

A 6 month randomized, double blind, placebo controlled, multi-center trial of high dose atorvastatin on myocardial perfusion abnormalities by positron emission tomography in coronary artery disease

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Background In coronary artery disease (CAD), statins decrease morbidity and mortality but changes in myocardial perfusion abnormalities remain poorly defined.

Methods We completed a randomized, double blind, placebo controlled, multi-center trial of 145 patients, 43 to 86 years old, with CAD from seven community and academic centers for cardiac positron emission tomography (PET) randomized to 6 months of atorvastatin 80mg daily (72 patients) or placebo (73 patients). PET scans were obtained at baseline, 6 weeks and 6 months using N-13 ammonia or Rb-82 at rest and after dipyridamole or adenosine stress, submitted to the core PET laboratory in Houston. Change in stress induced perfusion defects from baseline to follow-up PET scans was scored by two independent, double blinded readers and by automated quantitative software.

Results Total and LDL cholesterol decreased by 37% and 51%, respectively in atorvastatin but not placebo groups ($P < .05$). The primary endpoint, quantitative severity (lowest mean quadrant activity), showed no significant difference between treatment and placebo. The secondary endpoint, predefined blinded visual change scores, improved significantly after atorvastatin compared to placebo at six months ($P = .02$). Ad-hoc subgroup analysis showed interaction between quantitative defect size and treatment response with perfusion defects in the upper tertile of size by automated software improving more in atorvastatin than placebo groups ($P = .016$).

Conclusion The primary endpoint, quantitative severity of myocardial perfusion abnormalities by PET, did not improve after 6 months of atorvastatin 80 mg daily compared to placebo. The secondary endpoint of predefined blinded visual change scores significantly improved, as did a subgroup in the upper tertile of defect size, compared to placebo. (*Am Heart J* 2008;155:245-53.)

The statin class of cholesterol lowering drugs reduces coronary events and improves survival in patients with coronary artery disease (CAD). Although effects of statins

on absolute myocardial perfusion have been described in small un-controlled studies, no randomized, placebo controlled, double blind, multi-center trial using positron emission tomography has been reported.

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Methods

Study population

The study tested the hypothesis that high dose atorvastatin treatment would improve stress induced myocardial perfusion defects by cardiac positron emission tomography (PET) in patients with CAD compared to placebo treated controls. Accordingly, 145 patients with CAD from seven PET centers were randomized to a prospective 6-month, double-blind, placebo-controlled, multi-center trial to assess the efficacy of aggressive lipid lowering with 80 mg daily of atorvastatin compared to placebo by rest-stress myocardial perfusion PET scanning at baseline, 6 weeks and 6 months follow-up.

All patients signed informed consent approved by the institutional Committee For the Protection of Human Subjects. All patients were instructed to follow the National Cholesterol

Education Program (NCEP) Step 2 Diet. The institutional Committee For the Protection of Human Subjects, the authors, the sponsors and the participating patients agreed that randomization to short term, supervised placebo treatment was justified for better understanding of each patient's status by PET perfusion imaging for subsequent lifelong treatment as well as for scientific knowledge.

Inclusion criteria

Men and women 18 years of age or older with documented CAD were enrolled based on the following criteria (i) at least 50% stenosis in at least one vessel on visual assessment of a coronary arteriogram, or (ii) history of myocardial infarction (iii) history of positive stress echo (iv) reversible perfusion defect on stress thallium or Sestimibi perfusion imaging or on stress perfusion PET scanning and (v) abnormal rest-stress PET perfusion scan with stress image having at least one quadrant or apical relative uptake value less than 75% of maximum relative uptake and no resting defect with over two quadrants having less than 60% of maximum normalized activity.

Exclusion criteria

Patients were excluded with clinically significant left main disease ($\geq 50\%$ stenosis), left main equivalent, unstable angina within 3 months of randomization, symptomatic heart failure, left ventricular ejection fraction $\leq 35\%$, significant valve dysfunction, resting perfusion defect with two quadrants of $< 60\%$ of maximum relative activity, myocardial infarction or revascularization procedure (PTCA, atherectomy, stents, CABG) within 6 months of randomization or planned during the study period, stroke or cerebral transient ischemic attack within 3 months of screening or hypersensitivity to HMG-CoA reductase inhibitors.

Randomization

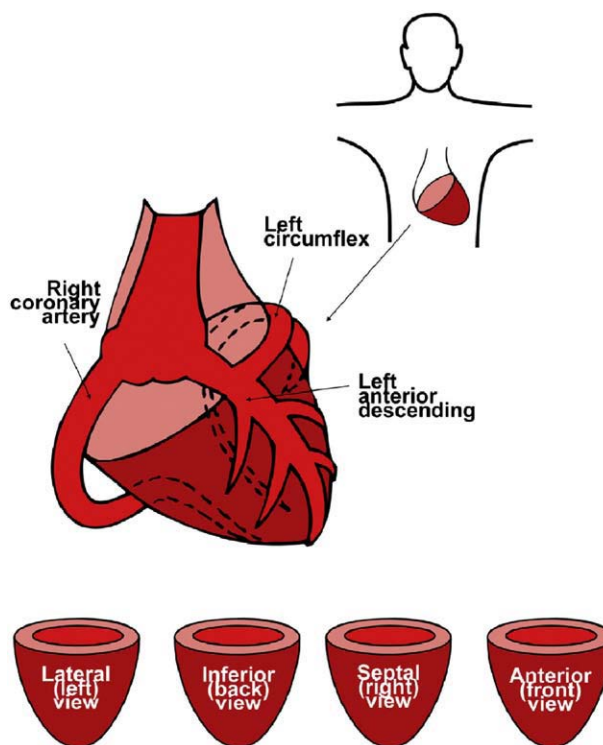
Eligible patients entered a one month lead-in phase, discontinued all lipid-lowering drugs, began the NIH NCEP Step 2 diet to stabilize baseline lipids, completed diet diaries for Food Record Rating scoring and had baseline PET before treatment randomization. After screening and baseline phases, patients were randomized to either 80 mg atorvastatin daily or placebo, provided as unlabelled study drug by Pfizer Global Research and Development, maintaining all investigators blinded to treatment group.

Other medications and monitoring

All patients were prescribed aspirin (≥ 80 mg daily). All lipid-regulating drugs including fish oil and Metamucil were discontinued at least one month prior to baseline PET perfusion imaging and baseline laboratory tests. Estrogen and antioxidant therapies were continued at the same dose but initiation of new treatment or change in any medication was prohibited. Approximately 52% of placebo and 69% of atorvastatin groups were taking lipid-altering medications before stopping them at beginning of one-month washout period.

Patients were monitored for drug toxicity and laboratory testing at four follow up visits over six-month follow-up. Investigators were blinded to lipid results but not safety lab data. There were no differences in side effects between treatment and placebo groups and no patient withdrew from the study due to

Figure 1



Schematic demonstrating four topographic views of myocardial perfusion by positron emission tomography; from left to right the views are left lateral, inferior, right or septal and anterior views with corresponding distribution of each coronary artery.

side effects. Data on patients withdrawing from the study for other reasons were carried forward to the end of the study at 6 months.

Positron emission tomography (PET)

PET scans were obtained on Positron Corporation PET scanners using the same imaging protocol, coded by PET number, saved on high density cassettes and sent to core PET laboratory in Houston, Texas for visual change scoring by two independent blinded readers and for automated quantitative changes in defect severity. All investigators were blinded to treatment agent. Patients fasted for 4 hours, abstained from caffeine and theophylline for 24 hours, stopped smoking for 12 hours before each PET study and stopped taking all medications except insulin, aspirin, and blood pressure medications.

As previously described,¹⁻⁷ PET imaging was carried out using University of Texas designed, Positron Posicam Auricle or Posicam HZL, BGO, 2-D multi-slice tomographs at resolution of 10 mm FWHM. With rotating rod source containing 4-5 mCi of Ge-68, transmission images to correct for photon attenuation contained 100 million counts. Emission images obtained following intravenous injection of 25 to 60 mCi of generator produced Rb-82 contained 40 million counts or after 18 mCi of

cyclotron produced nitrogen-13 contained 30 million counts. The same radionuclide was used for rest, stress and follow up images. Immediately after completing resting Rb-82 imaging or 30 minutes after administration of first dose of N-13 ammonia, dipyridamole (0.142 mg/kg/min) was infused for 4 min. At four minutes after completion of dipyridamole infusion, the same dose of same radionuclide was given intravenously and PET imaging repeated.

Image processing

A three-dimensional restructuring algorithm generates true short and long axis views from PET transaxial cardiac images, perpendicular to and parallel to long axis of left ventricle and three-dimensional topographic views of relative regional activity distribution displayed as lateral, inferior, septal (right) and anterior quadrant views corresponding to coronary arteries as previously described,¹⁻⁷ illustrated in Figure 1. Images were normalized to maximum 2% of pixels in whole heart data set and displayed on relative color scale with white as maximum activity and 5% relative uptake decrements to red, yellow, green, blue, purple and black being the lowest activity. Side-by-side baseline and follow-up stress scans were visually scored as worse or better by two experienced, independent, doubly blinded readers according to strict prospective per-study criteria as follows:

An entire quadrant was assessed for change in severity where each of four quadrants and apex region comprise 20% of left ventricle. A visual change score of 0 was assigned for no change, a visual score of 1 was assigned for a one-color difference, a score of 2 for a two-color difference and a score of 3 for a three color difference in each quadrant of side-by-side comparison of the baseline and follow-up scan displayed on the same scale on the CRT screen. Worsening was therefore visually scored on an integer scale as minimal worsening (-1 for a one color change), moderate worsening (-2 for a two color change), and maximal worsening (-3 for a three color change) where each integer step in worsening correlates with a one to three color worsening in each quadrant of follow-up compared to baseline scan. Improvement was visually scored on an integer scale as minimal improvement (+1 for a one color change), moderate improvement (+2 for a two color change), and maximal improvement (+3 for a three color change) where each integer step in improvement correlates with a one to three color improvement in each quadrant of follow-up compared to baseline scan. Scores were assigned to each quadrant, to apex and to whole heart.

Proper statistical analysis of change in severity of perfusion defects required that each patient contribute one data point. Accordingly, based on changes in one or more quadrants for each patient, an overall aggregate visual change in the follow-up PET was judged as better (mild+1 to marked +3), worse (mild-1 to marked -3), unchanged (0) or mixed (+1 or better in one quadrant but -1 or worse in another quadrant). In order to obtain a definite conclusion on benefit or no benefit of atorvastatin treatment, each patient contributed one data point in a binary classification into group B for better or group NB for no better that included patients scored as worse, mixed or no change. A score difference of greater than one between independent, doubly blinded readers was defined as a disagreement requiring blinded consensus final reading.

Table I. Baseline characteristics

Baseline characteristics differences between groups are not significant	Placebo N = 73	Atorvastatin N = 72
Men N(%)	62 (85%)	67 (93%)
Women N(%)	11 (15%)	5 (7%)
Age, years old Median	64	70
Current smoker N(%)	9 (12%)	12 (17%)
Total cholesterol, mg/dl, Mean ± SE	208 ± 3.7*	211 ± 3.2
LDL cholesterol, mg/dl, Mean ± SE	130 ± 3.4	129 ± 2.9
HDL cholesterol, mg/dl, Mean ± SE	44 ± 1.3	43 ± 1.2
Triglycerides, mg/dl, Mean±SE	179 ± 11.0	206 ± 14.8
Total exercise time in minutes	11.7 ± 0.4	11.6 ± 0.5
Severity % of max activity on stress PET	68 ± 0.8%	67 ± 0.6%
Severity % of max activity on resting PET	73 ± 0.5%	72 ± 0.7%
pts w stress/rest ratio <0.66 in >1% of LV	21 (23%)	21 (22%)

*Standard error of the mean.

Perfusion defects on PET images were also quantified by automated software as previously described¹⁻⁷ for changes from baseline to follow-up in (i) severity defined as the lowest average quadrant relative activity (ii) combined size and severity defined as % of left ventricle with a stress/rest relative ratio of ≤ 0.66 indicating % of heart with relative activity on stress scan that is reduced by 34% below, or to 66% of resting baseline image, a severe defect (iii) combined size and severity defined as % of left ventricle with a stress/rest relative ratio of 0.67 to 1.0 indicating % of heart with relative activity on stress scan that is reduced by less than 34% of resting baseline image, a mild to moderate defect.

Statistical analysis

All statistical analysis was done at the Pfizer Data Center. A sample size of 140 subjects was calculated based on a 2-sided t-test at a 5% level of significance. All paired baseline to follow-up stress PET images were scored independently by two blinded readers and statistical analysis conducted by the Pfizer statistical analysis center. Percent changes from baseline to follow-up in LDL, HDL, triglycerides and total cholesterol were analyzed using ANCOVA (analysis of covariance), reported as mean ± 1 standard error of the mean. PET scores for Better or Not Better from baseline to follow-up scans for atorvastatin was compared to placebo using Cochran-Mantel-Haenszel analysis. Analysis of change in quantitative measures, lowest average quadrant relative activity and % of left ventricle with a stress/rest relative ratio, were analyzed using ANCOVA with baseline measure as the covariate.

Ad-hoc analysis for interaction of treatment response with size of defects was conducted on combined placebo and atorvastatin patients in low, middle and high size tertiles of mild to moderate defects having a stress/rest relative ratio of 0.67 to 1.0. This analysis used ANOVA (analysis of variance) and tertile groups were subjects having % of heart with a mild to moderate defects comprising <47%, 47% to 64%, and $\geq 64\%$ of the left

Table II. Changes in lipids

Cholesterol Units, mg/dl	Placebo			Atorvastatin		Mean % change & P value
	Baseline	6 months	Mean % change	Baseline	6 months	
Total ± SE	208 ± 3.7	215 ± 4.5	+2%	210 ± 3.1	134 ± 2.8	-37%*
LDL ± SE	130 ± 3.5	134 ± 4.1	+3%	128 ± 2.8	63 ± 2.4	-51%*
HDL ± SE	43 ± 1.2	44 ± 1.2	+2%	43 ± 1.2	45 ± 1.2	+6%
Triglycerides	181 ± 11.2	195 ± 15.5	+7%	207 ± 15.0	131 ± 9.1	-34%*

*P < .05.

Table III. Changes from baseline in automated quantitative severity

Lowest quadrant average	Placebo	Atorvastatin
N	73	72
Baseline Mean ± SE	67.9 ± 0.8	66.9 ± 1.0
Treatment Mean ± SE	68.2 ± 0.9	66.3 ± 1.1
Change from Baseline ± SE	-0.5	-1.4
Treatment Difference		-0.9
P-value		.27

Table IV. Changes in PET perfusion images by pre-defined blinded visual change scores.

PET images at 6 months	Placebo	Atorvastatin	Significance of diff
Group B, better	20 (27%)	32 (44%)	P = .02
Group NB, not better	53 (73%)	40 (56%)	

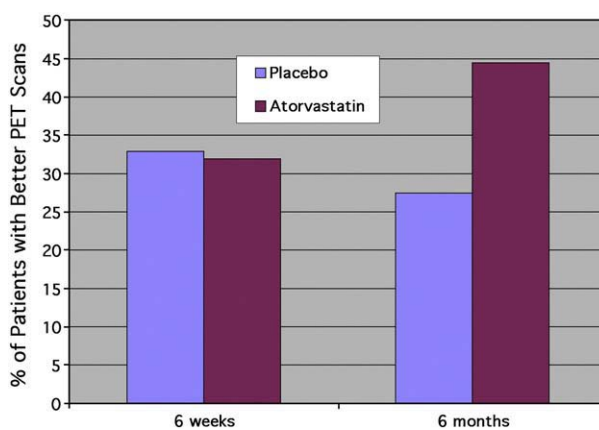
ventricle. All analyses were done using a 2-sided significance level of 5%.

Results

Seventy-three patients were randomized to placebo and 72 patients to atorvastatin for a total of 145 subjects. Three placebo and one atorvastatin treated patients withdrew from the study due to adverse events unrelated to study drug with one death associated with acute myocardial infarction in the placebo group. Three placebo and 4 atorvastatin treated patients withdrew for administrative reasons; 134 patients completed 6 months treatment. By clinic visit inquiry and tablet count, compliance was ≥90% for both groups and concurrent medications were similar.

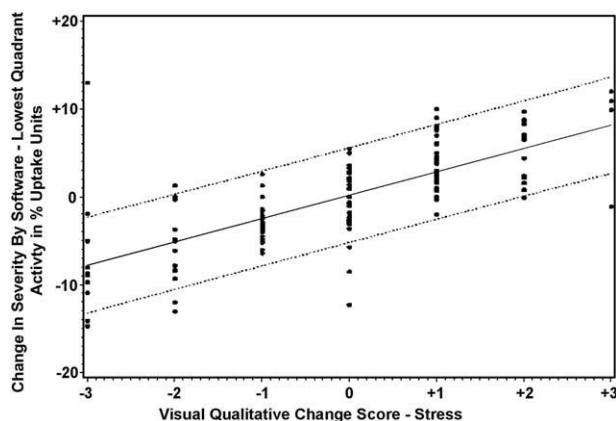
There were no significant differences in baseline characteristics between the treated and placebo groups (Table I) with exercise duration relatively good and comparable between groups. Baseline cholesterol levels

Figure 2



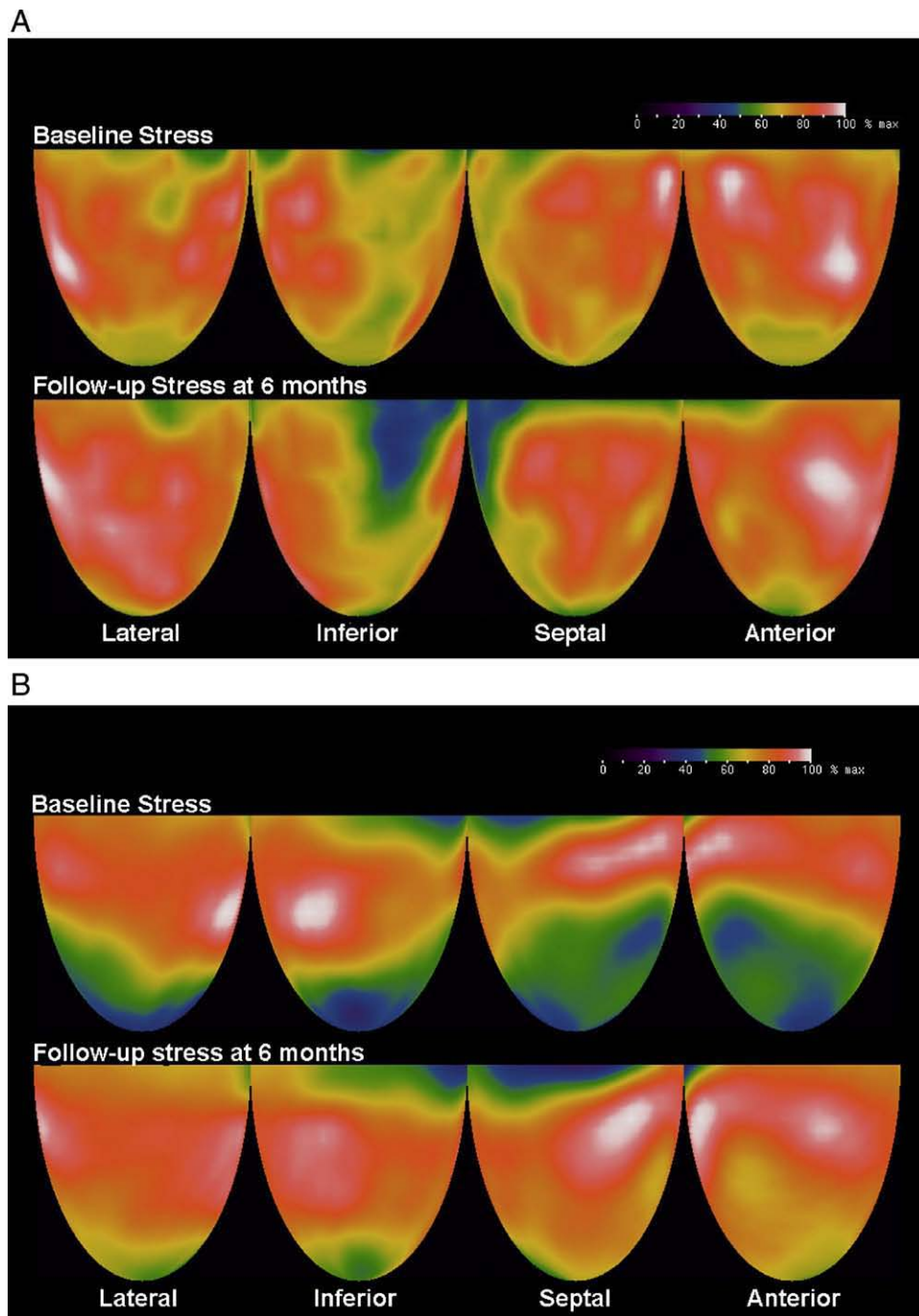
Percent of patients with improved myocardial perfusion defects by PET in placebo and atorvastatin treated patients at 6 weeks and 6 months.

Figure 3



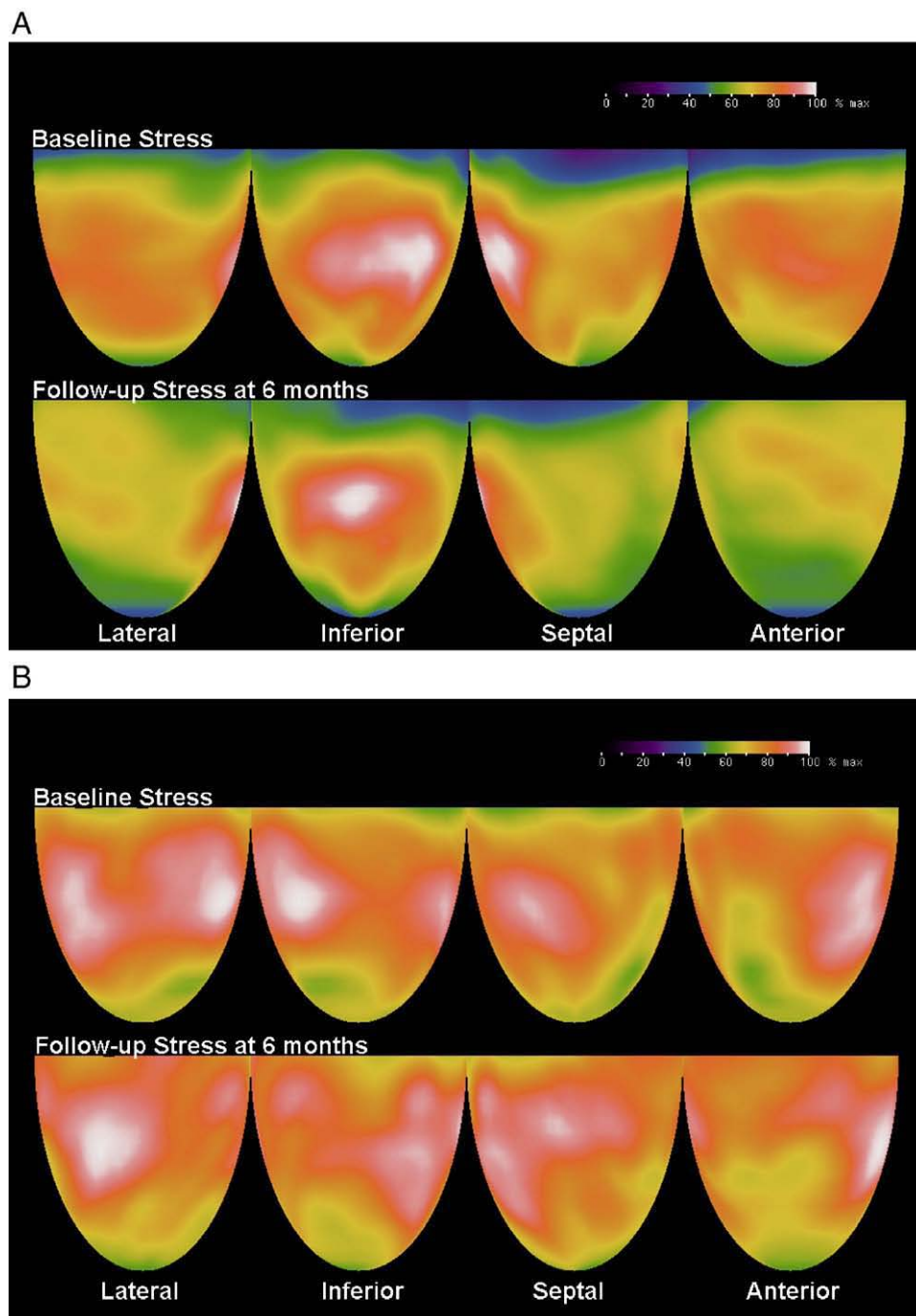
Relation of predefined blinded visual change scores from baseline to 6 months and objective measures of change in severity by automated software expressed for the lowest average quadrant activity as % of maximum activity.

Figure 4



(A) Example of dipyridamole PET at baseline (upper row) and at six-month follow-up (lower row) with a worsening severe perfusion abnormality in a patient in the placebo treated group. White indicates the highest flow, red the next highest in decreasing steps to yellow, green, blue and purple indicating the lowest activity in continuous graded steps according to the color bar where the scale is expressed as % of maximum activity (white). **(B)** Example of dipyridamole PET with a severe defect at baseline (upper row) and at six-month follow-up (lower row) with improvement in a patient in the atorvastatin treated group.

Figure 5

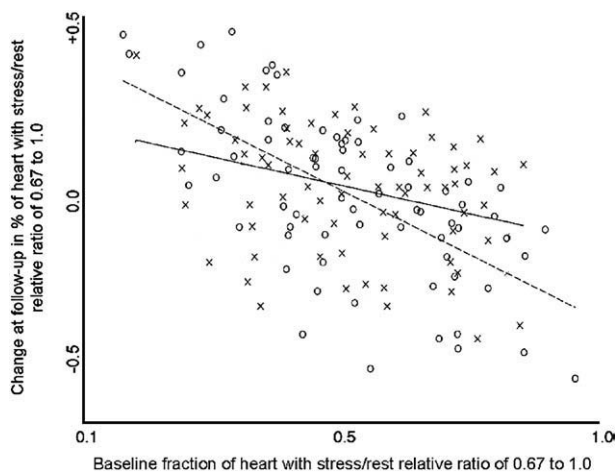


(A) Example of dipyridamole PET at baseline (upper row) and at six-month follow-up (lower row) with a mild worsening perfusion abnormality in a patient from the placebo treated group. (B) Example of dipyridamole PET with a mild defect at baseline (upper row) and at six-month follow-up (lower row) with improvement in a patient from the atorvastatin treated group. Color scale is the same as in prior illustration.

were only mildly elevated and fell significantly in atorvastatin but not in placebo groups (Table II). Average severity or lowest quadrant average of resting images in study subjects was 73%

comparable to 76% of the normal reference database of 23 subjects and for stress images was 68% that was modestly less than 78% of normal reference database.

Figure 6



Interaction of baseline size-severity (horizontal axis) with treatment (regression lines) in relation to quantitative change in size-severity at six months (vertical axis) for mild to moderate perfusion defects defined as fraction of the heart with a stress/rest relative ratio 0.67 to 1.0. X-axis points and solid line are for placebo; open circles and dashed line are for atorvastatin. Slope of relation for atorvastatin group (dashed line) is significantly greater than the slope for placebo (solid line), where $P = .008$, indicating significant size-treatment response interaction.

The primary endpoint, severity of perfusion abnormalities on stress PET images, defined as lowest quadrant average relative activity expressed as % of maximum activity, was not different between treated and placebo groups (Table III). The secondary endpoint, predefined, blinded change scores on baseline to follow-up stress PET images showed significant improvement in treated compared to placebo groups at 6 months (Table IV) ($P = .02$) but not at six weeks, Figure 2. Agreement between blinded independent readers was 97.7% with few differences resolved by blinded mutual consensus reading. Quantitative changes in severity of perfusion defects by automated software correlated closely with blinded visual change scores, $P = .0001$, Figure 3.

Figure 4 illustrates marked changes in stress perfusion PET at baseline and at six-month follow-up for placebo showing worsening and for atorvastatin groups showing improvement. However, severe stress induced perfusion defects were uncommon with Figure 5 showing more common milder defects and milder changes.

Minimum average quadrant relative activity was $72 \pm 6\%$ of maximum at rest and $67 \pm 9\%$ after dipyridamole compared to $76 \pm 6\%$ at rest and $78 \pm 7\%$ after dipyridamole in 23 healthy normal controls. Average stress severity of $67 \pm 9\%$ falls inside the two standard deviation limit for stress images in normals ($78\% - 2 \times$

$7\% = 64\%$), indicating mildness of the perfusion defects. Only 9 of the 145 study patients (4 in placebo, 5 in atorvastatin groups) or 6% had severe defects of greater than 10% of the heart with a stress/rest relative ratio ≤ 0.66 ($<3SD$ of normal reference database).

Ad-hoc analysis of 6 month stress images in combined placebo and atorvastatin groups showed significant interaction of treatment response with defect size categorized by size tertiles of mild to moderate perfusion defects defined as fraction of the heart with a stress/rest relative ratio of 0.67 to 1.0, Figure 6. Slopes of regression lines for placebo and atorvastatin groups in Figure 6 are significantly different ($P = .008$) indicating significant interaction among defect size and treatment response. Subjects having $\geq 64\%$ of their heart with mild to moderate perfusion defects, i.e., a stress/rest relative ratio of 0.67 to 1.0, showed significant reductions on treatment compared to placebo, $P = .0163$, Table V. Subjects with smaller percent of heart with mild to moderate defects (subjects with $<47\%$ and with 47 to 64% of heart having mild to moderate defects) showed no significant differences between atorvastatin and placebo. Although adhoc analysis based on tertiles of size could result in regression to the mean, it would not result in a treatment response.

Discussion

Several nonrandomized or uncontrolled studies reported increased myocardial perfusion by PET imaging after statin treatment⁸⁻¹⁴ in contrast to this randomized multi-center trial failing to show improved quantitative severity of stress PET perfusion abnormalities. However, the secondary endpoint, predefined blinded change scores showed significant improvement in treated compared to placebo groups at 6 months ($P = .02$) as did add-hoc analysis indicating significant improvement after atorvastatin compared to placebo for patients with larger stress perfusion defects.

While our primary endpoint is negative, the positive secondary endpoint and ad-hoc subgroup analysis raise important issues about randomized trials using PET perfusion imaging for assessing changes of CAD. With documented long-term benefit of statins, a short washout period reduces treatment-placebo differences but longer washout periods are inappropriate.

The entry criteria of PET severity here, one quadrant with relative activity $<75\%$ of maximum, was chosen based on the fact that a whole quadrant having relative uptake averaging 73% of maximum is visually, obviously worse than a whole quadrant having normal relative uptake averaging 78% of maximum, a difference of 5% relative uptake units. Interestingly, in Figure 3 correlating visual change scores with automated quantitative severity, the standard deviation of quantitative changes about the regression line is 5.5% relative uptake

Table V. Changes from baseline in fraction of heart with mild to moderate perfusion defects (Stress/rest relative ratio of 0.67 to 1.0) overall and by baseline tertile subgroups

Baseline group % of heart with defect	Treatment	N	Mean change \pm SE	Treatment difference	P-value
All Subjects	Placebo	73	0.000 \pm 0.025	-.023	.4353
	Atorvastatin	72	-0.023 \pm 0.025		
Baseline <47% of heart with defect	Placebo	24	0.075 \pm 0.053	.057	.3217
	Atorvastatin	24	0.132 \pm 0.046		
Baseline 47-64% of heart with defect	Placebo	26	-0.014 \pm 0.040	.005	.9171
	Atorvastatin	24	-0.009 \pm 0.048		
Baseline \geq 64% of heart with defect	Placebo	23	-0.058 \pm 0.046	-.128	.0163
	Atorvastatin	24	-0.186 \pm 0.042		

units, just larger than the difference between the normal 78% and our entry threshold criteria of 73% relative uptake units. In retrospect, this entry criteria led to enrollment of patients with such mild PET abnormalities that quantitative baseline to follow-up changes were not large enough to be significant against variability of automated quantitative measurements.

In contrast to failure of quantitative severity to show significant atorvastatin-placebo differences, the predefined blinded visual change scores showed significant atorvastatin benefit over placebo, suggesting that well-defined blinded visual comparisons may be more sensitive than our automated quantification of severity. Having recognized this problem after completion of the study, we did post-hoc subgroup analysis using a combined rest-to-stress-size-severity endpoint described above to discover an objective statistical interaction between quantitative PET changes and size of mild to moderate defects characterizing the study population since only 6% of stress PET scans had severe defects. In our prior studies, perfusion abnormalities were more severe that did not require this endpoint used for add-hoc analysis.

The final issue concerns what PET measurement is appropriate for a single trial endpoint from many alternatives for quantifying rest stress myocardial perfusion or perfusion defects- rest to stress change, stress images alone, size, severity of relative perfusion defects, absolute maximal myocardial perfusion in cc/min/gm or coronary flow reserve and, if absolute perfusion, how defined in terms of size and severity, for age, heart rate, blood pressure, for operator selected regions of interest or automated objective measurements. Our review of 23 publications reporting absolute perfusion measurements by PET in normal subjects showed great variability where the standard deviation expressed as a % of the mean value of cc/min/gm averaged 24% for rest and 29% for stress perfusion. By comparison in our normal reference database of 23 subjects, the variability in relative uptake with the standard deviation expressed as a % of the mean uptake is 8% for resting and 9% for stress

PET perfusion images, substantially less variability than absolute perfusion.

Study limitations

Enrollment criteria for quantitative severity of perfusion abnormalities on baseline stress PET images was too mild with consequent insufficiently severe flow limiting stenosis for the primary quantitative endpoint chosen, although suitable for blinded visual change scoring.

Our low inter-observer variability for visual change scores might be challenged but is consistent with our prior reports.¹⁻⁷ Bulls-eye displays distort spatial perfusion anatomy by compressing central data and expanding basal data. Based on extensive studies of PET and SPECT with Jaszczak cold spot phantoms and correlation of PET perfusion defects with over 1000 coronary arteriograms,⁵ the multiple, small, pie segment bulls-eye display artificially compartmentalizes myocardial images unrelated to branching coronary tree structure or to the longitudinal base to apex perfusion gradient characterizing diffuse CAD.³ Accordingly, reading whole quadrants of PET images may provide more consistent interpretations than smaller compartmentalization subject to greater variability and inter-observer variability.

Conclusions

The primary endpoint of this randomized, double blind, placebo-controlled, multi-center trial, automated quantitative severity of perfusion abnormalities on stress PET images, showed no improvement after 6 months of high dose atorvastatin compared to placebo. The secondary endpoint of predefined blinded visual change scores on stress PET perfusion images showed significantly greater improvement after 6 months of atorvastatin compared to placebo. Ad hoc subgroup analysis of automated measures of changes in combined rest-stress-size-severity of stress PET images showed significant improvement after atorvastatin compared to placebo for a subgroup with mild to moderate perfusion defects in the upper tertile of size. Although our study provides no definitive conclusions, it suggests that randomized trials using quantitative

perfusion imaging as an endpoint requires specific technology-physiology matching. The technical requirements for this match are complex and unclear for both imaging technology and for physiologic flow measurements needed. This report illustrates essential issues for future randomized trials with myocardial perfusion imaging as an endpoint.

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Appendix A. Contributing centers

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D. Sprecher, MD- Cleveland, OH

Correction

The e-mail address for the corresponding author, Hideya Yamamoto, MD, is incorrect for the simple-article entitled "Comprehensive Evaluation of Non-calcified Coronary Plaque Characteristics Detected Using 64-Slice Computed Tomography in Patients With Proven or Suspected Coronary Artery Disease" that appeared in *Am Heart J* 2007;154:1191-8. The correct e-mail address is hideyayama@hiroshima-u.ac.jp.