



UNIVERSITÀ
DEGLI STUDI
FIRENZE

FLORE

Repository istituzionale dell'Università degli Studi di Firenze

Effect of atorvastatin on circulating hsCRP concentrations: a sub-study of the achieve cholesterol targets fast with atorvastatin

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

Effect of atorvastatin on circulating hsCRP concentrations: a sub-study of the achieve cholesterol targets fast with atorvastatin stratified titration (ACTFAST) study / G.F. Gensini; A.M. Gori; B. Di Laghi; C. Rostagno; A. Gaw; L.M. Blanco-Colio; E. De Teresa; J. Egido; C. Farsang; L.A. Leiter; P. Martineau; A. Nozza; A. Langer. - In: INTERNATIONAL JOURNAL OF CARDIOLOGY. - ISSN 0167-5273. - STAMPA. - 142:

Availability:

The webpage <https://hdl.handle.net/2158/393520> of the repository was last updated on 2018-02-28T18:15:52Z

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

Publisher copyright claim:

La data sopra indicata si riferisce all'ultimo aggiornamento della scheda del Repository FloRe - The above-mentioned date refers to the last update of the record in the Institutional Repository FloRe

(Article begins on next page)

Effect of atorvastatin on circulating hsCRP concentrations: A sub-study of the Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study[☆]

G.F. Gensini^{a,b}, A.M. Gori^{a,b}, B. Dilaghi^{a,b}, C. Rostagno^{a,b}, A. Gaw^c, L.M. Blanco-Colio^d,
E. de Teresa^{e,f}, J. Egido^d, C. Farsang^g, L.A. Leiter^{h,i}, P. Martineau^j,
A. Nozza^j, A. Langer^{h,i,k,*}
on behalf of the ACTFAST investigators

^a Department of Medical and Surgical Critical Care, University of Florence, Azienda Ospedaliero-Universitaria Careggi Hospital, Firenze, Italy

^b Department of Heart and Vessels, Azienda Ospedaliero-Universitaria Careggi Hospital, Firenze, Italy

^c University of Glasgow, Glasgow, UK

^d Vascular Research Laboratory, Fundación Jimenez Díaz, Autonoma University, Madrid, Spain

^e University of Malaga, Avda. Cervantes, 2, 29071 Málaga, Spain

^f V. de la Victoria Hospital, Malaga, Spain

^g 1st Department of Medicine, Semmelweis University, Budapest, Hungary

^h University of Toronto, Toronto, ON, Canada

ⁱ St-Michael's Hospital, Toronto, ON, Canada

^j Medical Division, Pfizer Canada, Kirkland, QC, Canada

^k Canadian Heart Research Centre, 438 University Avenue, Suite 300, Toronto, ON, Canada M5G-2P9

Received 18 May 2008; received in revised form 17 November 2008; accepted 30 December 2008

Available online 12 February 2009

Abstract

Background: Elevated C-reactive protein (CRP) concentration is a risk factor for cardiovascular events that may add prognostic information. Statin treatment is associated with significant reductions in CRP concentrations, which appear to be unrelated to the magnitude of LDL-cholesterol reduction. We investigated the effect of atorvastatin, across its dose range, on high sensitivity (hs)CRP in subjects at high cardiovascular risk.

Methods: ACTFAST was a 12 week, prospective, multicenter, open-label trial in which high-risk subjects were assigned a starting dose of atorvastatin (10, 20, 40 or 80 mg/d) based on LDL-C and status of statin use at screening (1345 statin-free [SF] and 772 previously statin-treated [ST]).

Results: At baseline, ST subjects had significantly lower hsCRP levels than SF subjects (ST group 2.31, 95% CI 2.15, 2.48 mg/L vs. SF group 3.16, 95% CI 2.98, 3.34 mg/L, $p < 0.05$). In the SF group, atorvastatin 10 to 80 mg significantly ($p < 0.01$) reduced hsCRP levels in a dose dependent-manner. In ST group, additional hsCRP reductions were observed over the statin used at baseline, which were not dose-dependent. Atorvastatin significantly decreased hsCRP concentrations in subjects with or without diabetes or the metabolic syndrome.

Conclusions: Atorvastatin treatment at different doses, particularly 80 mg, significantly reduced hsCRP serum concentrations. This reduction was observed in both SF and ST groups and was independent of the presence of metabolic syndrome and/or diabetes. The beneficial effect of atorvastatin was evident at 6 weeks, supporting the practice of early introduction of higher doses of atorvastatin in high-risk patients.

© 2009 Elsevier Ireland Ltd. All rights reserved.

Keywords: Dyslipidemia; Coronary artery disease; Statins; Atorvastatin; C-reactive protein (hsCRP)

[☆] www.clinicaltrials.gov identification number: ACTFAST 1 (NCT00442845) <http://www.clinicaltrials.gov/ct/search.jsessionid=EBE8171E2B-CE4E1CF769BACC6F067646?term=NCT00442845>.

* Corresponding author. Canadian Heart Research Centre, 438 University Avenue, Suite 300, Toronto, ON, Canada M5G-2P9. Tel.: +1 416 977 8010.

E-mail address: Langer@chrc.net (A. Langer).

1. Introduction

Evidence has accumulated on the role of inflammation in the pathogenesis of atherosclerosis [1,2]. Atherosclerosis, formerly considered a disease of lipid accumulation, is characterized by chronic low-grade vascular inflammation [3,4].

Despite progress in the prevention and treatment of cardiovascular disease, about half of all myocardial infarctions (MI) and strokes occur in individuals with so-called “normal” LDL cholesterol (LDL-C) levels [5]. Commonly used risk algorithms, such as the Framingham Risk Score, fail to identify all at-risk individuals, thus, the need for additional risk factors to improve identification and subsequent care of subjects at higher risk for coronary heart disease (CHD).

Acute phase reactant C-reactive protein (CRP) is a circulating pentraxin that plays a crucial role in the innate immune response and provides a stable plasma biomarker for low-grade systemic inflammation [6]. Although its role as a biomarker or a mediator of atherosclerosis is still debated, CRP actively contributes to all stages of atherogenesis, including endothelial dysfunction, atherosclerotic-plaque formation, maturation, destabilization and eventual rupture [1,7–9]. A high concentration of hsCRP has been shown to be a strong independent risk factor for cardiovascular events [1,2,10–12], thus, adding prognostic information to traditional risk factors.

In addition to their effects on LDL-C, statins have anti-inflammatory properties [13,14], as shown by significant reductions in hsCRP levels that appear to be unrelated to the magnitude of LDL-C reduction [15–18]. Statins are highly effective in reducing the risk of cardiovascular events in both primary and secondary prevention, to a degree that is greater than predicted on the basis of LDL-C lowering alone. This may be related to their anti-inflammatory actions. In the Cholesterol and Recurrent Events (CARE) and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the magnitude of risk reduction associated with statin therapy was higher among those with elevated hsCRP levels [19,20]. Furthermore, patients who had lower hsCRP levels after statin therapy had better clinical outcomes than those with higher levels [21,22].

The main ACTFAST study investigated the benefits of selecting the starting dose of atorvastatin based on baseline LDL-C and current CAD risk status [24]. As a sub-study to ACTFAST, we investigated the effect of atorvastatin 10, 20, 40 and 80 mg on circulating concentrations of hsCRP in subjects at high cardiovascular risk, including pre-specified subgroups of subjects with the metabolic syndrome or diabetes.

2. Methods

2.1. Study design

ACTFAST was a 12 week, prospective, multicenter, open-label trial that enrolled subjects (either statin-free [SF], never previously prescribed a statin or off therapy for at least 2 months; or statin-treated [ST] at baseline) with CHD, a CHD-equivalent (defined as diabetes, peripheral vascular disease or cerebrovascular disease) or a 10 year CHD risk >20% [23]. Subjects had

LDL-C >2.6 mmol/L and ≤5.7 mmol/L, triglycerides ≤6.8 mmol/L, and had to be willing to follow the NCEP III multifaceted lifestyle approach (or equivalent). The key exclusion criteria included: current use of atorvastatin or high dose (>40 mg/d) statin, use of other lipid lowering therapy (eg niacin, fibrates,...) that could not be discontinued 2 months prior to enrolment, or use of strong CYP3A4 inhibitors. Subjects were also excluded if they suffered from significant hepatic or renal impairment, uncontrolled diabetes, uncontrolled hypertension, uncontrolled primary hypothyroidism, clinically relevant gastrointestinal disease, elevation of creatine kinase (CK) level, alcohol or other drug abuse, or any severe disease or surgical procedure within 3 months of screening. A complete description of inclusion and exclusion criteria has been published elsewhere [24].

Diabetes was defined according to the 2003 American Diabetes Association criteria [26] and metabolic syndrome was defined according to the 2001 National Cholesterol Education Program (NCEP)-III [23].

The institutional review board of all participating centers approved the ACTFAST study protocol and all participants provided written informed consent. This study was conducted in compliance with the Declaration of Helsinki [25].

2.2. Treatment

One week after screening, subjects were assigned to 6 weeks of open-label treatment with atorvastatin according to their baseline LDL-C level and prior statin use, followed by an additional 6 weeks of treatment, during which subjects who had not reached LDL-C targets, were titrated to the next highest dose of atorvastatin if possible [24]. SF subjects with a baseline LDL-C of 100–149 mg/dL (2.6–3.8 mmol/L), 150–159 (3.9–4.1 mmol/L), 160–169 (4.2–4.4 mmol/L) and 170–220 mg/dL (4.5–5.7 mmol/L) were assigned to 10, 20, 40 and 80 mg of atorvastatin, respectively. Based on comparative potency with other statins, a decision was made that subjects who were on statin therapy at baseline but whose LDL-C remained above target would receive double the atorvastatin dose for the same baseline LDL-C level as compared to their untreated counterparts (up to a maximum of 80 mg), without any washout period [24]. Subjects initially allocated to atorvastatin 80 mg who did not reach LDL-C targets, were continued at that dose and a more intense therapeutic lifestyle intervention (NCEP III step 2 diet or equivalent) was recommended [23].

2.3. Laboratory determinations

All assays were performed by a central laboratory (Bio-Inova Life Sciences International, Paris and Montreal offices). Fasting venous blood samples were collected at baseline, and after 6 and 12 weeks of atorvastatin treatment for the measurement of plasma lipids, routine hematology and chemistry. Direct LDL-C measurement was performed, regardless of triglyceride levels.

Serum hsCRP was assessed using a high-sensitivity, latex microparticle-enhanced immunoturbidimetric assay (Tina-Quant; Roche Diagnostics GmbH) and measured in batches. The minimum detectable concentration of hsCRP was 0.03 mg/L. Intra-assay and inter-assay coefficients of variation of hsCRP assay were 1.34% and 5.70%, respectively. A single measurement was performed at every time point.

2.4. Statistical analysis

All analyses were performed using the SAS statistical package version 8.2. *P*-values less than 0.05 were considered statistically significant. Due to the skewed distribution of serum hsCRP levels, log-transformed values were used in the analyses, and back transformed for data presentation, yielding geometric means and 95% confidence intervals (CI). Computed values for the absolute and percent change in hsCRP concentrations over time for each study subject were not normally distributed. Thus, after logarithmic transformation, *t*-test for paired data was applied to evaluate the significance of any difference in hsCRP changes over time, both overall and within each group.

Table 1
Baseline characteristics according to statin group—intent-to-treat study population.

Characteristics	Statin-free N=1345	Statin-treated N=772	All subjects N=2117
Male (N, %)	877 (65.2)	552 (71.5)	1429 (67.5)
Caucasian (N, %)	1254 (93.2)	724 (93.8)	1978 (93.4)
Mean age (y) (mean±SD)	63.0±11.0	63.5±10.1	63.2±10.7
Weight (kg) (mean±SD)	82.3±16.9	80.5±14.7	81.6±16.1
Systolic/diastolic blood pressure (mean±SD)	136.7±16.3/ 79.4±10.0	133.4±16.9/ 76.9±10.1	135.5±16.6/ 78.5±10.1
Smoking (N, %)	308 (22.9)	146 (18.9)	454 (21.4)
Diabetes (N, %)	611 (45.4)*	217 (28.1)	828 (39.1)
CHD (N, %)	675 (50.2)*	625 (81.0)	1300 (61.4)
Metabolic syndrome (N, %)	667 (49.6)	315 (40.8)	982 (46.4)
Hypertension (N, %)	930 (69.1)	509 (65.9)	1439 (68.0)
Current statin used at baseline (N, %)	†Fibrates 11(0.8) Statins 3 (0.2) Resins 1 (0.1)	Fluvastatin 56 (7.3) Lovastatin 42 (5.4) Pravastatin 238 (30.8) Rosuvastatin 6 (0.8) Simvastatin 427 (55.3) Other LLT 10 (1.3)‡	
Total cholesterol (mmol/L) mean (sd)	5.8 (0.9)*	5.4 (0.8)	5.7 (0.8)
LDL-C (mmol/L) mean (sd)	3.9 (0.7)*	3.5 (0.6)	3.7 (0.7)
HDL-C (mmol/L) mean (sd)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)
Triglycerides (mmol/L) mean (sd)	1.9 (1.0)	1.9 (0.9)	1.9 (0.9)
hsCRP (mg/L) (mean, 95% CI)	3.16 (2.98–3.34)*	2.31 (2.15–2.48)	2.82 (2.69–2.94)

* $p<0.05$ vs. statin-treated.

†These subjects were not eligible since any LLT at baseline was prohibited in the statin-free group. However, they were retained in intention-to-treat analyses.

‡These 10 subjects were using other LLT (ezetimibe, fibrates, cholestyramine and niacin) at baseline and thus, were not eligible for the study. However, they were retained in intention-to-treat analyses.

LLT: lipid lowering therapy.

Differences in demographic, clinical and laboratory characteristics between SF and ST patients were determined using *t*-test for unpaired data after log-transformation of the skewed variables (i.e., hsCRP) or Chi-square test for categorical data. Correlation coefficients were computed to assess any association between hsCRP levels and various parameters. Furthermore, the correlations between the change in hsCRP observed over time and the change observed for other continuous variables were calculated by using Spearman's correlation analysis.

Data were analyzed on an intention-to-treat (ITT) and per-protocol basis, with last observation carried forward (LOCF) being used for missing data. The ITT population consisted of all subjects assigned a starting dose, who took at least one dose of study medication, and had at least one subsequent assessment. The per protocol population consisted of those ITT subjects who: completed the study as per protocol, were exempt of major protocol violations, were compliant with study treatment, had a baseline hs-CRP ≤ 10 mg/L, without acute infectious or inflammatory episode or acute trauma at the time of blood sampling, and who did not use any anti-inflammatory/immuno-modulating drugs during the study.

3. Results

The ITT population comprised 2117 subjects (686 on 10 mg (32.4%), 773 on 20 mg (36.5%), 234 on 40 mg (11.1%) and 424 on 80 mg (20.0%)). The proportions of subjects who completed the study were 94%, 95%, 94% and 90% for the 10, 20, 40 and 80 mg doses, respectively.

Participants were mainly Caucasians (93%) and male (68%), with a mean age of 63 years (Table 1). Overall, 21% were current smokers, 39% had diabetes (97.2% were type 2), and 61% had prior CHD. A lower prevalence of diabetes and higher prevalence of CHD was observed in the ST group. As expected from the dose assignment scheme based on LDL-C and statin use at baseline, the mean baseline TC and LDL-C differed significantly between the two groups (Table 1). In the ST group, baseline serum hsCRP was

significantly lower than in the SF group (ST group 2.31, 95%CI 2.15, 2.48 mg/L vs. SF group 3.16, 95% CI 2.98, 3.34 mg/L). Approximately 46% of the ITT population had baseline hsCRP circulating levels of ≥ 3 mg/L.

3.1. Effect of atorvastatin on hsCRP concentrations

In the SF group, the mean change from baseline in hsCRP level was significant ($p<0.0001$) for all doses (Fig. 1) (10 mg –20.8%, 95% CI –26.1%, –15.0%; 20 mg –28.0%, 95% CI –36.1%, –18.8%; 40 mg –23.1%, 95% CI –32.4%, –12.4%; 80 mg –33.6%, 95% CI –40.0%,

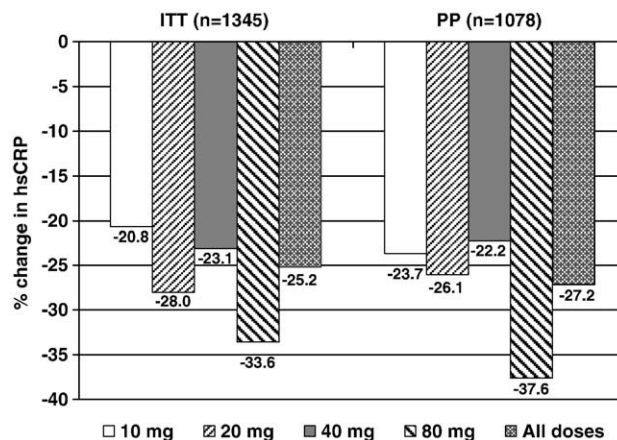


Fig. 1. Percent change from screening in hsCRP plasma levels in statin-free subjects. ITT, intention-to-treat; PP, per protocol. All $p<0.05$.

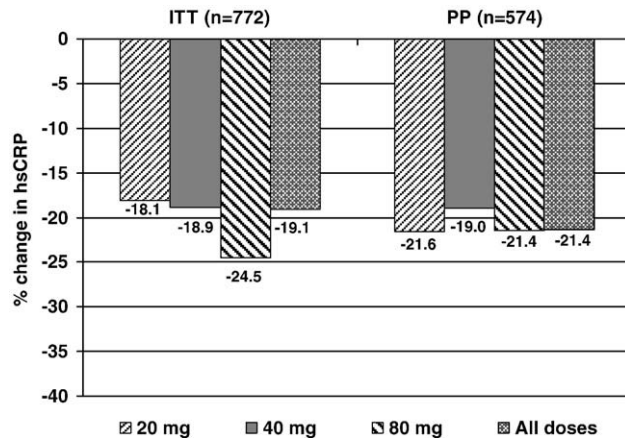


Fig. 2. Percent change from screening in hsCRP plasma levels in statin-treated subjects. ITT, intention-to-treat; PP, per protocol. All $p < 0.05$.

–26.5%). There was a statistically significant dose-response relationship at study end ($p < 0.05$). The per protocol analysis confirmed the ITT results. There were significant reductions in hsCRP compared to baseline at both 6 and 12 weeks of treatment ($p < 0.01$), with further reductions between week 6 and 12 with atorvastatin 20 mg (–13.28%, 95% CI –24.62%, –0.23%, $p < 0.05$) and 80 mg (–12.14%, 95% CI –20.38%, –3.04%; $p = 0.01$).

In the ST group, the mean percent change from baseline in hsCRP level was significant ($p < 0.05$) for all doses (20 mg: –18.1%, 95% CI –23.8%, –12.0%; 40 mg –18.9%, 95% CI –31.4%, –4.0%; 80 mg: –24.5%, 95% CI –36.7%, –9.9%), but was not dose-dependent (Fig. 2). Similar results were seen in the per protocol population. Reductions in hsCRP levels were significant after 6 weeks with atorvastatin 20 and 80 mg doses, and after 12 weeks with all doses. Further decreases in hsCRP between week 6 and 12 were observed with the 20 (–9.0%; 95% CI –15.0%, –2.5%, $p = 0.007$) and 40 mg (–20.7%, 95% CI –34.7%, –3.6%, $p = 0.02$) doses.

3.2. Effect of atorvastatin on hsCRP concentrations according to hsCRP subgroup

The ITT population was divided into two groups according to baseline hsCRP of < 3 or ≥ 3 mg/L. At baseline, 52.9% of 10 mg, 40.9% of 20 mg, 40.2% of 40 mg and 48.8% of 80 mg atorvastatin treated subjects had serum hsCRP levels ≥ 3 mg/L.

In SF group, there were significant reductions in hsCRP levels in subjects with baseline hsCRP levels ≥ 3 mg/mL, but not in those with levels < 3 mg/L, with the 10 to 40 mg doses compared to baseline, and in both hsCRP subgroups with the 80 mg dose (Table 2). In ST subjects, there were significant reductions in hsCRP concentrations when baseline was ≥ 3 mg/L with the 20 and 80 mg doses (Table 3).

Table 2

Change from screening in hsCRP, according to baseline hsCRP category in statin-free group—intent-to-treat population.

Dose	Baseline hsCRP	N	Change (%)	95% CI	p-value
10 mg	< 3 mg/L	323	–0.28	–8.76, 8.99	0.9509
	≥ 3 mg/L	363	–35.41	–41.70, –28.45	< 0.0001
20 mg	< 3 mg/L	89	–9.19	–23.45, 7.72	0.265
	≥ 3 mg/L	95	–42.04	–50.50, –32.13	< 0.0001
40 mg	< 3 mg/L	89	–8.6	–22.25, 7.44	0.272
	≥ 3 mg/L	71	–37.99	–49.42, –23.98	< 0.0001
80 mg	< 3 mg/L	153	–13.93	–25.65, –0.37	0.0446
	≥ 3 mg/L	162	–47.96	–54.39, –40.63	< 0.0001
All doses	< 3 mg/L	654	–6.0	–11.82, 0.21	0.0578
	≥ 3 mg/L	691	–39.76	–43.77, –35.47	< 0.0001

Table 3

Change from screening in hsCRP, according to baseline hsCRP category in statin-treated group—intent-to-treat population.

Dose	Baseline hsCRP	N	Change (%)	95% CI	p-value
20 mg	< 3 mg/L	368	–1.64	–9.23, 6.59	0.6859
	≥ 3 mg/L	221	–39.57	–46.84, –31.32	< 0.0001
40 mg	< 3 mg/L	51	–15.13	–28.41, 0.60	0.0583
	≥ 3 mg/L	23	–26.57	–51.20, 10.50	0.1314
80 mg	< 3 mg/L	64	–4.28	–25.30, 22.67	0.726
	≥ 3 mg/L	45	–46.09	–56.42, –33.30	< 0.0001
All doses	< 3 mg/L	483	–3.51	–10.15, 3.63	0.3257
	≥ 3 mg/L	289	–39.71	–45.86, –32.86	< 0.0001

3.3. Effect of atorvastatin on hsCRP concentrations according to metabolic syndrome status

In the SF group, baseline hsCRP levels were significantly higher in subjects with documented metabolic syndrome (defined according to the National Cholesterol Education Program (NCEP)-III [23], $n = 667$) than in those without ($n = 674$) (3.97, 95% CI 3.67, 4.28 mg/L vs. 2.52, 95% CI 2.33, 2.72 mg/L, $p < 0.0001$). Atorvastatin significantly decreased hsCRP levels in both subjects with and without metabolic syndrome (Fig. 3a).

In the ST group, subjects with metabolic syndrome ($n = 315$) also had significantly higher hsCRP levels at baseline (3.0, 95% CI 2.66, 3.37 mg/L)

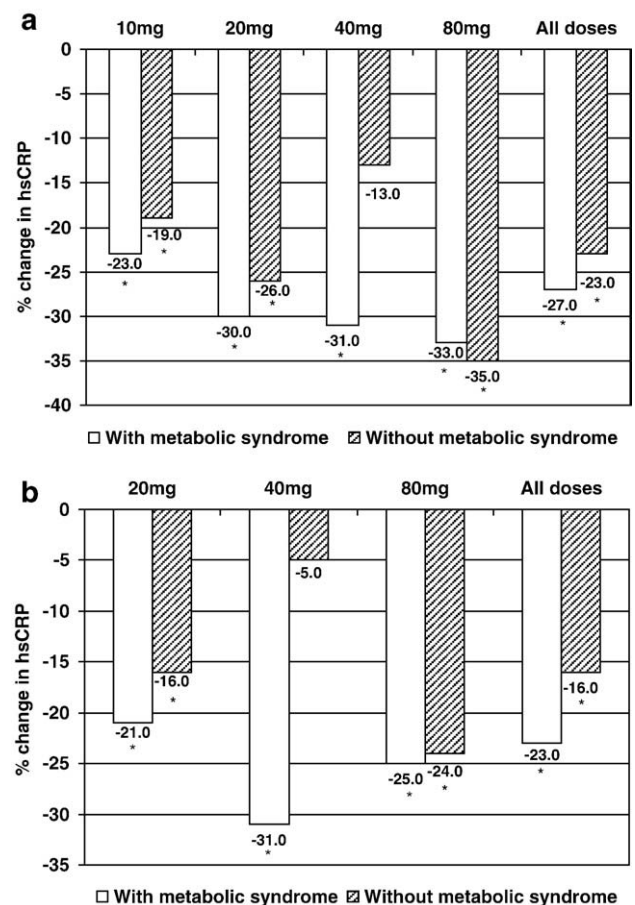


Fig. 3. a: Percent change from screening in hsCRP plasma levels in statin-free subjects with and without metabolic syndrome. $*p < 0.05$. b: Percent change from screening in hsCRP plasma levels in statin-treated subjects with and without metabolic syndrome. $*p < 0.05$.

than those without ($n=452$) (1.91, 95% CI 1.75, 2.08 mg/L, $p<0.0001$). Just as in the SF group, atorvastatin significantly reduced hsCRP concentrations, regardless of presence or absence of metabolic syndrome (Fig. 3b).

3.4. Effect of atorvastatin on hsCRP concentrations according to diabetes status

In the SF group, baseline hsCRP concentrations were not significantly different between subjects with diabetes (defined according to the American Diabetes Association [26], $n=611$) or without ($n=734$) (3.29, 95% CI 3.02, 3.59 mg/L vs. 3.05, 95% CI 2.83, 3.28 mg/L, $p=0.18$). Atorvastatin significantly decreased hsCRP levels in both subjects with and without diabetes (Fig. 4a).

Similarly, in the ST group, there were no differences in baseline hsCRP levels in subjects with ($n=217$) (2.41, 95% CI 2.10, 2.78 mg/L) or without diabetes ($n=555$) (2.27, 95% CI 2.09, 2.46 mg/L, $p=0.44$). The mean percent change in hsCRP from baseline was similar in subjects with or without diabetes (Fig. 4b).

3.5. Correlations with baseline hsCRP levels

In the overall study population, there were low, but significant ($p<0.0001$) correlations between baseline hsCRP levels and body weight, BMI, waist circumference and systolic blood pressure ($r=0.19$, $r=0.28$, $r=0.27$, $r=0.085$ respectively), but not with diastolic blood pressure ($p=0.14$). At study end, there were no significant correlations between

change in hsCRP and body weight ($r=-0.023$, $p=0.28$), BMI ($r=-0.023$, $p=0.28$), systolic and diastolic blood pressure ($r=0.042$ and 0.043 , respectively; $p=0.05$ for both).

There were small, but statistically significant correlations between change in hsCRP levels and change in LDL-C ($r^2=0.0117$, $p<0.0001$) or total cholesterol concentrations ($r^2=0.0105$, $p<0.0001$), but none of these were considered clinically significant.

Atorvastatin was well tolerated. Detailed safety results have been reported elsewhere [24].

4. Discussion

These results demonstrate that treatment with atorvastatin across its dose range, and particularly 80 mg, can effectively reduce circulating hsCRP serum concentrations. Reductions are observed in both patients who were statin free and those who were previously treated with a statin, and are independent of the presence of metabolic syndrome and diabetes. In ST subjects, additional reductions in hsCRP were achieved over what was obtained with the prior statin. The greatest reductions in hsCRP were observed in subjects with elevated serum hsCRP levels (≥ 3 mg/L) at baseline, suggesting that atorvastatin treatment, especially at the 80 mg dose, may be particularly effective in high risk subjects with chronic low-grade inflammation.

These results support the concept that the beneficial effects of statins may be mediated, in part, by anti-inflammatory effects. HsCRP is an independent risk factor for atherosclerotic disease [1,2,10–12]. Large randomized trials have demonstrated that statins significantly reduce the risk of MI and cardiovascular mortality [27–31], with a magnitude that is greater than expected based on LDL-C reduction alone. In addition, meta-analyses suggest that statins may reduce the risk of stroke to a greater extent than expected based on cholesterol lowering, and more than non-statin lipid lowering therapy [32–34]. This suggests that other factors, such as statin-induced hsCRP reduction, may have a role to play in reducing cardiovascular events.

In this study, 12 weeks of atorvastatin 80 mg therapy was associated with 34% and 24% (SF and ST, respectively) reductions in hsCRP levels, which were greater than those observed in studies with other statins [15,19,21,22,35–39]. Intensive dosing of atorvastatin helps to attenuate the inflammatory response present in high-risk patients [18,40]. Because the circulating levels of inflammatory markers are closely linked to cardiovascular outcomes, these results may explain the incremental beneficial effects of atorvastatin over less potent statins. This is supported by the REVERSAL trial [22], where intensive therapy with atorvastatin 80 mg slowed the progression of atherosclerosis more than moderate therapy with pravastatin 40 mg, and after adjustment for the reduction in lipid levels, the decrease in hsCRP levels was independently and significantly correlated with the rate of disease progression [22].

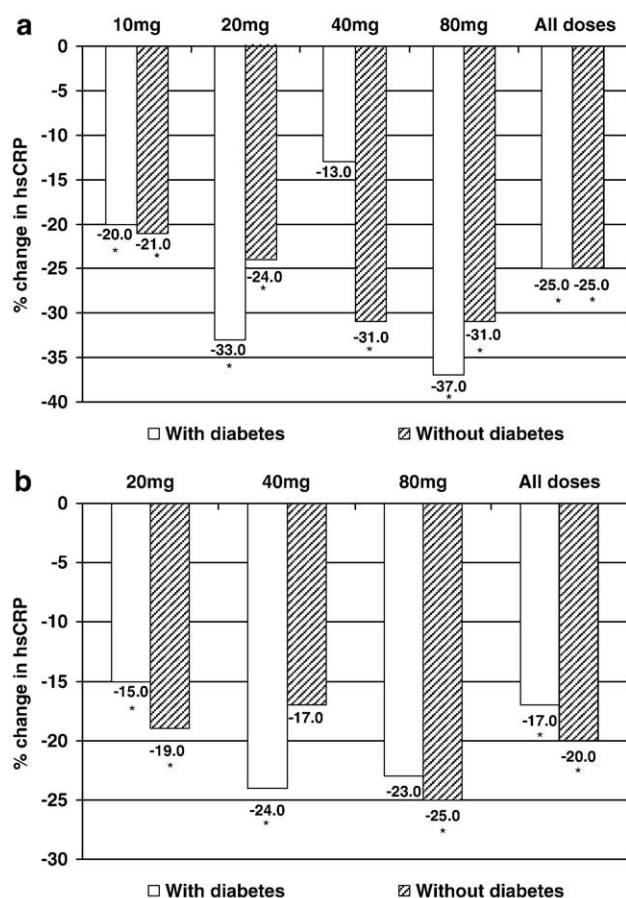


Fig. 4. a: Percent change from screening in hsCRP plasma levels in statin-free subjects with and without diabetes. * $p<0.05$. b: % Percent change from screening in hsCRP plasma levels in statin-treated subjects with and without diabetes. * $p<0.05$.

In ACTFAST, high-dose atorvastatin (80 mg) was associated with greater reductions in serum hsCRP levels than lower doses. Other studies in patients with stable coronary disease, acute coronary syndromes, or diabetes have also reported greater reductions in hsCRP with higher compared to lower doses of statins [16,38–40]. However, even the lowest dose, atorvastatin 10 mg was associated with significant reductions in hsCRP levels (SF group 18% (6 weeks) and 21% (12 weeks)). This is consistent with studies in patients with acute coronary syndromes [17], and hyperlipidemia [15,41]. Considering that dose groups were of unequal size, the study may have lacked power to find a difference between individual dosing groups, especially for the smallest one (e.g. 40 mg). However, when testing across the whole dose range, a significant dose-response relationship was evident.

In our study, a further significant decrease in hsCRP levels was observed from 6 to 12 weeks with most doses of atorvastatin in both SF (20, 80 mg) and ST (20, 40 mg) groups. In contrast, the SWiss Intervention Trial for lowering CHolesterol (SWITCH) study showed a significant decrease in hsCRP levels within the first 4 weeks and no further decrease at 12 weeks with atorvastatin 10 mg [42]. However, in the Comparative Atorvastatin Pleiotropic effects (CAP) study, atorvastatin 80 mg provided additional reductions in hsCRP concentrations when administered for 6 months (vs. 5 weeks), whereas a plateau was reached after 5 weeks with the 10 mg dose [18]. This suggests that optimum benefits of the highest dose (80 mg) may be achieved when treatment is continued for at least 6 months.

In the overall group, the percentage of patients with hsCRP ≥ 3 mg/L was relatively large (about 46%) compared with other populations [16]. We observed significant reductions in hsCRP levels at all doses in subjects with baseline hsCRP levels ≥ 3 mg/L, but only with the 80 mg dose in subjects with hsCRP levels < 3 mg/L. This suggests that a significant inhibitory effect of atorvastatin treatment takes place when high levels of inflammatory markers are present, but that high dose therapy may decrease inflammation, regardless of baseline level. This is consistent with previous results obtained with atorvastatin and other statins [17,19,42].

In ACTFAST, there were significant additional reductions of serum hsCRP levels in ST subjects over what was achieved with the previous statin used at baseline. This was most evident in subjects with high hsCRP levels (≥ 3 mg/L), emphasizing the capacity of higher starting doses of atorvastatin to reduce the inflammatory state in subjects in whom LDL-C levels remained above target despite the use of another statin.

Significant reductions in hsCRP were seen regardless of the presence of diabetes or metabolic syndrome. Significant reduction of hsCRP with pravastatin 40 mg have been shown to be independent of diabetes, cardiovascular disease, smoking, aspirin use, hormone replacement therapy (HRT) use, and lipid levels [19,43]. SF patients

with diabetes experienced reductions in hsCRP of 20% and 37% with atorvastatin 10 and 80 mg, respectively. This was similar to results of the Diabetes Atorvastatin Lipid Intervention (DALI) study [16], in which 197 patients with type 2 diabetes experienced reductions in hsCRP levels of 14.6% and 46.7% with 10 mg or 80 mg of atorvastatin.

As shown in other studies [2,19,21,44,45], the statin-mediated changes in hsCRP in ACTFAST were independent of LDL-C or total cholesterol changes. This strongly suggests that the statin-mediated reduction in hsCRP is unlikely to be a consequence of the reduction in LDL-C alone but, rather, is potentially mediated by independent pathways.

Limitations of our study must be considered: the trial was not blinded and the dosing groups (especially the 40 mg) were of unequal sizes. The study lacked a control group, due to ethical considerations. However, it is unlikely that reduction of hsCRP was due to chance or to the improvement of disease, since CHD is a chronic progressive disease and more than 68% of patients displayed a decrease in hsCRP compared to baseline. A single hsCRP sample was taken at each time point while the mean of two samples taken 2 weeks apart would have been preferable to account for variability in measurements [46]. Also, this study was not designed nor powered to investigate the impact of lowering hsCRP concentrations on the incidence of cardiovascular events, especially considering its short (12 weeks) follow-up period. Despite all the evidence behind the use of hsCRP for CHD risk stratification, studies are ongoing to determine if hsCRP should be used to guide therapy and what patient populations are most likely to benefit.

5. Conclusions

Elevated serum hsCRP concentrations provide a useful marker for cardiovascular risk which, when combined with traditional risk factors, may help improve global risk prediction. The reduction in hsCRP levels with statin therapy may explain the clinical benefits of statins, an effect that was shown to be independent of LDL-C and TC lowering in ACTFAST. In addition to effective LDL-C reduction, selecting a starting dose of atorvastatin tailored according to the required level of LDL-C reduction and status of statin use at baseline can help subjects at high risk achieve significant reduction of hsCRP concentrations. In ST subjects, such a regimen provided additional 18–24% reductions in hsCRP over what was attained with the current statin used at baseline. Our data provide strong evidence supporting the anti-inflammatory effects of atorvastatin, particularly the 80 mg dose. This effect is evident as early as 6 weeks and further supports the practice of introducing higher doses of atorvastatin early in the management of patients at high risk for coronary artery disease.

Acknowledgements

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [47].

References

- [1] Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. *Circ Res* 2001;89:763–71.
- [2] Libby P, Ridker PM. Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. *Am J Med* 2004;116(Suppl 6A):9S–16S.
- [3] Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol* 2005;46:937–54.
- [4] Viles-Gonzalez JF, Fuster V, Badimon JJ. Atherothrombosis: a widespread disease with unpredictable and life-threatening consequences. *Eur Heart J* 2004;25:1197–207.
- [5] Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997;337:1360–9.
- [6] Du Clos TW. Function of C-reactive protein. *Ann Med* 2000;32:274–8.
- [7] Verma S, Kuliszewski MA, Li SH, et al. C-reactive protein attenuates endothelial progenitor cell survival, differentiation, and function: further evidence of a mechanistic link between C-reactive protein and cardiovascular disease. *Circulation* 2004;109:2058–67.
- [8] Verma S, Li S, Badiwala M, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. *Circulation* 2002;105:1890–6.
- [9] Liang YJ, Shyu KG, Wang BW, Lai LP. C-reactive protein activates the nuclear factor-kappaB pathway and induces vascular cell adhesion molecule-1 expression through CD32 in human umbilical vein endothelial cells and aortic endothelial cells. *J Mol Cell Cardiol* 2006;40:412–20.
- [10] Schlager O, Exner M, Mlekusch W, et al. C-reactive protein predicts future cardiovascular events in patients with carotid stenosis. *Stroke* 2007;38:1263–8.
- [11] Sabatine MS, Morrow DA, Jablonski KA, et al. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. *Circulation* 2007;115:1528–36.
- [12] Everett BM, Kurth T, Buring JE, Ridker PM. The relative strength of C-reactive protein and lipid levels as determinants of ischemic stroke compared with coronary heart disease in women. *J Am Coll Cardiol* 2006;48:2235–42.
- [13] Wierzbicki AS, Poston R, Ferro A. The lipid and non-lipid effects of statins. *Pharmacol Ther* 2003;99:95–112.
- [14] Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 2004;109:III39–43.
- [15] Jialal I, Stein D, Balis D, et al. Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation* 2001;103:1933–5.
- [16] van de Ree MA, Huisman MV, Princen HM, Meinders AE, Kluft C. Strong decrease of high sensitivity C-reactive protein with high-dose atorvastatin in patients with type 2 diabetes mellitus. *Atherosclerosis* 2003;166:129–35.
- [17] Macin SM, Perna ER, Farias EF, et al. Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome: results of a randomized, double-blind, placebo-controlled study. *Am Heart J* 2005;149:451–7.
- [18] Bonnet J, McPherson R, Tedgui A, et al. Comparative effects of 10-mg versus 80-mg atorvastatin on high-sensitivity C-reactive protein in patients with stable coronary artery disease: Results of the CAP (Comparative Atorvastatin Pleiotropic Effects) study. *Clin Ther* 2008;30(12):2298–313.
- [19] Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) investigators. *Circulation* 1999;100:230–5.
- [20] Ridker P, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344:1959–65.
- [21] Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20–8.
- [22] Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005;352:29–38.
- [23] Executive summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–97.
- [24] Martineau P, Gaw A, de Teresa E, et al. Effect of individualizing starting doses of a statin according to baseline LDL-cholesterol levels on achieving cholesterol targets: The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study. *Atherosclerosis* 2007;191:135–46.
- [25] World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Int Bioethique* 2004;15:124–9.
- [26] Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003;26(Suppl 1):S5–S20.
- [27] Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1997;96:4211–8.
- [28] Flaker GC, Warnica JW, Sacks FM, et al. Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. Cholesterol and Recurrent Events (CARE) investigators. *J Am Coll Cardiol* 1999;34:106–12.
- [29] Pyorala K, Ballantyne CM, Gumbiner B, et al. Reduction of cardiovascular events by simvastatin in nondiabetic coronary heart disease patients with and without the metabolic syndrome: subgroup analyses of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 2004;27:1735–40.
- [30] Cannon C, Braunwald E, McCabe C, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–504.
- [31] Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–96.
- [32] Corvol JC, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomised trials. *Arch Intern Med* 2003;163:669–76.
- [33] Briel M, Studer M, Glass TR, Bucher HC. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* 2004;117:596–606.
- [34] Amarenco P, Labreuche J, Lavalley P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004;35:2902–9.
- [35] van Wissen S, Trip MD, Smilde TJ, et al. Differential hs-CRP reduction in patients with familial hypercholesterolemia treated with aggressive or conventional statin therapy. *Atherosclerosis* 2002;165:361–6.
- [36] Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 2004;110:3512–7.

- [37] Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Taylor AJ. Effect of atorvastatin and pravastatin on serum C-reactive protein. *Am Heart J* 2003;145:e8.
- [38] Taylor AJ, Kent SM, Flaherty PJ, et al. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002;106:2055–60.
- [39] Kinlay S, Timms T, Clark M, et al. Comparison of effect of intensive lipid lowering with atorvastatin to less intensive lowering with lovastatin on C-reactive protein in patients with stable angina pectoris and inducible myocardial ischemia. *Am J Cardiol* 2002;89:1205–7.
- [40] Ordulu E, Erdogan O. Early effects of low versus high dose atorvastatin treatment on coagulation and inflammation parameters in patients with acute coronary syndromes. *Int J Cardiol* 2008;128:282–4.
- [41] Sugiyama M, Ohashi M, Takase H, et al. Effects of atorvastatin on inflammation and oxidative stress. *Heart Vessels* 2005;20:133–6.
- [42] Riesen WF, Engler H, Risch M, Korte W, Nosedá G. Short-term effects of atorvastatin on C-reactive protein. *Eur Heart J* 2002;23:794–9.
- [43] Albert M, Danielson E, Rifai N, Ridker P. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001;286:64–70.
- [44] Kinlay S, Schwartz G, Olsson A, et al. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation* 2003;108:1560–6.
- [45] Correia LC, Sposito AC, Passos LC, et al. Short-term effect of atorvastatin (80 mg) on plasma lipids of patients with unstable angina pectoris or non-Q-wave acute myocardial infarction. *Am J Cardiol* 2002;90:162–4.
- [46] Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511.
- [47] Coats AJ. Ethical authorship and publishing. *Int J Cardiol* 2009;131:149–50.