Lipoproteins in Acute Coronary Syndromes – Measure, Treat or Disregard?

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Despite the impressive results achieved in secondary prevention studies using statins and other lipid-modifying agents [1–3] and evidence showing the cost-effectiveness of such treatment [4], these drugs are still underutilized in patients with coronary heart disease [5–7]. Although the majority of patients with CHD require lipid-lowering medications to achieve the recommended lipoprotein target goals, it is yet unclear if all such patients would benefit from drug therapy. In the CARE and LIPID studies, which recruited patients with evidence of CHD and average cholesterol levels, only patients with low density lipoprotein cholesterol levels of 125 mg/dl or above had a significant benefit from pravastatin therapy, while morbidity and mortality of patients with lower baseline LDL cholesterol levels were not significantly different between pravastatin-treated and placebo-treated patients [2]. In contrast, other primary and secondary prevention studies suggest that even patients with lower LDL cholesterol levels might benefit from statin therapy [8]. Current practice guidelines recommend performing a lipoprotein analysis for every patient with proven CHD and reducing the LDL cholesterol levels below 100–115 mg/dl [9,10]. Therapeutic lifestyle changes are recommended for all CHD patients with LDL cholesterol levels above 100 mg/dl. Additional drug therapy is indicated for patients with LDL cholesterol levels above 130 mg/dl and is optional in those with LDL cholesterol levels between 100 and 129 mg/dl. However, adherence of primary care practitioners to the recommended guidelines has generally been shown to be less than desirable. The reasons for this probably relate to inadequate time and low priority rather than lack of knowledge [11,12].

One method of improving the implementation of preventive strategies in patients with acute coronary syndromes is to measure their lipoprotein profile and identify patients who require pharmacologic treatment prior to discharge from the hospital. This is based on the notion that physicians in coronary care units and internal medicine wards may be more aware of the importance of secondary prevention in this subset of high risk patients and would be more able to incorporate lipoprotein measurements as part of their unit's routine. In addition, it has been hypothesized that early treatment with statins during ACS may confer additional advantage and reduce the incidence of early complications by virtue of its effects on the endothelium and plaque structure [13–15]. However, specific guidelines on this issue do not exist.

This article reviews the evidence related to the benefit of measuring and treating lipoproteins in patients with ACS and to propose evidence-based recommendations for cardiologists and internists involved in the care of patients with ACS.

Theoretical advantages of early statin treatment in ACS

The evaluation and treatment of dyslipidemia during the hospitalization phase of ACS has several theoretical potential benefits in the secondary prevention of CHD. These benefits might occur due to improved logistics in the identification and treatment of dyslipidemia, as well as to the effects of statins on the endothelium and plaque stabilization.

The major risk factors for atherosclerosis include hypertension, diabetes mellitus, smoking, a family history of coronary heart disease, elevated LDL levels and decreased high density lipoprotein levels. Several other markers, termed "emerging risk-factors," have been implicated in the pathogenesis of atherosclerosis but still lack sufficient evidence to be included in the "major risk factor" category [9]. Some of these include the serum triglyceride, lipoprotein remnants, small dense LDL particles, homocysteine, lipoprotein (a), oxidative stress and prothrombotic factors. Abundant evidence exists to support a fundamental role for chronic inflammation in mediating all stages of atherosclerosis [16]. The inflammatory response stimulates migration and proliferation of smooth muscle cells that become intermixed within the area of inflammation.

The pathogenesis of acute myocardial infarction involves the destabilization and rupture of unstable coronary plaques, most of which do not cause high grade stenosis before the acute event [17,18]. Vulnerable lesions usually contain a large lipid core, a thin fibrous cap and evidence of inflammation [19]. Stabilization of lesions probably occurs as a result of modification of the structure and content of the plaque, rather than simple improvement in the

CHD = coronary heart disease
LDL = low density lipoprotein

ACS = acute cardiac syndromes

Table 1. Randomized and observational studies of pre-discharge statin treatment in patients with acute coronary syndromes

[Ref.]	No. of patients	Admission diagnosis	Treatment	Control	Average length of follow-up	Major endpoints	RR reduction in major endpoints	Reduction in overall mortality
Randomized trials								
[29]	3,086	UA & NQMI	Atorvastatin 80 mg	Placebo	16 weeks	Total mortality, MI, SD, symptomatic ischemia	16%	NS
[30]	126	Acute MI or PCI d/t UA	Pravastatin 20–40 mg	Usual care	2 years	Total mortality, cardiovascular death, non-fatal MI, PCI, stroke, PVD	56%	NS
[31]	540	MI	Fluvastatin 80 mg	Placebo	1 year	Residual ischemia on ambulatory ECG monitoring	NS	NS
Observational studies								
[32]	20,809	ACS	Any LLD	No LLD	6 months	Total mortality		33%
[33]	600	Angiographic evidence of CAD	Prescription for a statin	No prescription for a statin	3 years	Total mortality		51%
[34]	19,599	Acute MI	Any statin	No statin	1 year	Total mortality		25%
[35]	525	Restenosis after coronary stenting	Any statin	No statin	6 months	MI or TVR		24%

RR = relative reduction, ACS = acute coronary syndrome, NQMI = non Q-wave myocardial infarction, UA = unstable angina, SD = sudden death, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease, CAD = coronary artery disease, LLD = lipid-lowering drugs, TVR = target vessel revascularization, NS = not significant.

luminal diameter [20]. It has been suggested that lowering the serum LDL cholesterol with statins increases the bioavailability of nitric oxide, thus favorably influencing lesion stabilization and improving endothelial-dependent vasodilation [21,22]. In addition to lowering the LDL cholesterol, statins have a variety of pleiotropic, or cholesterol-independent, effects that modulate the inflammatory response within the vessel wall, reduce cellular proliferation, decrease the adherence of platelets to the ruptured plaque, modulate the activity of the extrinsic coagulation cascade pathway, and reduce cellular oxidation [23–25]. Some differences in these pleiotropic effects have been noted between the various statins; whether this might translate into unique effects in preventing atherosclerosis or its complications is still unclear [26].

Long-term statin therapy of patients with CHD results in a 24–40% reduction in recurrent cardiovascular events and reduces the risk of death from any cause by about 30% [1,2]. Therapy with a statin also reduces the risk of angina pectoris and cerebrovascular accidents and decreases the need for coronary artery bypass grafting and angioplasty Current practice guidelines recommend performing a lipoprotein analysis in every patient with evidence of CHD and reducing the LDL cholesterol levels to below 100–115 mg/dl [9,10]. However, despite this compelling evidence, CHD prevention surveys reveal a wide therapeutic gap between scientific evidence and practice in the secondary prevention of CHD. These surveys revealed a high prevalence of dyslipidemia and low levels of lipid-lowering treatment months after discharge from hospitals following a coronary event [5–7,27]. Physicians are poorly compliant with the National Cholesterol Education Project guidelines for risk factor assessment and counseling, even in patients at high risk for CHD. NCEP criteria seem to influence the decision to initiate lipid-lowering therapy, but significant numbers of eligible patients remain untreated [28]. It has been proposed that beginning therapy in indicated patients at the time of discharge from the hospital has the potential to attenuate this "treatment gap" and improve long-term medication compliance. This is based on the notion that physicians in the coronary care unit and internal medicine wards may be more aware of the importance of secondary prevention in this subset of high risk patients and would be more able to incorporate lipoprotein measurements as part of their routine management.

Randomized trials of early treatment with statins in ACS

A number of trials have been initiated to investigate the benefit of statin therapy early in the course of acute coronary events [29], but to date only three have been published [Table 1]. In the MIRACL study [30], 3,086 patients with unstable angina or non-Q wave AMI were randomly assigned to receive treatment with high dose

NCEP = National Cholesterol Education Project
AMI = acute myocardial infarction

atorvastatin or placebo between 24 and 96 hours after hospital admission. Primary endpoint events were defined as death, non-fatal AMI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization. A primary endpoint event occurred in 228 patients (14.8%) in the atorvastatin group and 269 patients (17.4%) in the placebo group (relative risk 0.84, 95% confidence interval 0.70–1.00, $P = 0.048$). There were no significant differences in the risk of death, non-fatal myocardial infarction or cardiac arrest between the atorvastatin group and the placebo group, although the atorvastatin group had a lower risk of symptomatic ischemia with objective evidence and requiring emergency rehospitalization (6.2% vs. 8.4%, RR 0.74, 95%CI 0.57–0.95, $P = 0.02$). Likewise, there were no significant differences between the atorvastatin group and the placebo group in the incidence of secondary outcomes of coronary revascularization procedures, worsening heart failure or worsening angina, although there were fewer strokes in the atorvastatin group than in the placebo group (12 vs. 24 events, $P = 0.045$).

A prospective, randomized study evaluated the effect of an early-initiated, intensified therapy to usual care anti-lipidemic therapy in 126 patients with an AMI and/or PTCA secondary to unstable angina [31]. On average, 6 days after the acute event the patients were randomized to either pravastatin (combined, when necessary, with cholestyramine and/or nicotinic acid) to achieve LDL cholesterol levels of $\leqslant$ 130 mg/dl (group A) or to usual lipid-lowering therapy as determined by their family physicians (group B). Quantitative coronary angiography was performed at inclusion and at 6 and 24 month follow-ups. The combined clinical endpoints were total mortality, cardiovascular death, non-fatal myocardial infarction, need for coronary intervention, stroke and onset of new peripheral vascular disease. Minimal lumen diameter in group A increased by 0.05 ± 0.20 mm after 6 months and 0.13 ± 0.29 mm after 24 months, whereas it decreased by 0.08 ± 0.20 mm and 0.18 ± 0.27 mm, respectively, in group B ($P = 0.004$ at 6 months and <0.001 at 24 months). After 2 years, 29 of 56 patients in group B, but only 16 of 70 patients in group A, experienced a clinical endpoint (OR 0.28, 95%CI 0.13–0.6, $P = 0.005$).

In the FLORIDA study [32], the drug fluvastatin had no significant effect on the incidence of ischemia when started early after a myocardial infarction. Within 2 weeks of experiencing a myocardial infarction, 540 patients were randomized to receive 40 mg fluvastatin twice a day or a placebo. The primary endpoint of the trial was the presence of residual ischemia on 48 hour ambulatory ECG monitoring at 1 year or any clinical event (death, recurrent heart attack, recurrent ischemia requiring hospitalization or the need for PTCA, or coronary artery bypass grafting). At 1 year, 30% of the fluvastatin group had experienced at least one of the primary endpoint events compared with 36% of the placebo group. The researchers concluded that the study indicated no significant benefit from fluvastatin when given early after an AMI.

RR = relative risk
CI = confidence interval
PTCA = percutaneous transluminal coronary angioplasty

Observational studies of pre-discharge statin treatment

A number of non-randomized studies have looked into the benefit of pre-discharge statin prescription in patients with ACS [Table 1]. Aronow et al. [33] used data from two randomized trials, the GUSTO IIb and PURSUIT, to compare all-cause mortality among patients with ACS who were discharged on lipid-lowering agents (n=3,653) with those who were not (n=17,156). Lipid-lowering therapy was associated with a smaller proportion of deaths at 30 days (0.5% vs. 1.0%, $P = 0.001$) and at 6 months (1.7% vs. 3.5%, $P < 0.0001$). After adjustment for the propensity to be prescribed lipid-lowering agents and other potential confounders, prescription of a lipid-lowering agent at discharge remained associated with a reduced risk of death at 6 months (RR 0.67, CI 0.48–0.95, $P = 0.02$).

Muhlestein and colleagues [34] prospectively followed 600 patients with angiographically demonstrated CAD who met the NCEP guidelines for statin therapy for an average of 3 years (range 2–4.6). Seventy-seven percent of the patients initially presented with acute ischemic syndrome and 64 (10.7%) died during follow-up. Overall, 105 patients (17.5%) were discharged from the initial hospitalization with a statin prescription. At long-term follow-up, the number of patients taking statins had increased to 47%. However, long-term statin compliance was significantly higher among patients initially discharged with a statin prescription than those who were not (77 vs. 40%, $P < 0.0001$). Additionally, those patients discharged with a statin prescription had a significantly reduced mortality rate at long-term follow-up (5.7 vs. 11.7%, $P = 0.05$).

Stenestrand et al. [35] performed a prospective cohort study using data from the Swedish Register of Cardiac Intensive Care on patients admitted to the coronary care units of 58 Swedish hospitals with first registry-recorded AMI and discharged alive from the hospital. Altogether, 5,528 patients had received statins at or before discharge and 14,071 did not. At 1 year, unadjusted mortality was 9.3% (1,307 deaths) in the no-statin group and 4.0% (219 deaths) in the statin treatment group. In a regression analysis adjusting for confounding factors and propensity score for statin use, early statin treatment was associated with a reduction in the 1 year mortality (RR 0.75, CI 0.63–0.89, $P = 0.001$) in hospital survivors of AMI. This reduction in mortality was similar among all subgroups based on age, gender, baseline characteristics, previous disease manifestations and medications.

Finally, Walter and co-workers [36] evaluated the effect of statins on the development of restenosis and clinical outcome after coronary stent implantation in a retrospective analysis of 525 consecutive patients. Statin therapy was associated with a significantly improved survival ($P < 0.04$) free of myocardial infarction and a significant reduction in repeat target vessel revascularization procedures (28% vs. 37%, $P < 0.05$) at the 6 month follow-up.

Lipoprotein changes during ACS

The interpretation of lipoprotein values during the course of AMI is not simple. A fast of at least 12 hours is required for the measurement of serum triglycerides, from which the very low density cholesterol and LDL cholesterol levels are calculated

according to the Friedewald equation. Thus, admission values may not be valid in these cases. Further, the total and LDL cholesterol levels begin to decline within 24–48 hours after admission for AMI [37], making in-hospital LDL cholesterol measurements difficult to interpret. Similarly, the HDL cholesterol level begins to decline within several days after admission [38]. Smaller magnitude decreases in LDL cholesterol were also seen in patients with unstable angina [39]. Despite these changes, it has been shown that an LDL cholesterol level $\geqslant$ 130 mg/dl, measured the morning after admission to the coronary care unit, correctly identifies the majority of patients who will require statin therapy after discharge, especially in patients in whom the entry triglyceride levels were not elevated [39]. Although thrombolytic therapy appeared to influence the rate of changes in lipoproteins during hospitalization, it had no adverse effect on the predictive value of the morning-after LDL cholesterol level. Most guidelines currently recommend measuring lipoprotein levels either within the first 24 hours or after a delay of 1–2 months post-discharge.

Can we formulate evidence-based recommendations for managing lipoproteins in ACS?

Any recommendation for the appropriate way to manage lipoproteins in patients with ACS should take into account the degree to which each action will affect the acute and long-term outcome of the acute event, as well as logistic and cost-benefit aspects of the action taken. Four possible strategies are available:

- Disregard lipoprotein levels during hospitalization and rely on the ambulatory healthcare system to follow the existing guidelines regarding measurement and treatment of lipoproteins post-discharge.
- Measure fasting lipoprotein levels within 24 hours of admission to the hospital and recommend lipid-lowering therapy in the patient's discharge letter from the hospital where appropriate
- Measure fasting lipoprotein levels within 24 hours of admission and begin lipid-lowering therapy in indicated cases as soon as the results become available.
- Provide statin therapy to all patients with ACS soon after admission, regardless of lipoprotein levels.

In view of the data showing improved compliance and outcome of patients discharged from the hospital with a statin, it seems prudent to urge all physicians taking care of patients with ACS to assume a role in improving the current suboptimal management of secondary CHD prevention. Thus, disregarding the need for lipid-lowering therapy in these patients during hospitalization (the first option) is not a desirable mode of action.

At the other end of the treatment spectrum, one could opt to begin statin treatment in all patients hospitalized with CHD who had not received such treatment previously. We feel that the results of the MIRACL study are not convincing enough to warrant high dose atorvastatin therapy in all patients with ACS during the initial phase of hospitalization. Such treatment is expensive and will probably not be approved by most hospital administrations. However, beginning a standard dose of a statin before discharge in all patients with ACS, with a strong recommendation to reevaluate lipoprotein levels 6–8 weeks after discharge, and concomitant modification of the treatment regimen based on the results remains a viable option, especially in view of the results of the Heart Protection Study. This study recruited over 20,500 subjects at high risk for CHD and used a 2 x 2 factorial design investigating prolonged use (>5 years) of simvastatin (40 mg) and a cocktail of antioxidant vitamins (650 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene). The results suggest a benefit from simvastatin treatment across all patient groups regardless of age, gender or baseline cholesterol value [40]. Specifically, in this group of high risk patients there was no threshold cholesterol value below which statin therapy was not associated with benefit. All patients undergoing percutaneous interventions should probably also receive statin therapy during hospitalization. Patients who are on statin treatment should certainly continue such treatment after admission for ACS, as withdrawal of statins after admission may be associated with an increased cardiac event rate during the first week after onset of symptoms, as compared with patients who continue to receive statins and possibly even compared with patients who do not receive statins [41]. The recent reduction in statin prices, as a result of emerging generic products, should make the option of non-selective statin treatment in hospitalized patients attractive from a cost-benefit aspect. The hazard of this strategy is that some physicians may not continue long-term lipid-lowering therapy if the patient is not labeled as "dyslipidemic" and when follow-up blood tests reveal desirable lipoprotein levels.

Should lipoprotein levels be measured during hospitalization and used as the basis for stratifying patients to appropriate lipid-lowering therapy? Although somewhat controversial, we feel that evaluating lipoprotein levels within 24 hours of hospital admission is desirable. Such measurement will enable the detection of patients with severe hypertriglyceridemia who might benefit from triglyceride-lowering medications, as well as patients with very high LDL cholesterol levels who may need higher initial statin doses. In addition, the recently updated ATP III guidelines still recommend LDL cholesterol levels of 130 mg/dl as the cutoff for beginning statin therapy in the secondary prevention of CHD [9], and LDL cholesterol measurements taken the morning after admission seem reliable for identifying such patients [39]. Although a formal cost-benefit analysis of such an approach has not been published, the potential benefits gained by the selective treatment of patients with elevated LDL cholesterol probably justify the additional cost of one lipoprotein analysis in every patient admitted for ACS. While such a strategy may be viewed as conservative by some experts, we feel that additional data are required before recommending a more aggressive approach.

Conclusions

In order to improve the compliance of primary care physicians with secondary prevention guidelines, we recommend that all patients with ACS have a lipoprotein profile analysis within 24 hours of admission to the hospital. Labeling dyslipidemic patients in the discharge letter diagnosis list, as well as appropriate recommendation(s) for pharmacologic treatment of dyslipidemia should be

HDL = high density lipoprotein

routine for all such patients. Recently published guidelines suggest treatment with statins and diet for LDL cholesterol levels greater than 100 mg/dl begun 24 to 96 hours after admission and continued at hospital discharge (class IIa recommendation) [40]. Although the evidence in favor of initiating statin therapy in the hospital is not conclusive, we recommend such action where treatment is deemed appropriate.

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