CMRO

Current Medical Research & Opinion Vol. 26, No. 6, 2010, 1277–1284

0300-7995
doi:10.1185/03007991003751496

Article 5210/475671

Original article

Full-dose atorvastatin versus conventional medical therapy after non-ST-elevation acute myocardial infarction in patients with advanced non-revascularisable coronary artery disease

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Key words:
Atorvastatin – Acute coronary syndrome – Advanced coronary artery disease

Accepted: 5 March 2010; published online: 31 March 2010
Citation: Curr Med Res Opin 2010; 26:1277–84

Abstract

Aims:
This study tested the hypothesis that the addition of full-dose atorvastatin (80 mg/day) to conventional medical treatment could reduce ischaemic recurrences after non-ST-elevation acute myocardial infarction (NSTE-AMI) in patients with severe and diffuse coronary artery disease (CAD) not amenable to any form of mechanical revascularisation.

Methods and results:
The study was an open-label, randomised, controlled, blinded end-point classification trial, employing the PROBE (Prospective Open Treatment and Blinded End Point Evaluation) design. A total of 290 patients (mean age 74.6 ± 9.6 years) with NSTE-AMI and angiographic evidence of severe and diffuse CAD, not amenable to revascularisation by either coronary surgery or angioplasty, were randomised to atorvastatin 80 mg/day ($n = 144$) or conventional medical treatment ($n = 146$). A primary end point event (combination of cardiovascular death, non-fatal acute myocardial reinfarction and disabling stroke within 12 months of randomisation) occurred in 16.0% of patients treated with atorvastatin 80 mg/day and in 26.7% of patients receiving conventional treatment (HR 0.56; 95% CI 0.33–0.93, $p = 0.027$).

The study was not blinded. Consequently, a bias in the assessment of clinical outcome cannot be completely excluded.

Conclusions:
In conclusion, when compared with a conventional treatment strategy, full-dose therapy with atorvastatin 80 mg/day provides greater protection against ischaemic recurrences after NSTE-AMI in patients with severe, diffuse, non-revascularisable CAD.

Introduction

In recent years, therapeutic options for the management of coronary artery disease (CAD) have progressively improved. In particular, the increase of scientific knowledge on the underlying causes and mechanisms of myocardial ischaemia has led to a rational therapeutic approach, including both pharmacological and revascularisation therapies[1]. Despite all of these advances, the practising physician increasingly faces patients with chronic advanced CAD, which is often refractory to medical therapy and not amenable to any form of direct mechanical revascularisation[2]. These subjects usually show a high short-term cardiac morbidity and a severe impairment in their quality of life[2,3]. In fact, the syndrome is

usually characterised by a high recurrence of cardiac and vascular events, resulting in frequent hospital admissions and permanent disability. In order to improve both the long-term prognosis and the quality of life of this increasing subset of patients with end-stage no-option CAD, several evolving therapeutic approaches have been proposed, including enhanced external counterpulsation, therapeutic angiogenesis, neurostimulation, and transmyocardial laser revascularisation[2,3].

Statin therapy reduces cardiovascular morbidity and mortality in patients with established CAD[4]. Furthermore, two recent small trials have shown that intensive statin therapy with atorvastatin 80 mg/day may actually improve the clinical outcome of patients with chronic advanced CAD that is not amenable to traditional revascularisation treatments[5,6].

Accordingly, this clinical investigation was designed and undertaken to test the hypothesis that the addition of full-dose atorvastatin (80 mg/day) to conventional medical treatment could prevent major cardiovascular events in patients with advanced, non-revascularisable CAD after an acute coronary syndrome.

Methods

Study population

Consecutive patients admitted to four Italian cardiovascular institutions between September 2003 and February 2007 for non-ST-segment elevation acute myocardial infarction[7] were prospectively screened for inclusion in the study (see the Acknowledgements section for the list of institutions). Only patients undergoing early coronary angiography within 48 hours from admission were considered for inclusion in the study. To be enrolled in the trial, patients were required to show angiographic evidence of severe and diffuse coronary artery disease, which was not amenable to conventional direct revascularisation techniques by either coronary artery by-pass graft surgery (CABG) or percutaneous coronary intervention (PCI), as jointly determined by both a cardiac surgeon and an interventional cardiologist during the index admission. Exclusion criteria were ST-segment elevation acute myocardial infarction, clinical history of heart failure and of any clinical evidence of heart failure during the index admission, left ventricular ejection fraction <35%, any form of severe valvular dysfunction, previous implantation or indication to implant a cardioverter-defibrillator during the index admission, any increase in liver enzymes, history of any liver or muscle disease, renal failure with serum creatinine >2.5 mg/dL (221 μmol/L), need for continued use of intravenous medications to relieve anginal symptoms, and presence of any major comorbidity with life expectancy <24 months.

Study design

The study was planned as a prospective, randomised, controlled, open-label, blinded end-point classification trial, employing the PROBE (Prospective Open Treatment and Blinded End Point Evaluation) design[8].

The main goal of the study was to compare the effects of full-dose atorvastatin (80 mg/day) with the conventional approach, including adherence with current guidelines for cholesterol reduction[9], in the prevention of major adverse cardiovascular events after an acute coronary syndrome in patients with advanced, severe, non-revascularisable CAD.

During the index admission, all patients received standard medical treatments in accordance with current clinical guidelines[1]. In addition, immediately after completion of the angiographic procedure and exclusion of any option for conventional revascularisation, patients were assigned to one of the two study arms according to a computer-generated randomisation list.

Group 1 conventional medical treatment: For patients randomised to this arm, adherence to the National Cholesterol Education Program, Adult Treatment Panel III guidelines was required[9]. In particular, in these patients, atorvastatin was started at the initial dosage of 20 mg/day immediately after randomisation. Subsequently, atorvastatin dosage was titrated in order to attain low-density lipoprotein cholesterol (LDL-C) levels <100 mg/dL (2.5 mmol/L).

Group 2 conventional medical treatment plus atorvastatin in the fixed dose of 80 mg/day: For patients randomised to this arm, atorvastatin in the fixed dose of 80 mg/day was started immediately after randomisation.

During follow-up, patient adherence to statin therapy in both groups was assessed by pill counting.

Patients who dropped out owing to intolerable side-effects, adverse reactions, lack of adequate response to treatment or any other reason were taken as complete cases for the intention-to-treat analysis.

The study protocol is shown in Figure 1 and conformed to good clinical practice for trials and to the Declaration of Helsinki on medical research in humans. Approval of the local ethics committees of the participating centres before the beginning of the trial was obtained. All patients were required to give informed written consent. The study was independently conceived, conducted, and analysed under the responsibility of the Steering Committee.

Follow-up and outcome measures

Clinical monitoring for major adverse cardiovascular events for 12 months after randomisation was planned.

A control for LDL-C levels was performed in all patients 7, 14, 30, 90, 180 and 360 days after randomisation. In patients randomised to conventional medical

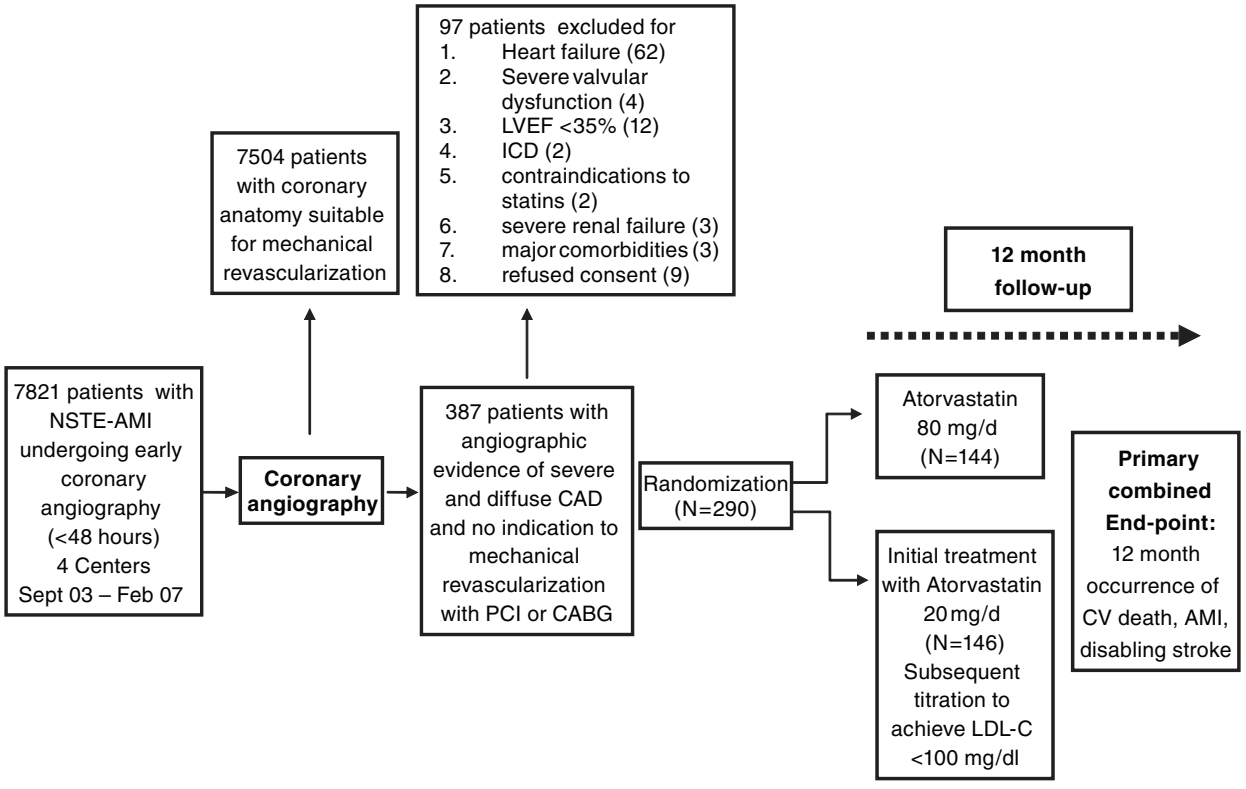

Figure 1. Study protocol.

treatment (group 1), in order to achieve recommended LDL-C levels, atorvastatin dosage was increased from 20 to 40 mg in cases of LDL-C values >100 mg/dL (2.5 mmol/L) in any of the planned controls. A clinical follow-up visit, including physical examination, a 12-lead electrocardiogram and general blood chemistry was performed 30, 90, 180 and 360 days after randomisation.

The primary end point of the study was prospectively defined as the combination of cardiovascular death, non-fatal acute myocardial re-infarction (re-AMI) and disabling non-fatal stroke. Secondary end points were the occurrence of each primary end-point component. All end points were independently adjudicated by a blinded Endpoint Validation Committee according to the PROBE format, which has already been used in other major cardiovascular trials[8]. Medical records were examined to verify all end points. End points were defined by using standard TIMI (Thrombolysis in Myocardial Infarction Investigators) group definitions[10]. All definitions can also be found at www.timi.org. For all included patients, formal study participation ended in the cases of occurrence of any primary end point component.

Statistical analysis

The trial was designed as a time-to-event study. The primary efficacy outcome measure was then the time from randomisation until the first occurrence of a component of the primary end point. The primary analysis of all outcomes was by intention-to-treat. Estimates of the hazard ratios (HR) and associated 95% confidence intervals (CI) comparing full-dose atorvastatin and conventional treatment were obtained with the use of the Cox proportional hazards model, with randomised treatment as the covariate. The cumulative risk of experiencing a component of the primary end point in the two study groups was estimated according to the Kaplan–Meier method.

Means (±SD) were calculated for continuous variables, and frequencies were measured for categorical variables. Differences between groups were analysed by unpaired Student's *t*-test for continuous variables and χ^2 for categorical variables.

According to the results of a previous Italian study[5], sample size calculation was based on an expected 28% cumulative rate of cardiovascular death, non-fatal acute myocardial re-AMI and stroke over a 12-month follow-up in the control group. As treatment with full-dose atorvastatin was expected to reduce such incidence rate by 40%, a sample size of 225 patients per arm in a 12-month period was calculated ($\beta = 0.80$, $\alpha = 0.05$ two-tailed). According to the study protocol, an interim analysis of safety and efficacy was planned every 6 months during the study.

Data analysis was performed by using the SPSS statistical software package (SPSS 12.0). A *p*-value <0.05 was considered statistically significant.

Table 1. Baseline characteristics of the study groups.

	Conventional treatment	Atorvastatin 80 mg/day
Patients	146	144
Age – mean (SD)	73.9 (9.4)	75.2 (9.9)
Females – number (%)	70 (47.9)	71 (49.3)
Diabetes – number (%)	102 (69.8)	104 (72.2)
Hypertension – number (%)	131 (89.7)	128 (88.8)
Previous ACS – number (%)	105 (71.9)	108 (75.0)
LVEF (%) – mean (SD)	46 (8)	47 (7)
Previous CABG – number (%)	82 (56.1)	84 (58.3)
Previous PCI – number (%)	101 (69.1)	99 (68.7)
Previous CABG or PCI – number (%)	132 (90.4)	130 (90.2)
Serum creatinine (mg) – mean (SD)	1.3 (0.7)	1.4 (0.6)
Statin therapy before admission – number (%)	68 (46.5)	71 (49.3)
Total cholesterol (mg) – mean (SD)	218 (37)	223 (41)
LDL-cholesterol (mg) – mean (SD)	123 (28)	126 (27)
HDL-cholesterol (mg) – mean (SD)	39 (10)	40 (12)
Triglycerides (mg) – mean (SD)	165 (39)	169 (42)

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SD, standard deviation.

Results

Enrolment was started in September 2003 and the seventh planned formal interim analysis was performed on March 10, 2007. By that time, 290 patients had been enrolled and follow-up data were available in all cases. The interim analysis showed a significant effect in favour of full-dose atorvastatin as compared to conventional medical treatment. Consequently, in accordance with the Study Safety and Efficacy Monitor, a decision was made to terminate enrolment and follow-up. The study results were then reported as of April 10, 2007.

During the recruitment period, 7821 potentially eligible patients were initially screened. Among all of these patients, 290 subjects (3.7%; 141 women and 149 men, mean age 74.6 ± 9.6) met all inclusion and exclusion criteria, provided informed consent and were randomised to one of the two treatment groups. The mean time between hospitalisation for the inclusion event, randomisation and beginning of statin therapy was 23.6 ± 12.3 hours. Overall, 146 patients were assigned to conventional medical therapy (group 1), while 144 patients were assigned to receive full-dose atorvastatin (80 mg/day) in addition to their pharmacological treatment (group 2). All patients were followed up for at least 60 days after randomisation (mean duration of follow-up 258 ± 144 days). No patient was lost to follow-up. The baseline characteristics of the two groups were similar and are shown in Table 1.

Efficacy outcomes

In the intention-to-treat analysis, a primary end point event occurred in 39/146 patients in group 1 (26.7%; 13 cardiovascular deaths, 22 non-fatal re-AMI, and four disabling strokes) and in 23/144 patients in group 2 (16.0%; 9 cardiovascular deaths, 12 non-fatal re-AMI, and two disabling strokes). Consequently, when compared with standard moderate statin therapy, full-dose atorvastatin significantly reduced the risk of the primary combined end point (HR 0.56; 95% CI 0.33–0.93, $p = 0.027$).

Even if there were no significant differences in the occurrence of each primary end-point component in the two study arms, the significant reduction in the relative risk of the primary combined end-point was mainly due to a reduced incidence of non-fatal re-AMI (HR 0.51; 95% CI 0.25–1.03, $p = 0.063$).

The Kaplan–Meier actuarial estimates of first occurrence of a component of the primary end point are shown in Figure 2.

Serum lipid levels

Serum lipid levels at randomisation were similar in the two groups (Table 1), while during follow-up LDL-C levels decreased significantly in both groups. Mean values (±SD) for LDL-C at 7, 14, 30, 90, 180 and 360 days after randomisation are provided in Figure 3.

During all the study period, as well as at the end of the trial, mean LDL-C levels were significantly lower in patients on full-dose atorvastatin. In fact, mean LDL-C levels at the end of the study were 62 ± 5 mg/dL (1.6 ± 0.13 mmol/L) in patients in the full-dose atorvastatin arm and 94 ± 4 mg/dL (2.4 ± 0.10 mmol/L) in patients from the conventional treatment arm ($p < 0.0001$).

In the conventional treatment arm, 111 patients (76.0%) required 20 mg/day and 35 patients (24.0%) 40 mg/day of atorvastatin to achieve the recommended LDL-C levels < 100 mg/dL (2.5 mmol/L). Overall, patients randomised to conventional treatment received a mean dose of 24.8 ± 8.6 mg/day of atorvastatin during the study. Titration from 20 to 40 mg/day was performed in all cases following the first LDL-C control 1 week after randomisation. Fourteen days after randomisation, mean LDL-C levels in the conventional treatment arm were 92 ± 6 mg/dL (2.3 ± 0.15 mmol/L), without any patient exceeding the recommended target for LDL-C (Figure 3). However, despite treatment, in 26/146 patients included in the conventional treatment arm (17.8%), LDL-C levels exceeded 100 mg/dL (2.5 mmol/L) in at least one of the subsequent controls performed during the study (two patients at 30 days, 11 at 90 days, 10 at 180 days and 3 at 360 days).

Concurrent medications

A similar antianginal and antiplatelet pharmacological treatment was administrated to patients included in the

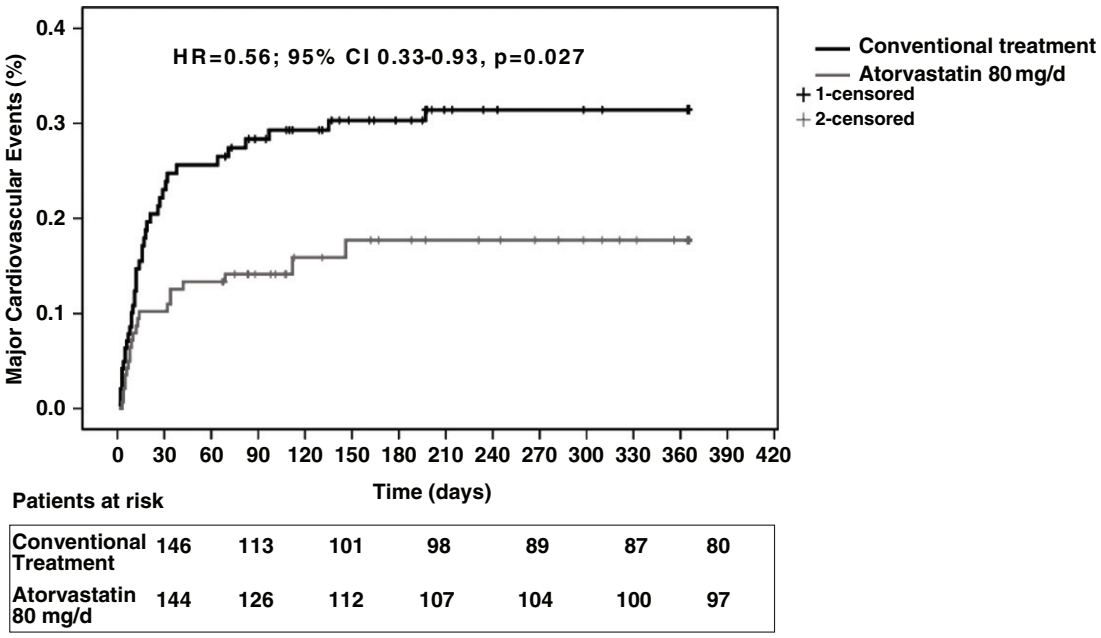

Figure 2. Actuarial estimates of the first occurrence of a component of the primary end-point in the two study groups.

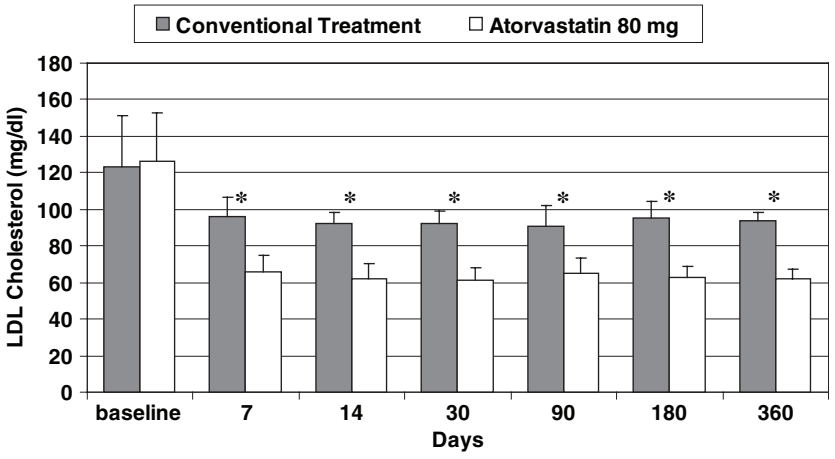

Figure 3. Low density lipoprotein cholesterol levels during the study. *$p < 0.0001$.

two study arms, both during the index admission and the follow-up period (Table 2).

Side-effects and adverse events

In two patients included in group 2 (1.4%), atorvastatin was withdrawn after 2 months of treatment, following the appearance of persistent muscle pain, associated with a significant rise in total serum CK (twice the upper limit of normal). Both abnormalities resolved following discontinuation of the drug. One patient in group 1 (0.7%) and two patients in group 2 (1.4%) had elevations in alanine aminotransferase levels that were more than three times the upper limit of normal.

Discussion

This clinical trial was aimed at assessing the effects of full-dose atorvastatin therapy in the specific subset of patients with advanced, non-revascularisable CAD. The trial was terminated early after 290 of the initially planned 450 patients had undergone randomisation and had been followed for a mean of 258 days. The decision to interrupt enrolment and follow-up was taken, in accordance with the Study Safety and Efficacy Monitor, following the interim analysis which showed a significant effect in favour of full-dose atorvastatin as compared to conventional medical treatment.

In the randomised high-risk population of patients with severe advanced CAD, the addition of atorvastatin

Table 2. Medications in the study groups.

	Conventional treatment	Atorvastatin 80 mg/day
During the index admission		
Aspirin – number (%)	145 (99.3)	144 (100)
Clopidogrel – number (%)	124 (84.9)	121 (82.8)
Heparin – number (%)	144 (98.6)	142 (98.6)
Glycoprotein IIb/IIIa receptor antagonists – number (%)	125 (85.6)	126 (87.5)
Nitrates – number (%)	145 (99.3)	143 (99.3)
Beta-blockers – number (%)	132 (90.4)	129 (89.5)
Calcium-channel blockers – number (%)	86 (58.9)	84 (57.5)
ACE-inhibitors – number (%)	92 (63.0)	90 (62.5)
Angiotensin receptor blockers – number (%)	26 (17.8)	23 (16.0)
During follow-up		
Aspirin – number (%)	139 (95.2)	140 (97.2)
Clopidogrel – number (%)	64 (43.8)	61 (42.3)
Warfarin – number (%)	24 (16.6)	22 (15.1)
Nitrates – number (%)	136 (93.1)	132 (91.6)
Beta-blockers – number (%)	124 (84.9)	125 (86.8)
Calcium channel blockers – number (%)	87 (59.5)	91 (63.1)
ACE-inhibitors – number (%)	103 (70.5)	101 (70.1)
Angiotensin receptor blockers - number (%)	28 (19.1)	25 (17.4)

80 mg/day to conventional medical therapy significantly reduced the incidence of major adverse cardiovascular events over a 12-month period after an acute coronary syndrome. In particular, a 10.7% absolute reduction in the incidence of the primary combined end point, which included cardiovascular death, non-fatal AMI, and disabling stroke, was noted. Treatment of approximately 9 patients was required to prevent one major cardiovascular event. Notably, full-dose atorvastatin therapy was associated with a lower incidence of the primary combined end point within 15 days from randomisation, with the actuarial curves describing event-free survival showing statistical significance after 4 weeks of therapy, which was maintained through follow-up. These results appear of particular interest as, unlike previous trials[11], patients in the control group were treated according to current recommendations regarding lipid-lowering therapy[9] rather than with a fixed statin dose. In fact, a LDL-C level <100 mg/dL (2.5 mmol/L) was reached in almost all control patients, but required a mean atorvastatin dose of about 25 mg/day.

In clinical practice, the subset of patients with advanced CAD is progressively increasing as a result of the aging population, the more extensive use of revascularisation procedures, and the availability of more effective medical therapies[2,3]. As many as 900 000 individuals in the United States are believed to have severe chronic CAD that is not amenable to traditional revascularisation, while 25 000–75 000 new cases may be diagnosed each year[12,13]. In Europe, 30 000–50 000 patients present each year with the clinical features of advanced CAD[14]. The clinical management of such patients is particularly demanding for the practicing physician, as most conventional therapeutic options have usually been exhausted and recurrent ischaemic episodes may lead to frequent admissions and significant disability. Newer approaches, which include enhanced external counterpulsation, therapeutic angiogenesis, neurostimulation, and transmyocardial laser revascularisation, have been developed for the management of these patients[2,3]. However, such largely experimental methodologies may not be available for many clinicians and patients[3]. Consequently, simple and readily available therapeutic measures should be developed to allow the effective management of patients with severe advanced CAD in everyday practice.

Large randomised clinical trials have shown that, when compared with moderate lipid-lowering treatment, intensive statin therapy can reduce cardiovascular events in both patients with stable CAD and those with acute coronary syndromes[11]. Two recent small trials, including 141 patients, have shown that intensive statin therapy with atorvastatin 80 mg/day may reduce the ischaemic burden and improve the clinical outcome of patients with advanced CAD[5,6]. Both studies included patients with angiographic evidence of severe and diffuse CAD, which was not amenable to any form of direct mechanical revascularisation with either PCI or CABG surgery. Despite the small sample size, these two studies provided early evidence that intensive statin therapy with full-dose atorvastatin could be effective in reducing the incidence of major adverse cardiovascular events in patients with severe non-revascularisable CAD. This trial confirms that intensive statin treatment with atorvastatin 80 mg/day is effective in improving the cardiovascular outcome of patients with severe CAD over the short term. Furthermore, this study provides further evidence that, even in extremely fragile elderly patients with severe advanced CAD, intensive statin therapy is safe, as atorvastatin 80 mg/day was not associated with an increased incidence of adverse reactions. In fact, a recent analysis of 49 trials demonstrated that atorvastatin 80 mg/day was safe and well-tolerated[15]. Despite such evidence, practicing physicians often avoid the use of more intensive statin therapy due to the fear of adverse events or of driving LDL-C level below a theoretical safe value.

In this study, patients treated with 80 mg/day of atorvastatin showed LDL-C levels which remained about 40 mg (1 mmol) below the currently recommended target of 100 mg/dL (2.5 mmol/L) throughout the study period. In the authors' opinion, the additional clinical benefit provided by full-dose atorvastatin in this trial is mostly explained by such relevant reduction of LDL-C. However, the early efficacy of full-dose atorvastatin in this study may also suggest a relatively short-term biological effect inherent to this therapeutic approach, possibly involving effective plaque stabilisation. In fact, recent data have suggested that high-dose atorvastatin might have

more relevant anti-inflammatory effects than conventional statin therapy[16]. Such stabilising effects could be of particular relevance in patients with end-stage CAD who have just suffered an acute coronary syndrome. These specific patients deserve particular attention as they have a significant coronary atherosclerotic burden together with a higher amount of unstable plaques which might be active at multiple sites.

Limitations of the study

The study was not blinded. Consequently, a bias in the assessment of clinical outcome cannot be completely excluded, even if the outcome events were adjudicated by an independent committee blinded to treatment assignment according to the PROBE design.

Conclusions

In conclusion, this trial provides evidence that adding an early full-dose atorvastatin treatment on top of optimal combination therapy reduces, to a significant extent, cardiac ischaemic recurrences after an acute coronary syndrome in patients with advanced non-revascularisable CAD. These results are clinically relevant, since the number of such high risk patients is expected to further increase in the future owing to the advances in secondary prevention, as well as technical improvements in invasive revascularisation procedures.

Transparency

Declaration of funding
This study has been financially supported by the Lazio Regional Section of the Italian National Association of Hospital Cardiologists (ANMCO), which is the scientific association of cardiologists working in public hospitals of the Italian National Health Service (www.anmco.it). All authors are active members of this scientific association.

The study was independently designed and conducted by the investigators and was not supported nor funded by any industry. All authors have contributed significantly to the preparation of the final report, have participated in the writing of the manuscript and approved the final version.

Declaration of financial/other relationships
All authors have neither financial relationships nor conflicts of interest to disclose in relation to this study. Peer reviewers may receive honoraria for their review work for CMRO. The peer reviewers have disclosed that they have no relevant financial relationships.

Acknowledgements
The investigators acknowledge the secretarial assistance during the study and in the preparation of the final report of Mrs Irene Di Pinto, whose work was entirely funded by the Lazio Regional Section of Italian National Association of Hospital Cardiologists (ANMCO).

The results of the study have been partially presented as an abstract at the European Congress of Cardiology 2008, Munich, Germany

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