Rationale of the REPARATOR study

A randomised trial with serial cardiac MRI follow-up testing the ability of atorvastatin to reduce reperfusion damage after primary PCI for acute MI

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The REPARATOR study is a multicentre clinical trial in which the effect of 80 mg atorvastatin on microvascular (re)perfusion and late ventricular remodelling, and infarct size in patients presenting with an acute ST-elevation myocardial infarction is studied. Primary endpoint is end-systolic volume index at three months measured by quantitative cine magnetic resonance imaging (MRI). Secondary endpoints are cardiac MI (CMR) measurements of global and regional left ventricular function, MRI measurements of infarct size on admission, one week and three months as well as changes between MRI investigations, biochemical markers of infarct size, blush grade, and TIMI frame count. A total of 50 patients will be enrolled. Including three months follow-up, the study will last for six months. (*Neth Heart J* 2006;14:95-9.)

Left ventricular (LV) remodelling after a myocardial infarction (MI) refers to changes in shape and function of both the infarcted area as well as the non-infarcted myocardium that begins minutes after acute myocardial infarction and may continue for months or years. These changes include: (a) thinning and dilation of the infarct zone (infarct expansion); (b) subsequent dilation of the remote, noninfarcted myocardium with compensatory hypertrophy; (c) interstitial fibrosis and impairment of contraction; and (d) global LV change from an elongated ellipse to a more spherical shape.[1,2]

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Infarct expansion occurs soon after onset of coronary occlusion. It is reversible if coronary flow is re-established rapidly; however, it may progress in a time-dependent manner if flow is not re-established or late.[3] Infarct expansion involves no additional myocardial necrosis but refers to an increment of the functional infarct size with a greater percentage of the LV wall being composed of necrotic myocardium or scar.

Long-term global remodelling with dilation and long-term impairment of noninfarcted myocardial segments begins soon after a large infarction and progresses for months to years. LV volume strongly correlates with long-term mortality.

Early reperfusion therapy, either medically with thrombolytics or mechanically with angioplasty, can achieve epicardial reperfusion in 60% (thrombolytics) to >95% (angioplasty) of patients. Reperfusion after an increasing period of ischaemia leads to a spectrum of reperfusion-associated pathologies collectively called 'reperfusion injury'. Reperfusion injury results in myocardial dysfunction and damage through stunning, no reflow and irreversible cell death and necrosis.[4-6] Stunning implies reversibility over time and can be picked up by serial measures of left ventricular function. The no-reflow phenomenon is probably caused by interstitial oedema, intense vasoconstriction of the microvasculature and plugging of the microvasculature with thrombus and macrophages. The severity and reversibility of the microvascular underperfusion can be assessed by grading the speed of contrast passage through the epicardial coronary artery (TIMI flow grade, TIMI frame count), by grading the density of contrast in the myocardium after contrast injection in the infarct-related artery (blush grade) and by serial ST-T analysis of the electrocardiogram. All these measures of microvascular perfusion correlate well with global infarct size and clinical outcome.

Regional and global left ventricular function and morphology can be quantified with high reproducibility by magnetic resonance imaging (MRI). The method is safe, noninvasive, well validated and has become a routine investigation in most cardiology/radiology departments. It is therefore an ideal tool to

Table 1. Exclusion criteria of the REPARATOR study.

- Previous myocardial infarction
- Previous coronary artery bypass grafting (CABG)
- Cardiac rhythm is other than normal sinus rhythm
- Electrical instability
- The patient is in Killip class 3 or 4 of heart failure
- Need for intra-aortic balloon counterpulsation therapy
- The patient is unable to hold his/her breath for up to 20 seconds due to age or concomitant illness
- Implanted electronic devices are present: pacemakers, internal defibrillators, ECG-registration devices, neurostimulators, implanted drug infusion devices, cochlear implants, etc
- Previous vascular surgery: aneurysm clip, carotid artery vascular clamp, aortic clips, venous umbrella
- Prosthesis (orbital/penile, etc.)
- Spinal/intraventricular shunts
- Swann-Ganz catheter, transdermal delivery systems
- Metal fragments: eye, head, ear, skin
- Implants held by magnets
- Known allergy to MR contrast media
- Prior use of statins
- No PCI performed
- No recanalisation achieved

assess changes in left ventricular shape and function after myocardial infarction. White et al. showed that the best predictor of survival after initial recovery from myocardial infarction is left ventricular end-systolic volume (ESV).[7] ESV measured by cine MRI is therefore an attractive surrogate endpoint in hypothesis-forming randomised trials aimed at reducing post-infarction remodelling.[8-10]

In a murine model of acute myocardial infarction and reperfusion atorvastatin, administered at the onset of reperfusion, reduced infarct size in a dose-dependent manner.[11] It was shown that rapid upregulation (in seconds) of the PI3K/Akt cell survival pathway led to a significant and parallel increase in eNOS phosphorylation. Activation of this pathway confers protection on the reperfused myocardium independent of the effects of atorvastatin on cholesterol and endothelial function. These findings suggest that atorvastatin might reduce reperfusion injury in humans in the setting of primary PCI for ST-elevation myocardial infarction.

Aim

The aim of this trial is to study the effect of atorvastatin on microvascular (re)perfusion, early and late left ventricular remodelling and infarct size in patients presenting with an acute ST-elevation myocardial infarction. Atorvastatin will be administered orally *before* catheter-based reperfusion therapy. Early and late left ventricular function and infarct size will be measured by serial MRI imaging. Microvascular (re)perfusion will be assessed by angiographic and electrocardiographic measurements (TIMI frame count, TIMI flow grade, blush score and ST-T segment measurements).

Patients

Consecutive patients (age >18 years) who are to undergo a primary PTCA for a first acute ST-elevation myocardial infarction will be asked to participate in this study. The exclusion criteria are presented in table 1.

Endpoints

The primary endpoint is end-systolic volume index at three months measured by quantitative cine MRI. Secondary endpoints are other CMR measurements of global and regional left ventricular function, MRI measurements of infarct size at admission, one week and three months, as well as changes in these measures between MRI investigations, biochemical markers of infarct size, blush grade and TIMI frame count.

Informed consent

Oral informed consent will be obtained prior to the emergency coronary angiography. Written informed consent will be obtained after the procedure when the medical condition has stabilised.

Randomisation

Randomisation will take place before emergency coronary angiography in the emergency department at both sites. Randomisation will be done in blocks of eight and is performed by pulling a sealed envelop containing the study medication assignment (A or B).

Study medication and rationale for medication dose

Study subjects will either be treated with atorvastatin 80 mg once daily or matching placebo. Study medication will stop after day 7. From day 8 all subjects will be treated with atorvastatin 80 mg once daily. Dose adjustment can be done at the discretion of the treating physician from day 10 or if adverse events presumably related to study medication occur. Blinding of medication will be done by the pharmacy of the St Antonius Hospital, Nieuwegein, the Netherlands. Cholesterol values will not be determined before day 10.

Atorvastatin is registered in the Netherlands for the treatment of primary hypercholesterolaemia and can be prescribed in doses ranging from 10 to 80 mg per day. Recently it was shown that 80 mg of atorvastatin per day stopped progression of coronary atherosclerosis as assessed by intravascular ultrasound.[19] In a large clinical trial, 80 mg of atorvastatin was found to be superior to 40 mg of pravastatin with respect to reduction of major cardiac adverse events in patients after an acute coronary syndrome.[19,20] In both studies the 80 mg dose was safe and well tolerated. Adverse events were not different between the atorvastatin group and the control group.

The difference in IVUS full and clinical outcomes could not be completely explained by the difference in LDL reduction. This suggests the existence of a dose-dependent pleiotropic effect of atorvastatin.

Since atorvastatin has no effect on haemodynamics, the 80 mg dose is safe and its effect on infarct size seems to be dose dependent in animal studies. Therefore we choose the 80 mg dose for our study.

Sample size calculation

The best predictor of survival after initial recovery from myocardial infarction is left ventricular end-systolic volume.[4] Grothues et al. determined the reproducibility of MR measurements of LV volumes.[12] The interstudy standard deviation of ESV index (ESV normalised for body surface area) was 2.8 ml/m^2. In the GUSTO-1 trial ESVI one week after MI was 27 ml/m^2. A reduction of 10% in ESVI by the index treatment at three months i.e. an ESVI of 24.3 ml/m^2 in the atorvastatin arm is considered clinically relevant. With a power of 0.9 and an α error of 0.05, 24 patients per treatment arm have to be enrolled. To allow for dropout a total of 50 patients will be enrolled.

PCI procedure

Standard emergency coronary angiography of both right and left coronary arteries will be performed (figure 1). TIMI flow, TIMI frame count and corrected TIMI frame count of the infarct-related artery will be assessed from these angiograms. Patients will be treated with unfractionated heparin 5000 to 10,000 IU bolus and additional boluses to keep the activated clotting time >300 seconds, clopidogrel 300 mg loading dose and acetylsalicylic acid. Standard PCI techniques will be used to achieve recanalisation and revascularisation of the infarct-related artery. From post PCI angiograms TIMI flow, (corrected) TIMI frame count and myocardial blush grade will be determined after intracoronary injection of 1 to 3 mg of nitroglycerin.[13,14]

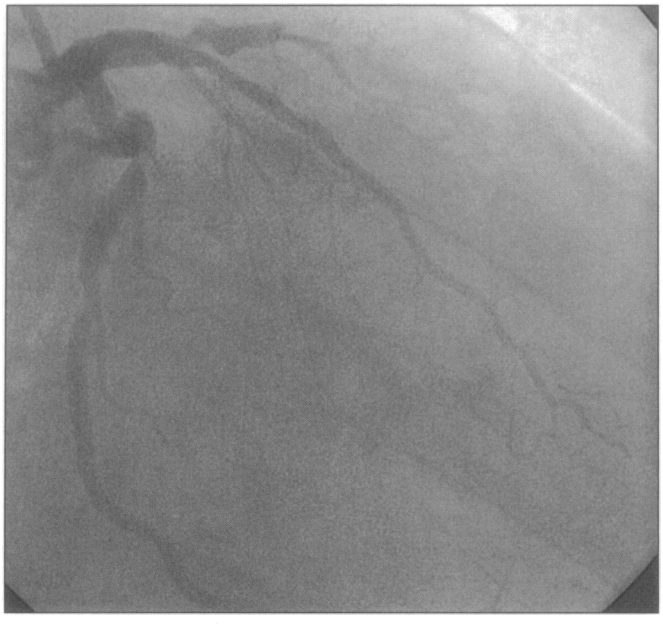

Figure 1. Acute occlusion LAD, pre PCI.

Post PCI medical treatment

All patients will be treated with clopidogrel 75 mg per day for six months, and lifelong aspirin. Beta blockers, diuretics and other medication are prescribed at the discretion of the treating physician.

MRI

To follow the process of infarct expansion and left ventricular remodelling three MRI investigations are planned. The first cardiac MRI will be performed within 24 hours after reperfusion therapy, the second on day 7 or on the day of hospital discharge, the third MRI investigation will be performed at three months follow-up, as shown in figures 2, 3 and 4.

Imaging protocol

The dedicated cardiovascular scanner is a 1.5 T Philips Intera MRI scanner stationed at the radiology departments of the participating centres. Software is installed to analyse global and regional left ventricular function data, viability and infarct size data and myocardial perfusion data.

Left ventricular function

Steady state free precession (SSFP) cine sequences of eight to ten short-axis views and two long-axis views are acquired. All images are acquired during an end-expiratory breathhold and are ECG gated. At least 25 phases per heart cycle will be recorded. The short-axis acquisition begins 1 cm under the mitral valve plane and continues with 1 cm increments through the left ventricle.

Myocardial viability, infarct size determination

A bolus of gadolinium contrast (0.4 mmol/kg) will be administered intravenously.

Fifteen minutes later eight to ten contrast-enhanced, short-axis scans, covering the complete left ventricle, will be acquired in the same views as those used for the short-axis cine MRI of the left ventricle. Images will be made using a segmented inversion recovery sequence to differentiate between regions of viable and nonviable myocardium and to determine infarct size.

ECG and markers for infarct size

Serial ECGs will be recorded (before PTCA, immediately after the procedure, at one and three hours after the PTCA procedure and before discharge) to assess early reperfusion and Q-wave formation. In addition, serial markers for infarct size (CK, CK-MB) will be determined every eight hours for 36 hours.

Angiographic markers for reperfusion

TIMI frame count, corrected TIMI frame count and blush grade after PCI will be determined as previously

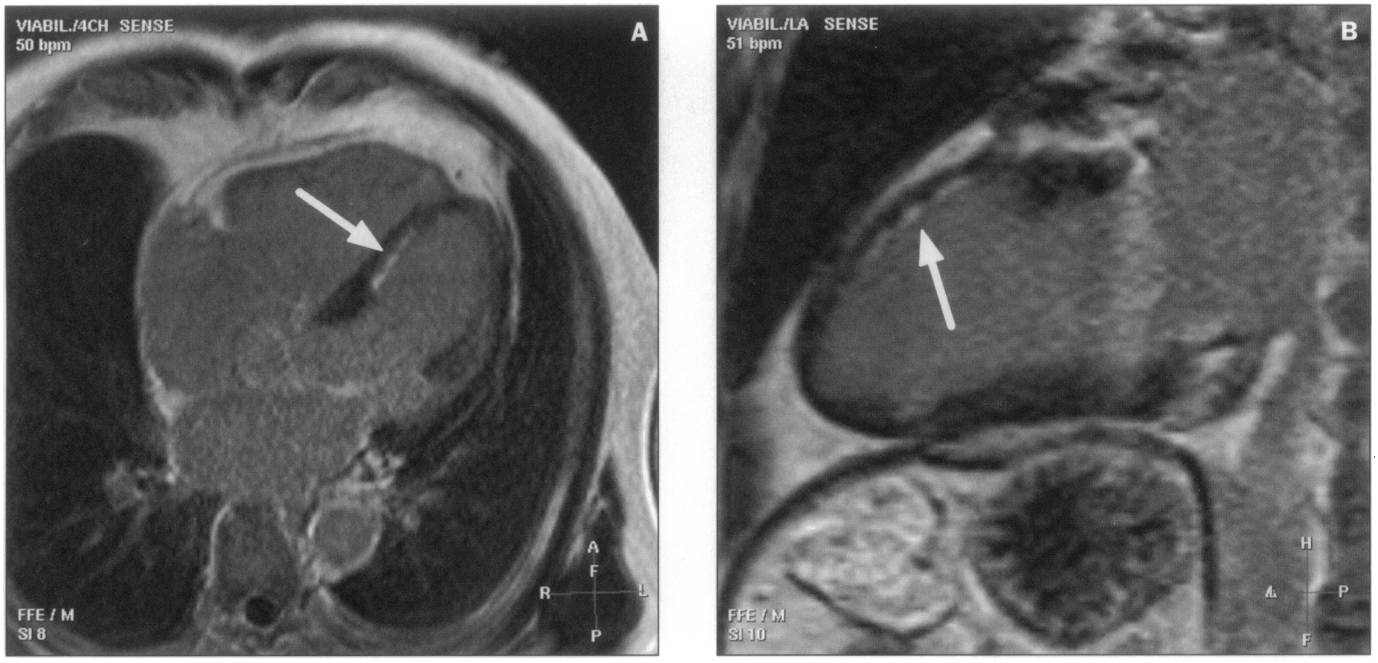

Figure 2. Late enhancement MRI at three months follow-up. Arrows: limited subendocardial anteroseptal infarction.

described.[13,14] Angiograms for assessment of blush grade and TIMI frame count will be preceded by intracoronary injection of 1 to 3 mg of nitroglycerin.

Timelines

The study will be performed at both cardiology departments of the Heart Lung Centre Utrecht (University Medical Centre Utrecht and St Antonius Hospital). It is expected that both departments will enrol 25 patients. Randomisation will be balanced between the two departments. The study is expected to start at the beginning of February 2006. With an expected enrolment of one to two patients per week, enrolment should be completed by the end of May 2006. The last follow-up MRI at three months and study closure is thus expected in August 2006 (table 2). ■

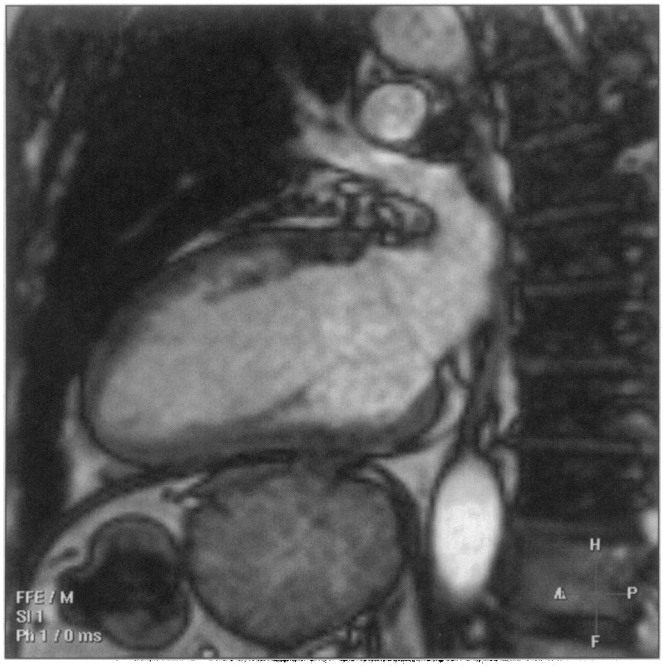

Figure 3. Three months follow-up, end-diastolic frame.

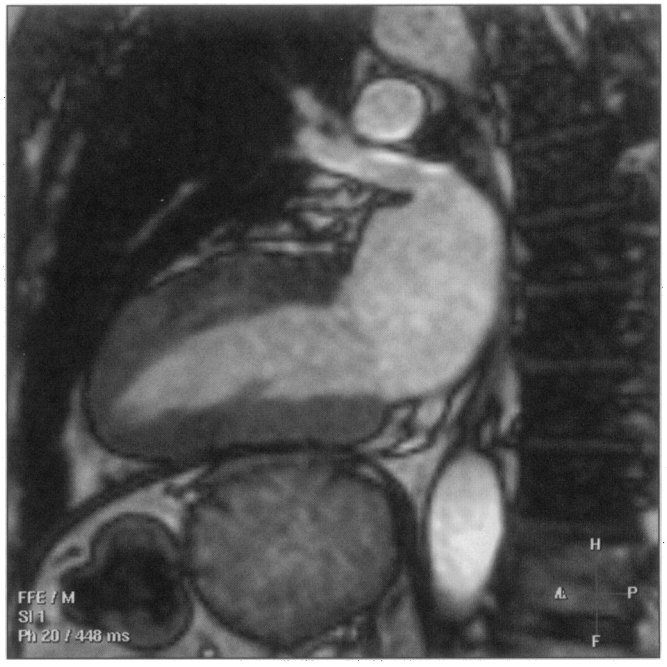

Figure 4. Three months follow-up, end-systolic frame.

Table 2. Timing of investigations.

	S	PCI	1-72 hrs	7 days	3 months
Angiography	x				
History/events	x	x		x	x
Medications	x			x	x
Physical examination	x				x
Electrocardiography	x		x	x	x
Blood analysis					
- CK, CK-MB	x		x		x
- Routine laboratory	x		x		x
- Cholesterol	x				x
Cardiac MRI			x	x	x

S=preprocedural screening, 1-72 hrs=electrocardiography at 1, 3, 24 hours after the PCI, CK and CK-MB at 8, 16, 36 hours after the PCI and cardiac MRI at 36 hours after the PCI.

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