The current role of statins in acute coronary syndrome

Amit Kumar[1], Christopher P. Cannon[2]

[1]UMass Marlborough Health System, Marlborough, MA, USA
[2]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

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Corresponding author:
Dr. Christopher P. Cannon
at the TIMI Study Group
Cardiovascular Division,
Brigham and Women's Hospital
75 Francis Street, Boston
MA 02115, USA
Phone: 617 278 0146
Fax: 617 734 7329
E-mail: cpcannon@partners.org

Abstract

Statins have long been known to be effective for primary and secondary prevention of coronary heart disease (CHD), and reduction of low density lipoprotein-cholesterol (LDC-C) levels over time was thought to be the mechanism by which statins exerted their clinical effectiveness. Data from recent large randomized trials have established the efficacy and safety of intensive statin therapy started early after ACS and have provided new insights into the mechanism of action of statins. While the early benefits appear to be related more to dose dependent LDL-C independent "pleiotropic" effects and reduction in C-reactive protein (CRP), which is an inflammatory biomarker, the long-term benefits are related to reductions in both LDL-C and CRP. The current state of evidence, based upon key trials of statins in ACS, supports a central role for statin therapy, in particular intensive statin therapy, in the management of patients with ACS.

Key words: ACS, intensive statin therapy, CRP, pleiotropic effects.

Introduction

Acute coronary syndrome (ACS), either as a primary or secondary diagnosis, is responsible for more than 1.5 million hospitalizations each year in the United States [1]. Following an ACS, the risk of adverse cardiovascular events is highest in the first 6 months and slowly diminishes over time [2]. There is an almost linear relationship between low density lipoprotein-cholesterol (LDL-C) level and coronary heart disease (CHD) event rate after ACS without any definite threshold below which risk declines (Figure 1) [3]. Statins are a class of drugs that reduce LDL-C levels by blocking the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the liver. Beyond LDL-C lowering, statins have several dose-dependent actions collectively referred to as "pleiotropic" effects. These include reduction of systemic inflammation, improvement of endothelial dysfunction and stabilization of atherosclerotic plaque amongst others. ACS is a pan-coronary process with multiple vulnerable or ruptured plaques in addition to the ruptured lesion that caused the ACS (Figure 2). While angioplasty and stenting treat a culprit lesion effectively, potent systemic therapy is required to passivate other vulnerable sites (Figure 3) [4]. Statins, by virtue of their multiple mechanisms of action, especially at high doses, have become established as the cornerstone drugs for management of ACS. This paper will review the key trials of statins with an emphasis on intensive statin therapy that have established the efficacy and safety of these agents and laid the foundation stone for their use in ACS.

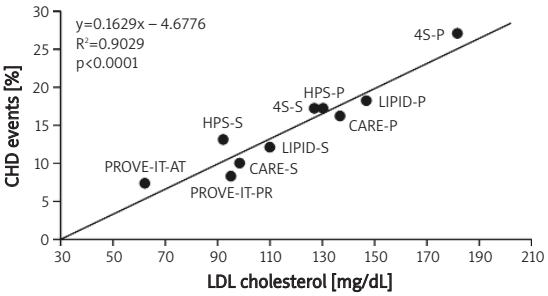

Figure 1. Coronary heart disease (CHD) event rates in secondary prevention and acute coronary syndrome trials; LDL – low density lipoprotein. Reprinted from O'Keefe JH Jr, et al. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. J Am Coll Cardiol 2004; 43: 2142-6. Copyright (2004), with permission from Elsevier

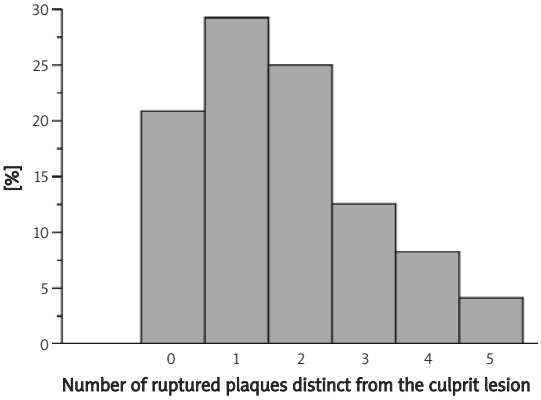

Figure 2. Number of ruptured plaques in addition to ruptured lesion in acute coronary syndrome (80% of patients with ≥1 ruptured plaque). Reprinted from Rioufol G, Finet G, Ginon I, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. Circulation 2002; 106: 804-8.

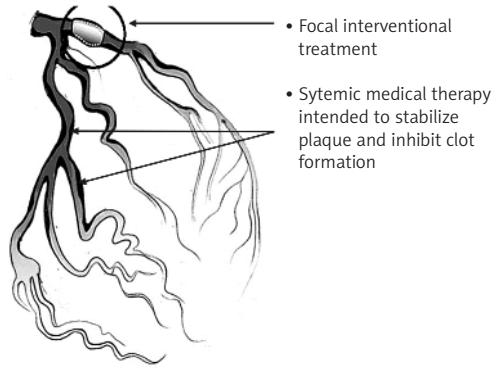

Figure 3. Integrated approach to managing patients with acute coronary syndrome

Early secondary prevention statin trials

The early secondary prevention statin trials excluded patients within the first 4-6 months following an ACS. The first of these trials was the Scandinavian Simvastatin Survival Study (4S) which randomized 4444 patients with angina pectoris or previous myocardial infarction (MI) and serum cholesterol 215-312 mg/dL (5.5-8.0 mmol/L) on a lipid-lowering diet to double-blind treatment with simvastatin or placebo [5]. Over the 5.4 years median follow-up period, simvastatin produced mean changes in total cholesterol and LDL-C of 25 and 35%, respectively, with few adverse effects. Statin therapy was associated with an absolute 4% reduction and a 30% relative risk reduction in all-cause mortality (p=0.0003). Significant reductions were also observed for CHD mortality (42%), major coronary event (34%) and coronary revascularization (37%). Benefit was observed in all subgroups including women and patients aged >60 years.

The Cholesterol and Recurrent Events (CARE) trial quickly followed 4S and demonstrated that the benefit of cholesterol-lowering therapy extends to the majority of patients with CHD who have average cholesterol levels. 4159 patients with MI who had plasma total cholesterol levels below 240 mg/dL and LDL-C levels of 115 to 174 mg/dL were randomized to pravastatin 40 mg daily vs. placebo [6]. The frequency of the primary endpoint (fatal coronary event or a nonfatal myocardial infarction) was reduced from 13.2% in the placebo group to 10.2% in the pravastatin group, an absolute difference of 3 percentage points (p=0.003). There were also significant risk reductions in coronary revascularization (26% reduction coronary bypass surgery and 23% reduction angioplasty) and stroke (31%).

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial was the largest of the three early secondary prevention trials and confirmed the mortality findings of 4S in a population with a broad range of initial cholesterol levels. A total of 9014 patients with a history of MI or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg/dL were randomized to pravastatin 40 mg daily vs. placebo [7]. The incidence of CHD death was reduced from 8.3% in the placebo group to 6.4% in the pravastatin group (relative reduction in risk [RR] 24%; 95% confidence interval [CI] 12 to 35%; p=0.001) and overall mortality was reduced from 14.1% in the placebo group to 11.0% in the pravastatin group (RR 22%; CI 13 to 31%; p=0.001). There were also reductions in the risk of recurrent MI (29%), stroke (19%) and coronary revascularization (20%). There were no clinically significant adverse effects of treatment with pravastatin.

Moderate dose statin therapy in ACS

Although the secondary prevention of CHD by statins beginning at ≥3 months after an ACS was established by the above trials, the impact of immediate initiation of statin therapy on clinical outcomes in patients with ACS was unknown. An initial pilot study, the Lipid-Coronary Artery Disease (L-CAD) study, randomized 126 patients, on average, 6 days after an acute MI and/or percutaneous transluminal coronary angioplasty for unstable angina, to pravastatin (combined, when necessary, with cholestyramine and/or nicotinic acid) to achieve LDL-C of ≤130 mg/dL vs. usual care [8]. The combined clinical endpoints were total mortality, cardiovascular death, nonfatal MI, need for coronary intervention, stroke, and new onset of peripheral vascular disease. After 2 years, there was a 72% reduction in the primary endpoint (odds ratio [OR] 0.28; CI 0.13 to 0.6; p=0.005). Despite the pronounced clinical benefit, the study was too small to provide large-scale evidence of benefit.

The Fluvastatin On Risk Diminishment after Acute Myocardial Infarction (FLORIDA) study was another small trial which randomized 540 ACS patients to treatment with fluvastatin 80 mg daily vs. placebo within 14 days of an ACS and followed them up for up to 12 months [9]. By the end of the study, LDL-C was reduced by 21% in the fluvastatin group vs. a rise of 9% in the placebo group (p<0.001 between groups). Fluvastatin treatment affected neither the end point of ischemia measured by 48-hour ambulatory ECG monitoring nor the occurrence of any major clinical events as compared to placebo. However, the study was underpowered to detect a significant benefit on clinical endpoints as a result of the small sample size.

Pravastatin in Acute Coronary Treatment (PACT) studied the effects of a moderate dose of statin therapy (pravastatin 20-40 mg daily) administered within 24 hours of ACS [10]. Patient recruitment of 10,000 with 1200 endpoints was planned, but the trial was stopped early due to difficulties with recruitment. A total of 3408 patients were randomly assigned to treatment with pravastatin or matching placebo for 4 weeks. The primary endpoint of the study was a composite of death, recurrent MI, or readmission to hospital for unstable angina within 30 days. The composite endpoint tended to be lower in the statin group but failed to achieve statistical significance (hazard ratio [HR] 0.94; p=0.48). Interestingly, the HR among patients receiving pravastatin 20 mg was 1, but among patients receiving pravastatin 40 mg the HR tended to be lower, suggesting a possible dose effect for statins in the immediate management of ACS. No adverse effects were seen with pravastatin.

Intensive statin therapy in ACS

MIRACL

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial provided the first clinical evidence that intensive statin therapy started early after ACS reduced recurrent ischemic events. A total of 3086 patients with non-ST elevation ACS were randomized within 24-96 hours of hospital admission to atorvastatin 80 mg vs. placebo [11]. Primary endpoint was defined as a composite of death, nonfatal MI, cardiac arrest with resuscitation, or recurrent symptomatic ischemia with objective evidence requiring emergency rehospitalization at 16 weeks. The mean LDL-C declined from 124 mg/dL (3.2 mmol/L) to 72 mg/dL (1.9 mmol/L) in patients given atorvastatin, reflecting a reduction of 42% vs. placebo. At 4 months, the rate of primary endpoint was reduced by 16% in the atorvastatin group compared with placebo (HR 0.84; p=0.048). The benefit of atorvastatin was due to reduction in the rate of symptomatic ischemia requiring rehospitalization. There were no significant differences in the risk of death, nonfatal MI or cardiac arrest between the two groups. Abnormal liver transaminases were more common in the atorvastatin group than in the placebo group (2.5 vs. 0.6%; p<0.001). While this trial suggested a beneficial role of intensive statin therapy early after ACS, the long-term efficacy and safety of such a strategy remained to be defined.

PROVE IT-TIMI 22

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT–TIMI 22) trial also studied ACS patients but compared intensive statin therapy to standard dose statin therapy. In this trial, 4162 patients within 10 days of hospitalization for an ACS were randomized to 40 mg of pravastatin daily (standard therapy) or 80 mg of atorvastatin daily (intensive therapy) [12]. Sixty-nine percent of patients had percutaneous coronary intervention for management of their ACS immediately prior to randomization. The primary endpoint was a composite of death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Patients were followed on average for a total of 2 years. The median LDL-C achieved during treatment was 95 mg/dL (2.46 mmol/L) in the standard-dose pravastatin group and 62 mg/dL (1.60 mmol/L) in the high-dose atorvastatin group (p<0.001). Kaplan-Meier estimates of the rates of the primary endpoint at 2 years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, reflecting a 16% reduction in the HR in favor of atorvastatin (HR 0.84; CI 0.74–0.95; p=0.005)

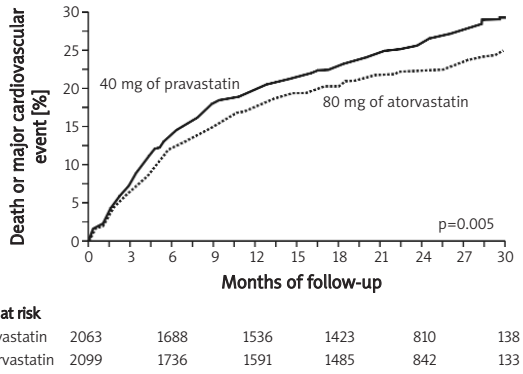

Figure 4. Kaplan-Meier estimates of the incidence of primary endpoint of death from any cause or a major cardiovascular event in PROVE IT-TIMI 22.
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(Figure 4). The benefit appeared very early (within 30 days) and the Kaplan-Meier event-free survival curves continued to diverge, suggesting sustained and continued benefit of the intensive regimen over 2 years [13]. Of note, the greatest benefit was seen in patients who underwent PCI, with the rate of the primary endpoint falling from 26.8% in the pravastatin group to 21.5% in the atorvastatin group among patients who underwent PCI with a relative risk reduction of 22%, p=0.002 [14]. The rates of adverse events were similar in the two groups with the exception of a transient increase in liver transaminases (3.3% in the atorvastatin group vs. 1.1% in the pravastatin group), suggesting that high doses of statins were as safe as moderate doses.

A to Z

A to Z (Aggrastat to Zocor) was another ACS trial which compared early initiation of an intensive statin regimen with delayed initiation of a less intensive statin regimen. A total of 4497 patients with ACS were randomized either to 40 mg/day of simvastatin for 1 month followed by 80 mg/day or to placebo for 4 months followed by 20 mg/day of simvastatin [15]. Follow-up was for at least 6 months and up to 24 months. The rate of the primary endpoint (composite of cardiovascular death, nonfatal MI, readmission for ACS and stroke) was 16.7% in the placebo plus simvastatin group compared to 14.4% in the simvastatin only group (40 mg/80 mg) (HR 0.89; CI 0.76-1.04; p=0.14). No difference was evident during the first 4 months between the groups for the primary endpoint (HR 1.01; CI 0.83-1.25; p=0.89) but from 4 months to the end of the study, the primary endpoint was significantly reduced in the simvastatin only group (HR 0.75; CI 0.60-0.95; p=0.02). Myopathy (creatine kinase >10 times the upper limit of normal associated with muscle symptoms) occurred in 9 patients (0.4%) receiving simvastatin 80 mg/day, in no patients receiving lower doses of simvastatin, and in 1 patient receiving placebo (p=0.02).

Comparing and contrasting PROVE IT-TIMI 22 and A to Z

The A to Z and PROVE IT trials compared intensive and moderate statin therapy after ACS, with seemingly disparate results during the early phases of the trials. The design, implementation and results of the two trials were analyzed in a subsequent study in an attempt to clarify the effects of early intensive statin therapy after ACS [14]. With common endpoints, an early favorable separation of event curves was seen in PROVE IT but not in A to Z. However, clinical endpoint rates and reductions were similar in both trials starting after 4 months. Factors that may explain this disparity (benefit in PROVE IT and no benefit in A to Z) include the intensity of statin therapy in the early phase, timing and magnitude of LDL-C and C-reactive protein (CRP) lowering, differences in baseline demographic characteristics and differences in early revascularization. Subjects in A to Z had higher-risk demographics. More PROVE IT subjects were enrolled in the United States and underwent pre-randomization revascularization. The LDL-C difference was greater in A to Z than in PROVE IT early (≤4 months) but less late. Significant CRP reduction was earlier in PROVE IT. Taking everything together, the results of these trials support a strategy of early intensive statin therapy coupled with revascularization when appropriate in patients after ACS [14].

Early and late benefits of intensive statin therapy after ACS

Although the PROVE IT-TIMI 22 trial established the benefit of intensive statin therapy in improving clinical outcomes over two years in ACS patients, the timing of benefit with intensive statin therapy and the relative contributions of early or late effects to the overall clinical efficacy of intensive therapy were not clear. This question was assessed by a further analysis of PROVE IT which studied the cumulative risk of death, MI or rehospitalization for ACS within 30 days of ACS and the conditional hazard after 6 months in subjects free from clinical events [13]. At 30 days, the composite triple endpoint occurred in 3.0% of patients receiving atorvastatin 80 mg vs. 4.2% of patients receiving pravastatin 40 mg (HR 0.72; CI 0.52 to 0.99; p=0.046). Commencing 6 months after ACS to the end of the study, atorvastatin 80 mg was associated with a composite event rate of 9.6% vs. rate of 13.1% in

the pravastatin 40 mg group (HR 0.72; CI 0.58 to 0.89; p=0.003). In conclusion, intensive statin therapy after ACS leads to an early reduction in clinical events at 30 days, and in stable patients continues to provide long-term reduction in clinical events. Thus, ACS patients should be started in-hospital and continued long-term on intensive statin therapy.

Potential mechanisms of early benefit

ACS may result from several underlying mechanisms including plaque rupture or erosion with superimposed thrombus (a process referred to as "atherothrombosis"), dynamic obstruction or progressive mechanical obstruction, and is accompanied by a number of changes in inflammation, endothelial function and coagulation [16, 17]. Statins have several dose-dependent lipid-independent rapid effects collectively referred to as "pleiotropic effects" (Figure 5) [4, 18, 19]. These include inhibition of inflammatory responses, stabilization of atherosclerotic plaques, normalization of endothelial dysfunction, and anti-oxidant effects. Additional effects include the ability to recruit endothelial progenitor cells, immunomodulation, and inhibition of myocardial hypertrophy. These and several other emergent properties could act in concert with the potent LDL-C lowering effects of statins to exert early as well as lasting cardiovascular protective effects. The very early benefits of statin therapy appeared to be correlated with reductions in CRP. The dose/potency of the statin regimen is crucial since the greatest pleiotropic effects are observed using the highest doses of statins *in vitro*, and in clinical trials there is little or no evidence of an early beneficial effect from moderate doses of statins.

CRP levels and outcomes

In PROVE IT-TIMI 22, the mean CRP level was reduced from 12 mg/L at study entry to 1.6 mg/L in the intensive therapy group and 2.3 mg/L in the moderate therapy group at day 30. Whether reduction of CRP levels affected long-term clinical outcomes was not known. The relationships between LDL-C and CRP levels achieved after treatment with intensive vs. moderate statin therapy and the risk of recurrent MI or CHD death were analyzed in a subsequent study [20]. Subjects who achieved both a low LDL-C (<70 mg/dl) and a low CRP (<2 mg/L) at 30 days had the lowest rates of CHD death and recurrent MI (Figure 6). An even greater benefit was observed amongst those who achieved a CRP <1 mg/L as well as LDL-C <70 mg/dl. Thus, LDL-C and CRP achieved at 30 days provided equal independent prognostic information, implying that a strategy aimed at achieving the dual goals of intensive LDL-C and CRP reduction is associated with a greater clinical benefit than strategies which reduce LDL-C alone. Although meeting these targets was more important in determining the outcomes than was the specific choice of therapy, patients were more likely to achieve dual goals if they were on intensive vs. moderate statin regimen (44 vs. 11%, p<0.001) [21].

A further analysis of PROVE IT assessed the relationship between uncontrolled cardiovascular risk factors and CRP level at four months after enrollment [22]. In a multivariate model, several risk

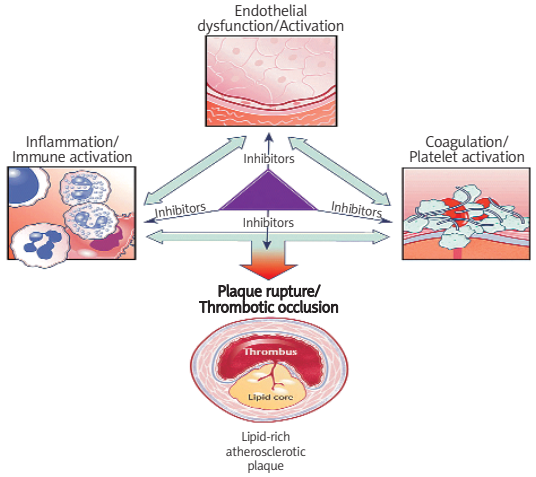

Figure 5. "Pleiotropic" effects of statins in acute coronary syndrome

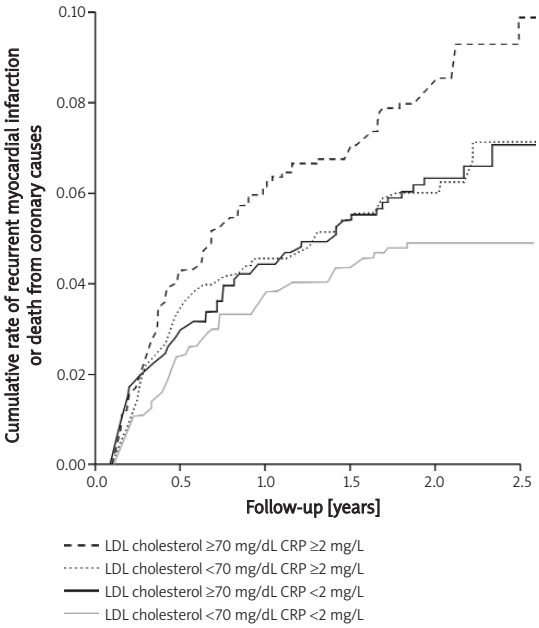

Figure 6. Cumulative incidence of recurrent myocardial infarction or death from coronary causes according to the achieved levels of both low density lipoprotein (LDL) cholesterol and C-reactive protein (CRP) in PROVE IT-TIMI 22.
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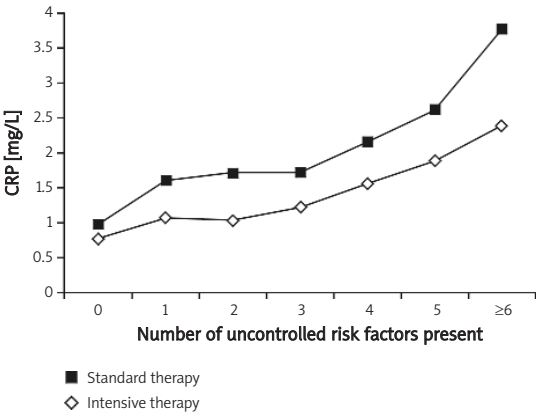


Figure 7. Relationship between the number of uncontrolled risk factors present and the median C-reactive protein (CRP) level for standard versus intensive statin therapy in PROVE IT-TIMI 22; p<0.0001 across the range of risk factors for each statin regimen.
Reprinted from Ray KK, et al. Relationship between uncontrolled risk factors and C-reactive protein levels in patients receiving standard or intensive statin therapy for acute coronary syndromes in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2005; 46: 1417-24. Copyright (2005), with permission from Elsevier

factors were weakly but independently associated with higher CRP levels: age, gender (with or without hormone replacement therapy), body mass index >25 kg/m^2, smoking, LDL-C ≥70 mg/dL, glucose >110 mg/dL, HDL-C <50 mg/dL, triglycerides >150 mg/dL, and the intensity of statin therapy. A direct relationship between the number of uncontrolled risk factors present and CRP levels (p<0.0001) was observed for both statin regimens. Among patients allocated standard therapy, CRP level was 3.8 mg/L (interquartile range [IQR]: 1.9, 7.8) when six to seven uncontrolled risk factors were present and 1.0 mg/L (IQR: 0.7, 2.1) when none were present, p<0.0001 for trend. Among patients allocated intensive therapy, the corresponding CRP levels were lower and ranged from 2.4 mg/L (IQR: 1.7, 5.7) to 0.8 mg/L (IQR: 0.4, 1.2), p<0.0001 for trend (Figure 7). Prior randomization to intensive statin therapy was associated with a lower CRP level (p<0.0001) independent of risk factors. Although the levels of both LDL-C and CRP were reduced by intensive statin therapy, the correlation between the achieved LDL-C and CRP was weak (r=0.16, p=0.001), suggesting independent effects of statins on lipids and inflammation.

Taken together, these data suggest that CRP level, as a marker of systemic inflammation, is an independent predictor of long-term cardiac risk. Intensive statin therapy reduces CRP levels and inflammation to a greater extent than moderate doses of statins. Beyond intensive statin therapy, better control of cardiovascular risk factors is a possible means to further reduce systemic inflammation. CRP may serve as a useful "global barometer" to monitor uncontrolled risk factors and guide further therapy.

Intensive statin therapy in stable CHD

The results of PROVE IT-TIMI 22 along with the analyses of the Heart Protection Study (HPS) led the National Cholesterol Education Program (NCEP) to add a new therapeutic recommendation of an "optional LDL-C goal" of <70 mg/dL in high-risk patients, including those with ACS. However, questions remained as to whether intensive statin therapy was safe over a longer period of time. The TNT and IDEAL trials addressed this issue by providing approximately 50,000 patient years of data on the safety of intensive statin therapy in addition to establishing its efficacy in subjects with stable CHD.

TNT

Treating to New Targets (TNT) was a randomized, double-blind trial that enrolled 10,001 patients with clinically evident CHD who had LDL-C levels of less than 130 mg/dL (3.4 mmol/L), and followed them for a median of 4.9 years [23]. Individuals qualified for the study if they had a previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic coronary disease, or had undergone coronary revascularization. All patients enrolled in the study were treated with 10 mg of atorvastatin for 8 weeks. After this open-label phase, patients were randomized to either 10 mg/day or 80 mg/day of atorvastatin. The primary endpoint was the occurrence of a first major cardiovascular event, defined as CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, and fatal or non-fatal stroke. During the open label phase, LDL-C fell from a mean of 152 mg/dL (3.9 mmol/L) to a mean of 98 mg/dL (2.6 mmol/L). It stayed at the same level in the 10 mg group and fell further by 21.4% to 77 mg/dL (2 mmol/L) in the 80 mg group. A primary event occurred in 8.7% of patients receiving 80 mg of atorvastatin and in 10.9% of patients receiving 10 mg of atorvastatin, representing a 2.2% absolute risk reduction and a 22% relative risk reduction (HR 0.78; CI 0.69-0.89; p<0.001). There was no difference between the two treatment groups in overall mortality. Overall, intensive therapy was safe, with a 1% higher absolute risk of elevations in liver transaminases.

IDEAL

The Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL) trial was an open-label trial that randomized 8888 patients (recruited months to years after the index MI) to

high-dose atorvastatin (80 mg/day) or usual-dose simvastatin (20 mg/day), and followed them for an average of 4.8 years [24]. The primary clinical outcome was the time to first occurrence of a major coronary event, defined as CHD death, hospitalization for nonfatal acute MI, or cardiac arrest with resuscitation. The mean LDL-C was 104 mg/dL in the simvastatin group and 81 mg/dL in the atorvastatin group. The primary outcome was reduced by 11% with atorvastatin compared with simvastatin but it did not reach statistical significance (HR 0.89; CI 0.78-1.01; p=0.07). Major cardiovascular events and any coronary event were significantly reduced by 13% (p=0.02) and 16% (p<0.001), respectively, in the atorvastatin 80 mg group. There were no differences in cardiovascular or all-cause mortality. A slightly higher number of patients stopped atorvastatin than simvastatin due to myalgia or gastrointestinal adverse events, but none of these adverse events were considered serious. Elevation in liver enzymes was also more common in the atorvastatin group but the proportion of patients was small (1%) and the elevations were transient.

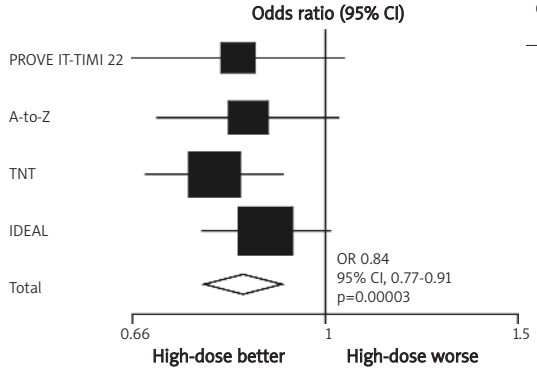
Meta-analysis of intensive versus standard statin therapy

The four trials of intensive vs. standard statin therapy discussed above (PROVE IT-TIMI 22, A to Z, TNT and IDEAL) all showed beneficial effects of intensive statin therapy but they used different endpoints to assess clinical outcomes and were each underpowered to assess the "historical" end point of CHD death or non-fatal MI. A meta-analysis of these four trials was conducted providing information on 27,548 patients and having approximately 120,000 years of patient follow-up data [25]. The primary endpoint was the composite of CHD death or non-fatal MI. The average pooled baseline LDL-C in the 4 trials was 130 mg/dL, which was reduced on average to 101 mg/dL with moderate statin therapy and to 75 mg/dL with intensive statin therapy. The combined analysis yielded a significant 16% reduction in the risk of CHD death or nonfatal MI with intensive statin therapy compared to standard therapy (OR 0.84; CI 0.77-0.91; p=0.00003) (Figure 8) as well as a significant 16% reduction in the risk of CHD death or any cardiovascular event (OR 0.84; CI 0.80-0.89; p<0.0001). No difference was observed in total or non-cardiovascular mortality but a trend toward decreased cardiovascular mortality (OR 0.88; p=0.054) was observed. Reductions were also observed for stroke (OR 0.82; CI 0.71-0.96; p=0.012).

The meta-analysis provided strong evidence for clinical benefit of early intensive statin therapy in ACS. Given the chronic lifelong nature of atherosclerosis, the 16% reduction observed in the rate of CHD death or nonfatal MI or any major cardiovascular event over 2-5 years might be expected to translate into greater absolute benefits throughout an individual's lifetime by prevention of recurrent adverse cardiovascular events.

Statins to prevent heart failure after ACS

While PROVE IT-TIMI 22 firmly established the benefit of intensive statin therapy in preventing recurrent ischemic events after ACS, its efficacy in preventing heart failure (HF) was not well defined. A further analysis of this trial examined the relationship between intensive statin therapy and the risk of hospitalization for HF after ACS [26]. Treatment with atorvastatin 80 mg significantly reduced the rate of hospitalization for HF compared to pravastatin 40 mg (1.6 vs. 3.1%; HR 0.55; CI 0.35 to 0.85; p=0.008) independently of a recurrent MI or prior history of HF. The risk of HF increased steadily with increasing quartiles of BNP (HR 2.6; CI 1.2 to 5.5; p=0.016 for the highest quartile compared with the lowest). Among patients with elevated levels of BNP (>80 pg/mL), treatment with atorvastatin significantly reduced the risk of HF



Odds reduction	Event rates No./Total (%) High dose	Std dose
–17%	147/2099 (7.0)	172/2063 (8.3)
–15%	205/2265 (9.1)	235/2232 (10.5)
–21%	334/4995 (6.7)	418/5006 (8.3)
–12%	411/4439 (9.3)	463/4449 (10.4)
–16%	1097/13798 (8.0)	1288/13750 (9.4)

Figure 8. Individual trials and pooled analysis showing a highly significant 16% reduction in the risk of coronary death or myocardial infarction (p<0.0001); CI – confidence interval, OR – odds ratio
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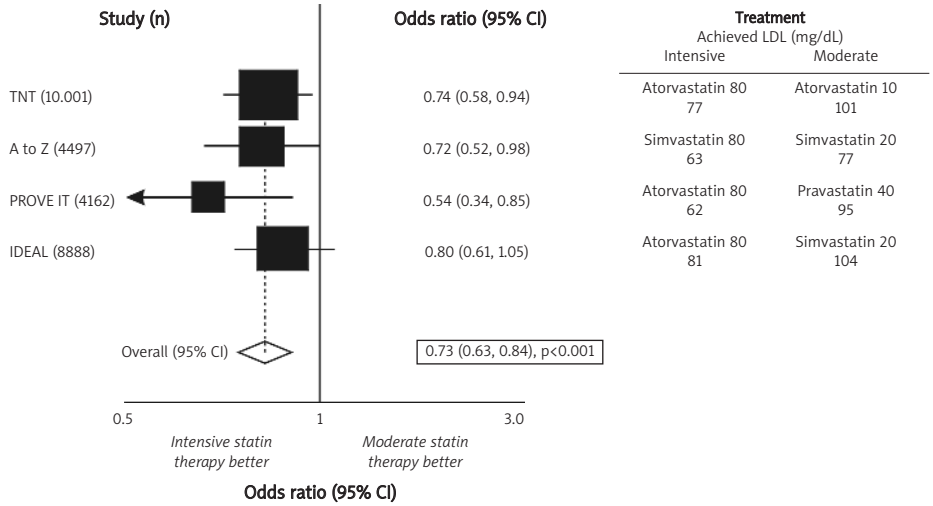

Figure 9. Benefit of intensive statin therapy versus moderate statin therapy in reducing the risk of hospitalization for heart failure in a meta-analysis of 27,546 patients
Reprinted from Scirica BM, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. J Am Coll Cardiol 2006; 47: 2326-31. Copyright (2006), with permission from Elsevier

compared with pravastatin (HR 0.32; CI 0.13 to 0.8; p=0.014). The TNT trial also found a significant decrease in the incidence of hospitalization for HF with intensive statin therapy (2.4% in the atorvastatin 80-mg arm vs. 3.3% in the atorvastatin 10-mg arm; HR 0.74; CI 0.59 to 0.94; p=0.0116) [27]. A meta-analysis of the four large randomized trials of intensive vs. moderate statin therapy (PROVE IT-TIMI 22, A to Z, TNT and IDEAL) demonstrated a 27% reduction in the odds of hospitalization for HF with intensive statin therapy (OR 0.73; CI 0.63 to 0.84; p<0.001) (Figure 9) [26]. The mechanisms responsible for the observed benefit in reduction of HF after ACS might be related to the "pleiotropic" actions of statins such as reduction of systemic inflammation, normalization of endothelial dysfunction, inhibition of neurohormonal activation, prevention of ventricular remodeling and anti-oxidant effects.

Efficacy and safety of achieving ultra-low LDL-C

Intensive statin therapy to reduce clinical events after ACS may result in LDL-C levels markedly below guideline recommendations. The efficacy and safety of achieving such ultra-low LDL-C levels was assessed by an analysis of the intensive arm of PROVE IT-TIMI 22, which examined the relationship between achieved LDL-C at 4 months with atorvastatin 80 mg and long-term risk of death or major cardiovascular event [28]. The patients were divided into subgroups by achieved 4 month LDL-C levels (>80-100, >60-80, >40-60, ≤40 mg/dL). Compared to the reference group (LDL-C 80-100 mg/dL), the multivariate adjusted hazard of death, MI, recurrent ischemia, revascularization and stroke was lower among patients with an LDL-C of >40-60 (HR 0.67; CI 0.50 to 0.92) and lowest among those with an LDL-C ≤40 mg/dL (HR 0.61; CI 0.40 to 0.91) (Figure 10). There were no significant differences in safety parameters, including muscle, liver, or retinal abnormalities, intracranial hemorrhage, or death, in the very low LDL-C groups. Similar findings were observed in a post-hoc analysis of TNT, with the risk of major cardiovascular events the least among subjects with the lowest quintile of LDL-C and increasing steadily across each successive quintile of achieved LDL-C (Figure 11) [29]. There was no observed excess of any side effects among subjects in the lowest LDL-C quintile compared to those with higher LDL-C quintiles. In another post-hoc analysis of TNT, HDL-C levels at 3 months were predictive of major cardiovascular events irrespective of LDL-C levels [30]. These data suggest that additional benefits might be seen if one can achieve so-called "physiological levels" of LDL-C (30-50 mg/dL), levels that are observed in nature in newborn and primates, who typically do not have atherosclerosis. The ongoing Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is comparing simvastatin 40 mg vs. ezetimibe/simvastatin combination 10 mg/40 mg to achieve a target LDL-C of approximately 65 vs. 50 mg/dL in stabilized high-risk ACS patients.

Intensive statin therapy in elderly patients with ACS

There are concerns about using high dose statins in elderly patients with ACS due to issues related to tolerability, safety and efficacy. An analysis of the

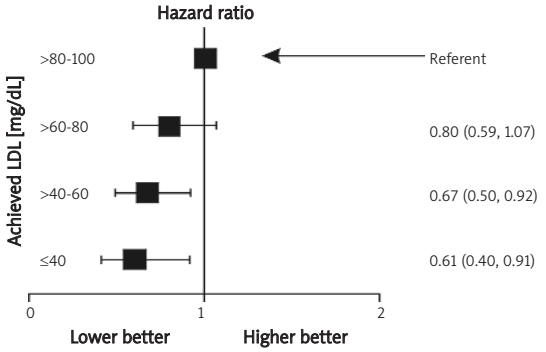

Figure 10. Level of low density lipoprotein cholesterol achieved at 4 months and the long-term risk of death or major cardiovascular event
Reprinted from Wiviott SD, et al. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. J Am Coll Cardiol 2005; 46: 1411-6. Copyright (2005), with permission from Elsevier

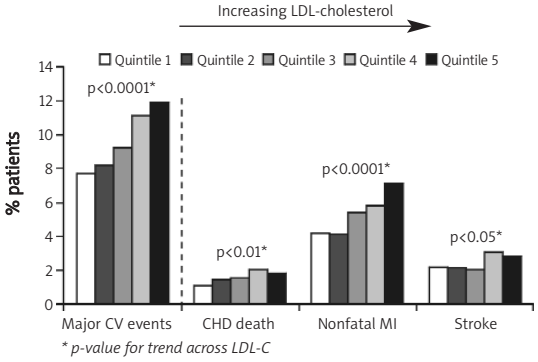

Figure 11. Risk of major cardiovascular events according to quintile of achieved low density lipoprotein (LDL) cholesterol in Treating to New Targets study
Reprinted from LaRosa JC, et al. Safety and efficacy of atorvastatin-induced very low-density lipoprotein cholesterol levels in patients with coronary heart disease (a post-hoc analysis of the Treating to New Targets [TNT] study). Am J Cardiol 2007; 100: 747-52. Copyright (2007), with permission from Elsevier

PROVE-IT-TIMI 22 trial assessed the efficacy and safety of achieving the NCEP LDL-C optional goal of <70 mg/dL (1.8 mmol/L) in elderly patients with ACS [31]. There were 634 elderly patients (≥70 years age) and 3150 younger patients (<70 years age) who remained free of events at 30 days (87 and 92% of each original group, respectively). Among elderly patients, the achievement of the LDL-C goal of <70 mg/dL at day 30 was associated with an 8% absolute and a 40% relative lower risk of events (HR 0.60; CI 0.41-0.87; p=0.008) vs. elderly patients who did not reach the goal. Among younger patients, the achievement of the LDL-C optional goal was associated with a 2.3% absolute and a 26% lower relative risk vs. younger patients who did not reach the goal (HR 0.74; CI 0.59-0.94; p=0.013). The incidence of major side effects among the elderly was similar to that in younger patients. Thus, among elderly ACS patients, achieving the NCEP LDL-C optional goal of <70 mg/dL as part of a secondary prevention strategy appears to be as safe and effective as in younger patients but with a greater absolute benefit since elderly patients are at higher risk.

Intensive statin therapy and atherosclerosis

The significant benefits of intensive statin therapy in reducing cardiovascular morbidity and mortality in patients with ACS as well as stable CHD sparked a series of trials which examined whether it was possible to halt or even reverse atherosclerosis disease burden with high dose statins. Results of these trials have shown that there is a direct relationship between LDL-C and the rate of progression of coronary atherosclerosis (Figure 12).

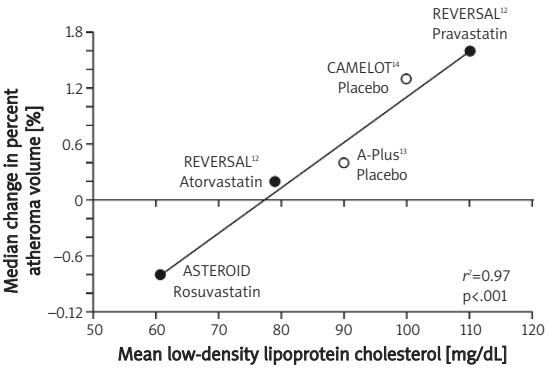

Figure 12. Recent coronary intravascular ultrasound trials (relationship between mean low density lipoprotein cholesterol level and progression rate of coronary atherosclerosis)
From Nissen SE, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295: 1556-65, with permission. Copyright © 2006, American Medical Association. All rights reserved

REVERSAL

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial randomized 654 patients with symptomatic coronary artery disease (20% or greater stenosis by angiography) to moderate (pravastatin 40 mg/day) or intensive (atorvastatin 80 mg/day) statin regimen and assessed progression of coronary atherosclerosis using intravascular ultrasound (IVUS) [32]. The primary efficacy parameter was the percentage change in atheroma volume (follow-up at 18 months minus baseline). Baseline LDL-C fell from 150.2 mg/dL in both treatment groups to 110 mg/dL in the pravastatin group and 79 mg/dL in

the atorvastatin group (p<0.001). CRP decreased by 5.2% with pravastatin and 36.4% with atorvastatin (p<0.001). The primary efficacy parameter showed a 2.7% increase in the pravastatin group (p=0.001) and a 0.4% reduction in the atorvastatin group (p=0.98), p=0.02 for difference between groups. Similar differences between groups were observed for secondary efficacy parameters, including change in total atheroma volume (p=0.02), change in percentage atheroma volume (p<0.001), and change in atheroma volume in the most severely diseased 10-mm vessel subsegment (p<0.01).

ASTEROID

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) was a single arm study designed to assess whether very intensive statin therapy could regress coronary atherosclerosis as determined by IVUS [33]. A series of 507 patients received intensive statin therapy with rosuvastatin 40 mg/day. A motorized IVUS pullback was used to assess coronary atheroma burden at baseline and after 24 months of treatment. The pre-specified primary efficacy parameters were the change in percent atheroma volume and the change in nominal atheroma volume in the 10-mm subsegment with the greatest disease severity at baseline. A secondary efficacy variable, change in total atheroma volume for the entire artery, was also pre-specified. The mean baseline LDL-C level of 130.4 mg/dL declined to 60.8 mg/dL, a mean reduction of 53.2% (p<0.001), while mean HDL-C level increased from 43.1 mg/dL at baseline to 49.0 mg/dL, an increase of 14.7% (p<0.001). The mean change in percent atheroma volume for the entire vessel was -0.98%, the mean change in atheroma volume in the most diseased 10-mm subsegment was -6.1 mm^3 and the mean change in total atheroma volume was -14.7 mm^3 (p<0.001 vs. baseline). Adverse events were infrequent and similar to other statin trials. The authors concluded that very high intensity statin therapy to reduce LDL-C levels below currently accepted guidelines, when accompanied by significant HDL-C increases, can regress atherosclerosis in coronary artery disease patients.

In conclusion, the efficacy and safety of statin therapy, especially intensive statin therapy, has been well established in ACS and such therapy should now be considered a standard part of ACS care. Intensive statin therapy beginning soon after ACS provides a rapid early reduction in clinical events the speed of which might be related to non LDL-C lowering "pleiotropic" effects which reduce inflammation. The long-term risk of death or major coronary event after ACS is related to the absolute level of LDL-C and CRP achieved with statin, leading to the mantra 'the lower the better'. It is possible to halt or even reverse atherosclerosis plaque burden with high dose statins. There are several ongoing trials of statins in ACS which will shed further light on mechanisms of action of statins and provide additional efficacy and safety data. Included are trials evaluating the combination of statins with drugs such as ezetimibe, nicotinic acid and fibrates. Beyond statin therapy, better control of cardiac risk factors is a possible means to further reduce systemic inflammation. Prospective trials are needed to establish the principle of targeting inflammation as a means of decreasing atherosclerosis and improving clinical outcomes.

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