Effects of Age, Gender, Obesity, and Diabetes on the Efficacy and Safety of the Selective A2A Agonist Regadenoson Versus Adenosine in Myocardial Perfusion Imaging : Integrated ADVANCE-MPI Trial Results

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Objectives

To compare the effects of age, gender, body mass index, and diabetes on the safety and efficacy of regadenoson stress myocardial perfusion imaging, and to assess the noninferiority of regadenoson to adenosine for the detection of reversible myocardial perfusion defects.

Background

Previous reports have shown that a fixed unit bolus of regadenoson is safe and noninferior to adenosine for the detection of reversible perfusion defects by radionuclide imaging.

Methods

Using a database of 2,015 patients, we evaluated the effects of age, gender, body mass index, and diabetes on the safety and efficacy of regadenoson compared to adenosine.

Results

For detection of ischemia relative to adenosine, noninferiority was demonstrated for all patients (agreement rate difference 0%, 95% CI −6.2% to +6.8%). The average agreement rate between adenosine-adenosine and adenosine-regadenoson were 0.62 ± 0.03 and 0.63 ± 0.02. Detection of ischemia was also comparable in specific subgroups. Agreement was less for both agents in women versus men with moderate and large areas of ischemia. Compared to adenosine, regadenoson had a lower combined symptom score and less chest pain, flushing, and throat, neck, or jaw pain, but more headache and gastrointestinal discomfort. This was true in nearly all subgroups. Regadenoson patients reported feeling more comfortable (1.7 ± .02 vs. 1.9 ± 0.03, $p < 0.001$). Based on the overall

tolerability score, women felt less comfortable than men with both stress agents. Image quality was rated good or excellent in 92% for both agents.

Conclusions

Regadenoson can be safely administered as a fixed unit bolus and is as efficacious as adenosine in detecting ischemia regardless of age, gender, body mass index, and diabetes. Regadenoson is better tolerated overall and across various subgroups.

Abbreviations and acronyms

AV, atrioventricular;

BMI, body mass index;

DM, diabetes mellitus;

MPI, myocardial perfusion imaging;

SDS, summed difference score;

SPECT, Single photon emission computed tomography;

SSS, summed stress score

Adenosine and dipyridamole are the most commonly used pharmacologic stress agents with single photon emission computed tomography (SPECT) for myocardial perfusion imaging (MPI) (1). These agents stimulate all 4 adenosine receptor subtypes, each with unique pharmacologic properties (2 and 3). The A2A receptor stimulation causes the differential coronary arterial dilation required for SPECT MPI. Activation of the other receptors causes undesired symptoms and safety concerns that mandate rigorous pre-screening and monitoring (4 and 5). Furthermore, these agents require weight-adjusted dosing and a continuous infusion pump, adding additional steps and increasing the potential for dosing errors (6).

Regadenoson, a selective A2A adenosine receptor agonist, is administered as a fixed unit bolus that induces a 2- to 3-fold increase in myocardial blood flow for 3 to 4 min (7 and 8). The ADVANCE MPI 1 and 2 (ADenoscan Versus regAdenosoN Comparative Evaluation for Myocardial Perfusion Imaging) trials are multicenter phase 3 trials designed to demonstrate noninferiority of regadenoson compared to adenosine (9, 10 and 11). The results of ADVANCE MPI 2 (12) have shown that regadenoson is noninferior to adenosine for the detection of reversible defects and is safe and better tolerated. The results of the second trial are presented with the combined dataset including specific subgroup analyses (1, 5 and 13).

The goals of this investigation were: 1) to compare the efficacy, safety, and tolerability of adenosine and regadenoson stress MPI in the subgroups of age, gender, body mass index (BMI), and diabetes (DM); and 2) to further assess the noninferiority of regadenoson to adenosine for the detection of reversible myocardial perfusion defects.

Methods

Study design and stress protocol

We combined data from 2 identical double-blind, randomized, active-comparator, double dummy, multicenter phase 3 trials designed to show that the strength of agreement between sequential adenosine-regadenoson images is noninferior to the strength of agreement between sequential adenosine images. Informed consent was obtained in all patients. All patients had an adenosine study and were randomized to either regadenoson or adenosine in a 2 to 1 ratio. The trial protocols limited the number of patients with “no to minimal” reversible defects based on the site investigator's interpretation of the initial adenosine study to ≤50% of the total number randomized to guarantee assessment across the full range of disease severity (14).

Patient population, imaging protocols, and SPECT analysis

The criteria for patient enrollment were identical in the 2 trials (12). All images were acquired according to guidelines (12 and 15). Separately for each trial, 3 expert readers independently scored the blinded images using a 17-segment model on a 5-point scale from 0 = normal to 4 = no activity (4). Segments were reversible if the stress score was greater than the rest score and the stress score was ≥2. Reversible defects were categorized as 0 to 1 (no to minimal), 2 to 4 (small to moderate), or ≥5 (large). Readers also assessed the overall diagnosis (normal, ischemia, ischemia + scar, scar) and overall image quality. When evaluating image quality, readers assessed lung uptake and subdiaphragmatic interference and recorded any evidence of excessive cardiac motion or breast shadow.

Reported symptom evaluation and hemodynamic

Reported symptoms following the randomized infusion were collected and rated as mild, moderate, or severe. In a pre-defined analysis, symptoms were combined into 7 groups corresponding to adverse reactions occurring with frequency greater than 10% according to the Adenoscan label. Summed scores on a scale of 0 = not reported to 3 = severe were calculated for the 3 most frequent groups, “flushing,” “chest pain,” and “dyspnea,” and for all 7 symptom groups. Hemodynamic measurements were performed at baseline and frequently over 45 min after dosing.

Tolerability questionnaire

At completion of the randomized study, patients were asked to rate how they felt using a 4-point scale of 1 = comfortable, 2 = a little uncomfortable, 3 = very uncomfortable, 4 = extremely uncomfortable. Patients were also asked how the second randomized procedure compared to the initial adenosine study using a 5-point scale (1 = much better, 2 = somewhat better, 3 = about the same, 4 = somewhat worse, 5 = much worse).

Statistical analysis

Demographic and baseline characteristics are summarized by median and range or count and percentage. Coronary artery disease risk was categorized based on the estimated pre-test probability of coronary artery disease (16).

The primary agreement measure was an average rate of agreement of the randomized study with the initial adenosine study on ischemia size category (0 to 1, 2 to 4, or ≥5 reversible defects using the median count across the 3 blinded readers). The average agreement rate was calculated as the equally weighted average across the 3 initial study categories: (1/3) (agreement rate for initial category 0 to 1 reversible segments) + (1/3) (agreement rate for initial category 2 to 4 reversible segments) + (1/3) (agreement rate for initial category ≥5 reversible segments). If the randomized study assessment is statistically independent of the initial assessment, the chance agreement rate is one-third when the initial study categories are weighted equally. The range from chance to perfect agreement on the average agreement scale is, therefore, 33.3% to 100%. Based on previous work (17), a 20% difference on a kappa scale of 0% (chance agreement) to 100% (perfect agreement) is considered substantial. Hence, a 20% difference on the average agreement scale ranging from chance agreement (33.3%) to perfect agreement (100%) is 13 1/3%, and therefore a noninferiority margin of 13 1/3% was selected.

The primary analysis tested the null hypothesis of inferiority of adenosine-regadenoson agreement to adenosine-adenosine agreement versus noninferiority. A 95% confidence interval for the difference between adenosine-regadenoson average agreement rate and repeat adenosine average agreement rate is calculated and the null hypothesis rejected when the lower limit is above −13 1/3%. Because the lower limit has a confidence coefficient of 97.5%, this corresponds to a 1-sided test at the 2.5% significance level (9, 10 and 11).

For the secondary efficacy analysis, summed stress score (SSS) was calculated as the rounded average of the 3 reader SSS values. Summed difference score (SDS) was calculated as the rounded average of the 3 reader SDS values, which were calculated as the sum of the positive stress–rest score differences. Mean and standard deviation of the difference between SDS and SSS scores from the initial and randomized scan are calculated.

The overall diagnostic categories of (normal, ischemia, ischemia + scar, scar) were collapsed into the presence (ischemia, ischemia + scar) and absence (normal, scar) of ischemia. Scores from the tolerability questionnaires 1 and 2 were collapsed into “comfortable” (1 and 2) and “uncomfortable” (3 and 4) and into “better” (1 and 2), “the same” (3), and “worse” (4 and 5), respectively.

Exploratory analyses were performed on the following subgroups: age (<65 or ≥65 years), male or female gender, BMI (≤30 kg/m2 or >30 kg/m2), and history or no history of DM.

All tests were performed at the 5% significance level, without adjusting for multiple comparisons. Wilcoxon's rank sum tests were used to compare means of continuous variables and chi-square and Cochran-Mantel-Haenszel tests were used to compare categorical variables.

Results

Randomization

Of the 3,469 patients with an initial adenosine study, 1,135 patients with normal images were not randomized to meet the pre-defined limit (≤50% in the 0 to 1 category). Forty-nine patients were not randomized due to major symptoms with the initial adenosine infusion. The efficacy analysis set included 1,871 patients (regadenoson 1,240, adenosine 631); 115 were withdrawn due to lack of defects assessed by the central lab after closure to the 0 to 1 category and 32 were withdrawn because of incomplete imaging data. Three patients were excluded because of nonevaluable safety data, leaving 2,015 patients (regadenoson 1,337, adenosine 678) in the safety analysis set. Efficacy analysis included 31% females, 55% ≥65 years, 38% BMI >30 kg/m2, and 32% DM. The safety analysis included 30% female, 56% ≥65 years, 38% BMI <30 kg/m2, and 33% DM. Subgroup proportions were similar for regadenoson and adenosine.

Baseline and demographic characteristics were comparable for both groups, including type of imaging protocol used and extent of ischemia on initial adenosine scan (Table 1, p is not significant for all comparisons) based upon the overall diagnosis determined by the central readers. Analysis by subgroups shows that patients ≥65 years old were more likely to be female, much less likely to be obese, and slightly less likely to have a reported history of DM; male patients were less likely to be obese and slightly less likely to have a reported history of DM; and obese patients were very much more likely to have a reported history of DM. Hence, as might be expected, age, gender, obesity, and DM are all confounded, and the association between DM and obesity is particularly strong.

Table 1.

Demographic and Baseline Characteristics and Medical History of Patients Included in ADVANCE MPI 1 and 2 Efficacy Analyses (n = 1,871)

Characteristic	Adenosine n = 631	Regadenoson n = 1,240	p Value
Age, yrs, median (range)	65 (26–91)	66 (27–93)	0.45
Male, n (%)	430 (68)	864 (70)	0.50
Caucasian, n (%)	472 (75)	935 (75)	0.78
BMI, kg/m^2, median (range)	28 (18–59)	29 (16–57)	0.47
Left ventricular ejection fraction ≥35%, n (%)†	553 (91)	1,084 (91)	0.63
Medical history, n (%)			
CAD	475 (75)	966 (78)	0.20
Hypertension	502 (80)	1012 (82)	0.28
Angina	387 (61)	789 (64)	0.33
CABG, PTCA, or PCI	323 (51)	627 (51)	0.80
MI	270 (43)	494 (40)	0.22
Arrhythmia	204 (32)	418 (34)	0.55
Diabetes	213 (34)	394 (32)	0.39
CHF	109 (17)	226 (18)	0.61
COPD	34 (5)	66 (5)	0.95
Estimated pretest probability of CAD >90%, n (%)‡	436 (69)	851 (69)	0.84
Imaging protocol			0.45
1-day ^{99m}Tc	193 (31)	415 (33)	
2-day ^{99m}Tc	288 (46)	541 (44)	
Dual isotope (^{201}Tl rest, ^{99}Tc stress)	150 (24)	284 (23)	
Days between initial adenosine and randomized scans (median)	7	7	0.71
Initial adenosine study results§			0.48
Normal	37%	35%	
Scar	15%	15%	
Ischemia	25%	25%	
Ischemia and scar	23%	25%	

ADVANCE MPI = ADenoscan Versus regAdenosoN Comparative Evaluation for Myocardial Perfusion Imaging; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty.

*For continuous variables (i.e., age, BMI, days between scans), approximate Wilcoxon's rank sum test p was used for comparing means. For categorical variables, chi-square test p was used for comparing proportions.

†Data were not available in all patients: missing data in adenosine = 22 (3%), regadenoson = 55 (4%).

‡Note: Patients with a history of MI or revascularization were reassigned to the “> 90%” category.

§Approximate p was used for comparing proportions with “reversible defects” or “fixed and reversible defects.”

Efficacy primary end point

In the 1,871 patients included in combined analysis (Fig. 1), the agreement rates between the initial adenosine and randomized adenosine or regadenoson imaging were almost identical (rate difference 0%, 95% CI −6.2% to +6.8%) and a lower limit of −6.2%, thereby meeting the noninferiority requirement (9, 17 and 18). The average agreement rate between adenosine-adenosine and adenosine-regadenoson were 0.62 ± 0.03 and 0.63 ± 0.02, respectively. For both agents, the interpretation agreement rate was best for the group with no or minimal ischemia.

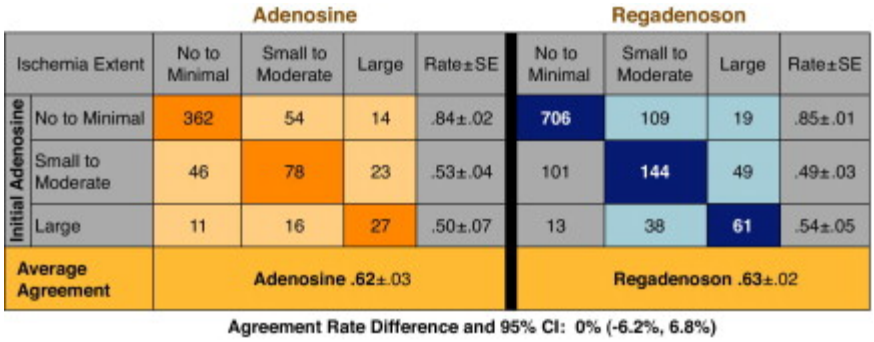

Figure 1.

Agreement Rates for Ischemia in Combined ADVANCE MPI 1 and 2

In 1,871 subjects, 3 blinded experts independently scored images on a 5-point scale using 17-segments and ischemia was categorized as 0 to 1 (no to minimal), 2 to 4 (small to moderate), or ≥5 (large). The overall average ischemia agreement rates between adenosine–adenosine and adenosine–regadenoson was 0.62 ± 0.03 and 0.63 ± 0.02 with an agreement difference of 0% (95% CI −6.2% to 6.8%), respectively. Regadenoson was noninferior to adenosine for detection of ischemia. ADVANCE MPI= ADenoscan Versus regAdenosoN Comparative Evaluation for Myocardial Perfusion Imaging; CI = confidence interval; SE = standard error.

Within age, gender, BMI, and DM subgroups, adenosine and regadenoson average agreement rates were similar, and adenosine and regadenoson agreement rates were also similar for each initial study ischemia size category. For both adenosine and regadenoson, average agreement rates ranged from ∼50% to 60% across all subgroups. In general, agreement rates were highest in the no ischemic category (∼80%) and lowest in the moderate to large ischemia extent categories (∼50%). For both adenosine and regadenoson, agreement rates were lower in females than in males for the initial study categories 2 to 4 and ≥5 reversible segments (Table 2).

Table 2.

Ischemia Size Category Agreement Rates Between Initial Adenosine and Repeat Adenosine or Regadenoson by Age, Gender, BMI, and DM

Subgroup	Agreement Rate for Reversible Ischemia (n)								95% CI for Difference*
	Adenosine–Adenosine				Adenosine–Regadenoson				
	Average	0 to 1	2 to 4	≥5	Average	0 to 1	2 to 4	≥5	
Age, yrs									
<65	56% (298)	81%	52%	35%	63% (544)	86%	50%	52%	−3%, 16%
≥65	68% (333)	87%	54%	64%	63% (696)	84%	48%	58%	−14%, 4%
Gender									
Female	57% (201)	88%	41%	42%	54% (376)	87%	35%	40%	−16%, 11%
Male	64% (430)	82%	57%	52%	65% (864)	83%	52%	59%	−6%, 8%
BMI, kg/m^2									
≤30	64% (389)	86%	59%	47%	62% (770)	83%	47%	56%	−10%, 7%
>30	60% (242)	82%	44%	55%	64% (470)	87%	52%	53%	−7%, 14%
History of diabetes									
Yes	59% (213)	84%	54%	38%	62% (394)	81%	48%	56%	−9%, 15%
No	63% (418)	84%	52%	54%	63% (846)	86%	50%	53%	−8%, 8%

CI = confidence interval; DM = diabetes mellitus; other abbreviations as in Table 1.

*The 95% confidence interval for adenosine-regadenoson average agreement rate minus repeat adenosine average agreement rate.

Efficacy secondary end points

For both adenosine-adenosine and adenosine-regadenoson, mean SSS differences were close to 0 and standard deviations were similar for the 2 arms for ADVANCE MPI 1 and 2, respectively: adenosine-adenosine mean ± SD = −0.1 ± 3.5 and 0.4 ± 4.6; adenosine-regadenoson mean ± SD = 0.0 ± 3.5 and 0.3 ± 4.2. The same was true of SDS: adenosine-adenosine mean ± SD = 0.1 ± 3.2 and 0.6 ± 3.9; adenosine-regadenoson mean ± SD = 0.0 ± 3.1 and 0.1 ± 3.8 (Fig. 2).

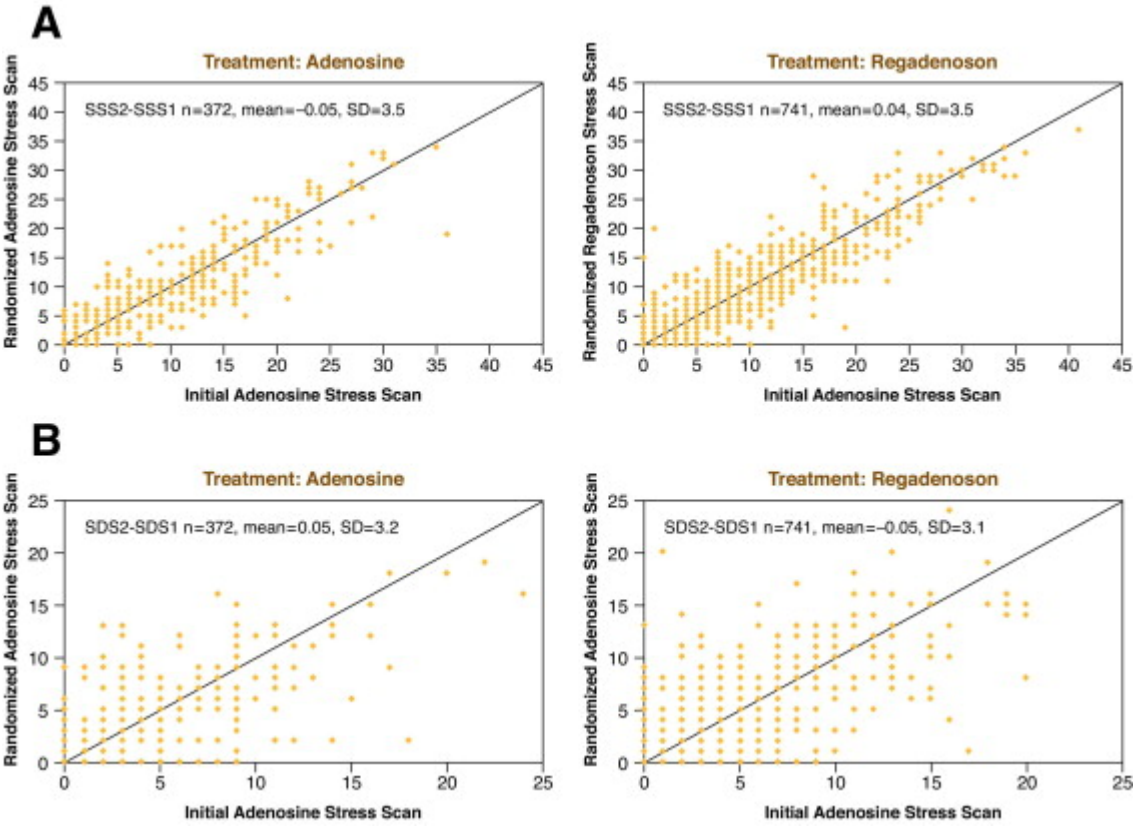

Figure 2.

Comparison of SSS and SDS for Initial Adenosine and Randomized Scan

Using the rounded average of 3 readers for adenosine-adenosine and adenosine-regadenoson scoring, mean summed stress score (SSS) (A) and summed difference score (SDS) (B) differences were close to 0 and standard deviations (SDs) were similar for the 2 arms for the ADVANCE MPI 1 and 2 trials. The differences between the initial adenosine and randomization to regadenoson were no different than randomization to repeat adenosine. Results of ADVANCE MPI 1 are shown.

Overall and for each subgroup, agreement rates were comparable for the presence and absence of ischemia. The average agreement rates between adenosine-adenosine and adenosine-regadenoson were 0.76 ± 0.03 and 0.77 ± 0.02 for the presence and 0.77 ± 0.02 and 0.78 ± 0.02 for the absence of ischemia, respectively.

For each stress agent, secondary end point simple agreement rates were also similar across age, sex, BMI, and DM subgroups.

Image quality

The majority of images were rated good or excellent (92%). Image quality was better in men compared with women for both stress agents ($p < 0.001$). For both stress agents, image quality was similar for nonobese and obese patients, for patients with and without a history of DM, and for patients <65 and ≥65 years of age.

Safety and tolerability

Comparing the incidences of pre-defined symptom groups (Table 3), regadenoson patients had a significantly reduced incidence of chest pain, flushing, and throat, neck, or jaw pain but significantly more headache and gastrointestinal discomfort ($p < 0.05$). These differences were similar across all subgroups.

Patients receiving regadenoson had a significantly lower mean summed score for the combination of chest pain, dyspnea, and flushing (0.9 ± 0.03 vs. 1.3 ± 0.05, $p < 0.05$) and the mean remained significantly lower when all symptoms were included (1.75 ± 0.05 vs. 1.94 ± 0.07, $p < 0.05$). For patients receiving both regadenoson and adenosine, females reported a higher summed symptom score than males. For regadenoson alone, patients <65 years reported a higher summed symptom score than patients ≥65.

Tolerability questionnaire—level of comfort with the randomized test

Patients randomized to regadenoson felt more comfortable compared to patients randomized to adenosine (92% vs. 81%) as demonstrated by a significantly lower tolerability score for regadenoson compared to adenosine (1.7 ± 0.02 vs. 1.9 ± 0.03, $p < 0.001$). Patients within each subgroup also reported feeling more comfortable with regadenoson. Based on the tolerability score, women reported feeling more uncomfortable than men did after receiving both regadenoson and adenosine.

Tolerability questionnaire—comparing the randomized test to initial adenosine

When patients were asked how the second test compared to the first (Table 4), 62% of those receiving regadenoson said it felt better versus 43% of those receiving adenosine. The average tolerability score for regadenoson was much lower than adenosine (2.2 ± 0.03 vs. 2.6 ± 0.04, $p < 0.001$), indicating a preference for regadenoson. Patients across all subgroups also favored regadenoson over adenosine (Table 4).

Table 3

	Any Symptom Group		Chest Pain		Dyspnea		Flushing		GI Discomfort		Headache		Lightheadedness/Dizziness		Throat, Neck, or Jaw Pain	
	Ado	**Reg**	**Ado**	**Reg**	**Ado**	**Reg**	**Ado**	**Reg**	**Ado**	**Reg**	**Ado**	**Reg**	**Ado**	**Reg**	**Ado**	**Reg**
All patients	79%	73%	41%	29%	26%	28%	34%	22%	17%	23%	17%	26%	7%	8%	14%	7%
Age, yrs																
<65	80%	75%	43%	32%†	27%	30%	32%	22%	20%	23%	17%	29%	7%	9%	16%	7%
≥65	77%	72%	40%	26%†	25%	27%	35%	21%	14%	24%	17%	24%	6%	7%	11%	7%
Gender																
Female	87%	80%†	48%	36%†	28%	31%	34%	17%†	22%	32%†	23%	37%†	8%	7%	17%	9%
Male	75%	70%†	38%	25%†	25%	27%	34%	23%†	14%	20%†	14%	22%†	6%	9%	12%	6%
BMI, kg/m^2																
≤30	76%	73%	39%	29%	23%	27%	30%	21%	16%	24%	16%	25%	6%	9%	12%	8%
>30	83%	73%	46%	28%	29%	29%	39%	23%	18%	22%	19%	27%	8%	7%	17%	6%
History of DM																
Yes	79%	73%	40%	29%	27%	24%†	33%	22%	21%	25%	14%	25%	7%	6%†	17%	5%
No	78%	73%	42%	28%	25%	30%†	34%	21%	14%	23%	19%	27%	7%	9%†	12%	8%

Table 4.

Tolerability Question 2: Responses and Overall Tolerability Score for Patients Receiving Adenosine and Regadenoson

	Better (Score 1 to 2)		Same (Score 3)		Worse (Score 4 to 5)		Mean Score ± SE	
	Ado	Reg	Ado	Reg	Ado	Reg	Ado	Reg
All patients	43%	62%	41%	24%	17%	14%	2.62 ± 0.038*	2.17 ± 0.031*
Age, yrs								
<65	46%	67%	38%	19%	15%	14%	2.56 ± 0.056*	2.08±0.046*†
≥65	40%	58%	43%	29%	17%	14%	2.67 ± 0.053*	2.23 ± 0.041*†
Gender								
Female	45%	64%	32%	20%	23%	17%	2.68 ± 0.078*	2.20 ± 0.059*
Male	42%	61%	45%	27%	13%	13%	2.59 ± 0.043*	2.15 ± 0.036*
BMI, kg/m^2								
≤30	43%	57%	42%	27%	14%	16%	2.58 ± 0.048*	2.30 ± 0.040*†
>30	42%	69%	38%	21%	19%	10%	2.68±0.065*	1.95±0.046*†
History of diabetes								
Yes	45%	63%	39%	25%	17%	12%	2.53 ± 0.070*	2.14 ± 0.052*
No	42%	61%	42%	24%	16%	15%	2.66±0.046*	2.18±0.038*

Question 2: How does this test compare to the first (initial open label adenosine) test?

SE = standard error; other abbreviations as in Table 1 and Table 3.

* Approximate Cochran-Mantel-Haenszel test of equality of regadenoson and adenosine means, $p < 0.05$.
† Approximate Cochran-Mantel-Haenszel test of equality of regadenoson means across subgroups, $p < 0.05$.

Efficacy primary end point

In the 1,871 patients included in combined analysis (Fig. 1), the agreement rates between the initial adenosine and randomized adenosine or regadenoson imaging were almost identical (rate difference 0%, 95% CI −6.2% to +6.8%) and a lower limit of −6.2%, thereby meeting the noninferiority requirement (9, 17 and 18). The average agreement rate between adenosine-adenosine and adenosine-regadenoson were 0.62 ± 0.03 and 0.63 ± 0.02, respectively. For both agents, the interpretation agreement rate was best for the group with no or minimal ischemia.

Hemodynamics

Hemodynamics were similar to those previously reported in ADVANCE MPI 2 (12) with no significant differences between subgroups.

ECG analysis

First-degree atrioventricular (AV) block (PR prolongation >220 ms) was noted in 34 (2.8%) regadenoson patients and 43 (7.0%) adenosine patients and second-degree AV block in 1 (0.1%) regadenoson patient and 9 (1.5%) adenosine patients (p = 0.001). The second-degree AV block of 1 beat at 3.5 min following regadenoson bolus was in a patient with baseline first-degree AV block and PR-related changes most consistent with atypical Wenckebach. Third-degree block did not occur. None of the episodes required intervention.

Discussion

In a large diverse high risk patient population using various imaging protocols and nuclear tracers, regadenoson is noninferior to adenosine for the detection of reversible myocardial perfusion defects (9, 10, 11, 17 and 18). Regadenoson can be safely administered as a unit bolus with good to excellent image quality. There were no clinical differences in efficacy or safety between the 2 agents overall and by age, gender, BMI, or DM. Regadenoson was better tolerated than adenosine based on patient questionnaires.

A2A selectivity

Advantage of regadenoson

Because of its high A2A adenosine receptor selectivity, regadenoson offers advantages over adenosine (7, 8 and 12). The safety profile of regadenoson may reflect its improved selectivity for the A2A receptor. Patients receiving regadenoson reported less flushing, chest pain, and throat, neck, or jaw pain, possibly reflecting less stimulation of peripheral adenosine receptors by regadenoson. Moreover, fewer cases of AV nodal block were seen, which is consistent with the weak activity on the A1 adenosine receptor. Patients receiving regadenoson, however, reported headache more frequently, which may result from differences in the degree of vasodilation and sympathetic stimulation produced by the 2 stress agents, which has been noted in animal models (19).

Fixed unit bolus

Unlike other agents, regadenoson can be safely administered as a fixed unit bolus because neither its central volume of distribution nor the clearance is significantly affected by body weight (20). The effect of the regadenoson bolus on the coronary circulation is due to its concentration during the first pass through the heart, which is predominately independent of the intravascular volume.

Insufficient levels of regadenoson are believed to be present at the second pass because of its short distribution half-life of ≤2 min. Thus, the drug effect is determined by dilution of the drug bolus as it mixes with venous blood on its way from the injection site to the coronary vasculature. The volume of venous blood diluting regadenoson during the short duration of administration as it reaches the heart for the first time determines the drug's effect. This volume is not expected to vary significantly with body weight. Because of adenosine's ultrashort half-life of <10 s (which is too short for adequate tracer uptake), it is not suitable for fixed bolus dosing. Furthermore, a fixed bolus dose eliminates the need to calculate dose by weight and the need for continuous computerized pump infusion, which may potentially reduce dosing errors. Subgroup analysis has confirmed fixed bolus dosing of regadenoson was both safe and efficacious regardless of age, BMI, gender, and DM.

Better tolerance

In addition to its good safety profile and ease of administration, more patients felt more comfortable following regadenoson than adenosine administration. This finding was consistent across all subgroups, including females who overall reported more symptoms than males.

Design features of the ADVANCE MPI trials

The ADVANCE MPI trials demonstrated the following distinctive design features: 1) reflection of real-world clinical practice; 2) noninferiority comparison; and 3) comparison of agreement rates for sequential imaging.

Real-world clinical practice

The ADVANCE MPI trials were designed to simulate real-world clinical practice by enrolling over 2,000 patients across 109 centers. Selection of protocols and radiotracers was at the discretion of the investigator and is comparable to those used in clinical practices worldwide (21).

Noninferiority design

The ADVANCE MPI trials adhere to the 4 requirements proposed for noninferiority trials: 1) comparison to a reference standard, 2) use of established outcome measurements, 3) establishment of a pre-defined margin of inferiority, and 4) avoidance of design features that will increase the risk of falsely concluding noninferiority (9, 10, 11, 17 and 18).

We used adenosine, which is an established pharmacologic agent for MPI studies (15 and 22). For the second requirement, outcome measurements similar to previous adenosine trials were used (13 and 23). The trials also pre-defined a margin of inferiority. The combined analysis revealed a difference of 0% between the 2 agents with a narrow confidence interval. Moreover, average agreement rates were comparable across different measures of efficacy and pre-defined subpopulations.

Finally, the primary end point comparison was designed to reduce the risk of wrongly concluding noninferiority by ensuring adequate representation of patients with reversible defects. Because the stress agent used should not affect results in patients without ischemia, the proportion of patients randomized with initial adenosine studies assessed by the site investigators as showing no or minimal reversible defects was limited to 50%, and the overall agreement rate was defined to give only one-third weight to patients in this category.

Variability in SPECT MPI

Another unique feature is comparison of agreement rates for sequential images. Knowing the inherent variability of SPECT imaging is critical to determining whether observed changes in scan interpretation can be ascribed to actual changes due to treatment, changes in the patient's condition, or the inherent procedure variability (14). There are few previous studies evaluating agreement rates for sequential imaging. These studies were single-center, included ≤20 patients, used polar map interpretation, and compared agreement rates using only 1 or 2 readers (24). The combined analysis suggests that there is a high degree of variability in SPECT MPI.

Although regadenoson is comparable to adenosine in determining the extent of reversible defects, the average agreement rate is approximately 60%. Previous studies (25, 26, 27 and 28) have reported higher agreement rates. However, the apparent discrepancy may be due to different methodologies used in the ADVANCE MPI trials and those used in previously reported studies.

First, the majority of studies in the literature have compared inter-reader interpretation of a single image and not 2 sequential images as performed in the ADVANCE MPI trials (25, 26, 27 and 28). Agreement rates for comparison of sequential images may be lower because acquisition of a second image introduces biological changes in the patient's clinical condition and in the medical regimen as well as technical variability in acquisition and image processing of the second image (14, 29 and 30).

Second, previous studies in the literature have used sample weighted averages to calculate agreement rates (25, 26, 27 and 28), which gives the category with the highest number of patients the greatest contribution to the average. Thus, studies tend to report higher agreement rates if they enroll more patients who have no ischemia. In the ADVANCE MPI trials, an unweighted average, which gives equal weight to all categories of ischemia, was used to calculate agreement rates. This provides a more conservative estimate of agreement and test of inferiority.

Finally, agreement rates in the literature are usually reported for the overall impression of the scan: normal versus abnormal or normal versus ischemia versus infarct. It is well known from previous studies on coronary angiography and SPECT that agreement rates are better when categories are limited (26 and 31). In the ADVANCE MPI trials, when ischemia categories are collapsed to presence versus absence of ischemia, agreement rates increase and approximate published values.

Similar to previous studies, the average agreement rates were highest in the no-to-minimal ischemia size category (~80%) and lower (~50%) in the moderate-to-severe ischemia size categories. Thus, readers often agreed upon the presence of ischemia, but they differed with respect to the extent of ischemia. The semiquantitative SSS and SDS for adenosine-adenosine comparisons showed relatively close agreement in the mean difference and standard deviations (Fig. 2). Another possible reason for the variability is that the degree of pharmacological stress produced by the agents differed between initial and randomized scans. This would primarily affect patients with ischemia. The degree of pharmacological stress would have no effect on patients without ischemia. Although the protocols were designed to ensure consistent infusion doses and medication usage, perfect consistency cannot be controlled. Similar agreement rates, however, were noted when collapsing diagnostic categories into the presence or absence of ischemia.

Study limitations

A major limitation of the ADVANCE MPI trials is that the trials excluded 2 important patient subsets: 1) patients who have contraindications to adenosine, and 2) patients who had significant symptoms on the initial adenosine scan. Although this does not affect the image comparison to adenosine, it underestimates the degree of side effects. Additional studies are needed to better evaluate the safety and tolerability of regadenoson in this subset of patients who may derive greater benefit from A2A selectivity. A second limitation of the study is that there was no formal evaluation of the reduction of dosing errors and improved lab efficiency associated with fixed, bolus dosing. This analysis, however, would have been challenging given the double dummy design. Finally, it is possible that quantitative analysis will decrease variability. Future analysis comparing the variability of sequential images using quantitative methods is ongoing.

Conclusions

Regadenoson can be safely administered as a fixed unit bolus and is as efficacious as adenosine in the detection of myocardial perfusion reversible defects. The safety and efficacy of regadenoson have been demonstrated in all patients regardless of age, gender, BMI, and presence or absence of diabetes. Regadenoson was better tolerated than adenosine by all patients and subgroups.

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