent registry and observational cohort studies such as the NMRI-4 registry (20) and the CHAMP (Cardiac Hospitalization Atherosclerosis Management Program) (61) and LTAP (Lipid Treatment Assessment Project) (62) trials have demonstrated improved short- and long-term adherence rates when statins, along with other cardioprotective medications, were started early before hospital discharge. However, these studies were limited by lack of randomization and lack of high-dose statin treatment. The drop-out rate associated with high-dose statin treatment in randomized trials is not trivial—nearly 11% over 4 months in the MIRACL trial (32) and nearly 30% over 2 years in both the PROVE-IT trial...
level in ACS remain to be defined. On the basis of these observations, and despite a compelling pathophysiologic rationale, the current evidence is insufficient to justify a Class I, Level of Evidence: A recommendation (as formerly defined) for initiating with ACS. More importantly, these limitations also call into question the recent elevation of this guideline to a performance measure (5), which is typically reserved for the highest level of evidence.

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Key Words: statins ▪ low-density lipoprotein ▪ unstable angina ▪ myocardial infarction ▪ guidelines ▪ cardiovascular outcomes.

APPENDIX

Search methodology. We searched EMBASE, MEDLINE, and the Cochrane Library until March 3, 2009. We used the following terms: statin(s), HMG-CoA reductase inhibitor(s), acute coronary syndrome(s), myocardial infarction(s), low-density lipoprotein (LDL), adherence, compliance, and guidelines. We focused on the randomized controlled trials and their meta-analyses, nonrandomized evaluations, editorials, and reviews to explore key issues relating to statins in acute coronary syndromes. All articles were limited to the English language.