

A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty

Final results of the fluvastatin angiographic restenosis (FLARE) trial

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Background The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors competitively inhibit biosynthesis of mevalonate, a precursor of non-sterol compounds involved in cell proliferation. Experimental evidence suggests that fluvastatin may, independent of any lipid lowering action, exert a greater direct inhibitory effect on proliferating vascular myocytes than other statins. The FLARE (Fluvastatin Angioplasty Restenosis) Trial was conceived to evaluate the ability of fluvastatin 40 mg twice daily to reduce restenosis after successful coronary balloon angioplasty (PTCA).

Methods Patients were randomized to either placebo or fluvastatin 40 mg twice daily beginning 2–4 weeks prior to planned PTCA and continuing after a successful PTCA (without the use of a stent), to follow-up angiography at 26 ± 2 weeks. Clinical follow-up was completed at 40 weeks. The primary end-point was angiographic restenosis, measured by quantitative coronary angiography at a core laboratory, as the loss in minimal luminal diameter during follow-up. Clinical end-points were death, myocardial infarction, coronary artery bypass graft surgery or re-intervention, up to 40 weeks after PTCA.

Results Of 1054 patients randomized, 526 were allocated to fluvastatin and 528 to placebo. Among these, 409 in the fluvastatin group and 427 in the placebo group were

included in the intention-to-treat analysis, having undergone a successful PTCA after a minimum of 2 weeks of pre-treatment. At the time of PTCA, fluvastatin had reduced LDL cholesterol by 37% and this was maintained at 33% at 26 weeks. There was no difference in the primary end-point between the treatment groups (fluvastatin 0.23 ± 0.49 mm vs placebo 0.23 ± 0.52 mm, $P=0.95$) or in the angiographic restenosis rate (fluvastatin 28%, placebo 31%, chi-square $P=0.42$), or in the incidence of the composite clinical end-point at 40 weeks (22.4% vs 23.3%; logrank $P=0.74$). However, a significantly lower incidence of total death and myocardial infarction was observed in six patients (1.4%) in the fluvastatin group and 17 (4.0%) in the placebo group (log rank $P=0.025$).

Conclusion Treatment with fluvastatin 80 mg daily did not affect the process of restenosis and is therefore not indicated for this purpose. However, the observed reduction in mortality and myocardial infarction 40 weeks after PTCA in the fluvastatin treated group has not been previously reported with statin therapy. Accordingly, a priori investigation of this finding is indicated and a new clinical trial with this intention is already underway. (Eur Heart J 1999; 20: 58–69)

Key Words: Prevention of restenosis, fluvastatin, balloon angioplasty.

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Introduction

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) are the most recently introduced class of agents aimed at the management of hyperlipidaemia. Many clinical studies have suggested that their beneficial effect on the progression of atherosclerosis is due to their lipid lowering properties^[1,2], although there is growing evidence that they may have additional effects beyond LDL cholesterol reduction^[3]. For example, *in vitro* studies have suggested that, by inhibiting mevalonate synthesis, they may limit the availability of isoprene units and as a consequence, retard such fundamental biological processes as cell growth and proliferation^[4].

A direct effect of four statins (simvastatin, lovastatin, pravastatin and fluvastatin) on smooth muscle cell proliferation, independent of any lipid lowering action was demonstrated in an experimental investigation in normocholesterolemic rabbits^[5]. Fluvastatin appeared to inhibit neointimal formation to the greatest extent and thus provided a rationale for investigation of the potential effect of fluvastatin for the prevention of restenosis after coronary balloon angioplasty in a large clinical trial. Accordingly, the FLARE—Fluvastatin Angioplasty Restenosis trial was designed.

Methods

Protocol development for this randomized double-blind placebo-controlled trial commenced as long ago as early 1992, in collaboration with a nucleus of committed expert physicians who subsequently formed the trial steering committee: the Cardialysis Clinical Trial Coordinating Centre, Rotterdam, Netherlands and Sandoz Pharma, AG, Basel (now Novartis Pharma, AG., the trial sponsors and proprietors of fluvastatin/lescol). To facilitate the successful performance of the trial, especially with regard to standardized performance of coronary angiography (suitable for optimal quantitative analysis at the core laboratory) by the 33 investigating centres, throughout seven European countries, extensive preparatory and background work was required. This included several national and international general investigators meetings to describe the protocol and trial documentation, visits by quantitative coronary angiography experts from the co-ordinating centre and representatives of the Sandoz Affiliated Companies to all centres, and the performance of angiographic test cases by investigators (with critical evaluation by the core laboratory), to demonstrate their suitability to participate in the trial. A number of prospective investigating centres, which were routinely recording angiograms on videotape instead of on cinefilm, had to be excluded from the trial after reproducibility testing at the core laboratory demonstrated unreliability of video as a substrate for image storage for subsequent quantitative coronary angiography analysis^[7].

Inclusion/exclusion

Patients to be included in the trial were those with symptomatic or ischaemia-producing coronary lesions suitable for balloon angioplasty, according to the local practice of the investigator, and an LDL cholesterol $<6.0 \text{ mmol} \cdot \text{l}^{-1}$. Initially, only patients requiring angioplasty of a single target lesion were to be included, but because of investigator opinion, that evolving clinical practice indicated an increasing proportion of multi-lesion procedures, the protocol was amended in January 1994 to allow planned multilesion angioplasty. Principal trial exclusion criteria were myocardial infarction within the previous 3 months (making measurement of some serum lipid fractions unreliable), restenotic lesions, lesion in a bypass graft, patients requiring urgent angioplasty or inability to defer angioplasty for 2 weeks in order to allow pre-treatment, and a fasting low-density lipoprotein cholesterol $>6 \text{ mmol} \cdot \text{l}^{-1}$ or triglycerides $>4.5 \text{ mmol} \cdot \text{l}^{-1}$ at screening.

Intention-to-treat population and sample size calculation

The trial commenced with inclusion of the first patient in October 1993. By July 1995 the recruitment target of 1000 patients had been exceeded, with a total of 1054 patients randomized to receive either fluvastatin 40 mg ($n=526$) or placebo ($n=528$), twice daily. This patient group formed the total population for evaluation of the safety of the trial medication. This was independently evaluated by a Safety and Data Monitoring Committee, formed by internationally recognized expert epidemiologists and cardiologists, not involved with patient treatment in the trial. The protocol was carefully designed primarily to investigate the influence of fluvastatin on restenosis after successful angioplasty. The intention-to-treat population was defined as 'those randomized patients who had taken at least one tablet of trial medication and undergone successful balloon angioplasty' (without the use of a stent) 2 ± 2 weeks later. At the time the protocol was finalized (mid 1993), limited data existed on the intermediate (6 month–1 year) results of stent implantation. The indications were uncertain and use varied widely throughout the participating countries. Accordingly, it was decided by the steering committee that all patients undergoing stent implantation during the initial angioplasty procedure would be considered to have had an unsuccessful balloon angioplasty and would be excluded from the intention-to-treat population. It seemed at that time that the incidence of so-called 'bail-out stent implantation' was generally less than 10% and this was taken into account in the estimation of patient inclusion required to test the trial hypothesis with 90% statistical certainty.

The calculation of sample size was based on the knowledge that the mean luminal loss during follow-up after successful PTCA among placebo-treated groups in

Table 1 Flow chart of all patients randomized (n=1054)

	Number of patients	
	Fluvastatin	Placebo
Safety population	526	528
Medication discontinued before PTCA	10	6
Consent withdrawn before PTCA	7	6
Delayed exclusion	10	9
PTCA cancelled	13	7
MACE before PTCA	4	3
MACE during PTCA	72	71
Protocol violation	1	1
Intention-to-treat population	409	425
Angiographic population	382	391

MACE=major cardiac events.

four previous trials with different agents was 0.30 mm^[8-10]. Thus it was assumed that the placebo group in the FLARE trial would demonstrate a similar degree of loss. The target treatment effect was decided upon by the steering committee as a 40% reduction in luminal loss by fluvastatin. In order to detect such a difference, with 90% power at an alpha level of 0.05, approximately 730 evaluable patients were required. Allowing for an estimated 'drop out' rate of 15% (based on experience with previous trials and taking account of the pre-treatment phase required in the FLARE trial), a total of 850 patients needed to be randomized. This number of evaluable patients also allowed the detection of a difference of 30% in the incidence of major adverse cardiac events (death, myocardial infarction, coronary artery bypass graft surgery or re-intervention) between the treated and placebo groups, with a power of >90% at an alpha level of 0.05. However, as a consequence of evolving angioplasty practice, principally the increasing use of coronary stents, a 22% 'drop out' rate was observed in the early months of the trial. The steering committee therefore took the decision to increase the recruitment target to 1000 patients to ensure that an adequate number of evaluable patients would be enrolled. Ultimately, 834 evaluable patients, 409 patients in the fluvastatin group and 425 in the placebo group, had a successful balloon and continued on trial medication until follow-up angiography at 26 ± 2 weeks after angioplasty (flow chart is shown in Table 1).

Trial chronology

The trial commenced (visit 1, 2-4 weeks before intervention) when eligible patients who had been screened and fulfilled all inclusion criteria^[12] and had given informed consent were randomized. After a minimum of 2 weeks, the patient returned for PTCA, prior to which clinical and laboratory assessments were carried out (visit 2, week 0). Patients undergoing successful PTCA (defined as diameter stenosis <50%) without reaching a major adverse cardiac event, continued on trial medication. A

clinical follow-up visit, with clinical evaluation and lipid and biochemical assessment was required 6 weeks after PTCA (visit 3, week 6) and a further visit with exercise testing (visit 4, 24 ± 2 weeks after angioplasty), was required prior to follow-up angiography, which was carried out 26 ± 2 weeks after PTCA (visit 5). In order to allow sufficient time for performance of justified (on the basis of recurrent symptoms or demonstrated exercised-induced ischaemia) elective re-intervention or bypass graft surgery arising from clinical and angiographic follow-up at 26 ± 2 weeks, the final clinical follow-up for evaluation of clinical end-points was at 40 weeks after PTCA (visit 6, week 40). Due to variable waiting times for elective surgical or non-surgical intervention throughout the participating countries, 40 weeks was agreed upon as the most practical timing for final clinical follow-up.

End-points

Primary end-point

The primary end-point for the FLARE trial was the absolute change in minimal luminal diameter, between the post-PTCA and follow-up angiogram, 26 ± 2 weeks later, measured by quantitative coronary angiography. If, for whatever reason, angiography was carried out prior to 14 weeks after PTCA, further angiography within the recommended time-window was required, unless a clinical end-point, as defined below, had been reached.

Secondary angiographic end-points

- (i) Minimal luminal diameter at follow up angiography;
- (ii) incidence of restenosis, as defined according to categorical angiographic criteria.

Clinical end-points

A clinical end-point was considered to have been reached upon the occurrence of any one of the major cardiac events described below, before 40 weeks post-PTCA, whereby for any patient experiencing more than one event, the first event reached was considered:

1. death—post-mortem examination was recommended in all patients randomized who died during the course of the trial. In the absence of clear evidence to the contrary, any deaths occurring during the trial were considered to be cardiac;
2. non-fatal myocardial infarction. The occurrence of myocardial infarction was defined as the finding of a typical temporal pattern of serum cardiac enzyme change, in particular, documented elevation of serum creatine phosphokinase levels to greater than twice the upper limit of normal for the laboratory and/or a greater than twofold increase in the creatine phosphokinase MB fraction, with return to within the accepted normal range. In the absence of unambiguous cardiac enzyme abnormalities, the finding of typical evolutionary ECG patterns of myocardial infarction, or of 'new' pathological Q waves were considered diagnostic of myocardial

infarction. Evidence to support the diagnosis of myocardial infarction had to be provided by the investigator, to facilitate final adjudication by the Critical Events and Safety and Data Monitoring Committees;

3. coronary artery bypass graft surgery (CABG);

4. re-intervention after completion of the initial PTCA procedure and before the end of the trial period, including requirement for repeat PTCA or intervention using an alternative percutaneous revascularization device (use of a perfusion balloon catheter at the discretion of the treating physician was acceptable and did not constitute an end-point or exclusion from the trial). Stent implantation during the index angioplasty procedure was considered to indicate unsuccessful balloon angioplasty and the patient was excluded from the intention-to-treat analysis.

Lipid and laboratory aspects

Patients with a measured fasting LDL cholesterol above $6.0 \text{ mmol} \cdot \text{l}^{-1}$ or fasting triglyceride level greater than $4.5 \text{ mmol} \cdot \text{l}^{-1}$ (by local laboratory) within 4 weeks of randomization were excluded from the trial, on the ethical principle that they required lipid-lowering therapy. The effect of trial medication on serum lipids was assessed by performing a comprehensive lipid profile (total cholesterol, low and high density lipoprotein cholesterol, lipoprotein (a), apolipoprotein A1 and B and triglycerides) at all clinical visits^[13]. Lipid parameters and temporal changes were compared between the two groups and correlated with the angiographic and clinical end-points. In addition, prior to randomization, all patients had to have documented haematological, hepatic and renal indices and creatine phosphokinase levels within the reference range for the analysing laboratory. At randomization, blood samples were taken for measurement of these parameters at a central laboratory. Similar laboratory tests were repeated at each attendance, to detect any potential adverse biochemical or haematological effects of trial medication. In the final analysis, the treatment and placebo groups were compared for frequency and severity of abnormalities detected. From randomization, all blood samples were specially packaged in protective containers and sent by courier to central laboratories for blinded analysis. Local laboratory results were used for screening and establishment of patient suitability for inclusion, as well as for diagnosis of acute adverse events (all data pertaining to such events were evaluated blindly by the Critical Events Committee and by the Safety and Data monitoring Committee). Central laboratory results were used to monitor the safety of trial medication and relevant laboratory abnormalities were reported to responsible investigators and to the Clinical Co-ordinating Centre.

Trial medication

Compliance, safety and tolerability

In addition to laboratory tests, compliance with trial medication was assessed at each visit and all adverse

experiences (any deterioration in clinical status during the course of the trial was considered an adverse experience; its relationship with trial medication was determined according to well known guidelines) were documented in the case record form. The trial medication was discontinued if: (1) the PTCA procedure was not performed for whatever reason; (2) the PTCA procedure was unsuccessful (failure to achieve a % diameter stenosis $<50\%$ post PTCA, without the use of a device other than balloon) whether or not a major cardiac event occurred; (3) a primary clinical end-point was reached, or another serious adverse event occurred; (4) a protocol violation occurred. Discontinuation of trial medication after successful angioplasty did not dictate withdrawal from the trial, and follow-up clinical observations had to be made as scheduled, to complete the evaluation and analysis.

Concomitant medication

All patients received acetyl salicylic acid up to 325 mg once daily throughout the trial period. Intracoronary injection of 1–3 mg isosorbide dinitrate or 0.1–0.3 mg glyceryl trinitrate, was systematically used to control vasomotor tone. Oral or sublingual nitrates could be given during the follow-up period where indicated. At the discretion of the treating physician, during the PTCA procedure or the in-hospital period, beta-blockers and calcium antagonists could be prescribed. Non-aspirin antiplatelet agents and oral anticoagulants were discouraged.

Excluded medications, which were considered to potentially interfere with evaluation or interpretation of study results, included: all other lipid lower agents; steroid hormones or oral contraceptive agents; thyroid hormone replacement, if not stable for at least 2 months prior to the study or likely to change during the study; erythromycin or ketoconazole; cyclosporin; anti-epileptic therapy; and, at the beginning of the trial, oral hypoglycaemic agents (this exclusion was cancelled within 3 months of the beginning of the trial, based on data from the manufacturing company).

Statistical analysis

Continuous variables, including in particular the change in minimal luminal diameter during follow-up and the minimal luminal diameter at follow-up, were compared by analysis of variance techniques, taking potential centre (investigating institution) interaction into account. Categorical variables were compared by Mantel–Haenszel test procedures. Major cardiac events were displayed using the Kaplan–Meier method; statistical comparisons were performed using the logrank test. Binary restenosis rates (according to the conventional definitions employed) were compared by Fisher's exact test.

Angioplasty procedure and angiographic protocol to facilitate quantitative analysis

The angioplasty technique was left to the discretion of the treating physician, except for the performance of coronary angiography before and after successful lesion treatment. To this end, all investigators were required to receive instruction from the core laboratory (Cardialysis, Rotterdam, the Netherlands) in the appropriate recording of angiograms to facilitate quantitative analysis. Two angiographic 'test runs' had to be submitted to the core lab for evaluation and approval before a centre could begin to recruit patients. Angiograms had to be recorded on cinefilm at a frame speed of 25 mm . s⁻¹; recordings pre-PTCA and the final post-PTCA recording had to be made after intracoronary injection of nitroglycerin or isosorbide dinitrate, beginning with the empty contrast catheter tip. Contrast opacification had to be optimal and in at least two projections (separated by at least 30° angulation) clearly showing the target lesion and adjoining segments proximal and distal. All film sequences, medications and materials used (including details of balloon inflations), a qualitative angiographic evaluation of the lesion morphology, angiographic outcome, and complications were recorded on a dedicated case record form (called the Technician's Worksheet). All further angiographic procedures, including intercurrent and follow-up angiograms and repeat angioplasty, had to be similarly documented in detail; angiographic film sequences had to be repeated in projections identical to those used during the index procedure.

Core laboratory angiographic evaluation procedures

All cineangiograms were evaluated by teams of two experienced observers for detailed qualitative features. The inter and intra-observer variability for evaluation of these features for this core laboratory had been previously published^[14]. Quantitative angiographic measurements were performed using the Cardiovascular Angiographic Analysis System (CAAS) using standardized methodology which has been extensively described^[15].

Results

Patients

Of the 1054 randomized patients, 34 in the fluvastatin group and 22 in the placebo group did not complete the pre-treatment period and undergo angioplasty (because of withdrawal of consent, discontinuation of trial medication, experience of a major adverse cardiac event or cancellation of angioplasty—Table 1). A further 83 patients in the fluvastatin group and 81 in the

placebo group underwent an angioplasty procedure, but had an unsuccessful or complicated outcome (including death n=2; myocardial infarction n=10; emergency coronary artery bypass graft surgery n=7; or necessity for bail-out stent implantation n=67) or had a previously unnoticed exclusion criterion and were later excluded from analysis. Ultimately, a total of 409 patients in the fluvastatin group and 425 in the placebo group had successful balloon angioplasty without adverse cardiac events and entered the intention-to-treat analysis.

Baseline clinical (Table 2) and angiographic characteristics (Table 3) were similarly distributed in the two groups. Patients (83% male) had predominantly single-vessel disease and underwent mainly single-lesion dilatation (85%). The majority of patients (71%) had stable class 0–2 anginal symptoms, although 40% gave a history of recent non-exertional angina. Lesions were located in the left anterior descending artery in a total of 42% of patients, in the right coronary artery in 27% and in the circumflex in 31%. Lesion type was mainly scored as ACC/AHA type B1 or B2 and a TIMI grade 0 or 1 occlusion was encountered in 7%. Additional features of interest include: lesion length was scored as <10 mm in 68% of the fluvastatin group and in 69% of the placebo group, as 10–20 mm in 23% of each group, as longer than 20 mm in 4% and 3%, and as not measurable in 5%. Calcification was scored in 18% of target lesions and thrombus in 1.8%, lesions were located in a tortuous segment in 16% of lesions in each group. A branch point was present in the stenosis, or was covered by the dilating balloon, in 45% of patients in the fluvastatin group and in 47% in the placebo group.

Lipid levels and other laboratory parameters (Tables 2 and 4)

Baseline lipid parameters were similar in the two groups. At the angioplasty visit (week zero, 2 weeks after commencing trial medication), LDL cholesterol was reduced by 37% in the fluvastatin group and maintained at 33% at the 26 week follow-up, whereas in the placebo group no significant change in LDL cholesterol was observed. In addition, at 26 weeks a 28% reduction in apolipoprotein B was observed, as well as a 13% reduction in triglycerides, in contrast to no significant change in the placebo group. No significant changes were observed in HDL cholesterol, apolipoprotein A1 or lipoprotein (a). A more than three-fold elevation above reference was observed in serum ALAT in 1.7% of patients in the fluvastatin group and in 0.7% in the placebo group, and in ASAT in 0.5% in each group. However, no patient showed such abnormalities in two consecutive samples. Elevation of total creatine phosphokinase to more than 10 times the upper range (the level required to define myopathy^[16]) was not observed.

Table 2 Baseline demographic characteristics of the intention-to-treat population (n=834)

	Fluvastatin (409 patients)		Placebo (425 patients)	
Age	60 ± 9		61 ± 9	
Male	339	83%	349	82%
Relevant medical history				
Diabetes mellitus	15	4%	19	5%
Prior MI	134	33%	141	33%
Prior CABG	18	4%	21	5%
Prior PTCA	38	9%	38	9%
Cerebrovascular disease	14	3%	15	4%
Hypertension	136	33%	140	33%
Peripheral vascular disease	35	9%	36	9%
Current smoking	125	31%	116	27%
Family history of coronary disease	134	33%	135	32%
Lipid profile				
Total cholesterol (mmol . l ⁻¹)	5.75 ± 1.01		5.77 ± 1.03	
LDL cholesterol (mmol . l ⁻¹)	3.96 ± 0.85		3.95 ± 0.87	
HDL (mmol . l ⁻¹)	1.06 ± 0.27		1.08 ± 0.28	
Triglycerides (mmol . l ⁻¹)	1.69 ± 0.84		1.6 ± 0.83	
Lipoprotein-a (mg . dl ⁻¹)	29.5 ± 40.0		32.2 ± 44.1	
Anginal status				
No angina	49	12%	45	11%
CCS class 1	57	14%	58	13%
CCS class 2	179	44%	207	49%
CCS class 3	111	27%	103	24%
CCS class 4	13	3%	12	3%
Recent history of non-exertional angina	163	40%	177	42%
Body mass index	26.7 ± 3.3		26.7 ± 3.2	
Extent of coronary artery disease				
Unknown	11	3%	2	21%
Single vessel disease	276	67%	316	74%
Two vessel disease	93	23%	88	21%
Triple vessel disease	29	7%	19	4%
Number of lesions	479		495	
Patients with multilesion PTCA	63	15%	59	14%

CCS=Canadian Cardiovascular Society.

Table 3 Baseline lesion characteristics of the intention-to-treat population (n=834)

	Fluvastatin (479 lesions)		Placebo (495 lesions)	
Lesion type (ACC/AHA)				
A	33	7%	40	8%
B1	202	42%	195	39%
B2	221	46%	242	49%
C	21	4%	18	4%
Missing	16	3%	18	4%
Lesion location				
Left anterior descending	210	44%	191	39%
Right coronary artery	128	7%	137	27%
Circumflex	141	29%	161	34%
TIMI flow status pre-PTCA				
TIMI 0	21	4%	22	4%
TIMI 1	14	3%	26	5%
TIMI 2	60	13%	48	10%
TIMI 3	383	80%	399	81%
Missing	1	0%	0	0%

ACC/AHA=American College of Cardiology/American Heart Association; TIMI=Thrombolysis in Myocardial Infarction.

Angiographic outcome (Table 5 and Fig. 1)

In the intention-to-treat population 773 patients (93% of those eligible) completed angiographic follow-up suitable for quantitative analysis. Target vessel size was 2.66 mm in each group. Minimal luminal diameter pre-angioplasty was 0.97 mm in the fluvastatin group and 0.96 mm in the placebo group, increasing to 1.78 mm in the fluvastatin group and 1.77 mm in the placebo group, giving an acute luminal gain of 0.81 mm and 0.80 mm, respectively. The frequency of angiographic dissection scored by the angiographic core laboratory was 44% in the fluvastatin and 47% in the placebo group. Late luminal loss was identical in both groups (0.23 mm) and follow-up minimal luminal diameter was similar at 1.55 mm in the fluvastatin group and 1.53 mm in the placebo group, reflected by superimposition of the cumulative frequency distribution curves in Fig. 1. The categorical restenosis rate (diameter stenosis >50%) was 28% in the fluvastatin group and 31% in the placebo group ($P=0.42$).

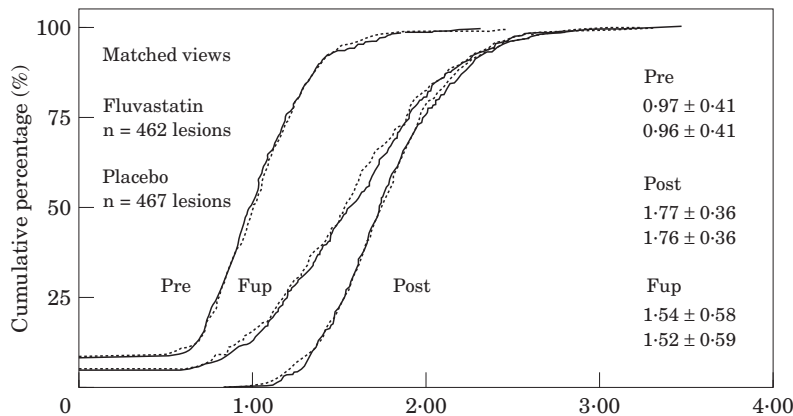
Table 4 LDL cholesterol volumes of intention-to-treat population during treatment period

	Fluvastatin (409 patients)	Placebo (425 patients)	Difference	
Week - 2 (baseline)	3.96 ± 0.85	3.95 ± 0.87	0.01	<i>P</i> =1.00
Week 0 (procedure)	2.46 ± 0.74	3.81 ± 0.79	0.35	<i>P</i> <0.0001*
Week 4	2.56 ± 0.71	3.88 ± 0.85	0.32	<i>P</i> <0.0001*
Week 26	2.63 ± 0.78	3.85 ± 0.84	0.22	<i>P</i> <0.0001*

**P* value adjusted for baseline value.

Table 5 Results of per lesion based offline Quantitative Coronary Angiographic analysis before and after angioplasty and at 6 month follow up in patients with evaluable angiograms (*n*=773)

	Fluvastatin (445 lesions in 382 patients)	Placebo (458 lesions in 391 patients)	<i>P</i> value for difference
Reference vessel diameter (mm)			
Pre-PTCA	2.66 ± 0.50	2.66 ± 0.54	<i>P</i> =0.99
Post-PTCA	2.75 ± 0.48	2.72 ± 0.51	<i>P</i> =0.56
Follow-up	2.79 ± 0.54	2.76 ± 0.60	<i>P</i> =0.79
Minimal luminal diameter (mm)			
Pre-PTCA	0.97 ± 0.41	0.96 ± 0.41	<i>P</i> =0.67
Post-PTCA	1.78 ± 0.36	1.77 ± 0.36	<i>P</i> =0.57
Follow-up	1.55 ± 0.59	1.53 ± 0.58	<i>P</i> =0.77
Percent diameter stenosis			
Pre-PTCA	63 ± 14%	63 ± 15%	<i>P</i> =0.79
Post-PTCA	35 ± 8%	35 ± 8%	<i>P</i> =0.72
Follow-up (mm)	44 ± 18%	44 ± 17%	<i>P</i> =0.96
Acute luminal gain (mm)	0.81 ± 0.42	0.80 ± 0.43	<i>P</i> =0.93
Late luminal loss (mm)	0.23 ± 0.49	0.23 ± 0.52	<i>P</i> =0.95
Net luminal gain (mm)	0.57 ± 0.55	0.57 ± 0.57	<i>P</i> =1.00
Restenosis rate (% diameter stenosis at follow up ≥ 50%)	126 28%	141 31%	<i>P</i> =0.42

**Figure 1** Cumulative frequency distribution curves for all evaluable lesions in the two treatment groups, showing minimal luminal diameter before (Pre) and after (Post) intervention and at follow-up (Fup).

Clinical results (Table 6 and Fig. 2(a) and (b))

Major cardiac events were observed in 92 patients in the fluvastatin group and in 99 in the placebo group (*P*=0.74). Death or myocardial infarction occurred in

1.4% of patients in the fluvastatin group compared with 4% of patients in the placebo group (*P*=0.03) and re-intervention (surgical or percutaneous) was carried out in 21% of the fluvastatin-treated patients and 19.3% of the placebo patients. At 26 weeks, prior to follow-up angiography, 69% of patients in the fluvastatin group and 70% in the placebo group were angina free.

Table 6 Major adverse cardiac events occurring during follow-up, assessed at 40 weeks after angioplasty in the intention-to-treat population (n=834)

	Fluvastatin (409 patients)		Placebo (425 patients)		Fluvastatin (409 patients)		Placebo (425 patients)		Difference	
Worst event					Cumulative events					
Death	3	0.7%	7	1.6%	Death	3	0.7%	7	1.6%	<i>P</i> =0.37
MI	3	0.7%	10	2.4%	Death/MI	6	1.4%	17	4.0%	<i>P</i> =0.03
CABG	18	4.4%	10	2.4%	Death/MI/CABG	24	5.8%	27	6.4%	<i>P</i> =0.88
rePTCA	68	16.6%	72	16.9%	Death/MI/CABG/rePTCA	92	22.4%	99	23.3%	<i>P</i> =0.85

MI=myocardial infarction; CABG=coronary artery bypass grafting; rePTCA=percutaneous transluminal coronary angioplasty reintervention.

Non-cardiac adverse events

A total of four patients (0.8%) in the fluvastatin group and 11 (2.1%) in the placebo group were diagnosed with malignant disease during the trial period. In 45% of patients in the fluvastatin group and 51% in the placebo group a minor adverse event was reported. Principal among these events, where more than a 1% difference existed between the two groups (fluvastatin vs placebo), were: headache (3.8% vs 1.7%), nausea (3.4% vs 2.3%), myalgia (1.7% vs 0.6%) or other pain (4.4% vs 2.5%); however, none of these differences was statistically significant.

Discussion

Design

The primary goal of this randomized placebo-controlled trial was to evaluate the effect of high dose fluvastatin (80 mg daily), with a pre-treatment period of 2–4 weeks and a duration of 26 weeks, on restenosis after successful balloon angioplasty, as measured by quantitative angiography. Accordingly, the study was powered to detect a 40% reduction in quantitative coronary angiography measured luminal loss, from an expected 0.30 mm in the placebo group to 0.18 mm in the fluvastatin group. Of the total recruitment of 1054 patients, 834 underwent a successful balloon angioplasty after receiving at least one dose of trial medication, thus forming a more than adequate intention-to-treat population. Angiographic follow-up of 93% provided a more than ample patient population to test the trial hypothesis.

The loss in minimal luminal diameter from post-angioplasty to follow-up angiography was used as a surrogate for intimal hyperplasia, since we were investigating the anti-proliferative effect of fluvastatin. Of course other angiographic measurements^[12] were also included as secondary and tertiary end-points and ultimately no differences were detected between the fluvastatin and placebo group so the outcome of the trial was negative.

It is noteworthy that the mean loss observed in this trial is the lowest ever published in a balloon

angioplasty population — 0.23 mm in both groups, compared with an average of 0.30 mm in the CARPORT, MERCATOR, MARCATOR and PARK trials^[17], all co-ordinated by this core laboratory. In two other restenosis trials using statins, the reported luminal loss was also greater, at 0.46 mm in the lovastatin trial^[18] and in the PREDICT (pravastatin)^[19] trial, although the minimal luminal diameter at follow-up is in the same range in all three studies (1.45 mm in lovastatin, 1.51 mm in PREDICT and 1.54 mm in FLARE) and the rate of revascularization during follow-up is consistent in all three trials (in the range of 21%). Differences in the patient populations may be responsible for the greater loss in the lovastatin trial compared with FLARE. In the lovastatin trials, the patient population included 55% CCS class 3 or 4 angina, compared to 30% in FLARE; diabetics formed 12% of the population in lovastatin and 4.5% in FLARE; females made up 29% of the lovastatin trial population compared with 19% in FLARE; 44% of patients in the lovastatin trials had multivessel disease compared with 33% in FLARE; 26% of patients had multilesion dilatation in lovastatin and 15% in FLARE; also, the intention-to-treat population in FLARE excluded the patients with stent implantation, which is known to be associated with greater luminal loss during follow-up than balloon angioplasty, despite the more favourable late outcome^[20]. Lastly differences in quantitative coronary angiography methodology may play a part, as has been previously published by our group^[21].

Effects of fluvastatin in FLARE

Why did fluvastatin not diminish restenosis?

For the first time, a pharmacological agent with proven ability to inhibit human smooth muscle cell proliferation *in vitro* has been tested in a clinical trial. *In-vitro* investigation of the pharmacological activity of sera from patients treated with either pravastatin or fluvastatin on proliferation of cultured human smooth muscle cells and on cholesterol biosynthesis, showed similar effects on plasma lipids and lipoproteins, but in addition, fluvastatin sera caused significant inhibition of smooth muscle cells proliferation (–28% cell growth),

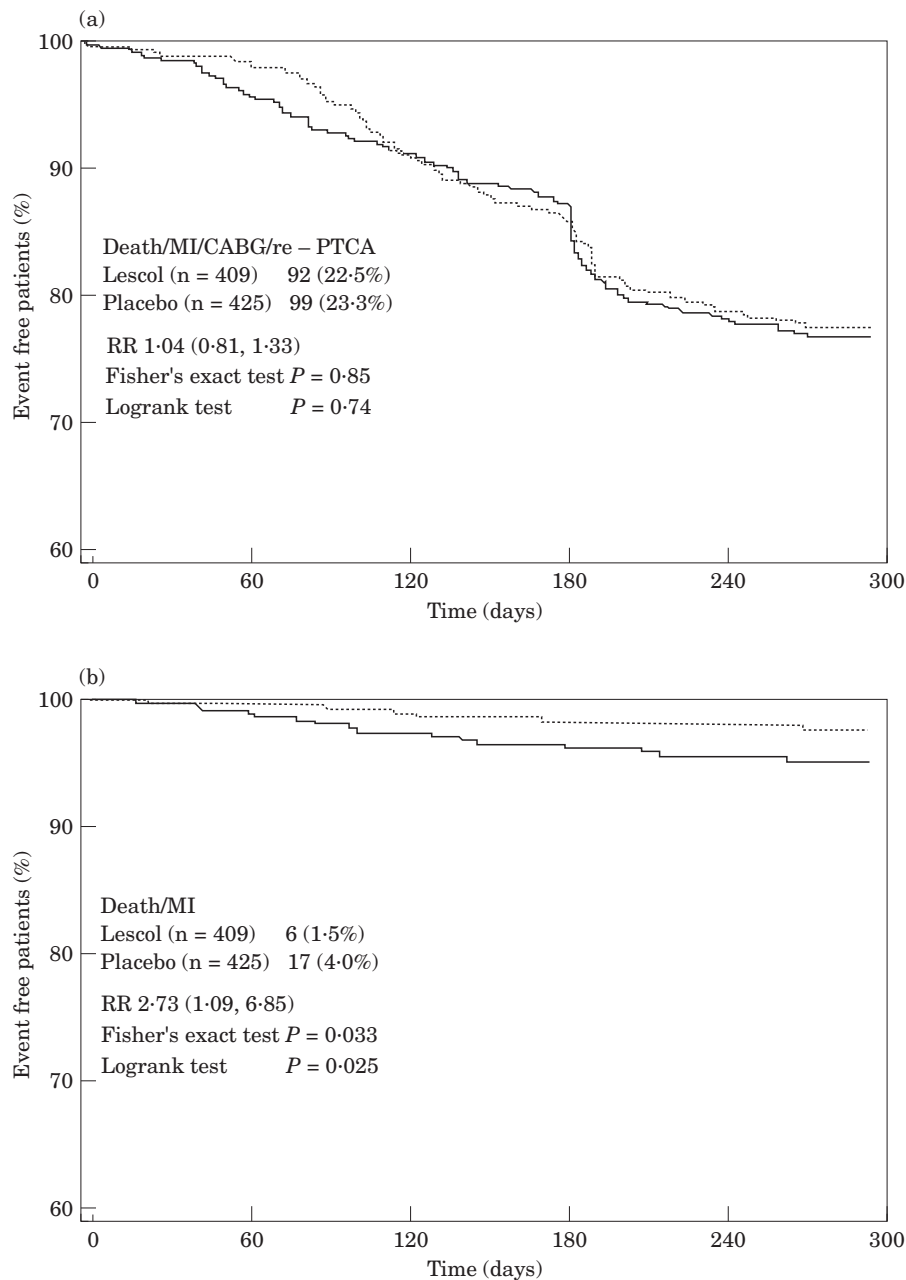


Figure 2 (a) Event-free survival curves with respect to all major cardiac events for both treatment groups. P values are calculated using the logrank test. (b) Event-free survival curves with respect to the combined end-point death and myocardial infarction (MI) for both treatment groups. P values are calculated using the logrank test.

whereas pravastatin sera exhibited no such effect^[26]. This was the first demonstration that a statin might inhibit human myocyte proliferation. Despite the achievement of effective serum levels and adequate pre-treatment to reach appropriate tissue levels, the in-vitro observed efficacy did not translate into in-vivo effect on restenosis, as measured by quantitative coronary angiography. Compliance with study medication was considered satisfactory, as judged by the LDL cholesterol changes already observed at the angioplasty visit

(2 weeks after initiating therapy) and maintained at follow-up angiography. To attempt to explain the apparent lack of effect, a number of scenarios may be considered. Firstly, although the experimental evidence indicates that the action of fluvastatin is observed in all activated cells (due to the inhibition of mevalonate synthetase), it is possible that the smooth muscle cells in culture may not appropriately model the hypertrophic, hyperplastic myocyte changes triggered by angioplasty. Experimental exposure of isolated

myocytes to fluvastatin in the culture medium may be quite different from the in-vivo situation, especially of proliferation after angioplasty is initiated from deep within the arterial media or adventitia^[22].

Secondly, examination of the results observed in the in-vitro human arterial model suggests that the inhibitory effect of fluvastatin in-vitro may be variable. In the clinical situation, which is characterized by fluctuations in the drug plasma level, it is conceivable that a steady state inhibition is not reached. Consequently, at times, growth suppression may be in abeyance, allowing sufficient proliferation to promote restenosis. Moreover, extensive studies of regional intracoronary pharmacokinetics (using radiolabelling) have revealed that even locally administered compounds in apparently effective doses, proportionally much higher than could be given orally, fail to reach adequate pharmacodynamic concentrations at the target site^[23].

Thirdly, restenosis is a much more complex process than simple proliferation. Cellular matrix production and the only recently intracoronary ultrasound demonstrated phenomenon of chronic vessel remodelling may explain at least 50% of the luminal loss in the 6 months after successful angioplasty^[24]. The implication of this is that since quantitative coronary angiography cannot provide measurements of these components of luminal renarrowing, a potential anti-proliferative effect of fluvastatin might have been masked by a lack of effect on vessel retraction or remodelling. Serial intracoronary ultrasound would be required to detect such subtle potential differences in the vessel wall response to balloon injury between the treatment groups, but when FLARE was conceived, intracoronary ultrasound was still very much investigational and not widely used and the described phenomena had not yet been recognized.

It is thus conceivable that fluvastatin may have had some inhibiting effect on smooth muscle cell proliferation in FLARE without actually affecting luminal loss, although the complete superimposition of the cumulative distribution curves for minimal luminal diameter indicate absence of even the slightest angiographically detectable difference between the treatment and placebo groups. It would be moot to suggest that either matrix production or chronic remodelling could be reasonably expected to be influenced by fluvastatin. Ultimately, the now recognized relative importance of chronic vessel remodelling mitigates against the likelihood of any systemically administered anti-proliferative agent exerting any detectable influence on restenosis after balloon angioplasty. Accordingly, future trials investigating anti-proliferative agents must use a predominantly proliferative clinical model, such as post successful stent implantation, where restenosis really represents new tissue growth^[25].

How can the increased infarct free survival in the fluvastatin treated group be explained?

Although this study had a primary angiographic end-point, it was adequately powered to detect a difference in major adverse cardiac events at 40 weeks. At 40 weeks

there was no difference in the incidence of the combined clinical end-points of death, myocardial infarction, CABG and re-intervention. However, a significantly lower incidence of death and non-fatal myocardial infarction (1.4% in the fluvastatin group, compared with 4% in the placebo group ($P=0.025$) relative risk reduction 0.37 [0.18, 0.89]) was observed in the fluvastatin group. This observation, which was not a pre-specified trial end-point in FLARE, was unexpected and has not been described in the lovastatin or PREDICT trials; in fact the frequency of these events was somewhat higher in the lovastatin and pravastatin groups compared to placebo in those trials. However, the finding is in keeping with reduced cardiovascular events observed in angiographic regression trials and the clinical lipid lower trials^[26–28]. Accordingly, despite the possibility that this is a chance finding (because of a type II error, reflected by the wide confidence intervals for the relative risk reduction in death or myocardial infarction by fluvastatin), it is possible to explain the finding on the basis of plaque stabilization secondary to effective and rapid reduction in total and LDL cholesterol and apolipoprotein B. There are also potential non-lipid effects of fluvastatin which could explain the observed clinical effect which deserve to be mentioned. Experimental data suggest that fluvastatin can favourably influence thrombogenic and hypofibrinolytic factors involved in acute vascular events. Colli and co-workers^[29] have recently demonstrated that fluvastatin, in a dose-dependent manner interferes with macrophage-derived tissue-factor production, while pravastatin had no such effect. The same group showed that fluvastatin can blunt the increased synthesis of endothelium derived PAI-1 induced by oxidized LDL. Additionally fluvastatin 40 mg daily in coronary patients significantly reduces circulating levels of tPa antigen^[30], which is considered a marker of endothelial damage. Accordingly, although the clinical benefits in FLARE may have arisen by chance, they do have plausible mechanistic explanations and evaluation in a definitive trial is indicated.

Conclusions

In this adequately powered randomized double-blind placebo-controlled trial, experimentally demonstrated anti-proliferative effects of fluvastatin on human arterial smooth muscle cells failed to translate into a clinical effect in reducing restenosis after successful coronary balloon angioplasty, despite a 2–4 week pre-angioplasty treatment period, whereby adequate tissue levels had been reached. A significantly lower incidence of death and myocardial infarction was, however, observed in the fluvastatin treatment group, representing the first demonstration of a potentially important secondary prevention effect of statin therapy only 6 months after successful angioplasty. Although the FLARE trial was not designed or powered to detect such an effect, and it could be serendipitous, this finding has prompted the

inauguration of a new double-blind randomized trial, now already in the inclusion phase, specifically intended to evaluate the effect of long term fluvastatin therapy on the occurrence of major adverse cardiac events after successful percutaneous coronary intervention.

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Appendix

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