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PTCA but not atorvastatin normalises dipyridamole induced myocardial perfusion and perfusion reserve in target vessel areas after 6 months.
A randomised study using positron emission tomography

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Submitted
ABSTRACT

Objective
To compare prospectively the effects of lipid-lowering therapy by atorvastatin with coronary angioplasty (PTCA) on myocardial perfusion assessed by positron emission tomography (PET), in a subgroup of patients enrolled in the AVERT study.

Methods
Of 23 patients scheduled for PTCA (target vessels) and mild angina (CCS < class III), 10 were randomised to PTCA and 13 to atorvastatin 80 mg per day. Dynamic $^{13}$N ammonia PET imaging was performed at rest and during dipyridamole infusion to assess myocardial perfusion and perfusion reserve in target and non-target vessel areas at baseline and after 6 months. Myocardial perfusion was also compared with data obtained in 13 healthy volunteers.

Results
At follow-up, LDL cholesterol was lowered by -7% in the PTCA group and by -53% in the atorvastatin group (p<0.0001). CCS class did not change in both groups and treatment did not influence resting myocardial perfusion. After 6 months, dipyridamole myocardial perfusion increased in target vessel areas in the PTCA group (+54%; p<0.01), whereas it remained unchanged in the atorvastatin group. Consequently, myocardial perfusion reserve in target vessel areas improved after PTCA from (1.57 (0.60) to 2.31 (0.64); p<0.01), whereas it did not change in the atorvastatin group (1.66 (0.56) to 1.71 (0.47); P=NS; p<0.05 vs PTCA). In the PTCA group myocardial perfusion normalised compared to healthy volunteers. In non-target vessel areas no significant changes were observed.

Conclusions
Successful PTCA, but not aggressive lipid-lowering therapy with atorvastatin, normalised myocardial perfusion in target vessel areas 6 months after treatment in patients with mild stable angina.
Lipid-lowering treatment with HMGCoA reductase inhibitors has been proven to significantly reduce the incidence of cardiovascular events, overall mortality, and the need for revascularization\textsuperscript{1,2}. One of the ancillary mechanisms of HMGCoA reductase inhibitors is a myocardial anti-ischaemic effect, as demonstrated by reduction of ischaemic events assessed by ambulatory electrocardiographic monitoring\textsuperscript{3,4}. The observed improvement of endothelial function\textsuperscript{6,7} and the enhancement of myocardial perfusion reserve\textsuperscript{5} by HMGCoA reductase inhibitor therapy may be contributing factors. Considering their anti–ischaemic properties, it was postulated that HMGCoA reductase inhibitors could prevent or delay revascularization also in patients with significant coronary lesions. When treated for two years with pravastatin, patients submitted to coronary angioplasty (PTCA) showed less ischaemic events after the procedure\textsuperscript{8}. In the Atorvastatin Versus Revascularization Treatments (AVERT) study, in which stable patients with a clinical indication for PTCA were randomised to either aggressive lipid-lowering with atorvastatin or PTCA, a significant reduction in late ischaemic events was found for patients randomised to atorvastatin 80 mg\textsuperscript{9}. As a substudy of the AVERT trial, we hypothesised that a substantial reduction in low-density lipoprotein (LDL) cholesterol after 6 months treatment with atorvastatin 80 mg would improve myocardial perfusion reserve in the target vessel areas to the same extent as PTCA of the target vessel. Furthermore, we investigated the effect of both treatments on non-target vessel areas. Myocardial perfusion reserve was assessed by positron emission tomography (PET); an accurate and reproducible method to assess myocardial perfusion and the effect of HMGCoA reductase inhibitors\textsuperscript{10,14}.

**METHODS**

**Study design**
Twenty-three patients enrolled in the AVERT trial at Groningen University Hospital (The Netherlands) constituted the population of this substudy and underwent PET imaging before and 6 months after treatment. The design of the AVERT study has been previously reported\textsuperscript{15}. Briefly, the study was an 18-month, open-label, randomised, multicenter study of 341 patients with stable coronary artery disease, a serum level of LDL-cholesterol...
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terol of at least 115 mg/dL, and a blood level of triglycerides of no more than 500 mg/dL. Patients had a significant stenosis (≥ 50%) in at least one coronary artery (target vessel) and had been recommended for PTCA. Patients were asymptomatic or had a mild degree of angina (Canadian Cardiovascular Society (CCS) class I or II angina), and were able to complete at least four minutes of a bicycle exercise test at 20 Watt per minute without relevant electrocardiographic ischaemic changes. Major exclusion criteria were: left main or three-vessel coronary artery disease, unstable angina or myocardial infarction within the previous two weeks, and left ventricular ejection fraction less than 40%. All patients gave written informed consent and the protocol was approved by the Institutional Review Board.

Treatment

The 23 patients were stratified according to whether they had one or two vessel disease. Ten patients had been randomised to undergo the recommended PTCA of the target vessel followed by usual care (which could include lipid-lowering therapy) and 13 to medical treatment with atorvastatin 80 mg.

Baseline characteristics of patients are summarised in Table 1. No differences were observed between the two groups, except for triglyceride levels (p<0.05). Before randomisation, the use of lipid-lowering therapy was 50% in the PTCA group and 31% in the atorvastatin group. Patients assigned to PTCA were allowed to continue their current drug regimen, which included lipid-lowering medication other than atorvastatin. Patients assigned to receive atorvastatin discontinued any other lipid-lowering medication without a washout period and received atorvastatin. In both groups no differences in baseline characteristics were found between patients receiving or not receiving lipid-lowering therapy before randomisation.

PET imaging was performed at baseline, either before PTCA or before start of atorvastatin treatment, and after 6 months. PET myocardial perfusion results in the study population were compared with data from a control group of 13 age and sex matched non-randomised non-concurrent normocholesterolemic healthy volunteers from our normal data base.

Positron emission tomography imaging protocol

PET imaging was performed in a 951 Siemens (ECAT) positron camera (Siemens AG, Knoxville, USA), with an in-plane spatial resolution of 6 mm full width at half maximum. Dynamic 13N-ammonia imaging was obtained
Table 1. Baseline Characteristics of the 23 AVERT Patients who Underwent PET Imaging.

<table>
<thead>
<tr>
<th></th>
<th>PTCA (n=10)</th>
<th>Atorvastatin (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>59.8 (9.4)</td>
<td>60.0 (0.2)</td>
</tr>
<tr>
<td>Male gender</td>
<td>8 (80%)</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>CCS angina class</td>
<td>1.6 (0.5)</td>
<td>1.4 (0.5)</td>
</tr>
<tr>
<td>One / Two vessel disease</td>
<td>7 (70%) / 3 (30%)</td>
<td>10 (77%) / 3 (23%)</td>
</tr>
<tr>
<td>Severity of stenosis [%]</td>
<td>82.4 (11.4)</td>
<td>88.3 (8.6)</td>
</tr>
<tr>
<td>Previous hypertension</td>
<td>3 (30%)</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Previous hyperlipidemia</td>
<td>4 (40%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Previous peripheral vascular disease</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Previous use lipid-lowering drug</td>
<td>5 (50%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>LDL-cholesterol [mg/dL]</td>
<td>148.0 (28.4)</td>
<td>150.8 (30.2)</td>
</tr>
<tr>
<td>HDL-cholesterol [mg/dL]</td>
<td>44.0 (12.0)</td>
<td>44.1 (11.2)</td>
</tr>
<tr>
<td>Triglycerides [mg/dL]</td>
<td>109.7 (35.3)</td>
<td>160.0 (80.3)</td>
</tr>
</tbody>
</table>

Continuous variables are mean (SD). Categorical variables are number (%). AVERT: atorvastatin versus revascularization treatments; PET: positron emission tomography; CCS: Canadian Cardiovascular Society; LDL: low-density lipoproteins; HDL: high-density lipoproteins. * p<0.05 for PTCA v atorvastatin.

at rest and during dipyridamole infusion (0.56 mg/kg in 4 minutes). Myocardial perfusion was calculated in milliliter per minute per 100 milliliter myocardial tissue [mL/min/100mL], according to the three-compartment model used in our institution and described by Hutchins et al. By means of a parametric polar map program, myocardial perfusion polar maps were constructed for each phase. On the basis of a predefined anatomical model, myocardial perfusion was calculated for areas supplied by the target vessel(s) (target vessel areas) and for areas not supplied by the target vessel(s) (non-target vessel areas). Myocardial perfusion reserve was computed as the ratio between dipyridamole-induced and rest myocardial perfusion. Perfusion results for target and non-target vessel areas obtained after six months were compared to baseline values. For detailed description of PET methods and analysis see appendix A.
Statistical analysis
The SPSS statistical package (Chicago IL, USA, version 9.0.) was used. Changes from baseline and between the groups were tested using a paired or non-paired Student t-test or the non-parametric Wilcoxon signed- or sum-rank test, when appropriate. Values are expressed as mean (standard deviation) or number (percentage). All p-values were two sided and a p-value < 0.05 was considered significant.

RESULTS

All PTCA procedures were successful and in the atorvastatin group none of the patients discontinued the study drug. In the PTCA group the use of lipid-lowering therapy did not change during follow-up. Changes in serum lipid values are shown in Figure 1. After 6 months LDL-cholesterol blood levels did not decrease significantly in the PTCA group (-7%, p=NS), whereas in the atorvastatin group LDL-cholesterol blood levels were significantly decreased (-53%, p<0.0001). In the PTCA group HDL-cholesterol blood levels did not change significantly (+5%, p=NS), but on atorvastatin therapy a significant increase was demonstrated (+9%, p<0.05). Triglycerides levels did not change significantly in the PTCA group (+11%, p=NS), whereas in the atorvastatin group triglycerides levels decreased significantly (-31%, p<0.0001).

![Figure 1. Changes in lipoprotein levels in the PTCA group and in the atorvastatin group. LDL, low density lipoproteins; HDL, high density lipoproteins.](image-url)
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p<0.01. After 6 months CCS class did not change significantly in both groups (from 1.6 (0.5) to 1.7 (0.5), p=NS; and from 1.4 (0.5) to 1.3 (0.4), p=NS; for PTCA and the atorvastatin group respectively).

**Positron emission tomography**

Results of myocardial perfusion and perfusion reserve are shown in Figures 2 and 3, respectively.

![Figure 2. Myocardial perfusion.](image)

Myocardial perfusion at rest and during dipyridamole infusion in target (2A) and non-target vessel areas (2B) before and after treatment. Myocardial perfusion data of healthy volunteers are shown as reference. In Figure 2A also change in dipyridamole myocardial perfusion from baseline after treatment was significantly different between PTCA and atorvastatin (p<0.01). PTCA; percutaneous transluminal coronary angioplasty.
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Baseline
At baseline, the PTCA group and the atorvastatin group did not show any significant difference in myocardial perfusion patterns. When groups were pooled, for target and non-target vessel areas, dipyridamole-induced myocardial perfusion was significantly lower in target vessel areas (129.3 (43.2) mL/min/100mL; p<0.05). For resting myocardial perfusion and myocardial perfusion reserve no significant differences were observed between target and non-target vessel areas (rest: 82.3 (22.8) mL/min/100mL; p=NS; reserve: 1.63 (0.57) mL/min/100mL; p=NS; target v non-target vessel area, respectively).

Six-months follow up
Rest myocardial perfusion did not change after treatment in both groups. In the PTCA group, dipyridamole-induced myocardial perfusion in target vessel areas significantly increased after treatment (+54 % v baseline; p<0.01), whereas no significant change was observed in the atorvastatin group (+1% v baseline; p=NS). Consequently, myocardial perfusion reserve in target vessel areas improved after treatment in the PTCA group and remained unchanged in the atorvastatin group. No different response to treatment was demonstrated between patients using lipid-lowering therapy before randomisation or not in the atorvastatin group, or between patients receiving or not receiving lipid-lowering therapy in the PTCA plus usual
care group. In non-target vessel areas, no significant change in myocardial perfusion and myocardial perfusion reserve was found after treatment in both groups.

**Comparison with healthy volunteers**

After PTCA dipyridamole-induced perfusion and perfusion reserve in target vessel areas normalised in respect to healthy volunteers.

**DISCUSSION**

This study showed that PTCA normalised dipyridamole induced myocardial perfusion and perfusion reserve in target vessel areas at 6 months after the procedure. Conversely, lipid-lowering treatment with atorvastatin did not improve myocardial perfusion reserve neither in target, nor in non-target vessel areas, despite a significant reduction in LDL-cholesterol blood levels and an increase in HDL-cholesterol.

Elevated blood cholesterol levels have been demonstrated responsible for vascular dysfunction, as revealed by an endothelial dysfunction, and an impaired response to vasodilatation related to cholesterol blood levels, both in patients with and without coronary artery disease. Vasodilatation with dipyridamole is considered an integrated measure of endothelial function and smooth muscle cell relaxation, mainly acting on coronary resistance and capillary vessels. As previously reported lovastatin treatment demonstrated an improvement in endothelial function, and other lipid-lowering therapies showed an improved perfusion response to vasodilatation, irrespective to the severity of any coronary stenosis. Although these studies provided direct evidence of the beneficial effect of lipid-lowering therapy on myocardial perfusion, they lacked a placebo-controlled and randomised design. To our knowledge, the present study is the first to report quantitative PET analysis in a randomised design.

It has previously been shown that successful PTCA is associated with an early improvement in regional myocardial perfusion reserve as assessed by PET imaging. Doppler-wire techniques have demonstrated that an improvement in myocardial flow immediately after PTCA is associated with a good long-term prognosis. The present study demonstrates that base-
line dipyridamole-induced myocardial perfusion in target vessel areas was impaired in comparison to non-target vessel areas and to healthy volunteers. PTCA showed an improvement in dipyridamole-induced myocardial perfusion that was still present 6 months after the procedure. Consequently, 6 months after PTCA, the myocardial areas supplied by the treated coronary arteries showed an improved myocardial perfusion reserve that was comparable with myocardial perfusion reserve of non-target vessel areas. Target vessel areas showed also normalisation of myocardial perfusion values compared to healthy volunteers. Although a better redistribution of blood flow in border ischaemic areas has been reported after PTCA, in our study no significant effect on myocardial perfusion of non-target vessel areas was found after PTCA.

Patients randomised to atorvastatin showed a significant reduction in LDL-cholesterol levels and increase in HDL-cholesterol levels regardless of the use of any lipid-lowering therapy at the time of randomisation. Therefore, atorvastatin treatment was anticipated to have a beneficial effect on myocardial perfusion response to vasodilatation, in both target and non-target vessel areas. Although both Guethlin et al. and Yokoyama et al. demonstrated an increase in global perfusion reserve, irrespective to the severity of any coronary stenosis after lipid-lowering assessed with PET imaging, our study did not show a beneficial effect of atorvastatin on myocardial perfusion in the target vessel areas. Similarly, atorvastatin did not influence myocardial perfusion in non-target vessel areas. This finding was also in contrast with previous results from our institution, which showed that fluvastatin treatment caused a cholesterol dependent increase in myocardial perfusion reserve in 13 healthy hypercholesterolemic subjects without coronary artery disease.

As part of the AVERT study design, some patients were receiving lipid-lowering medication before randomisation (22% in AVERT and 39% in the present substudy), and were allowed to continue lipid-lowering medication in the PTCA (plus usual care) group or started taking atorvastatin without a washout period. According to our previous findings, in which we demonstrated an association between total cholesterol and myocardial perfusion reserve, a further decrease in cholesterol was presumed to increase myocardial perfusion reserve, despite previous lipid-lowering therapy. Previous use of lipid-lowering therapy in the atorvastatin group, or usual care including lipid-lowering in the PTCA group did not show a difference in
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myocardial perfusion at baseline and in response to treatment compared to patients not receiving lipid-lowering before randomisation or during usual care.

Apart from the study design and probably more important, various HMGCoA reductase inhibitors exhibit different pleiotropic effects\textsuperscript{29,31}. Previous studies demonstrating amelioration of myocardial perfusion were performed with lipid-lowering therapy other than atorvastatin\textsuperscript{6,7}, and the present study is the first to examine the effects of atorvastatin on the coronary microcirculation. A beneficial effect of atorvastatin on endothelial function has been reported\textsuperscript{32}, but the complete range of its pleiotropic effects has not yet been extensively investigated. There is controversy whether treatment with atorvastatin increases plasma fibrinogen levels\textsuperscript{33,34}. A rise in fibrinogen levels may cause an increase in plasma viscosity and this could have a detrimental effect on coronary microcirculation. From the present results we are not able to make a conclusive statement whether this could be held responsible for the lack of improvement of myocardial perfusion, because fibrinogen and viscosity changes during atorvastatin treatment were not assessed. Furthermore, the duration of treatment may have influenced the effect of HMGCoA reductase inhibitor therapy. In the present study, a six-month period of treatment with atorvastatin might have been too short to achieve an effect on myocardial perfusion reserve, either by regression of the coronary stenosis or by improvement in microvascular function. In the REGRESS study, treatment with pravastatin resulted in a reduction in ischaemic events, and in less progression of angiographic coronary lesions after two years\textsuperscript{8}. On the other hand, after six months treatment with fluvastatin an improvement in myocardial perfusion was reported\textsuperscript{5}. In the AVERT study eighteen months of LDL-cholesterol reduction with atorvastatin demonstrated a significant reduction in ischaemic events, when compared to PTCA\textsuperscript{9}. The present substudy demonstrated a similar reduction in LDL-cholesterol (-53% \textit{v} 46% for substudy and AVERT, respectively). In the AVERT study, PTCA was significantly more effective in relieving anginal complaints, presumably as a result of an improvement in myocardial perfusion. However, in the PTCA group more ischaemic events were observed. After PTCA, plaque destabilisation and abrupt occlusion of the vessel can be held accountable for the ischaemic events occurring in the periprocedural period, while restenosis and progression of non-target lesions may be responsible for repeated revascularization in the mid-term and long term period. Conversely, by promoting plaque stabilisation,
atorvastatin was presumably able to reduce ischaemic cardiac events. According to results observed in the present study this may not have been accompanied by an improvement in myocardial perfusion reserve at 6 months despite a reduction in LDL-cholesterol.

**CONCLUSIONS AND CLINICAL IMPLICATIONS**

Successful PTCA, but not aggressive lipid-lowering therapy with atorvastatin, normalised dipyridamole myocardial perfusion and perfusion reserve in target vessel areas 6 months after treatment, in patients with mild angina and one or two vessel disease. From this substudy of the AVERT trial, the relationship between cholesterol lowering, myocardial perfusion and ischaemic events is less certain. PTCA has a beneficial effect on myocardial perfusion, which may reflect a relief from anginal symptoms. However, in 341 patients atorvastatin seems able to reduce ischaemic events\(^9\), while in this substudy with similar LDL-cholesterol reduction no significant change in myocardial perfusion is observed. Therefore, we speculate that the combination of PTCA and lipid-lowering therapy with atorvastatin is likely to enhance a favourable clinical mid and long-term outcome.

**APPENDIX A**

**Positron emission tomography imaging protocol**

All PET studies were performed after subjects had refrained from caffeinated beverage intake for a minimum of 12 hours before the investigation. Subjects were positioned in a 951 Siemens (ECAT) positron camera (Siemens AG, Knoxville, USA), which visualises 31 planes simultaneously over 10.8 cm. The in-plane spatial resolution of the camera is 6 mm FWHM. Data was automatically corrected for accidental coincidence and dead time. Subjects were positioned with the help of a rectilinear scan. Photon attenuation was measured using a rectilinear external ring source filled with \(^{68}\text{Ge}/^{68}\text{Ga}\). Continuous monitoring with 12-leads electrocardiography and blood pressure measurement were provided (Dynamap, 10 minutes interval and continuous monitoring during provocative test). Myocardial perfusion was studied using \(^{13}\text{N}\)-ammonia as tracer. Dynamic rest imaging was started at
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the time of $^{13}$N-ammonia injection (370 MBq) and continued for 16 minutes (frames, 12 x 5 seconds, 6 x 10 seconds, 4 x 30 seconds, 2 x 60 seconds, 2 x 120 seconds, 1 x 360 seconds). Pharmacological vasodilatation was achieved by intravenous infusion of dipyridamole (0.56 mg/kg body weight in 4 minutes). Myocardial imaging was performed by injecting 370 MBq $^{13}$N-ammonia, 6 minutes after beginning the dipyridamole infusion and continuing for 10 minutes (frames, 12 x 5 seconds, 6 x 10 seconds, 4 x 30 seconds, 2 x 60 seconds, 2 x 120 seconds). The total duration of the PET study was approximately 90 minutes.

**Positron emission tomography data analysis**

Data was reconstructed by filtered backprojection and a Hann filter with 0.5 cycles/pixel was applied. The matrix size was 128x128 and a zoom factor of 1.5 was used. Data from the $^{13}$N-ammonia provocative studies was corrected for remaining activity, by subtracting the last frame of the preceding study. After the subtraction procedure, a long axis was manually drawn in the left ventricle. Then, a fully automatic, non-operator-dependent, MATLAB-based program was used for reorientation to 10 short-axis images, contour detection was performed and each short-axis image was divided into 16 segments (22.5 degree each). The subendocardial layers of these segments were chosen as regions of interest, from which time-activity curves were calculated in all slices, for all segments. A left ventricular cavity region of interest was defined in three slices near the basis, the average of which was used to calculate a single blood-pool time-activity curve. For each segment, a fit procedure was performed, according to the three-compartment model described by Hutchins et al., and myocardial perfusion was calculated in milliliter per minute per 100 milliliter myocardial tissue [mL/min/100mL].

**Reproducibility**

For reproducibility of the above described PET imaging and analysis protocol, measurements for rest and dipyridamole-induced myocardial perfusion were repeated in a separate group of 7 stable coronary artery disease patients with mean interval 2.5 months. Both global and regional myocardial perfusion measurements were reproducible and in concordance with previous data reported by Sawada et al. (R=0.84; p<0.005; Y=1.08X – 4.29 mL/min/100mL and R=0.87; p<0.0001; Y=0.94X + 6.60 mL/min/100mL; for global and regional myocardial perfusion, respectively).
REFERENCES
