Benefits of lipid regulation in acute coronary syndrome

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Abstract

Lipid lowering therapy with statins has proven beneficial in patients with acute coronary syndrome (ACS). Outcome trials have demonstrated that the high risk of a recurrent coronary event or stroke can be reduced by about 15% using these agents. Further, greater benefit appears to be present when more aggressive treatment regimens (higher statin doses) are followed. Lipoprotein levels measured in the days following an ACS episode may not be a good guide to therapy due the effects of the acute phase response. Other lipid regulating modalities including HDL raising drugs are being explored. Theoretically, these approaches could be beneficial not only in facilitating reverse cholesterol transport but also in altering inflammatory and oxidative pathways. Their utility needs to be tested rigorously in clinical trials.

Key words: cholesterol, statins, lipoprotein, trials.

Introduction

Atherosclerosis is a decades long process in which continuous or repeated, episodic insults to the artery wall lead to remodeling and pathological changes. The "insults" make take the form of excessive levels of lipoproteins or bursts of free radicals or release of bioactive lipids that provoke an inflammatory response [1]. In time the disease process manifests itself clinically as sudden cardiac death, stable coronary ischemia, or acute coronary syndrome (ACS) which includes unstable angina and myocardial infarction. Risk factors for the development of atherosclerosis are well understood but what determines the severity of the clinical presentation is not yet clear. In order to target treatment it is important to understand the extent to which therapeutic strategies directed towards long term prevention of coronary artery disease (CAD) e.g. lipid lowering, smoking cessation and blood pressure reduction address adequately the needs of a patient experiencing an acute coronary event.

This article offers a brief review of the benefits of lipid regulation in ACS. The condition has proved amenable to improvements in clinical care and in intervention procedures, however optimal medical therapy has yet to be defined.

Lipoproteins as predictors of risk in acute coronary syndrome

Inflammation of the artery wall is believed to be the prime mechanism leading to the formation of focal, complex atherosclerotic plaques [2]. The key differences between plaques that are prone to rupture and hence give rise to an acute coronary event compared to stable lesions are

the presence of a thin fibrous cap heavily infiltrated with macrophages and lymphocytes, the accumulation of lipid in the core, and a relative deficiency of collagen and smooth muscle cells [1, 2]. Risk of a further event in those presenting with ACS is high particularly in the first 6 months; 7-12% of patients go on to suffer a fatal or non-fatal MI and there is a 10 fold increased risk of stroke [3-5].

Low density lipoprotein (LDL) is the principal cholesterol transporter in the blood and elevated levels of this particle are linked causally to the development of atherosclerotic plaque and CAD [6]. The association of LDL with risk of a future coronary event in ACS patients has been examined in a number of studies. In MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) it was observed that LDL cholesterol (LDLc) levels sampled within 4 days of hospital admission were not predictive of the primary endpoint (death, non fatal MI, cardiac arrest, worsening angina) over the next 16 weeks [7]. This may indicate a different pathology for ACS compared to chronic CAD, or more likely any aetiological relationship that might be present was confounded by the acute phase response which led to a decreased LDL in those most severely affected. Baseline LDL in the other major ACS lipid lowering trial, PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) was linked to the benefits of treatment in that those with highest LDL levels appeared to experience the greatest risk reduction on statin therapy [8].

Epidemiological studies have established a strong inverse association between high density lipoprotein (HDL) levels and CAD risk [6]. This has been attributed to atheroprotective properties of the lipoprotein class and its major protein apoA1 [9]; such properties include the facilitation of reverse cholesterol transport, anti oxidative actions and anti-inflammatory effects. Olsson *et al*. [7] reported that HDL cholesterol (HDLc) exhibited a negative association with risk of a recurrent coronary event in the MIRACL study; for each 1 mg/dl increase in HDLc there was an apparent 1.4% decrease in risk over the four month follow up (HDLc levels did not appear to be affected by the acute phase response to the index coronary event). A similar observation was made in a cohort study which followed ACS patients for 1 year. Those with low HDL (< 40 mg/dl in men, < 45 mg/dl in women) at baseline had a 2.6 fold increased risk of a major cardiac event or death over the next 12 months [10].

In many patients low HDL is part of a dyslipidaemic pattern termed "metabolic syndrome" which comprises central obesity, low HDL, raised triglyceride, hypertension and impaired glucose intolerance. Publication of a pragmatic definition of the syndrome [6] provoked a great deal of research into its possible aetiology and clinical sequelae. It has been linked to increased incidence of type 2 diabetes and CAD but there is controversy in the literature regarding the utility of metabolic syndrome as a construct for improving risk prediction in the general population [11]. A number of studies have evaluated whether patients with ACS who express metabolic syndrome are at increased risk. Schwartz *et al*. [12] carried out an analysis of recruits to the MIRACL study and found that 38% had metabolic syndrome. This sub group had a 19% incidence of the primary endpoint over the 16 week follow up compared to a rate of 14% in those not categorized as having the syndrome, a hazard ratio of 1.49 ($p < 0.0001$). The benefits of statin therapy were the same in both groups. A cohort study of the impact of metabolic syndrome in ACS patients who were unrecognized diabetics reported the syndrome to be a very strong predictor of 30 day and 1 year mortality with hazard ratios of 2.54 (CI 1.22-5.31) and 1.96 (CI 1.18-3.24) respectively [13]. In this study the presence of hyperglycemia in those admitted to hospital with ACS was particularly disadvantageous.

It is important that lipid abnormalities in ACS are set in the wider context of the consequences of the damage to the myocardium and systemic, stress related changes. There is a need to develop a cassette of biomarkers to aid in directing therapy in ACS patients [14, 15] as well as to provide further insight into the aetiology of the condition. An altered lipoprotein profile – raised LDL, reduced HDL, raised triglyceride (in Very Low Density Lipoproteins (VLDL) and remnants) – is well established as a potential causative factor leading to the chronic accretion of the lipid pool in atherosclerotic plaque (Figure 1). How lipoproteins contribute to the acute situation that leads to the precipitating event in ACS and to the greatly increased of a recurrent coronary episode over the next 6 months is not clear. Epidemiological associations and the effectiveness of statin therapy, suggest but do not prove a causal link since the drugs have pleiotropic effects and altered lipoproteins are linked to disturbances in the regulation of innate immunity and lipid oxidation. For example, LDL carries an enzyme lipoprotein-associated phospholipase A2 (Lp PLA2) which releases bioactive oxidized fatty acids from LDL and this entity is associated in ACS patients with increased CAD risk [16]. HDL, on the other hand, transports a powerful anti-oxidant enzyme, paraoxonase 1, which has been reported to be low in ACS patients and inversely correlated with severity of CAD [17, 18]. It is likely that a constellation of an exacerbation of inflammation, lipoprotein disturbances, change in oxidation status and the release of bioactive substances conspire to generate the plaque instability that is the hallmark

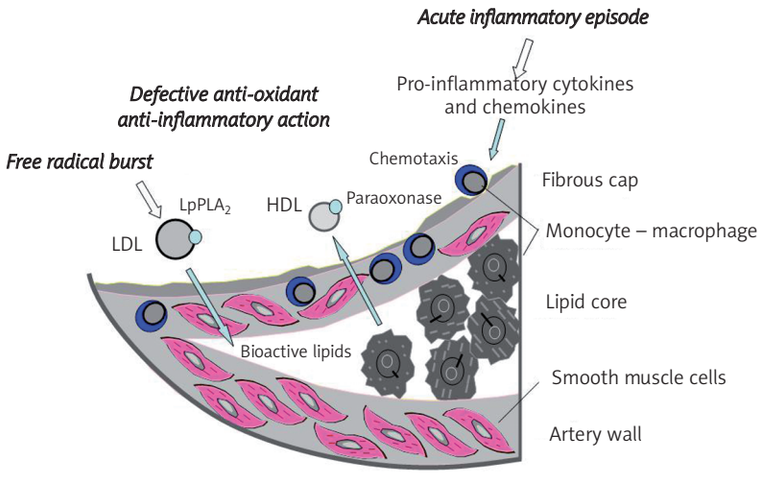

Figure 1. Potential role of lipoproteins in acute coronary syndrome
The diagram depicts the cross section of an atherosclerotic plaque. Cells of the monocyte macrophage line are present in the fibrous cap of the lesion and foam filled macrophage are contained in the lipid core.
Possible pathological events leading to plaque rupture (loss of integrity of the cap) are:
1) ehanced oxidation of LDL lipids with release of bioactive short chain fatty acids by action of lipoprotein-associated phospholipase A2,
2) low HDL and paraoxonase levels leading to decreased ability to detoxify oxidation products,
3) an acute exacerbation of the inflammatory state leading to increased generation of pro-inflammatory cytokines and increased penetration of the artery wall by inflammatory cells (monocytes)

of ACS (Figure 1). Lipid regulation, as described below, can go some way to protect patients against recurrent CAD and stroke [19] but it is not the whole answer.

Lipid lowering interventions trials in acute coronary syndrome

Evidence for the benefits of LDL lowering in ACS has been obtained from a number of large scale outcome studies using statin therapy. While a consistent pattern emerges from the trials, further in depth analysis has revealed as many questions as answers [20, 21].

MIRACL

Until this trial reported its findings in 2001 [22] it was not obvious that lipid lowering treatment could impact on the greatly increased risk of CAD associated death and stroke that followed an acute MI or episode of unstable angina. The study recruited 3,086 patients within 4 days of hospitalization for an acute coronary event to receive placebo or high dose statin treatment. The end point was a recurrent event within the 16 week follow up. Atorvastatin at 80 mg caused a 42% decrease in LDL cholesterol (Table I), a 23% drop in triglyceride but little change in HDLc [7, 22]. At 16 weeks statin therapy was associated with a 16% reduction (p = 0.048) in the primary endpoint and 50% decrease in stroke (p = 0.04) [22, 23]. No relationship between on treatment LDLc, plasma cholesterol or triglyceride levels and risk reduction on statin could be discerned [7]. Risk of stroke was related to levels of inflammatory factors (C-reactive protein [CRP], serum amyloid A [SAA] and interleukin 6 [IL-6]) at baseline in the placebo group; atorvastatin treatment abolished this association and lowered CRP by 34% SAA by 13% but had little impact in IL-6 [19]. Kinlay *et al*. [19] suggest that the reduction in high early risk of stroke was attributable to an anti-inflammatory action of the statin either through lipoprotein mediated or pleiotropic effects. Sub group analysis in MIRACL indicates that the treatment was equally effective in those with and without metabolic syndrome [12], and in those above and below 65 years of age [24].

PROVE-IT TIMI22

Debate over the pleiotropic properties of various statins led to this trial (Pravastatin or atorvastatin evaluation and infection therapy – thrombolysis in myocardial infarction 22) being designed as a comparison of pravastatin at 40 mg vs. atorvastatin at 80 mg/day. A total of 4,162 ACS patients were randomised to moderate or aggressive statin therapy (Table I). LDLc was 95 mg/dl (median) in the pravastatin group on treatment and 62 mg/dl in those who received atorvastatin [25]. The latter drug regimen was associated with a 16% reduction in risk of the primary endpoint compared to the former with little difference in adverse event rates between the two treatment arms. Follow up

Table I. Lipid lowering trials in ACS

Study (*n*)	Index event	Follow up [months]	Treatment regimen	Baseline LDLc	Moderate Rx LDLc	Intensive Rx LDLc	Moderate Rx 1ary endpoint incidence [%]	Intensive Rx 1ary endpoint incidence [%]	Hazard ratio	*P*
MIRACL (*n* = 3086)	Acute MI Unstable angina	4	Placebo vs. atorvastatin 80 mg	124[a]	135	72	17.4[b]	14.8	0.84	0.048
PROVE-IT (*n* = 4162)	Acute MI Unstable angina	24	Pravastatin 40 mg vs. atorvastatin 80 mg	106	95	62	26.3	22.4	0.84	0.005
A TO Z (*n* = 4497)	Acute MI Unstable angina	24	Placebo/simvastatin 20 mg vs. simvastatin 40/80 mg	111	77	62	16.7	14.4	0.89	0.14
LIPS (*n* = 1677)	PCI (49% had unstable angina	47	Placebo vs. fluvastatin 80 mg	132	147	110	26.7	21.4	0.78	0.01

[a]*LDL cholesterol in mg/dl; note baseline LDLc can be low due to acute phase response*
[b]*event rate relate to different periods of follow up and cannot be compared across studies*

was for longer than MIRACL at 2 years but time dependent analysis revealed that the reduced hazard ratio in the more aggressively treated subjects was evident within 3 months.

In contrast to MIRACL, baseline LDLc was a predictor of benefit in PROVE-IT. There was statistically significant interaction of LDLc at randomisation and risk reduction; those in the highest LDLc quartile (median 148 mg/dl) exhibited a 37% decreased risk ($p < 0.0002$) vs. those in the lowest (median 81 mg/dl) who had 7% ($p = 0.63$) decrease. Modeling of the whole trial population indicated no greater benefit on atorvastatin vs. pravastatin therapy if baseline LDLc was below 66 mg/dl. Note this fall off in efficacy relates to the differential effects of two statins and is not a test of aggressive LDL reduction itself.

Further exploration of the PROVE-IT study [26] led to the observation that both statins lowered CRP as well as LDL although the fall in these two variables was not correlated strongly. Achieved LDLc was related strongly to risk of a recurrent event and so was achieved CRP; the event rate in those with CRP < 2 mg/dl on treatment was similar to that seen in those with LDL < 70 mg/dl (the target for LDL in patients with ACS [27]). These findings have led to a call for ACS patients to be treated to a dual LDLc/CRP goal.

Low on-treatment triglyceride (< 150 mg/dl) was found also by the PROVE-IT investigators to be a factor linked to better outcome [28]. Statins lower triglyceride in those with high normal or elevated levels of this lipid approximately in proportion to the LDL reduction [29], and it was reported by Miller *et al*. [28] that for each 10 mg/dl decrement in triglyceride on statin the incidence of a coronary event decreased by 1.4% (after adjustment for LDLc, non-HDLc and other covariates). PROVE-IT patients who achieved the triple target of triglyceride < 150 mg/dl, CRP < 2 mg/dl and LDLc < 70 mg/dl had a 41% risk reduction ($p = 0.0002$). This substantial benefit may be due to a reduction in thrombotic potential linked to a triglyceride lowering [28], to a decrease the concentration of small, dense LDL (which is not formed at low triglyceride levels), or to a fall in the plasma concentration in remnant particles [30].

A to Z

Phase Z of the Aggrastat to Zocor study was an evaluation of the impact in ACS patients of intensive treatment with a statin (simvastatin at 40 mg for 1 month and then 80 mg/day) vs. a moderate regimen (placebo for 1 month followed by simvastatin at 20 mg/dl) [31]. LDLc, initially 111 mg/dl, was reduced at 24 months to 66 mg/dl in the intensively treated and to 81 mg/dl in the moderately treated subjects (Table I). The trial did not show a superior benefit for intensive treatment- the hazard ratio vs. moderate therapy was 0.89 ($p = 0.14$) – possibly because of reduced statistical power (low event rate) and the large number of drop outs.

Similarities in design between A to Z and PROVE-IT have prompted in depth comparison in order to explain better the apparently contrasting findings [20, 21]. Wiviott *et al*. [21] observed that the different in outcome between the two trials was due to the early benefit of intensive treatment seen within four months in PROVE IT but not in A to Z. This may have been linked to the nature of the population and prevailing ACS intervention strategies in different countries. Over the period from

4 months post randomisation to trial end there was no difference between studies, the risk reduction on intensive compared to moderate therapy was about 14%. Pooling of data at an individual level in PROVE-IT and A to Z provided further evidence of the benefits of aggressive therapy in preventing recurrent major coronary events [20].

LIPS

Entry to the Lescol Intervention Prevention Study (LIPS) was based on a successful outcome to a percutaneous coronary intervention (PCI) procedure rather than a clinical condition [32]. Of the 1,677 recruits about half had unstable angina as the indication for their index procedure. Patients were randomised within days of PCI to placebo or 80 mg fluvastatin and follow up was for 3-4 years. LDL was reduced 27% and the relative risk of a major coronary event was decreased 22% ($p = 0.01$). Separation of the event curves in the two treatment arms occurred about 6 months post randomisation and both those with stable and unstable angina appeared to receive similar benefits from statin therapy.

Potential benefits of HDL raising in acute coronary syndrome

The "LDL-atherosclerosis" paradigm is reasonably well understood in that excess lipoprotein in the bloodstream permeates the artery wall causing lipid accumulation and probably the release of noxious oxidation products which provoke an inflammatory response. Lowering plasma LDL slows this pathogenic sequence. The cardioprotective properties of HDL, however, are less well understood and it is far from clear that raising HDL levels in the circulation will lead to a reduction in CAD risk. Lipoproteins found in the "high density" range are small and highly variable in structure, and are engaged in a dynamic flux, exchanging components with each other, with other proteins and with tissues [9, 33]. Studies have attempted to identify the key structures or functions within HDL that help reduce risk of a coronary event. Apolipoprotein (apo) A1, the major HDL protein appears to have a critical role in reverse cholesterol transport, anti-inflammatory and anti-oxidation activities [33, 34].

Early trials of drug induced HDL alterations show some promise. The Coronary Drug Project had an arm that examined the effects of niacin on CAD risk in subjects with established chronic ischemic disease [35]. Treatment was associated with a rise in HDLc (niacin also alters plasma triglyceride and LDLc levels) and a significant reduction in risk. Studies using fibrates as an alternative way of increasing HDL have had variable success [36, 37].

If, as indicated in Figure 1, there is a need for a broad attack on atherosclerotic pathways – inflammation, lipid oxidation and cholesterol accretion by plaque – in ACS patients then HDL is a promising therapeutic target. However, it is likely that to have an impact in the acute situation the perturbation in HDL will need to be greater than what can be achieved using agents such as niacin and fibrates. In this regard inhibitors of cholesteryl ester transfer protein such as torcetrapib and JTT705 are worthy candidates since they increase by 25-50% the amount of HDL in the circulation [9]. However, torcetrapib has been found to be toxic and has been withdrawn from use [38].

One possible avenue to address the need for plaque stabilisation in ACS is the direct administration of HDL or apoA1. It has been shown that a short course (5 weeks) of infusion of apoA1-Milano (a naturally occurring mutant form of the protein) to ACS patients promoted atherosclerosis regression [39]. More recently, the results of the ERASE (Effect of rHDL on Atherosclerosis, Safety & Efficacy) study have been reported in which patients were given four weekly infusions of reconstituted HDL (rHDL) [40]. Safety issues were present with the highest does of rHDL (80 mg/kg). At 40 mg/kg there was a reduction in atheroma volume compared to baseline (–3.4%, $p < 0.001$) but no significance difference between the groups receiving placebo and rHDL ($p = 0.48$). There was, however, an indication from the plaque characterisation indices that the treatment was having a beneficial effect. An alternative to administering authentic apo A1 is to use peptides that possess some of the putative cardioprotective properties of the protein. These apoA1 mimetics are short amphipathic helical structures that can promote cholesterol efflux from tissues at least in model systems. How successful they will be in man is yet unclear [41].

Therapeutic goals and mechanisms of benefit

There is, as described above, an increasing body of evidence that LDL lowering with statins leads to a reduced risk of recurrent coronary events and stroke in ACS. These findings in patients with an acute, unstable condition mirrors closely those in subjects with stable CAD as demonstrated in a recent meta-analysis [42]; intensive therapy vs. moderately aggressive treatment with statin leads to approximately a 15% risk reduction virtually irrespective of concomitant risk factors and clinical presentation. This consistency in benefit suggests that the goals of therapy set in the more widely investigated chronic CAD setting could be transposed to ACS [27]. However, care is needed in adopting this approach until the mechanism of action of lipid lowering agents in ACS is known.

LDLc in the days following an acute coronary event – the time when treatment needs to be initiated – is affected by the acute phase response (Table I) and cannot therefore be a reliable guide in any treatment algorithm. HDLc does exhibit an inverse relationship to risk of an early recurrent event but this may linked to the anti-inflammatory or anti-oxidant properties of the lipoprotein class i.e. ACS patients with low HDL have a reduced capacity to handle the acute exacerbation of inflammation that precipitates plaque rupture.

Mechanistically, the immediate goal of therapy in ACS is plaque stabilisation and this can be influenced acutely by statin therapy. Takarada *et al.* [43] used serial optical coherence tomography imaging of coronary lesions to show that statin treatment following PCI led to increased thickening of the fibrous cap of plaque, and this was especially evident for lesions with an initial thin cap (i.e. "vulnerable" plaques). Similar results using intravenous ultrasound histology were reported for hyperlipidemic subjects [44]; statin treatment led to an increase in fibrous volume and a reduction in the lipid content of coronary lesions in patients with stable angina. How statins promote these changes in plaque composition, that theoretically lead to greater stability, is not clear. LDL lowering must be considered the primary mechanism (and the degree of LDL reduction in ACS was linked to outcome [8]) but other actions of the drugs cannot be ruled out. For example, the impact of statins on lesion size has been linked to the rise induced in HDL as well as LDL reduction [45]. Also, in MIRACL it was observed that the association of stroke with elevated levels of inflammatory markers was attenuated markedly in the atorvastatin treated group [19].

In conclusion, the goal of therapy in ACS patients (Table I) is a rapid reduction in risk of both early and late recurrent events. Aggressive statin therapy is indicated by the evidence base and it is arguable that patients should receive the highest tolerable dose of statin to produce the greatest benefit. As discussed above and in line with recent comments [46, 47] caution should be exercised in selecting patients for lipid lowering therapy of the basis of guidelines that apply to chronic CAD. Further, it is not obvious from recent trials observations that alternative means of reducing LDL will produce the same risk reduction [48]. Residual risk in optimally treated patients (using both surgical and medical interventions) is still high (Table I) and there is the potential of further benefit from additional regulating (HDL raising) treatments.

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