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STATE-OF-THE-ART PAPER

Regadenoson: A New Myocardial Stress Agent

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Vasodilator stress myocardial perfusion imaging (MPI) accounts for up to 50% of all stress MPI studies performed in the U.S. In 2008, the Food and Drug Administration approved regadenoson for stress testing in conjunction with MPI. Regadenoson, unlike adenosine, is a selective A_{2A} agonist that is given as an intravenous bolus at a fixed dose, with less undesirable side effects including atrioventricular block and bronchospasm. Unlike adenosine, regadenoson could be used in patients with mild-to-moderate reactive airway disease. This review will summarize the pre-clinical and clinical data on regadenoson, as they specifically relate to its use as a vasodilator stress agent, currently the only approved selective A_{2A} agonist. (J Am Coll Cardiol 2009;54:1123–30)
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Coronary artery disease accounts for 20% of the deaths in the U.S. (1). Myocardial perfusion imaging (MPI) is widely used for the detection of coronary artery disease, risk assessment, detection of viable myocardium, and evaluation of the effects of various therapeutic interventions (2).

At present, up to 50% of MPI studies are performed with vasodilators rather than with exercise (3). Adenosine and dipyridamole have been the mainstays of vasodilator stress testing for almost 2 decades since the approval by the Food and Drug Administration (FDA) of adenosine (Adenoscan, Alfa Aesar, Ward Hill, Massachusetts) in 1990. Dobutamine stress MPI is reserved for patients with contraindications for vasodilator testing (~5% of patients). Adenosine triphosphate is approved in Japan but not in the U.S. (2). In the past few years, several selective A_{2A} agonists have been examined as potential stress agents, and regadenoson (Lexiscan, Gilead Sciences Inc., Foster City, California) is the first one to be approved by the FDA. This review will summarize its current status and unique features in comparison with adenosine, which is a nonselective agonist.

Adenosine

The production and metabolism of adenosine have been extensively reviewed elsewhere and will not be discussed here (2,4,5). Adenosine nonselectively activates 4 receptor subtypes: A_1, A_{2A}, A_{2B}, and A_3. Activation of the Gi/o protein-bound A_1 and A_3 receptors reduces adenylyl cyclase activity and decreases intracellular cyclic adenosine monophosphate. However, activation of the Gs protein-bound A_{2A} and A_{2B} receptors increases adenylyl cyclase activity and cyclic adenosine monophosphate levels (6).

Activation of cardiac A_{2A} and A_{2B} adenosine receptors vasodilates the coronary and peripheral arterial beds, increases myocardial blood flow (MBF), and causes sympathoexcitation. Activation of cardiac A_1 receptors mediates the negative chronotropic, dromotropic, inotropic, and anti-beta-adrenergic effects. Stimulation of A_3 and A_{2B} receptors produces mast cell degranulation and bronchial constriction (7,8). The discovery of the various subtypes of adenosine receptors has paved the way for therapeutic potential of selective antagonists and agonists (9,10).

The use of adenosine for stress MPI is primarily related to the activation of A_{2A} receptors and the resultant increase in MBF; the activation of A_1, A_{2B}, and A_3 receptors produces short-term undesirable side effects. Furthermore, the very short half-life of adenosine necessitates a continuous intravenous infusion.

Regadenoson is the first selective A_{2A} receptor agonist that is approved by the FDA and is currently used clinically. It has many of the characteristics of an ideal stress perfusion agent, being a potent and a selective coronary vasodilator with a rapid onset of action, a short duration of action, and being administered as a fixed-dose bolus (not weight-based). Further, it has a good safety and tolerability profile including in patients with reactive airway disease, and finally its side effects can be readily reversed by an antagonist if needed (11–13).

Structure and Synthesis

The structural modification of adenosine derivatives provides different plasma stability, lipophilicity, and selective affinity for receptor subtypes. The 4-substituted pyrazole derivative (regadenoson) gives the molecule its highly selective A_{2A} receptor-binding properties (14,15).

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Abbreviations and Acronyms

COPD = chronic obstructive pulmonary disease

FDA = Food and Drug Administration

FEV_1 = forced expiratory volume (1 s)

LV = left ventricle/ventricular

MBF = myocardial blood flow

MPI = myocardial perfusion imaging

Regadenoson is a 2-[N-1-(4-N-methylcarboxamidopyrazolyl)]-adenosine derivative. It is synthesized from the condensation of 2-hydrazino-adenosine with ethoxycarbonylmalondialdehyde followed by aminolysis with methylamine, or from 2-cholo or 2-iodo adenosine derivatives (15) (Fig. 1).

Receptor Affinity

The selectivity of regadenoson was established in radioligand binding assays and was found to have low affinity for A_1, A_{2B}, and A_3 adenosine receptors (16). Trochu et al. (17) further showed in an animal model the lack of A_1 response in contradistinction to a dose-dependent A_{2A} response. Regadenoson was also shown to have absent bronchoconstrictive response in control and allergen-sensitized mice (18).

By design, regadenoson has a low affinity for the A_{2A} adenosine receptor. Affinity (Ki) is defined as the ratio of the rate of drug dissociation to the rate of drug association to the receptor (16). Because of the large A_{2A} receptor reserve in the coronary arterial bed, an ideal selective A_{2A} receptor agonist may have a relatively low binding affinity without affecting the maximal coronary vasodilation (19). Drugs with low affinity (high Ki) have a shorter duration of effect than drugs with high affinity. For example, the Ki value of adenosine is 2,700 to 5,600 while that of regadenoson is 1,200 (16).

The low affinity of a selective A_{2A} agonist in a large receptor reserve bed allows maximal vasodilation effect and rapid termination of action. The time required in reversing maximal increase of coronary conductance by 50% by adenosine and regadenoson was 1.6 and 5.2 min, respectively. Possibly other factors such as dose, metabolism, and volume of distribution also affect duration of action (16). Of note, the duration of action is at times defined in different ways such as how long a response exceeds some arbitrary threshold of peak MBF (i.e., 2 × resting flow) and not necessarily the time to return to baseline MBF.

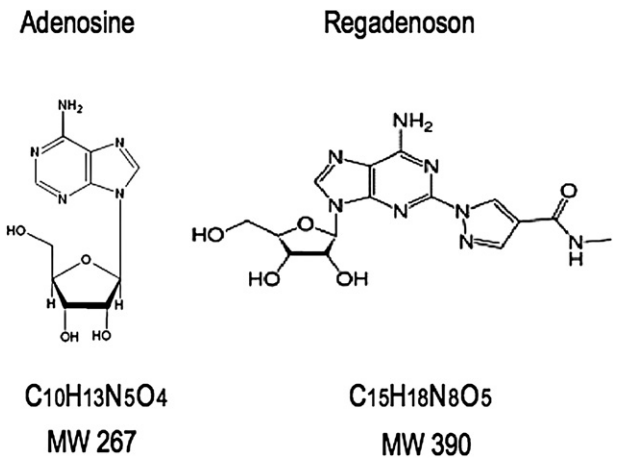

Figure 1 Chemical Structures of Adenosine and Regadenoson

MW = molecular weight.

Coronary Vasodilator Properties

In a dog model, intravenous bolus injection of regadenoson caused a dose-dependent increase in MBF comparable to that produced by adenosine infusion. Both drugs caused a dose-dependant decrease in coronary vascular resistance (maximal decrease of 73% by both). The maximal increase in MBF with regadenoson (2.5 μg/kg intravenous bolus) was approximately 84% of the peak MBF achieved by transient occlusion of the coronary artery. The increased MBF after bolus of regadenoson remained at least 2-fold above the baseline for 97 s as compared with 24 s with adenosine (267 μg/kg) ($p < 0.01$) (17).

Zhao et al. (20) showed similar data in a dog animal model; regadenoson and adenosine caused a dose-dependent increase in MBF, with nonstatistically different maximal values between the 2 drugs although regadenoson was 100× more potent than adenosine (ED_{50} = 0.45 vs. 47 μg/kg, respectively).

Hemodynamic Effects

Trochu et al. (17) used a solid-state pressure gauge in the left ventricular (LV) apex to measure the LV systolic pressure and its first derivative (LV dP/dt) during regadenoson and adenosine infusion. Regadenoson did not cause changes in the LV systolic pressure, while adenosine increased it by 12% and 18% at doses of 134 and 267 μg/kg, respectively. However, both regadenoson and adenosine increased LV dP/dt by 39% and 29%, respectively. Furthermore, the increase in heart rate and duration of the increase were greater with regadenoson than adenosine. The decreases in mean arterial blood pressure were 13 mm Hg and 18 mm Hg with regadenoson and adenosine, respectively (17). Similarly, the decrease in systemic vascular resistance was less with regadenoson than adenosine (Fig. 2). Neither drug caused a significant change in cardiac output (20).

Unlike adenosine, which caused a dose-dependent renal vasoconstriction at a 250-μg/kg dose (683 ± 197% increase in renal vascular resistance, and an 85 ± 4% decrease in renal blood flow), regadenoson (2.5 μg/kg) did not affect renal vascular resistance and caused a mild decrease in renal blood flow (11 ± 4%) (20). Aminophylline (20 mg/kg) administration prevented the coronary and systemic hemodynamic effects of 1 μg/kg of regadenoson and significantly reduced the effect of the higher dose of the drug (2.5 μg/kg) (17). In the phase 3 trials, aminophylline was seldom used with either adenosine or regadenoson. In clinical use, there has seldom been a need for aminophylline use in our

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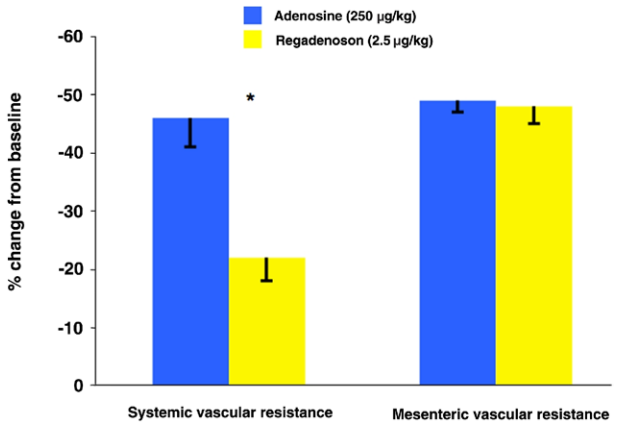

Figure 2 **Comparison of Regadenoson Versus Adenosine on Vascular Resistance in Dogs**

Regadenoson caused a smaller decrease in systemic vascular resistance compared with adenosine. Both drugs reduced mesenteric vascular resistance to the same extent. *p < 0.05. The **error bars** represent the standard error of the means.

experience to counteract undesirable side effects of regadenoson. In a dog animal model, caffeine did not affect the maximal MBF but decreased the duration of hyperemia from 8.6 ±1.2 min to 1.5 ± 0.4 min (21).

The mechanism of regadenoson-mediated tachycardia was further investigated by Dhalla et al. (22). In a rat heart model, regadenoson was shown to have a dose-dependent increase in heart rate and a decrease in mean arterial pressure at the higher doses. These changes were abolished using a selective A_{2A} antagonist. Pre-treatment with a beta-blocker reduced the tachycardia but not the hypotension, while pre-treatment with a ganglion blocker prevented the tachycardia but not the transient hypotension. Regadenoson also caused more than a 2-fold increase in serum norepinephrine and epinephrine. These results suggested that the A_{2A} receptor-mediated sinus tachycardia is mainly due to direct sympathoexcitation rather than being baroreflex mediated (22). A study conducted by Hage et al. (23) showed that the increase in heart rate by either adenosine or regadenoson was significantly blunted in diabetic than nondiabetic patients, possibly due sympathetic denervation in diabetic patients, hence reinforcing the sympathoexcitation mechanism (23).

Clinical Data

Regadenoson has a volume of distribution of 11.5 l and 78.7 l (at steady-state), and an estimated clearance of 37.8 l/h. It is renally excreted (58% of total elimination) with a terminal half-life of 33 to 108 min. Gordi et al. (24) showed that the lack of a correlation between the model estimates and various baseline patient demographics supports unit-based dose administration of regadenoson. There is no need to adjust the dose in patients with renal failure, as there were no adverse effects in patients with serum creatinine clearance of <30 ml/min after administration of a 400-μg regadenoson intravenous bolus (26). The pharmacokinetic and pharmacodynamic properties of regadenoson are summarized in Table 1 (2,24–26).

In 38 volunteer subjects, flow velocity (measured by intracoronary Doppler-tipped guidewire) increased more than 3-fold with 300-, 400-, and 500-μg bolus doses of regadenoson (26). The mean time to peak effect was 33 s (20 to 40 s); the durations of the increase in flow velocity greater than 2.5× the baseline were 2.3 and 2.4 min with the 400- and 500-μg doses, respectively. Aminophylline, a competitive inhibitor of adenosine, reversed the effect of regadenoson and reduced the coronary hyperemia duration (>2-fold increase in MBF) from 6.9 to 0.6 min (26) (Fig. 3).

Similar to the animal data, in a study using positron emission tomography to measure MBF in human volunteers, moderate caffeine consumption did not affect the maximal MBF (2.98 ± 0.14 ml/min/g vs. 3.05 ± 0.14 ml/min/g) or the coronary flow reserve (2.75 ± 0.16 vs. 2.97 ± 0.16, p = NS) (27). The duration of maximum hyperemia was not evaluated. The clinical results of masking ischemia by caffeine with adenosine have been inconsistent (28,29). Several other studies have examined the effects of caffeine on MBF (30), but it should be noted that effects of adenosine or regadenoson on MBF might be different from those on perfusion because of the nonlinear relationship between peak MBF and tracer concentration in the myocardium (2).

MPI Using Regadenoson

A phase 2 trial enrolled 36 patients who had reversible ischemia on adenosine MPI. The patients then had a repeat MPI with either 400- or 500-μg regadenoson given as an intravenous bolus. Images, interpreted by 3 blinded readers, had 89% and 76% agreement rates for the presence of

Table 1 **Comparison of Adenosine and Regadenoson Pharmacokinetic and Pharmacodynamic Properties in Human Volunteers**

	Adenosine	Regadenoson
Formula	$C_{10}H_{13}N_5O_4$	$C_{15}H_{18}N_8O_5.H_2O$
Molecular weight (g/mol)	267.24	408.37
Mode of action	Nonselective agonist	Selective A_{2A} agonist
Administration	Infusion	IV bolus
Dose	140 μg/kg/min	400 μg
Duration of infusion	4–6 min	10-s bolus
Radiotracer injection	Third minute of infusion	30 s after bolus
Terminal half-life	2–10 s	33–108 min
Time to peak	30 s	33 s
Duration of action	6 s*	2.3 min†
Elimination	Cellular uptake	Renal (57%)
Antidote	Aminophylline	Aminophylline

*Because adenosine is administered as an infusion, the duration of action is as long as the duration of the infusion; therefore, the 6-s value is misleading; †duration of action is defined as duration of coronary blood flow >2.5 × baseline.
IV = intravenous.

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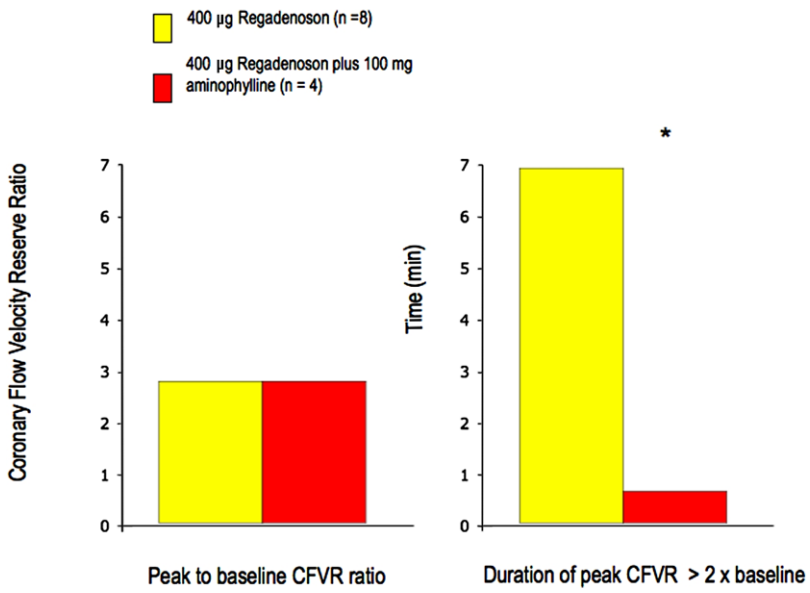

Figure 3 Effect of Aminophylline Infusion on Regadenoson-Mediated Coronary Vasodilation in Human Volunteers

Aminophylline injection (100 mg) did not affect the peak-to-baseline coronary flow velocity reserve (CFVR) ratio, but significantly blunted the duration of hyperemia (2-fold increase in CFVR above baseline). *$p < 0.05$.

ischemia with the 400- and 500-μg doses, respectively, compared with adenosine images. When patients were divided into 4 groups based on summed stress score (the score is based on a 17-segment model where each segment is scored on a scale of 0 to 4, where 0 = normal tracer activity and 4 = absent tracer activity) (0 to 3, 4 to 7, 8 to 11), the agreement rates between regadenoson and adenosine were 57% and 69% by visual and quantitative analysis, respectively (31).

The pivotal phase 3 trials that culminated in the FDA approval of this drug were 2 identical randomized, double-blind studies of over 2,000 patients in more than 100 sites (32,33). The patients had a baseline adenosine MPI and were then randomized in a 2:1 ratio to regadenoson (400-μg intravenous bolus in <10 s) and adenosine. Because there was no reason to expect the results with regadenoson to be superior to those with adenosine, the trials were designed as noninferiority studies (34,35).

The primary end point was to demonstrate that the difference between sequential adenosine–regadenoson images and adenosine–adenosine images, based on blinded reading, lay above a pre-specified noninferiority margin. The images were processed in a central core laboratory and interpreted by 3 blinded readers. The quality of the images was comparable; good or excellent in 88% to 90% of patients given either drug (Fig. 4).

The average agreement rate was 0.62 ± 0.03 for adenosine–adenosine and 0.63 ± 0.02 for adenosine–regadenoson images; the difference was above the lower limit of the 95% confidence interval in the entire group of patients as well as in pre-specified subgroups based on age, sex, body weight, and diabetes. Further, side-by-side image interpretation showed comparable agreement rates between the adenosine and regadenoson groups (0.76 ± 0.03 vs. 0.77 ± 0.02 and 0.77 ± 0.02 vs. 0.78 ± 0.02) for the presence and absence of ischemia, respectively (33). The problems associated with agreement rates by visual analysis have been previously addressed. Analysis of the same data by automated quantitative analysis showed >90% agreement rates for adenosine–adenosine as well as adenosine–regadenoson images (36).

Changes in Heart Rate and Blood Pressure

Regadenoson, like adenosine, produces a decrease in blood pressure and an increase in heart rate. The effects of regadenoson and adenosine to decrease the blood pressure were not significantly different. The heart rate response was higher with regadenoson than adenosine (32,33) (Fig. 5). The mechanism of the increase in heart rate was discussed earlier (22,23).

Safety and Adverse Events

The side effects of regadenoson observed in the phase 3 clinical trials are summarized in Table 2 (33). They were mild and transient in nature; none was life threatening or serious. There were no instances of high-degree atrioventricular block. However, patients who had atrioventricular block on entry MPI were excluded from the study. There were no reported deaths or life-threatening arrhythmias. There was no QT prolongation consistent with earlier animal data (37). Regadenoson was preferred over adenosine, based on patient satisfaction scores; the summed score due to flushing, chest pains, and dyspnea (the 3 most common side effects

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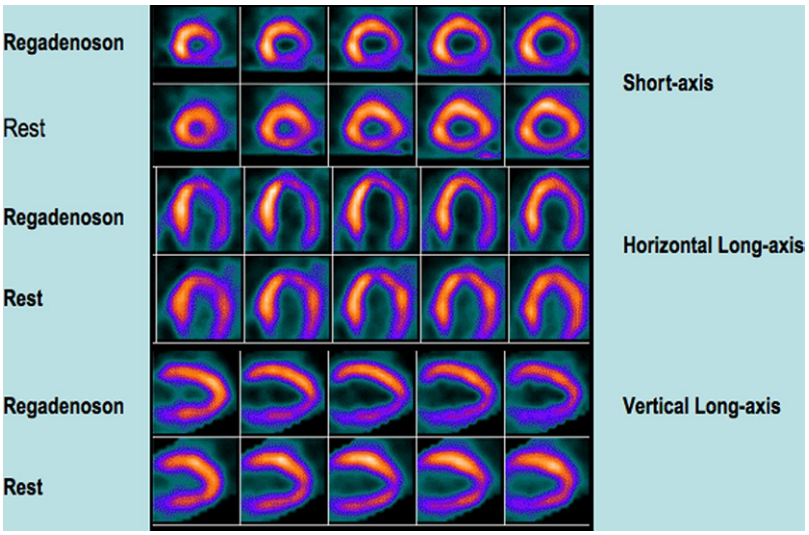

Figure 4 **Regadenoson/Rest SPECT Images Showing a Large Reversible Perfusion Abnormality in the Inferior and Lateral Segments of the LV Myocardium**

By quantitative analysis, the abnormality involved 29% of the myocardium. The patient is a 54-year-old man with chest pains. LV = left ventricular; SPECT = single-photon emission computed tomography.

with adenosine) was lower with regadenoson than with adenosine in the entire group of patients as well as in women and the elderly (32,33) (Fig. 6). The combination of low-level exercise with regadenoson has been shown in a small study to reduce the side effects (38).

Studies in Patients With Asthma and Chronic Obstructive Lung Disease

Adenosine might provoke bronchospasm in certain susceptible patients such as those with asthma or those on maintenance doses of bronchodilators or steroids. The selectivity of regadenoson was therefore of great interest to study for its safety and efficacy in such patients. The final answer is not yet in, and more studies are needed, but there are some preliminary data.

Prior studies have suggested that with prophylactic pretreatment with a B-2 agonist, adenosine could be given to patients with mild asthma or chronic obstructive lung disease (COPD). It should be noted the majority of patients with COPD but no bronchospasm could be tested with

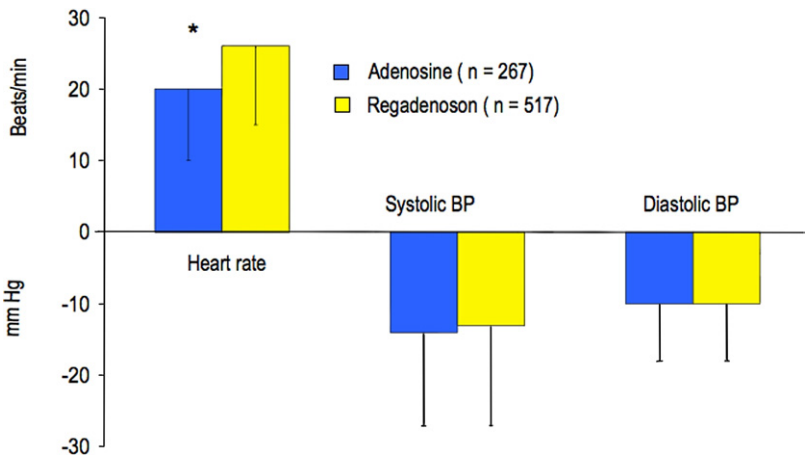

Figure 5 **Changes in HR and Blood Pressure With Regadenoson Versus Adenosine**

Regadenoson bolus administration caused a greater increase in maximal heart rate (HR) than did an adenosine infusion (*$p < 0.05$). Effects of regadenoson and adenosine on systolic and diastolic blood pressure (BP) were not statistically different. The **error bars** represent standard error of the mean.

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Table 2 Adverse Event Incidence of Regadenoson in All Patients and in Special Groups (Elderly, Women, Obese, and Patients With Diabetes)

	Any Event	Chest Pain	Dyspnea	Flushing	Headache	GI	Dizziness	Neck/Jaw Pain
All patients	73%	29%	28%	22%	23%	23%	8%	7%
Elderly (≥65 yrs)	72%	26%	27%	21%	24%	24%	7%	7%
Women	80%	36%	31%	17%	37%	32%	7%	9%
BMI >30 kg/m^2	73%	28%	29%	23%	27%	22%	7%	6%
Patients with diabetes	73%	29%	24%	22%	25%	25%	6%	5%

BMI = body mass index; GI = gastrointestinal.

adenosine without any serious problem (39). Further, tachypnea is common after adenosine infusion and is not due to changes in airway resistance or pulmonary capillary wedge pressure but rather to stimulation of carotid body receptors (40,41).

A randomized double-blind, placebo-controlled cross-over trial assessed the safety of regadenoson in 48 patients with proven mild (n = 24) or moderate (n = 24) asthma (positive challenge test) based on the global initiative for asthma guidelines (42). There was at least a 6-h abstention from the use of bronchodilators before the study. A dose of 400-μg regadenoson or a matching placebo was infused over 10 s. The mean forced expiratory volume at 1 s (FEV_1) at any time point was not statistically different between placebo and regadenoson-treated patients. Similarly, the incidence of bronchospasm was 4% in both groups (p = 0.99). No patient had oxygen desaturation (<92%) in either group. More patients experienced dyspnea with regadenoson than with placebo (43), although this was not associated with a decrease in FEV_1.

A similar double-blind, cross-over study enrolled 49 patients (mean age 67 years) with moderate (stage II) or severe (stage III) COPD (based on the Global Initiative for Chronic Obstructive Lung Disease Scientific Committee criteria) (44). Patients were randomized to 400-μg regadenoson/placebo sequence or placebo/400-μg regadenoson. Patients received their regular daily COPD medications except bronchodilators, which were withheld for at least 8 h before the study. Measurements included FEV_1, forced vital capacity, and pulse oximetry in addition to pulmonary physical examination.

There were no statistically significant differences in values of mean FEV_1 and forced vital capacity, mean oxygen saturation, bronchoconstriction, and new-onset wheezing at any time between groups. Dyspnea, however, was more common in the regadenoson group but was not related to a decline in FEV_1 or any objective finding (45).

These results suggest that regadenoson could be safely administered to patients with mild or moderate reactive airway disease. There is no comparable data on adenosine infusion in patients with moderate-to-severe asthma as this drug is contraindicated in this population. However, a larger and more definitive multisite study is needed to clearly define the safety of regadenoson use in patients with

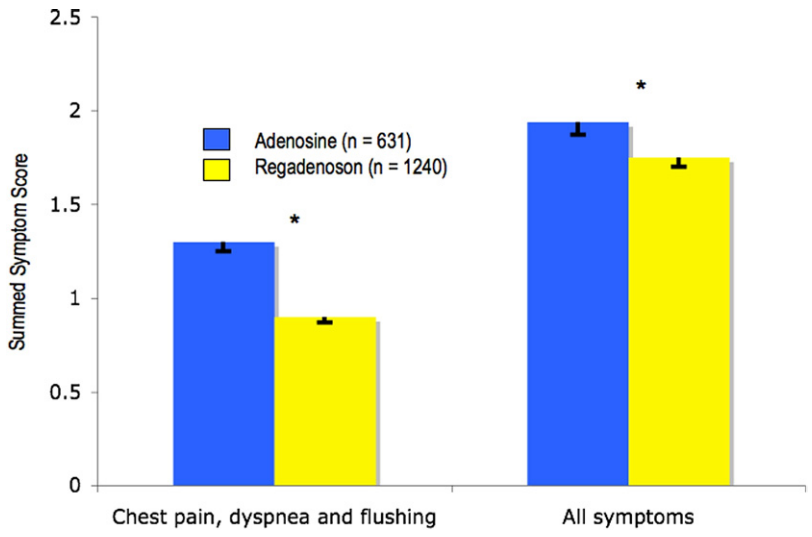

Figure 6 Summed Symptom Score With Regadenoson and Adenosine

The mean summed symptom score for chest pain, dyspnea, and flushing, and the mean summed score of all the symptoms were significantly lower in the regadenoson versus adenosine groups (*p < 0.05). The score for each symptom was calculated as: 0, absent; 1, mild; 2, moderate; and 3, severe. The **error bars** represent standard error of the mean.

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wheezing and in patients on maintenance doses of bronchodilators and/or steroids.

Regadenoson Market

Since the FDA approval of regadenoson on April 2008, the market share has increased steadily (2% in July 2008 vs. 11% in November 2008) together with a decline in the use of adenosine and no change in the use of dipyridamole. By October 2008, the market share of regadenoson has surpassed that of dobutamine (11% vs. 7%) (46). At present, the cost of regadenoson is slightly lower than adenosine, but that may change once adenosine becomes generic.

Summary and Future Perspectives

Regadenoson has appealing features for clinical use, ease of administration as a bolus, weight-unadjusted dose, a fast onset and short duration of action, sufficient hyperemic response, and comparable efficacy to adenosine but with less side effects. Unlike adenosine, regadenoson could also be used in patients with mild-to-moderate reactive airway disease and obstructive lung disease. The cost must be considered especially after a generic form of adenosine becomes available. These features are likely to expand the use of these agents beyond MPI to stress testing with other imaging modalities and to measure coronary hemodynamics in the cardiac catheterization laboratory with the flow-Doppler catheter (47). There are 2 other selective A_{2A} agonists at various stages of development: 1 completed phase 3 trials (binodenoson, MRE0470, King Pharma, Bristol, Tennessee) and the other is about to start large-scale studies (apadenoson, ATL146e, PgXHealth, LLC, a division of Clinical Data, Inc., Newton, Massachusetts) (48,49). We have no data comparing these new agents at present.

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Key Words: adenosine ■ regadenoson ■ myocardial perfusion imaging ■ single-photon emission computed tomography ■ stress testing.

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