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Regadenoson Induces Comparable Left Ventricular Perfusion Defects as Adenosine

A Quantitative Analysis From the ADVANCE MPI 2 Trial

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OBJECTIVES This study sought to determine whether regadenoson induces left ventricular perfusion defects of similar size and severity as seen with adenosine stress.

BACKGROUND Total and ischemic left ventricular perfusion defect size predict patient outcome. Therefore, it is important to show that newer stressor agents induce similar perfusion abnormalities as observed with currently available ones.

METHODS The ADVANCE MPI 2 (Adenosine versus Regadenoson Comparative Evaluation for Myocardial Perfusion Imaging) study was a prospective, double-blind, randomized trial comparing image results in patients undergoing standard gated adenosine single-photon emission computed tomography (SPECT) myocardial perfusion imaging who were then randomized in a 2:1 ratio to either regadenoson (N = 495) or a second adenosine SPECT (N = 260). Quantitative SPECT analysis was used to determine total left ventricular perfusion defect size and the extent of ischemia. Quantification was performed by a single observer who was blinded to randomization and image sequence.

RESULTS Baseline gated perfusion results were similar in patients randomized to adenosine or regadenoson. No significant differences in total (11.5 ± 15.7 vs. 11.4 ± 15.8, p = 0.88) or ischemic (4.8 ± 9.2 vs. 4.6 ± 8.9, p = 0.43) perfusion defect sizes were observed between the regadenoson and adenosine groups, respectively. Linear regression showed a close correlation between adenosine and regadenoson for total ($r = 0.97$, $p < 0.001$) and ischemic ($r = 0.95$, $p < 0.001$) left ventricular perfusion defects. Serial differences in total (−0.03 ± 3.89 vs. −0.13 ± 4.16, p = 0.73) and ischemic (0.15 ± 4.08 vs. 0.25 ± 3.81, p = 0.74) perfusion defect size and left ventricular ejection fraction (0.12 ± 0.32 vs. 0.15 ± 0.35, p = 0.27) from study 1 to study 2 were virtually identical in patients randomized to regadenoson versus adenosine, respectively. The good correlation between serial adenosine and regadenoson studies regarding total (0.41 ± 5.43 vs. 0.21 ± 5.23, p = 0.76) and ischemic (0.17 ± 5.31 vs. 0.23 ± 6.08, p = 0.94) perfusion defects persisted in the subgroup of 308 patients with an abnormal baseline SPECT.

CONCLUSIONS Applying quantitative analysis, regadenoson induces virtually identical scintigraphic results as adenosine regarding the size and severity of left ventricular perfusion defects and the extent of scintigraphic ischemia. (J Am Coll Cardiol Img 2009;2:959–68) © 2009 by the American College of Cardiology Foundation

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Stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging is widely used to diagnose (1) and to risk stratify (2) patients with suspected or known coronary artery disease based on the presence and extent of left ventricular (LV) perfusion defects (1,2), the extent of inducible ischemia (2,3), and the LV ejection fraction (EF) (4). The value of SPECT in these arenas has been shown using exercise or pharmacologic stressor modalities (2) and across patient populations at varying clinical risk, including those after infarction (5).

In this regard, it is essential that any newly introduced stressor agent be shown to induce similar perfusion and functional results as observed with more traditional ones. Quantitative SPECT techniques afford such accurate comparisons (6,7). In this substudy analysis of the ADVANCE MPI 2 (Adenosine versus Regadenoson Comparative Evaluation for Myocardial Perfusion Imaging) trial (8), we report the quantitative perfusion results for regadenoson, a selective A2A adenosine receptor agonist, as compared with those observed with the widely used nonselective pharmacologic vasodilator, adenosine. A quantitative approach was taken to better characterize the similarity in perfusion results observed between adenosine and regadenoson over the visual assessment used in the original study design (8).

ABBREVIATIONS AND ACRONYMS

EF = ejection fraction
LV = left ventricular
PDS = perfusion defect size
SDS = summed difference score
SPECT = single-photon emission computed tomography
SRS = summed rest score
SSS = summed stress score

METHODS

Study design. The ADVANCE MPI 2 trial was a double-blind, randomized trial assessing the strength of agreement between sequential adenosine–regadenoson and adenosine–adenosine SPECT based on visual interpretation of the image data. The study design and main trial results are published (8). Patients referred for a clinically indicated pharmacologic stress SPECT study were eligible for enrollment. Exclusion criteria included contraindications to adenosine, recent acute coronary syndrome (<3 months) or coronary revascularization (<6 months), severe valvular abnormalities, and hemodynamic instability (8). Contraindications to adenosine were: greater than 1st degree atrioventricular block, sick sinus syndrome in patients without a functioning artificial pacemaker, symptomatic bradycardia or high-degree atrioventricular block on the initial study, known or suspected bronchospastic lung disease, known hypersensitivity to adenosine, dipyridamole use within 30 h, and methylxanthine consumption within 12 h.

After the initial unblinded adenosine study, a second blinded study was performed within 4 weeks in patients who had no changes in their clinical status or cardiac medications. Before the second study, patients were randomized in a 2:1 fashion to receive either regadenoson or adenosine stress. Images were acquired according to American Society of Nuclear Cardiology guidelines using either 1- or 2-day (depending on body weight) technetium-99m tracer protocols or a dual-isotope (rest thallium–stress technetium-99m tracer) protocol (9). Investigators were blinded to vasodilator randomization by using a double-delivery technique in which each patient received both a 6-min infusion of adenosine or placebo through one intravenous line and a regadenoson or placebo bolus through a second intravenous line placed in the other arm.

Images were available for analysis in 755 of the 784 patients enrolled in the ADVANCE MPI 2 study (96%), of whom 260 were randomized to adenosine and 495 to regadenoson. In 29 patients the raw data SPECT images could not be obtained from the nuclear core laboratory. Both image sets could be analyzed in all 260 patients randomized to adenosine and in 493 of 495 patients randomized to regadenoson. In the latter 2 patients, the studies could not be processed because of technical difficulties.

SPECT analysis. All raw data of gated SPECT images (2 sets per patient) were electronically transferred to the Methodist DeBakey Heart and Vascular Center for analysis, where they were reconstructed by a single observer using standard back projection and identical filtering (Butterworth filter with a critical frequency of 0.4 cycles/s, order 5) (10). Motion correction was applied before image reconstruction if >1 pixel of x or y axis deviation was observed over the 180° acquisition.

Images were reoriented according to American Society of Nuclear Cardiology guidelines (9) and then visually assessed in all 3 standard projections, along with the gated SPECT and raw image data, to assess for image quality and study normalcy/abnormalcy. The study quality of each image set was graded as good, fair, or poor based on the presence of attenuation artifacts, patient motion during study acquisition, and extracardiac tracer uptake interfering with image interpretation. Visual interpretation of all SPECT studies was performed by one investigator (J.J.M.) and solely to allow comparison of quantified SPECT data obtained with the 2 vasodilator agents in the subgroup of

patients with an initially abnormal baseline adenosine study result. All references to SPECT abnormalcy are based on visual interpretation and not on the quantitative results.

Quantitative SPECT was performed using a previously validated automated program that determines the extent and severity of the stress-induced LV perfusion defect size (PDS) and the extent of scintigraphic scar and ischemia based on polar plot analysis (5). The LV defect severity within abnormally perfused regions of the patient's polar plot was defined on a pixel-by-pixel basis as mild, moderate, or severe based on its relation to expected normal pixel count activity in the normal database polar plot (>50%, 26% to 50%, and 0% to 25%, respectively). The number of pixels falling into each of these 3 categories was then summed to determine the percentage of the LV with a mild, moderate, or severe defect. Ischemia severity was calculated as the percent count improvement toward normal values within ischemic pixels and defined as minimal (0% to 25%), moderate (26% to 50%), or marked (>50%) improvement. Thus, if a pixel had a stress value of 20 and a rest value of 70, and the corresponding pixel in the normal database had a value of 80, the ischemia severity would be [(70 − 20)/(80 − 20)] or 83% (i.e., marked improvement). The number of pixels falling into each of these 3 categories was then summed to determine the percentage of the LV with minimal, moderate, or marked ischemia. Our quantitative program has been shown to be reproducible for assessing serial differences in myocardial perfusion (6,10) and accurate in risk stratification (5,11) and is currently incorporated within the 4DM-SPECT software platform. LVEF and cardiac volumes were calculated from gated SPECT images using standard 4DM-SPECT software (12). Quantification was performed by one individual (J.J.M.) who was blinded to patient randomization and image sequence. The value quantified for each SPECT variable was used in the analysis regardless of whether or not the study was interpreted as normal from a visual perspective.

Statistical analysis. The primary end point of this substudy was to determine whether serial differences in total and ischemic (reversible) LV PDS were similar between the adenosine–regadenoson and adenosine–adenosine studies. Based on a sample size of 758 patients, the study had 94% power to detect a small (0.9%) absolute difference in the change in LV PDS between serial adenosine–adenosine and adenosine–regadenoson studies at an alpha = 0.05, and assuming a standard deviation of 3.5.

All statistical analyses were carried out in SAS version 9.1 (SAS Institute Inc., Cary, North Carolina) on an XP-PRO platform (Microsoft Corp., Redmond, Washington). Data were collected in Access (Microsoft Corp.), and then exported to an SAS dataset (SAS Institute Inc.); all personal information was removed from the dataset in compliance with Health Insurance Portability and Accountability Act regulations. Secondary analyses assessed differences in total and ischemic PDS severities and functional parameters (i.e., cardiac volumes and LVEF) between the 2 randomized groups using unpaired *t* tests. Scintigraphic differences on the baseline adenosine studies in the 2 groups were assessed using unpaired *t* tests. Linear regression analysis was used to quantitate the relationship between adenosine- and regadenoson-induced scintigraphic variables. Mean differences, standard deviations, and 95% confidence intervals were calculated. Chi-square analysis was used to compare discrete variables. A p value <0.05 was considered significant.

RESULTS

Study quality and visual interpretation. Study quality was similar on serial adenosine–adenosine and adenosine–regadenoson image sets with both sets scored as good to excellent (175 or 67% vs. 361 or 73%); 1 good, 1 fair (26 or 10% vs. 43 or 9%); both fair (35 or 13% vs. 52 or 10%), or both poor (24 or 10% vs. 40 or 8%), respectively (p = NS).

The baseline adenosine SPECT results for the 2 randomized groups are shown in Table 1. A similar percentage of patients randomized to adenosine or regadenoson had an initial adenosine study that was visually interpreted as normal with approximately 40% of patients in each group having clearly abnormal perfusion results.

Serial imaging results based on visual interpretation are shown in Table 2. The overall agreement between adenosine–adenosine and adenosine–regadenoson image sets was comparable (247 of 260, 95% vs. 481 of 493, 97.5%, p = NS) with a similar percentage of patients randomized to adenosine or regadenoson showing abnormal perfusion on both SPECT studies (100 of 104, 96% vs. 202 of 204, 99%, p = NS).

Most (94.1%) of the baseline studies visually interpreted as normal were also normal by quantitative analysis (i.e., <3% total PDS) in both the

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Table 1. Baseline Adenosine Scintigraphic Results

	Adenosine Group (N = 260)	Regadenoson Group (N = 495)	p Value
Visual interpretation (%)			NS
Normal	144 (55%)	266 (54%)	
Probably normal	12 (5%)	24 (5%)	
Abnormal	104 (40%)	205 (41%)	
Quantitative analysis			
PDS (% LV)			
Total	10.2 ± 14.8	11.4 ± 15.8	0.287
Ischemia	4.2 ± 7.8	4.6 ± 8.9	0.538
Scar	6.0 ± 10.7	6.8 ± 11.3	0.316
PDS severity (% LV)			
Mild (>50%)	8.3 ± 10.9	9.1 ± 11.8	0.360
Moderate (26%–50%)	1.6 ± 4.5	1.9 ± 4.9	0.296
Severe (0%–25%)	0.3 ± 1.8	0.4 ± 2.1	0.659
Ischemia severity (% LV)			
Minimal (0%–25%)	0.3 ± 1.2	0.3 ± 1.1	0.874
Moderate (26%–50%)	1.5 ± 3.5	1.5 ± 3.5	0.903
Marked (>50%)	2.4 ± 4.8	2.8 ± 6.1	0.412
Gated SPECT variables*			
LVEF (%)	64.2 ± 13.7	63.2 ± 15.7	0.409
LV EDV (ml)	117.4 ± 58.5	118.3 ± 61.0	0.854
LV ESV (ml)	47.8 ± 44.2	51.2 ± 52.6	0.386

*n = 259 adenosine group; 488 regadenoson group.
EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; NS = not significant; PDS = perfusion defect size; SPECT = single-photon emission computed tomography.

adenosine (134 of 144, 93.1%) and the regadenoson (251 of 265, 94.7%) groups. Conversely, most (98.7%) of the baseline studies visually interpreted as abnormal were also abnormal by quantitative analysis in the adenosine (102 of 104, 98%) and regadenoson (202 of 204, 99%) groups.

Overall quantitative SPECT results. The baseline quantitative adenosine SPECT results for the 2 randomized groups were similar (Table 1). The overall total LV PDS was relatively small at approximately 11% of the myocardium, but this increased significantly when analysis was restricted to the 40% of patients with a visually abnormal study (adenosine group total PDS: 23.4 ± 15.5 %LV; regadenoson group total PDS: 25.7 ± 15.5 %LV). Likewise, the baseline ischemic PDS increased from 4.2 ± 7.8% to 10.0 ± 9.7% (adenosine group) and from 4.6 ± 8.9% to 10.8 ± 11.3% (regadenoson group) when only patients with visually abnormal studies were considered.

The differences in quantified SPECT variables from the baseline adenosine study to the regadenoson study are shown in Table 3. No significant differences in serial LV perfusion results were observed when regadenoson became the vasodilator. Significant but only minor differences in LVEF and end-systolic volume were observed between the 2 vasodilators. Linear regression analysis likewise showed a strong relationship between serial adenosine–regadenoson studies for total ($r = 0.97$, $p < 0.001$) (Fig. 1A), ischemia ($r = 0.95$, $p < 0.001$) (Fig. 1B), and scar ($r = 0.96$, $p < 0.001$) defect sizes and also LVEF ($r = 0.99$, $p < 0.001$).

The primary end point of this study was to determine whether sequential serial differences in stress-induced total and ischemic PDS could be identified between the 2 randomized groups. As shown in Table 4, there were no significant differences in any of the perfusion or gated SPECT variables between serial adenosine versus adenosine–regadenoson studies.

We have previously reported that a >9% absolute serial difference in total LV PDS represents the 95% confidence interval for a real patient change beyond variability (6). Consistent with the mean group findings, only a small and similar percentage of patients exceeded these limits when comparing serial adenosine (12 of 260 or 4.6%) versus adenosine–regadenoson (17 of 493 or 3.5%) LV PDS imaging results. Most patients randomized to adenosine or regadenoson had either no difference in their total PDS on serial imaging (102 or 39% vs. 211 or 43%, p = NS) or a ≤5% absolute difference (232 of 260 or 89% vs. 448 of 493 or 91%, p = NS). In both randomized groups, serial differences in total and ischemic PDS showed a typical Gaussian distribution (shown for regadenoson group) (Fig. 2).

Quantified SPECT results in patients with an initially abnormal adenosine SPECT. A separate analysis was performed on the 308 patients (104 adenosine group, 204 regadenoson group) who had a visually

Table 2. Visual Interpretation Results

	Normal	Probably Normal	Abnormal	Total
		Adenosine 2		
Adenosine 1				
Normal	140 (97.2%)	1 (0.7%)	3 (2.1%)	144
Probably normal	3 (25%)	7 (58.3%)	2 (16.7%)	12
Abnormal	4 (3.9%)	0	100 (96.1)	104
Total	147 (56.5%)	8 (3.1%)	105 (40.4%)	260
		Regadenoson		
Adenosine 1				
Normal	261 (98.5%)	0	4 (1.5%)	265
Probably normal	5 (20.8%)	18 (75%)	1 (4.2%)	24
Abnormal	2 (1.0%)	0	202 (99.0%)	204
Total	268 (54.4%)	18 (3.6%)	207 (42.0%)	493

Agreement between adenosine 1 and adenosine 2 studies: 247 of 260 = 95% and adenosine 1 and regadenoson studies: 481 of 493 = 97.5%.

abnormal baseline adenosine SPECT study. Most of these patients by quantitative analysis had a ≥5% baseline ischemic perfusion defect in both the adenosine (65 or 63%) and regadenoson (134 or 66%, p = NS) groups. The total and ischemic PDS did not differ significantly from study 1 to study 2 for the entire cohort or in either of the randomized groups (Fig. 3). As in the overall analysis, no significant differences in any of the imaging results were observed between the patients randomized to serial adenosine versus adenosine–regadenoson imaging (Table 4). The individual patient results likewise show that few had a >9% absolute difference in total PDS with serial imaging in either the adenosine–adenosine (7.7%) or adenosine–regadenoson (5.9%) randomized groups. A representative patient example is shown in Figure 4.

DISCUSSION

Stress SPECT is known to predict outcome across the entire spectrum of patients with suspected or known coronary artery disease based on the size of the stress-induced perfusion defect, the extent of ischemia, and the LVEF (2–5,11). This has been shown using exercise stress and pharmacologic vasodilators such as adenosine (2). Therefore, when considering the introduction of a new stressor agent, it is imperative that it not only be of similar diagnostic accuracy but also confer the same prognostic information as a standard agent.

Our results show based on an objective quantitative analysis of the ADVANCE MPI 2 study dataset that regadenoson induces virtually identical scintigraphic results as adenosine with regard to the size and severity of the total LV PDS and the extent of scintigraphic ischemia. This was true when analyzing mean group data or assessing serial differences in individual patients. In this regard, regadenoson is comparable to adenosine when used in conjunction with gated SPECT imaging.

Rationale for similar results with adenosine and regadenoson. The ability to increase myocardial blood flow during stress from basal resting levels is termed the coronary flow reserve of a vascular bed, and this is regulated primarily at the arteriolar level (13). Vascular beds supplied by stenosed arteries will utilize coronary flow reserve relative to stenosis severity to maintain adequate resting blood flow. Thus, during exercise (14), and particularly with pharmacologic stress (15), coronary blood flow to the vascular bed served by a normal artery will dramatically increase, whereas flow distal to a ste-

Table 3. Serial Differences in Scintigraphic Variables in Patients Randomized to Regadenoson (N = 493)

	Baseline Adenosine Study	Regadenoson Study	Δ	p Value
PDS (% LV)				
Total	11.4 ± 15.8	11.5 ± 15.7	−0.03 ± 3.9	0.88
Ischemia	4.6 ± 8.9	4.8 ± 9.2	0.15 ± 4.1	0.43
Scar	6.8 ± 11.3	6.7 ± 11.1	−0.12 ± 2.6	0.31
PDS severity (% LV)				
Mild (>50%)	9.1 ± 11.8	9.0 ± 11.4	0.05 ± 3.7	0.78
Moderate (26%–50%)	1.9 ± 4.9	2.0 ± 5.0	−0.05 ± 1.7	0.52
Severe (0%–25%)	0.4 ± 2.1	0.5 ± 2.1	−0.02 ± 0.89	0.54
Ischemia severity (% LV)				
Minimal (0%–25%)	0.3 ± 1.1	0.3 ± 1.2	−0.02 ± 0.69	0.43
Moderate (26%–50%)	1.5 ± 3.5	1.5 ± 3.5	0.10 ± 1.7	0.20
Marked (>50%)	2.8 ± 6.1	3.0 ± 6.3	−0.22 ± 3.6	0.17
Gated SPECT variables*				
LVEF (%)	63.2 ± 15.7	62.7 ± 15.5	0.48 ± 3.06	0.001
LV EDV (ml)	118.3 ± 61.0	118.6 ± 61.2	−0.86 ± 15.6	0.222
LV ESV (ml)	51.2 ± 52.6	52.2 ± 53.4	−1.4 ± 10.4	0.003

*N = 483 patients.
Abbreviations as in Table 1.

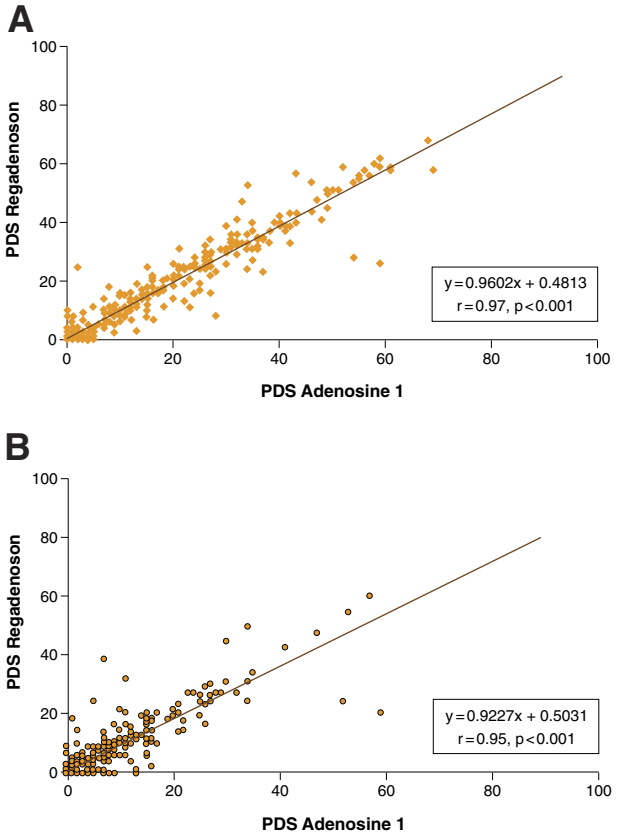

Figure 1. Linear Regression Analysis of Serial Adenosine–Regadenoson SPECT Results

Excellent agreement is seen between the adenosine and regadenoson induced total **(A)** and ischemic **(B)** perfusion defect size (PDS) results. SPECT = single-photon emission computed tomography.

Table 4. Comparison of Differences in Serial Imaging Results Between the Two Randomized Groups

	Adenosine Group	Regadenoson Group	Δ (95% Confidence Interval)	p Value
Total cohort	(N = 260)	(N = 493)		
Δ PDS (% LV)				
Total	−0.13 ± 4.16	−0.03 ± 3.89	−0.11 (−0.71 to 0.49)	0.73
Ischemia	0.25 ± 3.81	0.15 ± 4.08	0.10 (−0.50 to 0.70)	0.74
Scar	−0.11 ± 2.14	−0.12 ± 2.63	0.01 (−0.36 to 0.38)	0.96
Δ PDS severity (% LV)				
Mild (>50%)	0.06 ± 4.11	0.05 ± 3.66	0.01 (−0.56 to 0.59)	0.97
Moderate (26%–50%)	−0.18 ± 1.50	−0.05 ± 1.68	−0.13 (−0.38 to 0.11)	0.27
Severe (0%–25%)	−0.01 ± 0.90	−0.02 ± 0.89	0.01 (−0.12 to 0.14)	0.85
Δ Ischemia severity (% LV)				
Minimal (0%–25%)	−0.06 ± 0.86	−0.02 ± 0.69	−0.04 (−0.15 to 0.07)	0.55
Moderate (26%–50%)	−0.09 ± 1.95	−0.10 ± 1.75	−0.19 (−0.47 to 0.08)	0.18
Marked (>50%)	−0.09 ± 2.83	−0.22 ± 3.60	0.13 (−0.37 to 0.64)	0.58
Δ Gated SPECT variables*				
LVEF (%)	0.15 ± 0.35	0.12 ± 0.32	0.03 (−0.02 to 0.08)	0.27
LV EDV (ml)	−1.82 ± 12.17	−0.87 ± 15.57	−0.95 (−3.15 to 1.24)	0.36
LV ESV (ml)	−1.60 ± 7.14	−1.41 ± 10.41	−0.19 (−1.62 to 1.23)	0.77
Abnormal baseline study†	(N = 104)	(N = 204)		
Δ PDS (% LV)				
Total	0.41 ± 5.43	0.21 ± 5.23	0.20 (−0.34 to 0.75)	0.76
Ischemia	0.17 ± 5.31	0.23 ± 6.08	−0.05 (−0.62 to 0.52)	0.94
Scar	−0.58 ± 2.61	−0.43 ± 3.51	−0.15 (−0.58 to 0.28)	0.67
Δ PDS severity (% LV)				
Mild (>50%)	0.88 ± 5.28	0.35 ± 4.93	0.53 (0.00 to 1.06)	0.40
Moderate (26%–50%)	−0.45 ± 2.40	−0.09 ± 2.60	−0.36 (−0.73 to 0.02)	0.23
Severe (0%–25%)	−0.03 ± 1.36	−0.06 ± 1.38	0.30 (−0.25 to 0.31)	0.86
Δ Ischemia severity (% LV)				
Minimal (0%–25%)	−0.16 ± 1.36	−0.06 ± 1.07	−0.10 (−0.35 to 0.16)	0.53
Moderate (26%–50%)	−0.14 ± 3.05	0.23 ± 2.62	−0.37 (−0.77 to 0.02)	0.29
Marked (>50%)	0.12 ± 3.53	−0.40 ± 5.43	0.52 (0.00 to 1.04)	0.31
Δ Gated SPECT variables‡				
LVEF (%)	0.64 ± 2.92	0.29 ± 3.00	0.35 (−0.07 to 0.77)	0.34
LV EDV (ml)	−0.69 ± 14.46	−1.05 ± 18.97	0.36 (−0.65 to 1.38)	0.85
LV ESV (ml)	−1.36 ± 9.28	−1.61 ± 13.06	0.25 (−0.59 to 1.08)	0.85

*N = 259 (adenosine group); N = 483 (regadenoson group). †N = 104 (adenosine group); N = 204 (regadenoson group). ‡N = 99 (adenosine group); N = 198 (regadenoson group).
Abbreviations as in Table 1.

nosed artery may change minimally because of exhaustion of flow reserve under resting conditions. Because radiopharmaceutical tracer uptake is flow dependent, the relative myocardial radionuclide concentration will be greater in vascular beds supplied by normal versus stenosed arteries, leading to blood flow heterogeneity and development of a perfusion defect.

Both adenosine and regadenoson induce coronary arteriolar vasodilation through activation of the A2A adenosine receptor (15,16). However, adenosine activates all 4 adenosine receptors, whereas regadenoson is a selective A2A receptor agonist that theoretically should induce coronary hyperemia but limit the development of untoward side effects related to activation of the other receptors (17). In humans, regadenoson increases myocardial blood flow by more than 2.5-fold above baseline for at least 2 min when given intravenously as a 400-μg bolus (18). This degree of hyperemia is less than that observed with adenosine (18), but sufficient to discern relative regional differences in myocardial tracer uptake (19), and long enough to ensure maximal hyperemia during the time needed to clear the radiopharmaceutical from the blood pool (20). The similar quantitative results we report in the current study with adenosine and regadenoson are validation of these theoretical constructs.

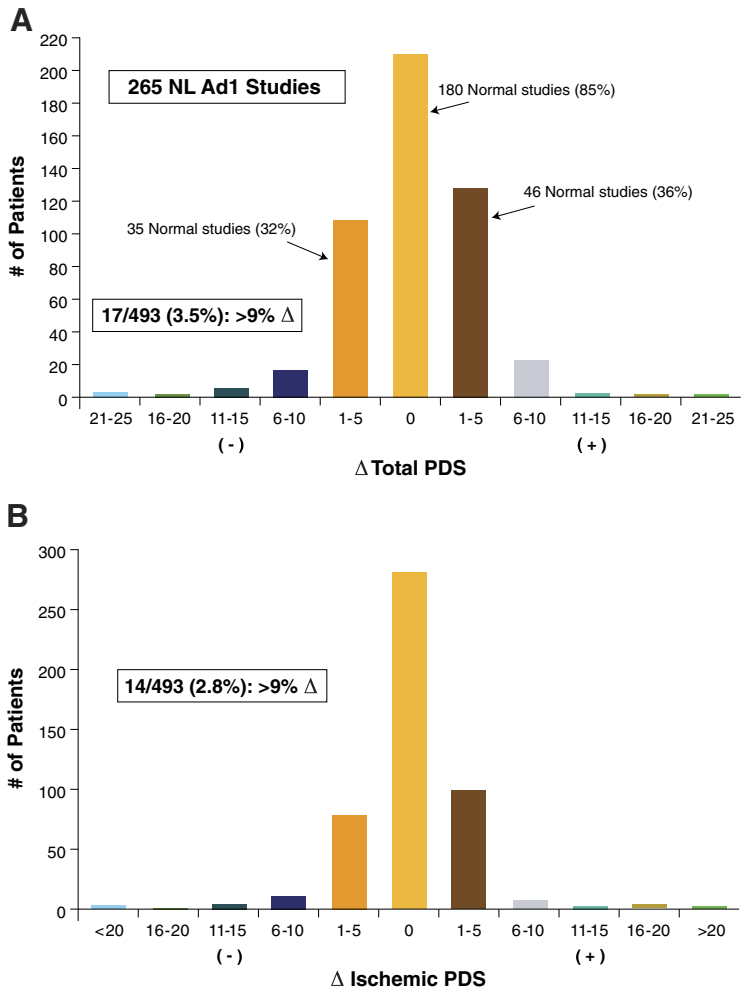

Figure 2. Absolute Differences in Serial Imaging Results

Shown are differences (**Δ**) in total perfusion defect size (PDS) **(A)** and ischemic PDS **(B)** from the initial adenosine study (Ad1) to the regadenoson study. The differences reflect a typical Gaussian distribution. − = decrease in PDS with regadenoson; + = increase in PDS with regadenoson; NL = normal.

Sources of variability in serial imaging. In clinical trials assessing patients with serial imaging, there are several sources of variability that need to be recognized and potentially avoided. The inherent patient biological variability is usually minimized by enrolling clinically stable patients who are reimaged within a relatively short time interval and in whom changes in medical and/or interventional antiischemic therapies have not occurred between studies. Variability in study acquisition parameters is also minimized by serially using the same radiopharmaceutical (at similar doses) and an identical imaging protocol. The previously mentioned sources of variability are generally controlled for in clinical trials, as was true in the ADVANCE MPI 2 trial (8). Finally, there is interpreter variability in visually assessing serial perfusion scans, which is the major source of disagreement and heterogeneity in imaging results. Currently, visual assessment of SPECT is most commonly used in clinical trials to determine the comparability of diagnostic information obtained with differing acquisition protocols, isotopes, and/or stressors. Visual assessment usually includes review of the raw image data for potential artifacts followed by a semiquantitative segmental analysis of the images to generate a summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS). Because of the inherent method of creating these scores from a 17-segment anatomic model, significant variability is inevitable. With quantitative analysis, the variability associated with investigator visual interpretation is removed,

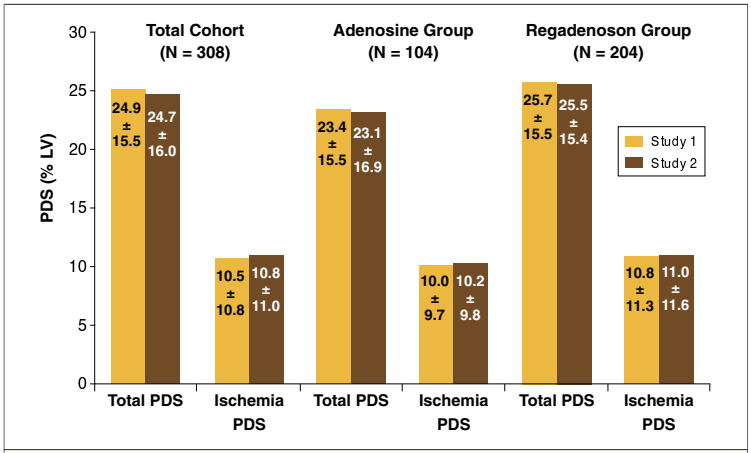

Figure 3. Scintigraphic Results in Patients With a Visually Abnormal Baseline Perfusion study

Serial mean total and ischemic left ventricular (LV) perfusion defect size (PDS) results are shown for the entire cohort and the 2 randomized groups. p = not significant, all comparisons study 1 to study 2.

making these techniques more reproducible (6) and therefore better suited for assessing serial changes after administration of differing tracers and/or stressors or after treatment with anti-ischemic therapies (7). A recent editorial underscored the limitations of visual assessments and the potential benefit of quantification to add objectivity when serially analyzing imaging studies (21).

Importance of quantitative analysis. In the ADVANCE MPI 2 trial, the primary end point was agreement by visual analysis of 3 independent readers for detecting 3 categories of ischemia (i.e., none to minimal, small to moderate, large) in patients undergoing serial adenosine versus adenosine–regadenoson imaging (8). Although agreement regarding the presence and absence of ischemia in serial images was comparably high between the groups (82%), there was significant heterogeneity in both randomized groups regarding perfusion defect extent (i.e., SSS) and the degree of scintigraphic ischemia (i.e., SDS) (22). In the combined ADVANCE MPI 1 and 2 studies, the overall visual agreement based on ischemia categories from study 1 to study 2 was comparably low at 62% (adenosine–adenosine) and 63% (adenosine–regadenoson) (p = NS) (22). Agreement between serial images worsened with increasing extent of ischemia on the baseline study in both groups. Thus, although visual analysis can be used to assess the relative diagnostic accuracy of serial SPECT

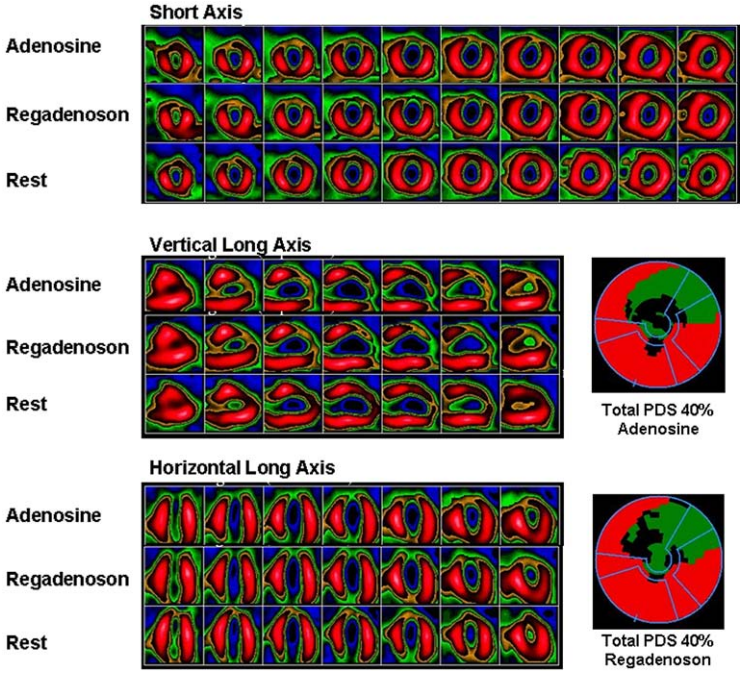

Figure 4. Representative Patient Example

The reoriented adenosine, regadenoson, and rest images are displayed in the short, vertical long, and horizontal long axes. The polar maps for adenosine and regadenoson both show a total perfusion defect size (PDS) of 40% with 27% ischemia (adenosine) and 25% ischemia (regadenoson) **(green)**.

based on broad categories of normalcy versus abnormalcy or ischemia, this may become problematic when assessing prognosis because of potentially large serial differences in the visually estimated PDS and extent residual ischemia.

Our quantitative analysis of the ADVANCE MPI 2 data shows significantly better agreement between serial adenosine and adenosine–regadenoson imaging variables than reported in the same patients using visual analysis (22). The correlation coefficients we report for total ($r = 0.97$, $p < 0.001$) and ischemic ($r = 0.95$, $p < 0.001$) PDS on serial adenosine–regadenoson studies were considerably higher than those reported for SSS ($r = 0.87$, $p < 0.001$) and SDS ($r = 0.64$, $p < 0.001$) when using visual analysis (22).

By quantitative analysis, the mean differences in perfusion results between serial adenosine–adenosine and adenosine–regadenoson studies were nominal for the primary end point variables of total ($-0.13 \pm 4.2\%$ vs. $-0.03 \pm 3.9\%$, $p = 0.73$) and ischemic ($0.25 \pm 3.8\%$ vs. $0.15 \pm 4.1\%$, $p = 0.74$) defect sizes, respectively. This was also true when only the 308 patients with clearly abnormal baseline adenosine studies were considered, in whom the largest degree of variability in serial imaging would be expected. Furthermore, over 90% of patients randomized to either group had a <5% absolute difference in their defect size from the first to the second study. In this regard, our results are not only consistent with, but solidify, the results observed in the main ADVANCE MPI 2 study.

Study limitations. The main limitation of this study was the large number (60%) of normal SPECT studies in both randomized groups. However, the 308 patients with abnormal baseline SPECT results represents the largest published series to date assessing 2 vasodilator agents when using quantitative techniques to analyze serial differences in SPECT results. Quantitative analysis in the abnormal patients showed minimal differences in adenosine–regadenoson results despite an anticipated greater disparity in serial images due to the larger baseline perfusion defect.

CONCLUSIONS

Applying quantitative analysis, regadenoson induces virtually identical scintigraphic results as adenosine with regard to the size and severity of LV PDS and the extent of scintigraphic ischemia.

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REFERENCES

1. Mahmarian JJ, Boyce TM, Goldberg RK, Cocanougher MK, Roberts R, Verani MS. Quantitative exercise thallium-201 single-photon emission computed tomography for the enhanced diagnosis of ischemic heart disease. J Am Coll Cardiol 1990;15:318–29.
2. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004;11:171–85.
3. Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. J Am Coll Cardiol 1993;22:665–70.
4. Sharir T, Germano G, Kavanagh PB, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 1999;100:1035–42.
5. Mahmarian JJ, Shaw LJ, Filipchuk NG, et al. A multinational study to establish the value of early adenosine technetium-99m sestamibi myocardial perfusion imaging in identifying a low-risk group for early hospital discharge after acute myocardial infarction. J Am Coll Cardiol 2006;48:2448–57.
6. Mahmarian JJ, Moye LA, Verani MS, Bloom MF, Pratt CM. High reproducibility of myocardial perfusion defects in patients undergoing serial exercise thallium-201 tomography. Am J Cardiol 1994;75:1116–9.
7. Mahmarian JJ. Monitoring medical therapy: the role of noninvasive imaging. In: Dilsizian V, Narula J, Braunwald E, editors. Atlas of Nuclear Cardiology. 2nd edition. Philadelphia, PA: Current Medicine, 2006:191–210.
8. Iskandrian AE, Bateman TM, Belardinelli L, et al. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. J Nucl Cardiol 2007;14:645–58.
9. Hansen CL, Goldstein RA, Akinboboye OO, et al., for the American Society of Nuclear Cardiology. Myocardial perfusion and function: single photon emission computed tomography. J Nucl Cardiol 2007;14:e39–60.
10. Mahmarian JJ, Dakik HA, Filipchuk NG, et al. An initial strategy of intensive medical therapy is comparable to that of coronary revascularization for suppression of scintigraphic ischemia in high risk but stable survivors of acute myocardial infarction. J Am Coll Cardiol 2006;48:2458–67.
11. Dakik HA, Wendt JA, Kimball K, Pratt CM, Mahmarian JJ. Prognostic value of adenosine thallium-201 myocardial perfusion imaging after acute myocardial infarction: results of a prospective clinical trial. J Nucl Cardiol 2005;12:276–83.
12. Ficaro EP, Lee BC, Kritzman JN, Corbett JR. Corridor4DM: the Michigan method for quantitative nuclear cardiology. J Nucl Cardiol 2007;14:455–65.
13. Marcus ML, Chilian WM, Kanatsuka H, Dellsperger KC, Eastham CL, Lamping KG. Understanding the coronary circulation through studies at the microvascular level. Circulation 1990;82:1–7.

14. Heiss HW, Barmeyer J, Wink K, et al. Studies on the regulation of myocardial blood flow in man. I.: training effects on blood flow and metabolism of the healthy heart at rest and during standardized heavy exercise. Basic Res Cardiology 1976;71:658–75.
15. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. Circulation 1990;82:1595–606.
16. Belardinelli L, Shryock JC, Snowdy S, et al. The A2A adenosine receptor mediates coronary vasodilation. J Pharmacol Exp Ther 1998;284:1066–73.
17. Cerqueira MD. The future of pharmacologic stress: selective A2A adenosine receptor agonists. Am J Cardiol 2004;94:33D–42D.
18. Lieu HD, Shryock JC, von Mering GO, et al. Regadenoson, a selective A2A adenosine receptor agonist, causes dose-dependent increases in coronary blood flow velocity in humans. J Nucl Cardiol 2007;14:514–20.
19. Gould KL. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation. I. Physiologic basis and experimental validation. Am J Cardiol 1978;41:267–78.
20. Wackers FJ, Berman DS, Maddahi J, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med 1989;30:301–11.
21. Udelson JE. Lessons from the development of new adenosine A_{2A} receptor agonists. J Am Coll Cardiol Img 2008;1:317–20.
22. Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE, on behalf of the ADVANCE-MPI Trial Investigators. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A_{2A} agonist regadenoson versus adenosine in myocardial perfusion imaging: integrated ADVANCE-MPI trial results. J Am Coll Cardiol Img 2008;1:307–16.

Key Words: single photon tomography ■ regadenoson ■ adenosine.