Prevention of Restenosis After Coronary Balloon Angioplasty: Rationale and Design of the Fluvastatin Angioplasty Restenosis (FLARE) Trial

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Prevention of restenosis after successful percutaneous transluminal coronary balloon angioplasty (PTCA) continues to present the greatest therapeutic challenge in interventional cardiology. Experimental and pathological studies describe restenosis as no more than the biologic healing response to arterial injury. Studies of serial quantitative coronary angiography have demonstrated that this biologic process may be measured as the loss in minimal luminal diameter (MLD) from post-PTCA to follow-up angiography and that it is essentially ubiquitous and normally distributed. Thus, quantitative coronary angiography has become the gold standard for evaluation of the angiographic outcome of clinical trials of new agents and devices aimed at prevention of restenosis. The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors inhibit biosynthesis of mevalonate, a precursor of non-sterol compounds involved in cell proliferation, and thus may control the neointimal response, which forms the kernel of restenosis. Experimental evidence suggests that fluvastatin may exert a greater direct inhibitory effect on proliferating vascular myocytes than other HMG-CoA reductase inhibitors, independent of any lipid-lowering action. The Fluvastatin Angioplasty Restenosis (FLARE) Trial was conceived, in collaboration between the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands, and Sandoz Pharma, to evaluate the ability of fluvastatin 40 mg twice daily to reduce restenosis after successful single-lesion PTCA. Treatment of suitable patients begins 2 weeks before PTCA and continues after successful PTCA (residual diameter stenosis <50%, without major cardiac complications) to follow-up angiography at 26 ± 2 weeks. Restenosis is measured by quantitative coronary angiography at a core laboratory as the loss in MLD from post-PTCA to follow-up angiography. It is calculated (90% power, $\alpha = 0.05$) that 730 evaluable patients will be needed to test the hypothesis that fluvastatin will reduce the expected post-PTCA loss in MLD by 40%. Serial lipid analysis will be carried out at a central laboratory. Trial evaluation is focused on the primary endpoint (change in MLD) but includes primary clinical endpoints (death, myocardial infarction, or the need for coronary artery bypass graft surgery or reintervention up to 40 weeks after PTCA) as well as secondary and tertiary clinical, angiographic, and laboratory endpoints. According to this methodologic approach, the effect of fluvastatin on luminal renarrowing and clinical events after successful PTCA as well as possible associations of lipid parameters with restenosis can be comprehensively investigated.

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Lesion recurrence, or restenosis, remains the bane of percutaneous transluminal coronary angioplasty (PTCA) in the treatment of obstructive coronary artery disease.[1] Much has been written on the pathobiologic nature of restenosis as well as conceptual, intellectual, and methodologic approaches to its study, elaboration, and discussion in the clinical field. The fundamental pathogenesis of restenosis appears to mimic, for the most part, the biologic tissue-healing response to injury.[2,3] A brief and general summary of the mechanisms and time course begins with the obliga-

tory intimal disruption caused by effective coronary angioplasty, in response to which there is immediate platelet aggregation and adhesion, with consequent release of a plethora of intracellular substances, including growth factors.[2,4-9] Many growth factors have been identified as participating in the process that culminates in neointimal hyperplasia,[10] but the complete picture of their complex interaction, at cellular and subcellular levels in vivo, remains to be clarified, although rapid and extensive progress is being made. Suffice it to say that the end result of the cascade of reactions initiated by vessel wall trauma is the conversion of the quiescent contractile smooth muscle cell to its synthetic proliferative phenotype.[4-10] According to the conventional understanding of the process,[2] this activation is initiated in the media,[11] but within the first few days, migration takes place into the disrupted intima, where endothelial cells are also proliferating in an attempt to restore an intact luminal surface.

Within the first few days after trauma, the synthetic smooth muscle cells already begin to produce abundant proteoglycan[11] (a bulky, extracellular matrix substance). By 2 weeks after injury, some of the synthetic smooth muscle cells already begin to readopt a quiescent, contractile appearance,[11,12] and this pattern progresses at a rate that depends on a number of factors, particularly the extent of injury, and parallels the gradual replacement of proteoglycan in the extracellular matrix by collagen during the succeeding months.[12,13] Throughout this period, the now characteristic histologic appearance of intimal hyperplasia may be observed, i.e., proliferating smooth muscle cells in varying concentrations, against a background of a loose, mainly proteoglycan, matrix.[12,13] By 6 months, basal conditions of the preinjury vessel wall tend to have been restored, with intact endothelial layer and predominance of contractile smooth muscle cells, now in a mainly collagenous matrix.[14] Few human postmortem studies have been conducted, and these involve small patient numbers; however, findings in lesions where PTCA had been carried out >2 years previously appear to be histologically indistinguishable from conventional atherosclerotic plaque.[12]

ASSESSMENT OF RESTENOSIS IN CLINICAL TRIALS

Contribution of Quantitative Coronary Angiography: Although improvement in the functional and symptomatic status of patients is the ultimate therapeutic goal when undertaking coronary intervention, evaluation of the effectiveness of therapy, using clinical parameters, is subjective and thus prone to considerable imprecision.[15] Similarly, the use of noninvasive tests of myocardial perfusion or function has been reported to be unreliable for this specific purpose.[15-17] Therefore, because coronary angiography has been (and is still) the only universally available coronary artery imaging technique, most clinical studies investigating restenosis have become angiographically oriented. This situation has been enhanced by the advent of sophisticated, objective, and reproducible quantitative coronary angiography analysis systems for measurement of coronary luminal dimensions.[18] Thus, traditional visual assessment of the angiogram has been superseded,[19] and increasing application of quantitative coronary angiography has considerably advanced understanding of the general process of restenosis after interventions. Further, the physiologic relevance of luminal measurements provided by reliable quantitative assessment systems has now been well described.[20,21] The most important contributions of quantitative coronary angiography have emerged from detailed study of large patient groups undergoing serial coronary angiography before and after intervention and at predesignated 6-month follow-up, in the context of multicenter clinical trials or large single-center experience. Luminal renarrowing after intervention is now universally perceived as a normally distributed phenomenon that affects treated lesions to variable degrees,[22,23] can be angiographically detected as early as 1 month after intervention, and tends to peak at about 6 months, with minimal further progression after that.[24,25] As already described, such a time course has been demonstrated in experimental models of tissue injury and arterial injury in particular, allowing the interpretative conclusion that the angiographic perception of restenosis as a normally distributed process of luminal renarrowing or loss[22,23] is well in keeping with the paradigm of a biologic phenomenon. The application of categorical definitions for the occurrence (or nonoccurrence) of restenosis, as has been carried out in many large trials until recent years, is therefore inappropriate and provides an incomplete and inaccurate evaluation of the process.[26-28] To compare the effects of alternative treatment options for prevention or control of the extent of this tissue response to injury, a continuous approach to evaluation is clearly mandatory, whereby all patients treated in a common manner are considered as a single group.[26-29]

As a consequence of the limited knowledge of

the specific pathobiologic pathways leading to neo-intimal hyperplasia, many different pharmacologic interventions, including antiplatelet agents, thromboxane receptor antagonists, serotonin antagonists, calcium antagonists, antimitotic agents, angiotensin-converting enzyme inhibitors, steroids, somatostatin analogues, anticoagulants, and fish oils have been used in prospective randomized trials to prevent restenosis, without conclusive success.[29-31] Until 1990, most clinical trials aimed at restenosis prevention were limited in their methodologic approach by 3 major shortcomings: (1) insufficient patient population, (2) incomplete angiographic follow-up, and (3) diversity in the angiographic definition of restenosis.[26] Since then, a number of large, carefully designed, randomized, placebo-controlled trials have been carried out in Europe and North America, with quantitative coronary angiographic endpoints and high rates of complete angiographic follow-up.[32-35] However, in 1994, it may still be confidently stated that to date no pharmacologic agent has been convincingly demonstrated to reduce or control the degree of luminal renarrowing after successful PTCA.[31]

Potential role of HMG-CoA reductase inhibitors in prevention of restenosis: The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are the most recently introduced class of agents aimed at management of hyperlipidemia. By inhibiting this enzyme, the reduction of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis, is prevented.[36] The result is primarily a reduction in low density lipoprotein cholesterol, because the low density lipoprotein cholesterol receptor is stimulated by depletion of the endogenous cholesterol pool. Data from many clinical investigations of these compounds have suggested that their beneficial effect on progression of atherosclerosis is due to their lipid-lowering properties.[37,38] Use of these compounds has also allowed the appreciation of the importance of mevalonate as a precursor of isoprenoid groups as well as cholesterol in such fundamental biologic processes as cell growth and proliferation.[39] In addition, mevalonate (or its product or products) has recently been shown to be necessary for esterification of intracellular cholesterol by acetylated low density lipoprotein cholesterol in macrophages,[40] a process that may lead to lipid accumulation in the arterial wall, which is a fundamental step in atheroma formation.[41]

Of even greater interest for restenosis prevention is a recent experimental study[42] in normocholesterolemic rabbits, which investigated a possible direct effect of 4 HMG-CoA reductase inhibitors on smooth muscle cell proliferation after carotid artery injury (imparted by surgical placement of a hollow external Silastic collar), independent of any lipid-lowering action. A direct independent myocyte inhibitory effect was indeed confirmed, and, further, considerable differences were unveiled in the degree of inhibition of neointimal formation between the 4 compounds evaluated, with fluvastatin (Sandoz) demonstrating the greatest effect (over simvastatin, lovastatin, and pravastatin, in that order). These differences in neointimal inhibitory effect between the compounds were attributed to diversities in relative lipophilicity, thus in tissue distribution and also in the relative efficacy of inhibition of HMG-CoA reductase. Because the inhibitory effects of HMG-CoA reductase inhibitors on myocyte proliferation have previously been prevented by addition of mevalonate to a culture of proliferating rat carotid smooth muscle cells, it has been concluded that blockade of intracellular mevalonic acid synthesis precludes cellular proliferation. In addition, because a number of studies have demonstrated that mevalonate and some of its metabolites are necessary for many cellular functions, ranging from cholesterol synthesis to growth control,[40] blockade of its synthesis by HMG-CoA reductase inhibitors may simultaneously inhibit myocyte proliferation through a number of mechanisms.

Trials with HMG-CoA reductase inhibitors in prevention of restenosis: Lovastatin has been used in 2 clinical trials to prevent restenosis after coronary angioplasty, with conflicting results.[43-45] In the first trial,[43] investigators reported a reduction in the frequency of recurrence of a diameter stenosis ≥50% that ranged from 45% in the untreated to 15% in the treated group. However, the study was not blinded, angiographic follow-up was available in only two thirds of treated and one third of untreated patients, and only 157 patients were included—thus covering each of the 3 major limitations of the clinical restenosis trials already mentioned.[26] In fact, the use of a categorical definition of angiographic restenosis has been widely demonstrated as unsatisfactory and insensitive for the objective evaluation of outcome of so-called restenosis prevention trials.[26-29] According to these criteria, this study must be considered to be fraught with weakness and the results of doubtful value.

The second lovastatin trial was designed as a multicenter, double-blind, placebo-controlled trial to determine whether administration of lovastatin,

40 mg orally twice daily, starting 7–10 days before and continuing for 6 months after PTCA, would reduce the rate of restenosis (defined as a diameter stenosis >50% at follow-up angiography) after successful PTCA.[45] The main working hypothesis was that by lowering serum lipids, lovastatin therapy might promote endothelial healing and restoration of normal endothelial-derived relaxation and thus prevent restenosis. Although significant lipid-lowering effects were indeed achieved by lovastatin compared with placebo in this trial, no prevention of restenosis could be demonstrated in terms of reduction in the frequency of recurrence of a diameter stenosis ≥50% or in the final angiographic minimal luminal diameter (MLD) at follow-up. Thus, it was concluded that lipid lowering does not prevent restenosis after successful coronary balloon angioplasty.[45]

THE FLUVASTATIN ANGIOPLASTY RESTENOSIS (FLARE) TRIAL

Design, aim, and working hypothesis: Fluvastatin is a novel, fully synthetic HMG-CoA reductase inhibitor that is subject to a high first-pass hepatic metabolism, with correspondingly low systemic bioavailability and a short plasma half-life. The Fluvastatin Angioplasty Restenosis (FLARE) Trial was conceived and inaugurated as a multicenter, multinational, randomized, double-blind, placebo-controlled trial to investigate whether fluvastatin, at a dosage of 40 mg twice daily for 2–4 weeks before and continued for 26 ± 2 weeks after successful coronary balloon angioplasty (see Appendix 1), could reduce the degree of luminal renarrowing during follow-up, measured by an automated quantitative angiographic system (Appendix 2) as the deterioration in MLD from post-PTCA to follow-up angiography. The working hypothesis was that fluvastatin would reduce luminal renarrowing by a direct inhibitory effect on proliferating smooth muscle cells through the action described above, based on previous experimental findings. Taking account of the aggressive immediate biologic reaction to arterial injury already described, it was decided to incorporate a 2-week pre-PTCA treatment phase in the FLARE Trial to allow sufficient time for tissue distribution and accumulation of fluvastatin in advance of balloon angioplasty.

Fundamental design and structural differences between the fluvastatin and lovastatin restenosis trials: Although the FLARE study was designed while the Lovastatin Restenosis Trial was still in progress, the steering committee (Appendix 3) and investigators (Appendix 4) were not deterred by the neutral preliminary results of the lovastatin trial for a number of reasons.

First, the primary working hypotheses of the 2 trials are inherently different: the FLARE study investigates fluvastatin's potentially beneficial direct inhibitory effect on the coronary vascular myocyte, independent of any influence on serum lipid concentrations, as stated previously, whereas the Lovastatin Restenosis Trial investigated aggressive lipid lowering as the putative antirestenosis mechanism.

Second, in experimental studies, although all the HMG-CoA reductase inhibitors were found to inhibit myocyte proliferation, fluvastatin demonstrated greater inhibitory effects on neointimal formation than did lovastatin.

Third, the pretreatment period in the FLARE Trial is 2–4 weeks before angioplasty, compared with 7–10 days in the lovastatin trial, to ensure adequate tissue distribution of fluvastatin.

Fourth, the primary categorical endpoint chosen by the lovastatin group could be considered insensitive for measuring prevention of luminal renarrowing by a pharmacologic agent, and also the target reduction of 50% in the angiographic restenosis rate could be considered a little overambitious; thus, a type II error may have been inadvertently made (only 322 patients had angiographic follow-up, compared with >500 patients in the CARPORT[32] Trial, >600 patients in each of the MERCATOR, PARK,[33,35] and REDUCE trials, and >1,200 patients in the MARCATOR[34] and HELVETICA trials). The sample size in the lovastatin trial, as calculated, was also reported to be sufficient to detect a difference of 0.36 mm in MLD at follow-up between the 2 groups, with 90% power and at an α level of 0.05. Such a treatment effect would again have to be retrospectively considered to be an ambitious target, because even randomized comparison of Palmaz-Schatz coronary stent implantation with balloon angioplasty in 520 patients demonstrated a superior MLD at follow-up of only 0.18 mm (favoring the stent group)—although this was, nevertheless, statistically significant (p = 0.004).[46]

In the FLARE Trial, 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 4 previous trials with different agents was 0.30 mm.[32–35] Thus, it was assumed that the placebo group in the FLARE Trial would demonstrate a similar degree of loss. With fluvastatin, the target treatment effect de-

	Visit (wk)				
TABLE I Chronological Study Schedule	1 (−4 to −2)	2 (0)	3 (6)	4/5 (26 ± 2)	6 (40)
Randomization	X				
Clinical assessment	X	X	X	X	X
Concomitant medication	X	X	X	X	X
Physical examination	X	X	X	X	X
Lipid assessment	X*	X	X	X*	
Safety laboratory evaluations	X	X	X	X	
Fibrinogen	X			X	
Electrocardiogram	X	X	X	X	X
Exercise test	±†			X‡	
Dispensing	X		X		
Angioplasty		X			
Angiography (for quantitative coronary angiography)		X		X	
Compliance check		X	X	X	
Adverse events check		X	X	X	X

*Lipoprotein(a) and apolipoprotein A1 and B will be measured only at visits 1 and 4.
†Exercise testing is done at the discretion of the investigator but is not a requirement of the trial.
‡Exercise testing must be performed no more than 2 weeks before follow-up angiography.

cided on was a 30% reduction in luminal loss. To detect such a difference with 90% power at an α level of 0.05, approximately 730 evaluable patients would be required. Allowing for an estimated dropout rate of 15% (based on experience with previous trials and taking account of the pretreatment phase required in the FLARE Trial), 830 patients would need to be randomized. Such a total number of evaluable patients would also allow the detection of a difference of 30% in the incidence of major adverse cardiac events (death, myocardial infarction, coronary artery bypass graft surgery, or reintervention) between the treated and placebo groups, with a power of > 90% at an α level of 0.05.

Trial chronology: The trial commences (visit 1, weeks −4 to −2, depending on when PTCA is performed; Table I) when eligible patients who have been screened and fulfill all inclusion and exclusion criteria (Table II) and have given informed consent are randomized to the control or treatment groups. Patients in the control group receive placebo twice daily and patients in the treatment group receive fluvastatin 40 mg twice daily to be taken orally for a continuous period of 28 ± 4 weeks (2–4 weeks before PTCA and until follow-up angiography at 26 ± 2 weeks).

After a minimum of 2 weeks, the patient returns for PTCA, prior to which clinical and laboratory assessments are carried out (visit 2, week 0). Trial medication is continued during the hospital stay, the length of which is at the discretion of the treating physician. Patients undergoing successful PTCA (defined as diameter stenosis <50%) without reaching a primary clinical endpoint continue on trial medication. A clinical follow-up visit is required 6 weeks after PTCA (visit 3, week 6). A further clinical assessment, with exercise testing, is required prior to follow-up angiography, which is carried out 26 ± 2 weeks after PTCA. The clinical and laboratory assessments and exercise test must be carried out prior to angiography but may be done during the same visit or on a separate day, according to the preference of the treating physician and individual patient (visits 4 and 5, weeks 24–28). The investigators decided that final clinical follow-up for evaluation of clinical endpoints would occur 40 weeks after PTCA (visit 6, week 40) to allow sufficient time for performance of justified (on the basis of recurrent symptoms or demonstrated exercise-induced ischemia) elective reintervention or bypass graft surgery as determined by clinical and angiographic follow-up at 26 ± 2 weeks. Because of variable waiting time for elective surgical or nonsurgical intervention throughout the participating countries, it was decided that 40 weeks was the most practical time for final clinical follow-up.

Primary angiographic endpoint: The primary endpoint for the FLARE Trial is the change in MLD, in millimeters, between the post-PTCA and the follow-up angiogram, 26 ± 2 weeks after the PTCA procedure, measured by quantitative coronary angiography. If, for whatever reason, angiography is carried out prior to 14 weeks after PTCA, further angiography within the recommended time window will be required, unless a primary clinical endpoint, as defined below, has been reached.

Secondary angiographic objectives: The secondary objectives are: (1) minimal luminal diameter at follow-up angiography; and (2) the relation between acute luminal gain and late luminal loss for the treatment and control groups, taking all other potentially confounding parameters into consideration, using multiple linear regression analysis techniques to investigate whether treatment with fluvastatin beneficially alters, or modifies, the healing response of the vessel wall to the injury imparted at PTCA.

Tertiary angiographic objective: Incidence of restenosis is defined according to a selection of

categorical angiographic criteria (see definitions in Appendix 1).

Primary clinical endpoints: A primary clinical endpoint will be considered to have been reached on the occurrence of any 1 of the major adverse cardiac events described later, before 40 weeks postsuccessful PTCA. At the outcome of the trial, the primary clinical endpoints will be described in terms of the incidence of the following events; for any patient experiencing > 1 event, the *first* event reached will be considered.

1. Death: Postmortem examination is recommended in all randomized patients who die during the course of the trial. If there is no clear evidence to the contrary, any deaths occurring during the trial will be considered to be cardiac.

2. Nonfatal myocardial infarction: The occurrence of myocardial infarction will be defined as the finding of a typical temporal pattern of serum cardiac enzyme change; in particular, documented elevation of serum creatine kinase levels to greater than twice the upper limit of normal for the laboratory and/or a > 2-fold increase in the creatine kinase-MB fraction, with return to within the accepted normal range. If there are no unambiguous cardiac enzyme abnormalities, the finding of typical evolutional electrocardiogram patterns of myocardial infarction or of "new" pathologic Q waves will be considered diagnostic of myocardial infarction. Evidence to support diagnosis of myocardial infarction must be provided by the investigator to facilitate final adjudication by the critical events and safety and data monitoring committees.

3. The need for coronary artery bypass graft surgery or for stent implantation (which is considered equivalent to the need for coronary artery bypass graft surgery).

4. Need for reintervention 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 perfusion balloon catheter at the discretion of the treating physician is acceptable and does not constitute an endpoint or exclusion from the trial.)

Secondary and tertiary clinical objectives: All clinical events occurring during the 40-week trial will be recorded, for the purpose of reporting both a ranked classification, as a secondary clinical objective, and a total event count (whereby multiple entries per patient are allowed) as a tertiary clinical objective of the trial. (Decisions made within the 40-week trial period to carry out further

TABLE II Patients—Inclusion and Exclusion Criteria in the FLARE Trial

Inclusion criteria

Men and women (who are not potentially childbearing) with native primary coronary artery disease amenable to PTCA. Patients with previous intervention of CABG surgery are acceptable if the target lesion is a native primary lesion only

Clinical status stable enough to allow at least 2 weeks treatment prior to PTCA

Patients must be suitable for CABG surgery, if required

Patients must be agreeable to follow-up angiography 26 ± 2 weeks following PTCA

Patients must give informed consent

Exclusion criteria

General criteria:

Lack of informed consent (for whatever reason)

Females of childbearing age (i.e., only women who are at least 2 years postmenopausal or who have been surgically sterilized for at least 1 year may be included; premenopausal women using contraceptive methods are ineligible)

Participation in another study of any investigational agent within the past 30 days or previous participation in this study

Malignant or other disease where life expectancy is < 1 year

Major surgery within previous 3 months

Impaired intellectual or cognitive function likely to prevent clear understanding of the trial purpose and requirements or to compromise compliance with trial procedures

History of drug, alcohol, or other substance abuse, making complete compliance with the requirements of the FLARE Trial unlikely

Specific exclusion criteria related to performance of PTCA or coronary angiography:

Allergy to contrast media

Allergy to or intolerance of aspirin

Target lesion in an unprotected left main coronary artery

Target lesion in a bypass graft (arterial or venous)

Previous intervention of the intended target lesion

Target lesion a totally occluded vessel of > 3 months' duration

Excessively tortuous or diseased peripheral arteries or complex peripheral arterial anatomy making PTCA or follow-up angiography difficult or dangerous

Known or suspected bleeding diathesis

Severe renal dysfunction (serum creatinine > 20 mg/liter [180 μmol/liter] or urea > 1,200 mg/liter)

History of a cerebrovascular accident or thromboembolic event within the previous 6 months

Presence of > 1 severe lesion requiring intervention

Intention to use any interventional device other than conventional balloon angioplasty

Uncontrolled systemic hypertension (diastolic blood pressure > 100 mm Hg or systolic blood pressure > 180 mm Hg, despite medical therapy)

Poor left ventricular function with an ejection fraction < 30%

Exclusion criteria related to lipids, lipid metabolism, and the use of fluvastatin

Known hypercholesterolemia or hypertriglyceridemia or detection of fasting low density lipoprotein cholesterol > 6.0 mmol/liter or triglycerides > 4.5 mmol/liter, according to the local laboratory, within 4 weeks prior to randomization

Evidence or history of medical condition that might place the patient at risk or obscure the evaluation of the safety, tolerability, or efficacy of fluvastatin (e.g., autoimmune diseases, nephrotic syndrome, multiple myeloma, dysglobulinemia or macroglobulinemia, glycogen storage disease, chronic pancreatitis, and porphyria)

Use of any lipid-lowering agent (including fish oils or nonprescription medication that is known to affect serum lipids) within the previous 4 weeks or exposure to probucol within the previous 12 months

Myocardial infarction in the previous 3 months associated with a rise in creatine kinase to more than twice the upper limit of normal for the local laboratory

Known preexisting gallbladder disease, liver disease, or abnormal liver function (aspartate or alanine aminotransferase or serum bilirubin, > 20% above the upper limit of normal for the local laboratory, within 4 weeks of randomization)

Chronic muscular disorder, wasting disease, or dystrophy

Non–insulin-dependent diabetes (a potential interaction between fluvastatin and sulfonylureas has not been completely ruled out)

CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angiography.

intervention after this time will not be included as clinical endpoints.)

Lipid and laboratory aspects: Patients with hyperlipidemia or those with a measured fasting low density lipoprotein cholesterol >6.0 mmol/liter or fasting triglyceride level >4.5 mmol/liter (by local laboratory) within 4 weeks of randomization are excluded from the trial on the ethical principle that they require lipid-lowering therapy. Prior to randomization, all patients must have documented evidence of fasting lipid levels below these limits within the previous 4 weeks.

The effect of trial medication on serum lipid levels will be assessed by performance of a comprehensive lipid profile [total cholesterol, low density and high density lipoprotein cholesterol, lipoprotein(a), apolipoproteins A1 and B, and triglycerides] at randomization and prior to angiographic follow-up at 26 ± 2 weeks after PTCA. Cholesterol and triglycerides will also be measured pre-PTCA (2–4 weeks after commencement of trial medication) and 6 weeks after PTCA. Lipid parameters and temporal changes therein will be compared between the 2 groups and correlated with the angiographic and clinical endpoints.

In addition to acceptable serum lipid levels, all patients must have documented hematologic, hepatic, and renal indices and creatine kinase levels within the acceptable range (Table II) according to local laboratory limits prior to randomization.

At randomization, blood samples will be taken for measurement of these parameters at a central laboratory. Similar laboratory tests will be repeated at each patient visit to detect any potential adverse biochemical or hematologic effects of trial medication. In the final analysis, the treatment and placebo groups will be compared for frequency and severity of abnormalities detected.

From randomization, all blood samples will be specially packaged in protective containers and sent by courier to central laboratories for blinded analysis. Local laboratory results will be 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 will be blindly evaluated by the critical events committee and by the safety and data monitoring committee, who will be unblinded). Central laboratory results will be used to monitor the safety of trial medication, and relevant laboratory abnormalities will be reported to responsible investigators and the data coordinating center.

Trial medication:

COMPLIANCE, SAFETY, AND TOLERABILITY: In addition to laboratory tests, compliance with trial medication will be assessed at each patient visit, and all adverse experiences (any deterioration in clinical status during the course of the trial is considered an adverse experience; its relation with trial medication is determined according to well-known guidelines) will be documented in the case record form.

DISCONTINUATION OF TRIAL MEDICATION: The trial medication is discontinued if: (1) PTCA is abandoned without the performance of balloon dilation or if PTCA is not performed, for whatever reason; (2) PTCA is unsuccessful (diameter stenosis >50% post-PTCA) whether or not a major adverse event occurs; (3) a primary clinical endpoint is reached or if a major adverse event (as defined in Appendix 1) occurs; (4) a protocol violation occurs. Discontinuation of trial medication does not imply withdrawal from the trial, and follow-up clinical observations must be made as scheduled to complete the safety and intention-to-treat evaluation and analysis.

CONCOMITANT MEDICATION: Other medications included: (1) All patients will receive acetylsalicylic acid up to 325 mg once daily throughout the trial period; (2) each set of angiographic recordings must be preceded by an intracoronary injection of 1–3 mg isosorbide dinitrate or 0.1–0.3 mg glyceryl trinitrate to control vasomotor tone. Oral or sublingual nitrates may be given during the follow-up period when indicated; (3) calcium antagonists may be given at the discretion of the treating physician, during the PTCA procedure or during the in-hospital period; (4) antiplatelet agents and oral anticoagulants should not be used during the trial period.

EXCLUDED MEDICATION: Excluded medications that may interfere with evaluation or interpretation of study results include all lipid-lowering agents, steroid hormones or oral contraceptive agents, thyroid hormone replacement (acceptable only if the patient is euthyroid and the dose being taken has not changed in the previous 2 months and is also unlikely to change during the trial; otherwise, the patient is excluded), erythromycin, ketoconazole, cyclosporine, and antiepileptic therapy.

STATISTICAL PLAN: The calculation of patient numbers required for appropriate evaluation of the trial outcome has already been described.

EVALUATION OF SAFETY: All patients randomized and receiving at least 1 dose of trial medica-

tion will be included in an evaluation of the safety of trial medication (Table III).

INTENTION-TO-TREAT ANALYSIS: The primary parameter for the confirmatory analysis is the angiographically determined change in MLD from the post-PTCA to the follow-up angiogram, using the intention-to-treat population (shown in Table II). The control and treatment groups will also be compared with respect to baseline clinical and angiographic parameters and angioplasty procedural data, the occurrence of primary clinical endpoints up to week 40 following angioplasty, and the secondary and tertiary clinical and angiographic endpoints or objectives, compliance with and tolerability of trial medication, use of concomitant medication, incidence of adverse events, lipid and biochemical parameters, clinical status at follow-up, and exercise test results prior to follow-up angiography. Continuous variables, especially the change in MLD during and at follow-up, will be compared by analysis-of-variance techniques, taking potential center (investigating institution) interaction into account. Categorical variables will be compared by Mantel-Haenszel test procedures. Incidence of clinical endpoints, adverse events, and patient dropout from the trial after randomization will be compared using contingency method tables (i.e., chi-square statistics). Binary restenosis rates (according to the conventional definitions employed) will be compared by Fisher's exact test.

Multiple logistic and linear regression analysis techniques will be used to relate primary angiographic outcome (change in MLD during follow-up) to primary clinical outcome (incidence of major adverse cardiac events, where only the first event experienced is counted for each patient) and to lipid outcome (change in lipid parameters during follow-up), taking all other potentially confounding factors into consideration (for example, luminal gain, MLD pre-PTCA, reference vessel diameter, lesion location, and duration of preexistent angina). In this manner, independent determinants of angiographic, clinical, and lipid outcome may also be investigated.

PER PROTOCOL ANALYSIS: A per protocol analysis will also be performed on patients as characterized in Table II. All assessments in the intention-to-treat analysis will also be evaluated by the per protocol analysis.

SUMMARY

The rationale for use of fluvastatin in the FLARE Trial is thus based on good experimental evidence that suggests potential treatment benefit

TABLE III Statistical Plan	
Patients	Parameter of Analysis
All randomized patients who received at least 1 dose of trial medication, whether or not PTCA was performed	Clinical events (safety analysis)
All randomized patients who received at least 1 dose of treatment and underwent successful PTCA	Clinical events Angiographic endpoints (intention-to-treat analysis)
Patients treated per protocol, i.e., all randomized patients who:	
Underwent successful PTCA as defined in the protocol	Clinical events Angiographic endpoints (per protocol analysis)
Completed the treatment course according to the protocol (28 weeks ± 15% missed medication is acceptable)	
Underwent angiography and clinical follow-up according to the protocol	

in reducing neointimal proliferation after successful angioplasty by direct inhibition of myocyte proliferation. The 2 central design features of the FLARE study are: (1) it is a prospective, randomized, double-blind, placebo-controlled trial with an objective primary angiographic endpoint, namely, the change in MLD from post-PTCA to follow-up angiography, measured by a computer-assisted, automated edge detection system in a central, independent, core laboratory; and (2) a pre-PTCA treatment phase of 2–4 weeks will allow adequate accumulation of fluvastatin in tissue before vessel injury occurs at PTCA. In addition, this trial provides an opportunity to compare prospectively and evaluate the relation of various lipid parameters and changes therein, as a consequence of therapy with fluvastatin, to the development of luminal renarrowing (and major adverse cardiac events) after successful PTCA in a large patient group.

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APPENDIX 1

Definitions:

COMPLIANCE: Compliance with trial medication is based on the pill count at each patient visit and will be considered unsatisfactory at 8 weeks (visit 3) if <90% of appropriate trial medication has been taken or if trial medication has been omitted for 3 consecutive days. At follow-up angiography (visit 5), if <80% of trial medication has been taken or if it has been omitted for >3 consecutive days. If a patient misses a scheduled visit by >1 week, noncompliance is also defined.

SUCCESSFUL PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY: Successful PTCA is defined as residual diameter stenosis after balloon angioplasty <50% visually assessed by the interventionalist without the use of an adjunctive interventional device and without the occurrence of a major adverse cardiac event (also described in the text).

PRIMARY CLINICAL ENDPOINT: Described in the text.

MAJOR ADVERSE CARDIAC EVENT: Defined as the occurrence of death, myocardial infarction (as defined in the text), or need for coronary artery bypass graft surgery or reintervention at any time after randomization but within 40 weeks of angioplasty.

PRIMARY ANGIOGRAPHIC ENDPOINT: Described in the text.

FOLLOW-UP ANGIOGRAM: The follow-up angiogram is defined as angiography carried out at the optimum time of 26 ± 2 weeks after PTCA and must be performed according to the instructions of the angiographic core laboratory as provided in the technician's work sheet.

INTERCURRENT ANGIOGRAPHY: Angiography carried out before 14 weeks post-PTCA is acceptable as the follow-up angiogram if the target vessel is now occluded or if significant renarrowing has occurred requiring reintervention or bypass graft surgery. Otherwise, further angiography within the recommended time window will be required. For good clinical indications, angiography after 14 weeks is acceptable as the follow-up angiogram.

RESTENOSIS: In this trial, restenosis is defined as the loss in MLD from post-PTCA to follow-up angiography. However, as already mentioned in the text, conventional categorical angiographic definitions of restenosis will be applied to the collected patient data and evaluated accordingly. These definitions include: (1) A diameter stenosis >50% at follow-up angiography (2) National Heart, Lung, and Blood Institute definition IV, i.e., loss during follow-up ≥50% of the initial gain achieved at PTCA; (3) loss of ≥0.40 mm in MLD during follow-up, which represents twice the post-PTCA lesion measurement variability for the cardiovascular angiographic analysis system quantitative coronary angiography system[47] under current standardized angiographic acquisition and analytical conditions.

APPENDIX 2

Quantitative coronary angiographic methodology:

STANDARDIZATION OF ANGIOGRAPHIC ACQUISITION PROCEDURES BY INVESTIGATORS TO FACILITATE QUANTITATIVE ANALYSIS: The following procedures have been standardized:

1. Intracoronary nitrate before angiography pre-PTCA, post-PTCA, and at follow-up
2. Use of nonionic contrast, prewarmed to 37° C
3. Contrast-empty catheter (at least 6F) filmed before each injection plus distal 20 cm sent with film for micrometric measurement by core laboratory
4. Optimal arterial opacification for at least 3 cardiac cycles
5. Avoidance of bony structures or closely parallel/overlapping branches
6. At least 2 projections ≥60° apart for right coronary artery lesions and at least 3 projections ≥30° apart for left coronary artery lesions
7. Identical projection angulations and table height, pre-PTCA, post-PTCA, and at follow-up
8. Radiopaque indicators filmed to identify balloon inflation pressures and administration of intracoronary nitrate
9. Guide wire and balloon catheter removed before final post-PTCA angiogram

CORE-LABORATORY STANDARDIZATION PROCEDURES FOR QUANTITATIVE ANALYSIS: Procedures standardized for quantitative analysis are:

1. Automated edge detection using the cardiovascular angiographic analysis system
2. Micrometrically measured catheter tip used as scaling device
3. Panel evaluation of projections and frames selected by investigator
4. Analysis of optimal end-diastolic frames in least foreshortened projections
5. Automatic corrections for pincushion distortion of image intensifier
6. Comprehensive range of measurements provided for each segment analyzed

7. Polaroid print of each analysis to confirm matching of projections pre-PTCA, post-PTCA, and at follow-up

8. Careful evaluation and error check before each analysis is verified and entered on database

9. Final measurements used are the means of the multiple matched projections

CARDIOVASCULAR ANGIOGRAPHIC ANALYSIS SYSTEM: The procedural and technical details of this system are beyond the scope of this article and have been described in detail elsewhere.[18,24] In summary:

1. An area measuring 6.9 × 6.9 mm (512 × 512 pixels) from the selected cineframe (18 × 24 mm), encompassing the arterial segment of interest, is digitized with a high-resolution charge coupling device camera

2. The segment of interest is analyzed between nearest proximal and distal side branches

3. Center points within the arterial segment are selected by the analyst (the accuracy of this process is unimportant, because the computer subsequently automatically readjusts the center line after contour detection)

4. Vessel contours are detected automatically, based on the weighted sum of first and second derivative functions, applied to the digitized brightness information, along scan lines perpendicular to the local center line directions of the arterial segment

5. An interpolated reference diameter is derived automatically. For this purpose, the lesion itself is excluded, using the curvature analysis (which identifies the proximal and distal ends of the lesion); then, in a continuous fashion, the arterial contours over the lesion are interpolated on the basis of the proximal and distal center line segments and a first-degree polynomial through all the diameter values, followed by a translation to the 80th percentile level, taking physiologic tapering of the vessel (beyond side branches) into account

6. Calculation of absolute dimensional measurements requires use of the contrast-free catheter tip as the scaling device[48]

7. The length of the lesion is determined from the diameter function on the basis of curvature analysis that identifies the proximal and distal extremities of the actual narrowed segment

8. Because the algorithm cannot measure total occlusions or lesions with Thrombolysis in Myocardial Infarction Study Group (TIMI) flow grade I, a value of 0 mm is substituted for the MLD and 100% for the percent diameter steno-

sis in these circumstances, and the interpolated reference diameter post-PTCA is used as the reference diameter pre-PTCA

APPENDIX 3
Trial organizational bodies:

STEERING COMMITTEE: A steering committee has been formed, consisting of: Prof. Patrick W. Serruys, Thoraxcenter, Erasmus University, Rotterdam, The Netherlands; the principal investigators from each of the 4 participating European countries; directors of each of the angiographic core laboratories, the clinical coordinating center, and the lipid core laboratory; chairpersons of each of the other committees; and representatives of the sponsor (Sandoz Pharma, Basel, Switzerland). The steering committee is the main policy and decision-making committee of the study and has final responsibility for the scientific conduct.

SPONSOR: Sandoz Pharma: Dr. P. J. Pfister, Corporate Management, Basel, Switzerland; Dr. A. DeBlander, Brussels, Belgium; Mr. M. T. Rudolphie, Uden, The Netherlands; Dr. I. Porta Pujol, Barcelona, Spain; Dr. J. Jewitt-Harris, Surrey, United Kingdom.

ANGIOGRAPHIC CORE LABORATORY: The angiographic core laboratory is at Cardialysis, Rotterdam, The Netherlands. The tasks of the core laboratory include: (1) working with investigators in setting up local procedures for angiography suitable for quantitative analysis; (2) performing quantitative analysis of study angiograms provided by investigators; (3) preparing, updating, and maintaining the angiographic computer database; and (4) liaising with the angiographic committee of the FLARE Trial to ensure provision of reliable angiographic data to the satisfaction of all participants in the trial.

DATA COORDINATING CENTER: The data coordinating center is located at Sandoz Pharmaceuticals, Surrey, United Kingdom, and is responsible for: (1) working with local investigators and study monitors to ensure accuracy and reliability of clinical data and punctual and efficient transfer of case record forms and clinical information from investigators; (2) preparing, updating, and maintaining the clinical database; and (3) liaising with the angiographic core laboratory, including regular transfer of data as required from time to time, to ensure provision of reliable clinical data to the satisfaction of all participants in the trial.

Each of the following committees has a chairperson who will be responsible for the committee performing its function in an efficient manner throughout the trial period.

ADVISORY AND DATA MONITORING COMMITTEE: This is an independent committee consisting of 4 acknowledged experts (Prof. P. G. Hugenholz, Mies, Switzerland; Prof. B. Meier, Geneva, Switzerland; Prof. D. W. Erkelens, Utrecht, Netherlands; Prof. L. Wilhelmsen, Göteborg, Sweden) in the relevant disciplines of interventional cardiology, lipidology, and epidemiology who are not otherwise associated with the trial and who will act in a senior advisory capacity on matters of safety of trial procedures and in evaluating the reliability of the data collected. This committee will also ensure that the study is performed in accordance with the Declaration of Helsinki. This committee periodically reviews, unblinded, treatment-monitoring reports for evidence of unexpected adverse or beneficial effect of trial medication. The committee is entitled to recommend

amendments of the protocol or early termination of the trial to the steering committee.

CRITICAL EVENTS COMMITTEE: A critical events committee consisting of 3 experienced investigators will blindly review clinical data to identify the occurrence of any major adverse cardiac events.

ANGIOGRAPHY COMMITTEE: The angiography committee, consisting of 3 members, will approve the procedures and evaluations applied and carried out by the angiographic core laboratory for quantitative analysis. Guidelines for interpretation of the angiograms and for quantitative analysis will be further elaborated by this committee, which will work in close collaboration with the angiographic core laboratory and provide arbitration of any angiographic difficulties and dilemmas arising during the trial.

PUBLICATIONS COMMITTEE: A publications committee consisting of the investigators will evaluate and report the results of the study, with the cooperation and permission of the sponsor.

APPENDIX 4
List of investigators:

BELGIUM: Dr. G. Heyndrickx, Onze Lieve Vrouwziekenhuis, Aalst; Dr. M. Vrolix, Algemeen Ziekenhuis Sint Jan, Genk; Dr. V. Legrand, CHU Sart Tilman, Liège; Dr. W. Wijns, U.C.L. Saint-Luc, Brussels; Dr. P. Materne, Hôpital de la Citadelle, Liège; Dr. Y. Taeymans, R.U., Gent.

THE NETHERLANDS: Dr. J. J. R. M. Bonnier, Catharina Ziekenhuis, EJ Eindhoven; Dr. A. van Boven, Academisch Ziekenhuis Groningen, Groningen; Dr. P. J. de Feyter, Academisch Ziekenhuis Dijkzigt, Rotterdam; Dr. G. J. Laarman, Onze Lieve Vrouwe Gasthuis, Amsterdam; Dr. H. Suryapranata, Ziekenhuis De Weezenlanden, Zwolle.

IRELAND: Dr. P. Crean, St. James Hospital, Dublin.

UNITED KINGDOM: Dr. P. Bloomfield, Royal Infirmary of Edinburgh, Edinburgh, Scotland; Dr. C. Handler, Northwick Park Hospital, Harrow, Middlesex, England; Dr. D. Dymond, St. Bartholomew's Hospital, London, England; Dr. I. Hutton, Royal Infirmary, Glasgow, Scotland; Dr. R. Foale, St. Mary's Hospital, London, England; Dr. C. Ilsley, Harefield Hospital, Harefield, Middlesex, England; Dr. A.H. Gershlick, Glenfield Hospital, Leicester, England; Dr. G. Jackson, Guys Hospital, London, England; Dr. R. Hall, University Hospital of Wales, Cardiff, Wales; Dr. D. Lipkin, The Royal Free Hospital, London, England; Dr. J. Ramsdale, Cardiothoracic Centre, Liverpool, England; Dr. M. Rothmann, The London Hospital, London, England; Dr. L. Shapiro, Papworth Hospital, Cambridge, England; Dr. A. Timmis, London Chest Hospital, London, England.

SPAIN: Dr. J. Escaned, Sanatorio Quirurgico Modelo, La Coruña; Dr. J. L. Delcan Dominguez, Hospital General Gregorio Maranon, Madrid; Dr. C. Macaya, Hospital Universitario San Carlos, Madrid; Dr. A. Betriu, Hospital Clinic i Provincial, Barcelona