

Selective adenosine agonists and myocardial perfusion imaging

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Selective adenosine receptor agonists have several advantages for use as stress agents in conjunction with myocardial perfusion imaging compared to the non selective agents such as adenosine and dipyridamole. This review will summarize the pre-clinical and clinical data on the selective adenosine agonist stress agents regadenoson (Lexiscan[®]), binodenoson (CorVue[™]) and apadenoson (Stedivaze[™]) that have been studied so far with focus on regadenoson that has the most clinical data published so far. The article will review the adenosine receptor types and properties. It will also review the various attributes of the selective adenosine agonists including their pharmacology, pharmacokinetics and pharmacodynamics, their coronary vasodilatory and hemodynamic effects, their safety and side effects, their interactions with other drugs and their use with myocardial perfusion imaging. The landmark trials of the selective adenosine agonists will be reviewed as well as their use in special patient populations undergoing stress myocardial perfusion imaging.

Key Words: Myocardial perfusion imaging • selective adenosine agonists • regadenoson • binodenoson • apadenoson

INTRODUCTION

Pharmacologic stress is used in conjunction with $\approx 50\%$ of the ≈ 10 million myocardial perfusion imaging (MPI) studies performed yearly in the United States for the evaluation of patients with known or suspected coronary artery disease (CAD). Pharmacologic stress is reserved for patients who cannot exercise, achieve adequate exercise end-points, or have a left-bundle branch block (LBBB) or electronically paced rhythms. Around 50% of outpatients and 75% of inpatients and $\approx 30\%$ of patients <75 years and $\approx 50\%$ of ≥ 75 years cannot perform adequate exercise MPI.¹ The pharmacologic stress agents include the vasodilator agents and the inotropic-chronotropic agents such as dobutamine or arbutamine. The vasodilator stress agents are classified, based on their action on the adenosine receptors, as non-selective agonists such as dipyridamole, adenosine, and

adenosine triphosphate (ATP) or as selective agonists such as regadenoson (Lexiscan[®], Gilead Sciences Inc), binodenoson (CorVue[™], King Pharmaceuticals) or apadenoson (Stedivaze[™], Forest Laboratories, Inc). Regadenoson, the only FDA approved agent so far, has become one of the more commonly used pharmacologic stress agents in use in the United States accounting for 68% of the market compared to 15% for adenosine, 13% for dipyridamole, and 4% for dobutamine.

VASODILATOR MPI

The vasodilator agents increase the myocardial blood flow (MBF) by 3-5-fold in normal coronary arteries independent of myocardial oxygen demand. The generation of perfusion defects during vasodilator MPI results from the disparity in MBF and radiotracer concentration between territories supplied by non-diseased compared to diseased coronary arteries that have limited ability to augment MBF. The capillaries and myocardial blood volume are important in determining the regional myocardial radiotracer concentration. Cellular exchange and radiotracer extraction depend primarily on capillaries that contain 90% of the myocardial blood volume.² A capillary pressure of ≥ 30 mm Hg is needed to maintain resting MBF and homeostasis and is achieved in the presence of coronary stenosis by recruitment of capillaries.^{2,3} In the presence of a significant

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Table 1. Distribution and action of the various adenosine receptors (reproduced from Zoghbi and Iskandrian⁴ with permission)

Receptor type	Location	Action
A1	Sinoatrial node Atrioventricular node Atrial myocytes Ventricular myocytes	Negative dromotropic, inotropic and chronotropic effects Preconditioning Chest pain production Tachypnea production
A2A	Smooth muscle cells	Coronary vasodilatation (predominant) Peripheral vasodilatation (partial) Anti-inflammatory effect Sympathetic stimulation
A2B	Smooth muscle cells	Vasodilatation in most vascular beds Vasoconstriction in renal afferent arterioles and hepatic veins Bronchiolar constriction
A3	Ventricular myocytes	Mast cell degranulation Preconditioning Bronchospasm

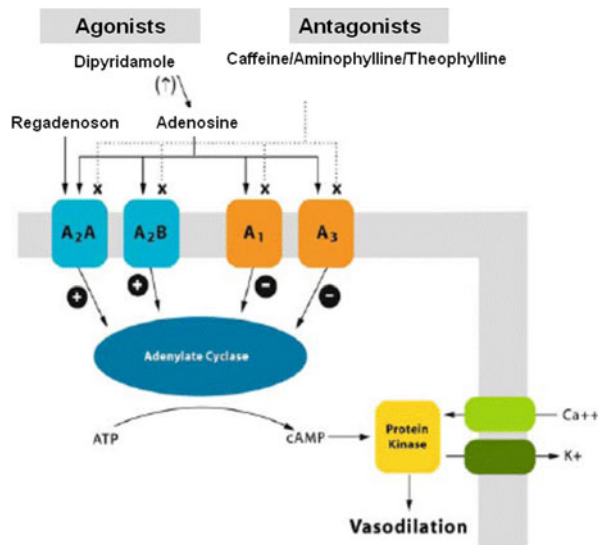


Figure 1. Adenosine receptor subtypes and mode of action (modified from Gemignani and Abbott⁵).

stenosis, the coronary MBF reserve and capillary recruitment are already maximal and can minimally increase further under vasodilator stress leading to the disparity in MBF and radiotracer concentration compared to a non-diseased coronary artery which is the basis for the generation of perfusion defects by single photon emission computed tomography (SPECT) MPI.

THE ADENOSINE RECEPTORS

The adenosine receptors are ubiquitously located in multiple tissue types and are divided into 4 subtypes: A1, A2A, A2B, and A3 (Table 1; Figure 1).^{4,5} The A1 and A3 receptors activate a Gi protein that decreases adenylyl cyclase activity leading to a decrease in intracellular cyclic adenosine monophosphate (cAMP) which increases potassium channel conductance and causes smooth muscle contraction.⁶⁻⁹ The A2A and A2B receptors activate a Gs protein that increases adenylyl cyclase activity leading to an increase in intracellular cAMP which opens potassium channels and inhibits the voltage-gated calcium channels resulting in smooth muscle relaxation and arteriolar vasodilation.⁷⁻⁹ Stimulation of the A2A receptors causes coronary vasodilation whereas stimulation of the other adenosine receptors causes the undesirable side effects. An ideal adenosine receptor agonist is one that causes vasodilation via selective stimulation of the A2A receptor and minimal or no stimulation of the other adenosine receptors that cause the side effects (Table 2). Most of the adenosine receptor agonists are derived from the purine nucleosides adenosine or xanthosine.⁹ The selective A2A agonists that have been studied so far as pharmacological stressors for MPI are apadenoson (BMS068645 or ATL146e), regadenoson (CVT-3146), and binodenoson (MRE-0470 and WRC-0470).

Table 2. Attributes of the ideal vasodilator for stress MPI^{7,10}

Selective A2A receptor agonist (selective coronary vasodilatation)
Rapid onset of action
Short duration of action
Long enough to allow radiotracer uptake during maximal coronary hyperemia
Coronary hyperemia: increase myocardial blood flow by 2-3-fold above baseline
Ease of administration (single and non weight- based bolus),
Acceptable safety and tolerability profile
Minimal side effects
Ease of reversing side effects with an antagonist

PHARMACOLOGY, PHARMACOKINETICS, AND PHARMACODYNAMICS

Regadenoson

Regadenoson is a 2-[N-1-(4-N-methylcarboxamidopyrazolyl)] pyrazole adenosine derivative (Figure 2).¹⁰ In contrast to adenosine, regadenoson is less rapidly metabolized by the cell membrane nucleoside transporter

or by the plasma adenosine deaminase permitting its administration as an intravenous (IV) bolus rather than a continuous IV infusion.¹¹ In pharmacokinetic and pharmacodynamic analyses of regadenoson in healthy male volunteers, adverse events were mainly related to vasodilation and increase in heart rate (HR) and were more prevalent at regadenoson doses >3 µg/kg in a dose-dependent effect.¹² The maximum tolerated doses of regadenoson were 20 µg/kg in the supine position and 10 µg/kg in the standing position.¹² The pharmacokinetics of regadenoson followed a 3-compartment model with linear clearance and rapid distribution throughout the body followed by a slower elimination half-life of approximately 2 hours following IV bolus administration.¹² Following IV bolus administration, regadenoson maximal venous plasma concentration was reached within 1-3 minutes.¹¹ The central compartment volume of distribution was 11.5 L and the steady state volume of distribution was 78.7 L with an estimated clearance of 37.8 L/h.¹² Renal excretion accounted for 58% of total regadenoson elimination.¹² Regadenoson's volume of distribution, terminal half life and excretion were dose independent.¹¹ The plasma regadenoson concentration causing a 50% increase in E_{max} (EC50) and the maximum HR increase (E_{max}) were 12.3 ng/mL and 76 beats/minute, respectively.¹² The elimination half life of a single IV

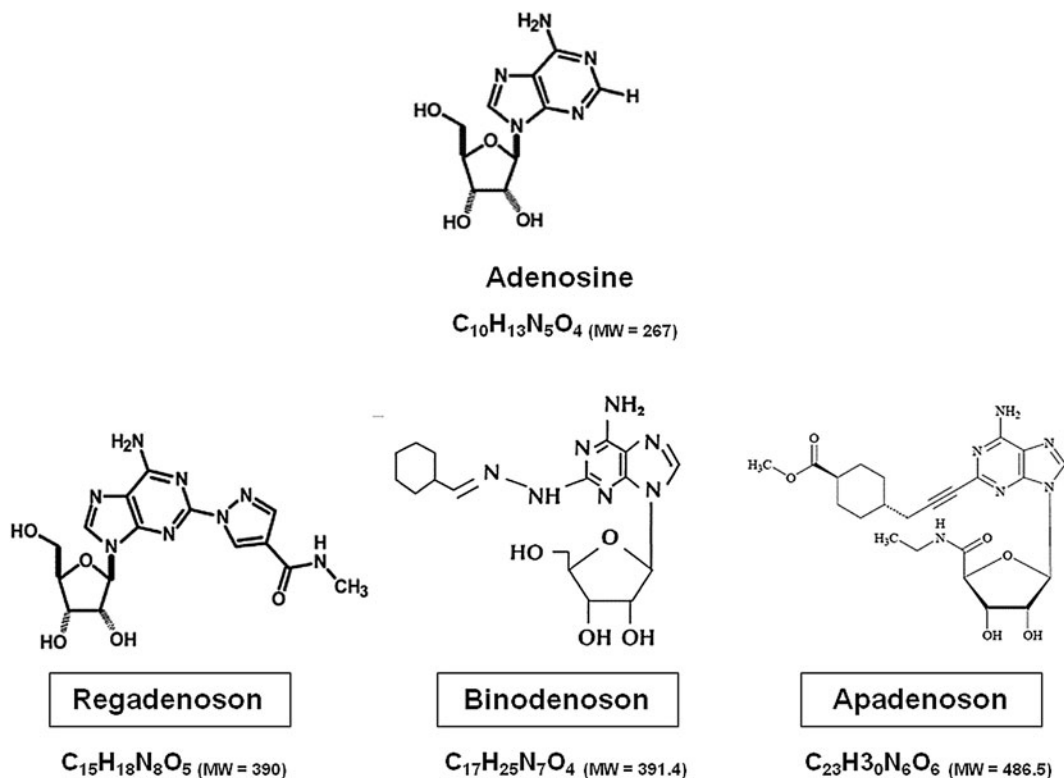


Figure 2. Chemical structures of adenosine and the selective adenosine A2A receptor agonists.

bolus of 400 µg of regadenoson was prolonged with decreasing renal function.¹³ However, regadenoson's maximal plasma concentrations, severity and number of adverse side effects did not differ significantly by renal function.¹³ Thus, dose adjustments of regadenoson are not necessary in patients with impaired renal function.¹³

Binodenoson

Binodenoson is a [(2-cyclohexylmethylene)hydrazine] adenosine derivative (Figure 2).¹⁴ The pharmacokinetics of binodenoson were studied after IV escalating doses (0.1, 0.2, 0.4, 0.6, 1, 2, 3, 4, 5, and 6 µg/kg) that were infused over 10 minutes in healthy volunteers.¹⁴ Binodenoson exhibited linear pharmacokinetics and a dose-related increase in side effects such as headache, nausea, vasodilation, and chest pain.¹⁴ Binodenoson distributed into the extracellular space and exhibited 2-compartment pharmacokinetics based on visual inspection of the semi-log plots of plasma concentration vs time curves.¹⁴ The distribution phase was apparent at higher doses over the first 10 minutes post-infusion and the terminal elimination phase was generally apparent after 10-15 minutes post-infusion with a terminal half life of 10 ± 4 minutes. Systemic clearance was independent of dose but correlated with body weight.¹⁴ Mean maximal plasma concentration (C_{max}) values increased with dose with a range from 0.09-12.11 ng/mL. C_{max} occurred at the end of the infusion with a corresponding mean time of maximum plasma concentration (T_{max}) of 7.5-11.3 minutes across all doses.¹⁴ The incidence of side effects was dose related.¹⁴

Apadenoson

Apadenoson (ATL-146e) is a 2-propynylcyclohexyl-5'-N-ethylcarboxamido derivative of adenosine (Figure 2).¹⁵ The pharmacokinetic and pharmacodynamic properties of apadenoson have not been published.

ADMINISTRATION

Regadenoson is marketed as Lexiscan® (Astellas Inc) and is packaged in 5 mL pre-filled syringes. It is administered as a single 400 µg IV bolus dose over 10 seconds followed by a 5 mL saline flush.⁵ The radiotracer is administered 20 seconds after the regadenoson bolus.⁵ Binodenoson has not been yet approved by the FDA for use. It will be marketed as CorVue™ (King Pharmaceuticals) and will be supplied in 250 µg vials. Binodenoson is administered as a single weight based IV bolus dose of 1.5 µg/kg over 30 seconds. The packaging information for apadenoson is not available.

ADENOSINE RECEPTOR BINDING AFFINITY AND SELECTIVITY

The properties of the selective A2A receptor agonists are summarized in Table 3. Compared to adenosine, regadenoson is 100 times more potent at the A2A receptor.^{7,10} In animal studies, regadenoson had greater affinity and more selectivity for the A2A receptor compared to the other adenosine receptors.¹⁶ In one study of isolated rat hearts, regadenoson increased coronary conductance via its action on the A2A receptors without affecting the atrioventricular conduction times that are mediated by the A1 receptor.¹⁶ Receptor

Table 3. Properties of the A2A receptor agonists (modified from Hendel et al,⁷ Al Jaroudi and Iskandrian¹⁰)

	Binodenoson	Apadenoson	Regadenoson
Selectivity	+++	++++	++
Affinity	+++	++++	+
Potency	+++	++++	++
Hyperemia onset	<1 minute	<1 minute	20-40 seconds
Hyperemia duration	10 minutes	4-5 minutes	2-3 minutes
Elimination			Renal (57%)
Administration	Bolus	Bolus	Bolus
Dose	Weight based	Fixed dose	Fixed dose
Antidote	Aminophylline	Aminophylline	Aminophylline
Clinical trials	Completed	Phase III	Completed
FDA approval	No	No	Yes

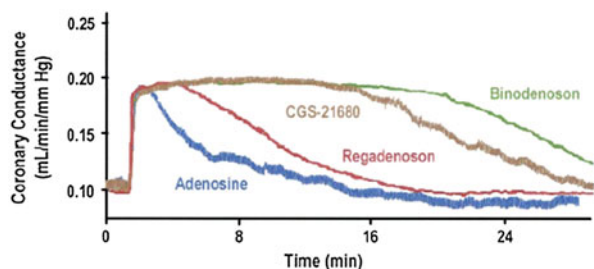


Figure 3. Duration and extent of coronary vasodilation of adenosine and the selective A2A agonists (from Cerqueira¹⁷ with permission).

affinity (K_i) is defined as the ratio of the rate of drug dissociation to the rate of drug association to the receptor in question.¹⁶ Thus, high affinity agonists have a lower K_i compared to low affinity agonists.¹⁶ The affinity of regadenoson to the A2A receptor was >13-fold compared to the A1A receptor.¹⁶ At the A2A receptor, regadenoson ($K_i = 1200$) has a lower affinity compared to CGS-21680 ($K_i = 157$) and binodenoson ($K_i = 21$) and a higher affinity compared to adenosine ($K_i = 2700-5600$).^{16,17} In dog studies, ATL-146e was equipotent to ATL-193 as agonist of A2A receptors and ≈ 6 and 35 times more potent than MRE-0470 (binodenoson) and CGS-21680, respectively. ATL-146e was more selective for the A2A over the A1 receptor.¹⁶ ATL-146e was 71 times more selective for the A2A over the A1 receptor compared with selectivity ratios of 37 and 6 for MRE-0470 and CGS-21680, respectively.¹⁶ Regadenoson produced a maximal coronary vasodilator response of similar magnitude compared with the higher affinity A2A agonists (Figure 3).^{16,17} Thus a lower affinity drug, such as regadenoson, can elicit a potent and rapid vasodilatory response due to the presence of a high density of A2A receptors and a large spare receptor capacity in the coronary arteries.^{16,17}

ANIMAL STUDIES

Coronary Vasodilatation

Intravenous adenosine (13-267 $\mu\text{g}/\text{kg}$) and regadenoson (0.1-5 $\mu\text{g}/\text{kg}$) were compared in a study of conscious dogs.¹⁸ Regadenoson caused a dose-dependent increase of coronary blood flow (CBF) with a comparable maximal increase to adenosine ($221\% \pm 18\%$ vs $227\% \pm 11\%$).¹⁸ Regadenoson ($\text{ED}_{50} = 0.34 \pm 0.08 \mu\text{g}/\text{kg}$) was more potent than adenosine ($\text{ED}_{50} = 51 \pm 15 \mu\text{g}/\text{kg}$, $P < .05$).¹⁸ Duration of $\text{CBF} \geq 2$ -fold above the baseline ranged from 97 ± 14 seconds to 247 ± 39 seconds for the minimal to maximal regadenoson doses compared to 24 ± 2 seconds after the maximal adenosine dose.¹⁸

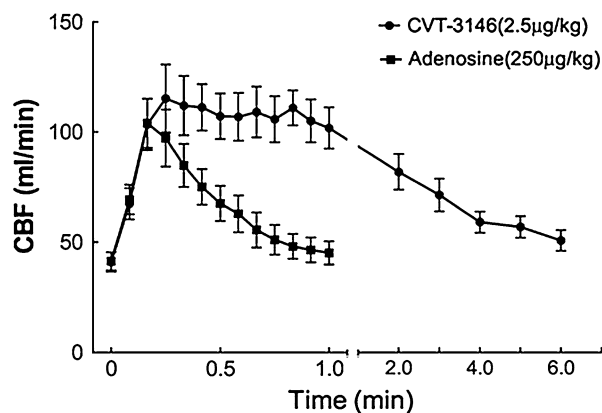


Figure 4. Time course of changes in coronary blood flow (CBF) by regadenoson (CVT-3146) and adenosine (reproduced from Zhao et al¹⁹ with permission).

In another study of conscious dogs, IV regadenoson (0.1-2.5 $\mu\text{g}/\text{kg}$) or adenosine (10-250 $\mu\text{g}/\text{kg}$) caused similar dose-dependent increases in CBF and dose-dependent decreases in the late diastolic coronary resistance.¹⁹ Regadenoson at 2.5 $\mu\text{g}/\text{kg}$ caused a similar increase in maximal CBF compared to 250 $\mu\text{g}/\text{kg}$ of adenosine though the increase in CBF was significantly of longer duration with regadenoson (Figure 4).¹⁹ Adenosine ($\text{ED}_{50} = 47 \pm 7.77 \mu\text{g}/\text{kg}$) was 100 times less potent than regadenoson ($\text{ED}_{50} = 0.45 \pm 0.07 \mu\text{g}/\text{kg}$).¹⁹

Regadenoson (2.5 $\mu\text{g}/\text{kg}$ IV bolus) and adenosine (4.5-minute infusion at 280 $\mu\text{g}/\text{kg}$) were studied in anesthetized dogs.²⁰ The biodistribution and clearance of 201-Tl and 99m-Tc sestamibi tracers and the hyperemic responses were comparable between regadenoson and adenosine.²⁰ During regadenoson stress, the relative microsphere flow deficit ($0.34\% \pm 0.02\%$) was significantly greater than the relative perfusion defect with 201-Tl ($0.53\% \pm 0.02\%$, $P < .001$) or 99m-Tc sestamibi ($0.69\% \pm 0.03\%$, $P < .001$) and the ex vivo single photon emission computed tomography (SPECT) perfusion defect score was larger with 201-Tl ($22\% \pm 2.8\%$) than with 99m-Tc sestamibi ($17\% \pm 1.7\%$).²⁰

Binodenoson (0.1-3 $\mu\text{g}/\text{kg}/\text{minute}$ infused for 10 minutes) produced dose-related vasodilatation in the left anterior descending (LAD) and left circumflex (LCx) arteries of 5 dogs without altering mean BP, HR, left atrial pressure, or left ventricular (LV) dP/dt .²¹ Infusion of adenosine at 300 $\mu\text{g}/\text{kg}/\text{minute}$ for 4 minutes to the same dogs produced coronary vasodilatation that was limited by significant hypotension.²¹ The maximal hyperemic effect of binodenoson was produced by the 1 $\mu\text{g}/\text{kg}/\text{minute}$ dose and was considerably greater than that produced by adenosine (Figure 5). In 6 dogs, LAD stenosis was created by snare ligation. Adenosine (250 $\mu\text{g}/\text{kg}/$

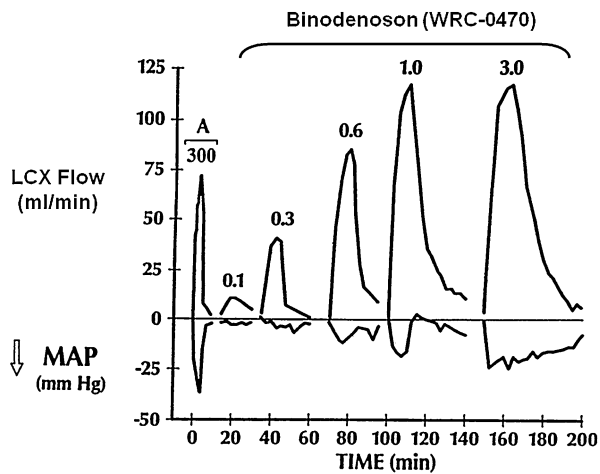


Figure 5. Dose-dependent increase in mean LCx coronary flow (Q_{cx}) in response to multiple doses of binodenoson in anesthetized dogs compared to a 300 $\mu\text{g}/\text{kg}/\text{minute}$ adenosine infusion (reproduced from Glover et al²¹ with permission).

minute infused until peak hyperemia was reached) caused LCx flow to increase approximately 3-fold from rest, whereas flow in the stenotic LAD did not significantly change (Figure 6). Adenosine caused a significant drop in mean systemic BP (Figure 6). Binodenoson (0.6 $\mu\text{g}/\text{kg}/\text{minute}$ for 10 minutes) caused LCx flow to increase 5-fold from rest, whereas flow in the stenotic LAD did not significantly change compared to rest with no associated hypotension (Figure 6).

ATL-146e (Apadenoson) was administered as a continuous (0.05, 0.1, 0.2, 0.3, and 0.4 $\mu\text{g}/\text{kg}/\text{minute}$ infused over 10 minutes compared to 250 $\mu\text{g}/\text{kg}/\text{minute}$ of adenosine for 3 minutes) or bolus (0.25, 0.5, 1.0, and 1.5 $\mu\text{g}/\text{kg}$ compared to 60, 250, 500, and 750 $\mu\text{g}/\text{kg}$ of adenosine boluses) infusions to normal dogs and to dogs with critical LAD stenosis.¹⁵ The 1.5 $\mu\text{g}/\text{kg}$ dose of ATL-146e caused an increase of CBF from 35.3 mL/minute at baseline to 142.3 mL/minute.¹⁵ The 1.0 $\mu\text{g}/\text{kg}$ dose of ATL-146e produced a larger increase in CBF than did the 500 $\mu\text{g}/\text{kg}$ dose of adenosine.¹⁵ ATL-146e bolus doses ≥ 0.5 $\mu\text{g}/\text{kg}$ produced approximately equal or greater increases in CBF as the adenosine infusion (250 $\mu\text{g}/\text{kg}/\text{minute}$ for 3 minutes) but without provoking significant hypotension (Figure 7).¹⁵ After a bolus apadenoson injection, CBF reached its peak in 2.3 minutes and remained elevated for several minutes and returned to baseline within 20 minutes (Figure 7).¹⁵ In dogs with critical LAD stenosis, LAD CBF remained unchanged while normal zone LCx flow increased ≈ 4 -fold after the ATL-146e bolus resulting in a 4:1 flow disparity between the stenotic LAD and normal LCx zones.¹⁵

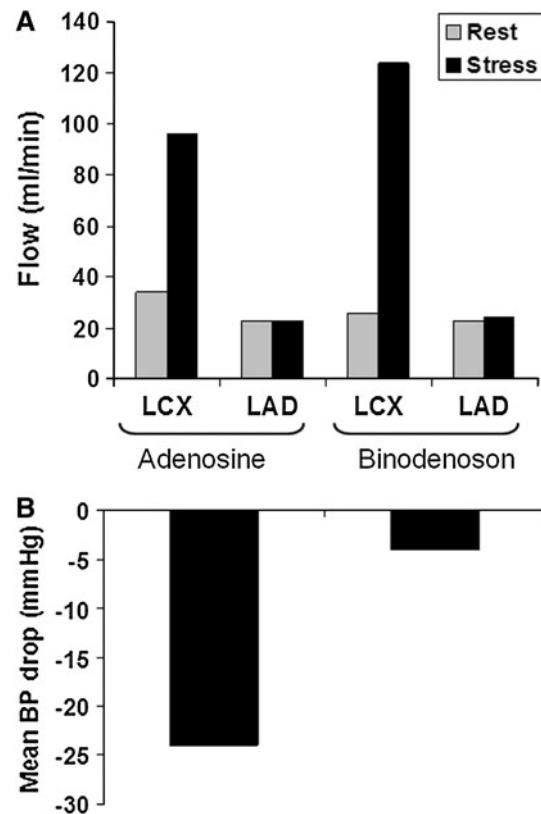


Figure 6. **A** Coronary blood flow at rest and after adenosine (250 $\mu\text{g}/\text{kg}/\text{min}$) and binodenoson 0.6 $\mu\text{g}/\text{kg}/\text{minute}$ infusions in normal LCx and critically stenosed LAD by snare ligation. **B** The effects of adenosine and binodenoson on mean BP (modified from Glover et al²¹).

Hemodynamic Effects

IV regadenoson (0.1-2.5 $\mu\text{g}/\text{kg}$) in conscious dogs caused a smaller decrease in total peripheral resistance and a smaller increase in the lower body flow compared to IV adenosine (10-250 $\mu\text{g}/\text{kg}$).¹⁹ Adenosine caused a dose-dependent renal vasoconstriction with a $683\% \pm 197\%$ increase in renal vascular resistance and an $85\% \pm 4\%$ decrease in renal blood flow with the maximal adenosine dose while the maximal regadenoson dose did not significantly affect the renal vascular resistance and caused a minimal decrease in renal blood flow ($-11\% \pm 4\%$).¹⁹ Adenosine and regadenoson caused comparable dose-dependent mesenteric vasodilation.¹⁹ The maximal regadenoson and adenosine doses caused similar increases in the cardiac outputs.¹⁹ The average peak CBF velocity increased by 3.3-fold, whereas the peak peripheral flow velocity increased by 1.1-fold after administration of 1 $\mu\text{g}/\text{kg}$ of IV regadenoson to anesthetized closed chest dogs.¹⁷ IV adenosine doses of 134 and 267 $\mu\text{g}/\text{kg}$ in conscious dogs increased LV systolic pressure by 12% and 18%, respectively,

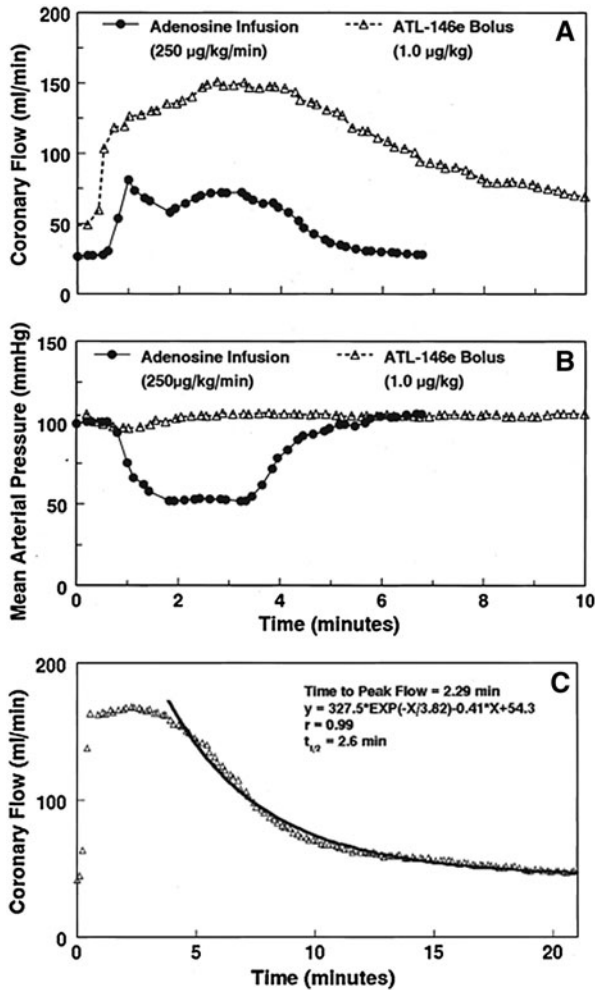


Figure 7. A CBF responses after 3-minute IV adenosine and 1.0 µg/kg IV bolus of binodenoson in the same dog. B Mean arterial BP responses in the same dog. C Time course of CBF after 1.0 µg/kg IV bolus of binodenoson (modified from Glover et al²¹).

with no changes with regadenoson (0.1-5 µg/kg).¹⁸ The LV dP/dt increased by 29% with adenosine and by 39% with regadenoson.¹⁸ The mean BP decreased by 13 mm Hg with regadenoson and by 18 mm Hg with adenosine.¹⁸ Regadenoson caused a lower decrease in the systemic vascular resistance compared to adenosine (-20% vs -45%), while both adenosine and regadenoson caused a 45% decrease in the mesenteric vascular resistance.¹⁸

Regadenoson caused a higher and a more prolonged increase in HR compared to adenosine.¹⁸ Regadenoson (0.3-50 µg/kg) caused a dose-dependent increase in HR and a decrease in mean BP at the higher doses in rats.²² The BP decrease and the HR increase caused by regadenoson were attenuated after pretreatment with an A2A receptor antagonist whereas pretreatment with

metoprolol (1 mg/kg) attenuated the HR increase with no effect on the hypotensive response.²² A ganglionic blocker prevented the tachycardia-mediated effect of regadenoson whereas the mean BP was further reduced. The plasma norepinephrine levels increased by 2-fold after 10 µg/kg of IV regadenoson.²² Regadenoson (5 and 10 µg/kg) did not cause a significant change in HR after administration of propranolol in dogs.²³ This dissociation of HR and BP responses suggests that regadenoson baroreflex-mediated tachycardia maybe more due to a direct stimulation of the sympathetic nervous system via activation of A2A adenosine receptors rather than an entirely baroreflex-mediated response.²²

Binodenoson (0.1-3 µg/kg/minute infused for 10 minutes) was compared to an infusion of adenosine at 300 µg/kg/minute for 4 minutes in 5 dogs.²¹ Binodenoson did not produce significant systemic hypotension (Figure 8).²¹ The highest dose of binodenoson decreased the mean BP from 104 ± 6 to 88 ± 13 mm Hg which was not statistically significant.²¹ Similar to adenosine, there was a reflex rise in HR with binodenoson. There was a trend toward a dose-related increase in LV dP/dt .²¹

In dogs, mean BP fell significantly at the higher doses of ATL-146e (13-18 mm Hg) but was markedly less than that produced by all of the adenosine doses (≈ 50 mm Hg).¹⁵ The decrease in mean BP was transient and lasted 1.5-6 minutes after injection. ATL-146e produced small but statistically significant increases in heart rate and dP/dt at several doses, whereas adenosine produced either no change or a decrease in heart rate at the higher doses.¹⁵

EFFECTS OF OTHER DRUGS

Pretreatment with 20 mg/kg of aminophylline abolished the peak CBF and hemodynamic effects caused by 1 µg/kg of regadenoson and attenuated the effects of the 2.5 µg/kg dose in conscious dogs.¹⁸ The effects of different doses of caffeine on 5 µg/kg of IV regadenoson were studied in 16 conscious dogs. Caffeine at 1, 2, 4, and 10 mg/kg did not significantly affect the 2-fold increase in CBF but decreased the duration of hyperemia by 17% ± 4%, 48% ± 8%, 62% ± 5%, and 82% ± 5%, respectively.²⁴ Caffeine at 4 and 10 mg/kg significantly attenuated regadenoson's effects on BP and HR.²⁴

CLINICAL STUDIES

Coronary Vasodilation

Rapid IV bolus of regadenoson (10-500 µg) increased coronary peak blood flow velocity (measured

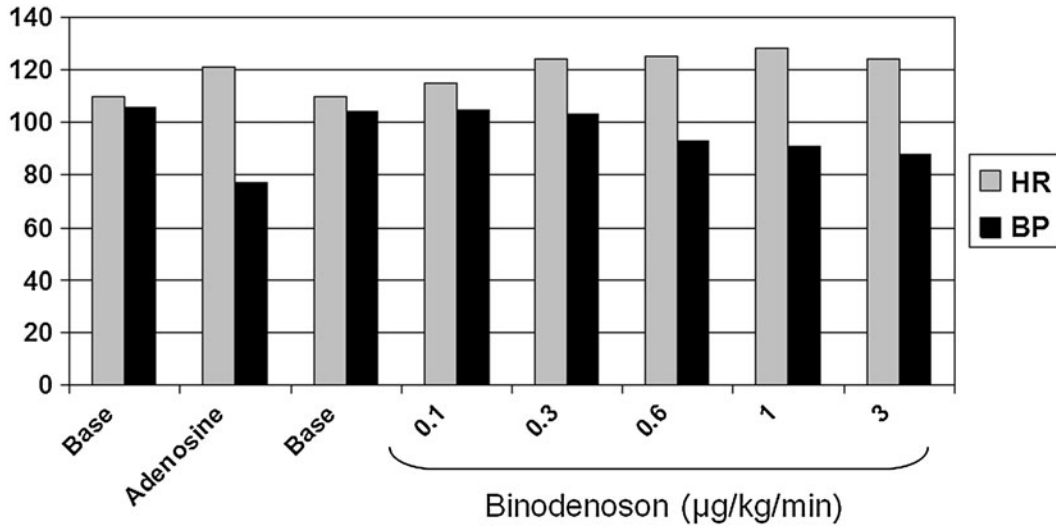


Figure 8. HR and BP responses to an infusion of adenosine at 300 $\mu\text{g}/\text{kg}/\text{minute}$ for 4 minutes and various binodenoson (0.1 to 3 $\mu\text{g}/\text{kg}/\text{minute}$ infused for 10 minutes) doses in dogs (from Glover et al²¹).

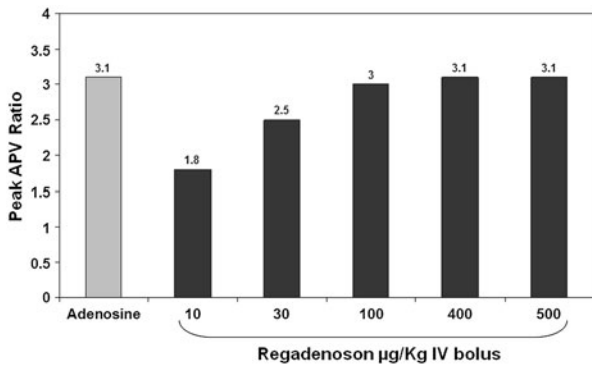


Figure 9. Dose-dependent increase of peak coronary flow velocity with 10-500 μg of regadenoson. Also shown is peak flow velocity after intracoronary administration of 18 μg of adenosine¹¹.

by a Doppler flow wire) by up to 3.1-fold in a dose-dependent manner (Figure 9).¹¹ The mean time to $\geq 85\%$ of maximum peak flow velocity was 33 seconds (range of 20-40 seconds) and was independent of regadenoson dose.¹¹ The peak flow velocity was reached within 0.5-2.3 minutes with the 400 μg dose.¹¹ The mean duration of >2.5 -fold increase of peak flow velocity was 2.3 and 2.4 minutes for the 400 and 500 μg regadenoson doses, respectively (Figure 10A).¹¹

Different doses of 3-minute IV infusions (0.3, 0.5, or 1.0 $\mu\text{g}/\text{kg}/\text{min}$) and bolus injections (1.5 or 3.0 $\mu\text{g}/\text{kg}$) of binodenoson were studied in patients who underwent diagnostic cardiac catheterization using a flow wire and were compared to hyperemia induced by intracoronary adenosine administration (Figure 11).²⁵ The 1.5 and

3 $\mu\text{g}/\text{kg}$ doses whether infused over 3 minutes or injected as boluses produced coronary hyperemia equivalent to that achieved by adenosine whereas the hyperemia of the 0.3 $\mu\text{g}/\text{kg}/\text{minute}$ dose was less.²⁵ The hyperemic responses occurred within seconds of administration. The 1.5 $\mu\text{g}/\text{kg}$ dose produced near-maximal hyperemia by 4.5 ± 3.7 minutes that was sustained for 7.4 ± 6.9 minutes, whereas the 3 $\mu\text{g}/\text{kg}$ dose produced near-maximal hyperemia by 6.0 ± 3.8 minutes that was sustained for 12.3 ± 9.6 minutes. The higher dose also resulted in higher HR, rate-pressure product and more subjective side effects. Thus the 1.5 $\mu\text{g}/\text{kg}$ dose was selected as the pharmacological stress agent to be used with MPI.²⁵

In one study of human subjects that has been published in abstract form, the effects of IV bolus doses of apadenoson (0.5, 1.0, 2.0, and 2.5 $\mu\text{g}/\text{kg}$) on CBF (measured by a flow wire) and hemodynamics were compared to a 140 $\mu\text{g}/\text{kg}/\text{minute}$ adenosine infusion over 6 minutes.²⁶ All apadenoson doses produced hyperemia within 1 minute.²⁶ The mean CBF velocity remained $>2\times$ baseline values for 3, 6, 7, and 8 minutes for the 0.5, 1.0, 2.0, and 2.5 $\mu\text{g}/\text{kg}$ doses, respectively (Figure 12).²⁶ The 1 $\mu\text{g}/\text{kg}$ apadenoson bolus dose produced a CFR response that was similar in extent and duration compared to an adenosine infusion.²⁶

Hemodynamic Effects

Rapid IV bolus of regadenoson (10-500 μg) caused a dose-dependent increase in HR and no dose-dependent

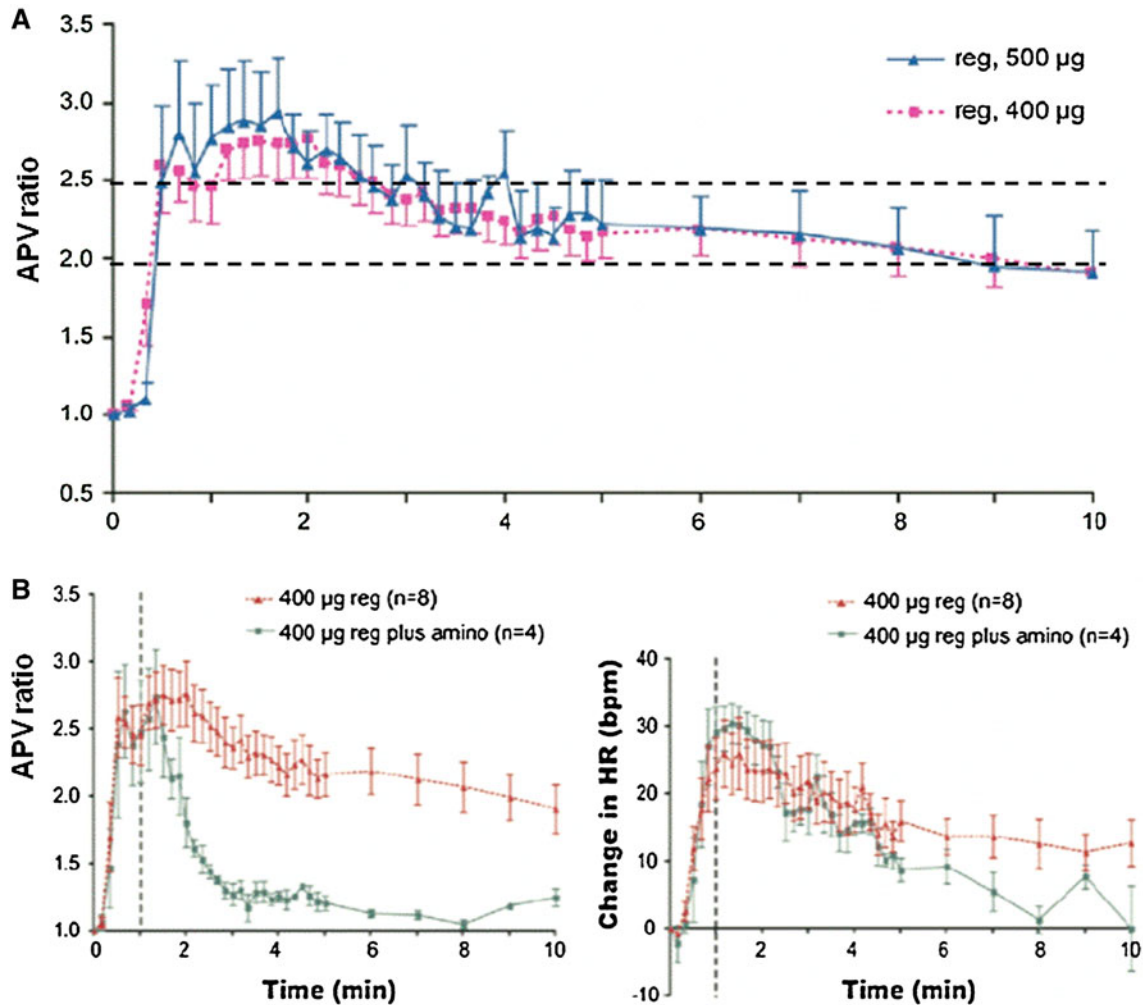


Figure 10. A Time dependence of 400 and 500 µg of regadenoson on average peak coronary flow velocity. B Effects of 400 µg of regadenoson on peak coronary flow velocity and heart rate before and after administration of 100 mg of IV aminophylline (modified from Lieu et al¹¹).

drop in BP. The 400 µg regadenoson dose increased the HR by 21 ± 21 beats/minute, decreased the systolic BP by 24 ± 15 mm and the diastolic BP by 12 ± 10 mm Hg.¹¹ The maximal BP changes occurred within 5 minutes of regadenoson administration and returned to near baseline within 15 minutes.¹¹ In the phase II and III trials, IV regadenoson boluses (400 and 500 µg) decreased the systolic and diastolic BP and increased the HR (Figure 13).^{27,28} In the larger phase III trial, regadenoson caused a greater increase in peak HR compared to adenosine though the BP nadir was similar.²⁸ The peak HR was reached within 2 minutes and returned to near-baseline within 30-40 minutes of regadenoson administration.²⁸ In the 400 µg regadenoson group from the phase II trial, 5% of subjects had > 25 mm Hg decrease in SBP and none had a drop in systolic BP to < 90 mm Hg.²⁷ The nadir systolic BP occurred at 3 minutes after regadenoson

administration.²⁷ In one study, patients with DM, particularly those on insulin therapy, had blunting of the adenosine- and regadenoson-mediated increases in HR.²⁹ A blunting in the HR response to adenosine and regadenoson was also seen in patients with the metabolic syndrome.³⁰ An increase in the number of features of the metabolic syndrome was associated with a stepwise decrease in the HR response (-0.92% per metabolic syndrome criterion, $P < .05$), irrespective of the presence of DM. Increasing blood sugar levels caused blunting of the HR response even after controlling for DM and the metabolic syndrome ($0.60\% \pm 0.08\%$ per 10 mg/dL, $P < .001$). The metabolic syndrome was independently related to the HR response on top of DM, renal function, left ventricular function, gender, age, baseline HR, BP, and beta-blocker use.³⁰ In summary, regadenoson causes a faster and greater increase in HR and a comparable

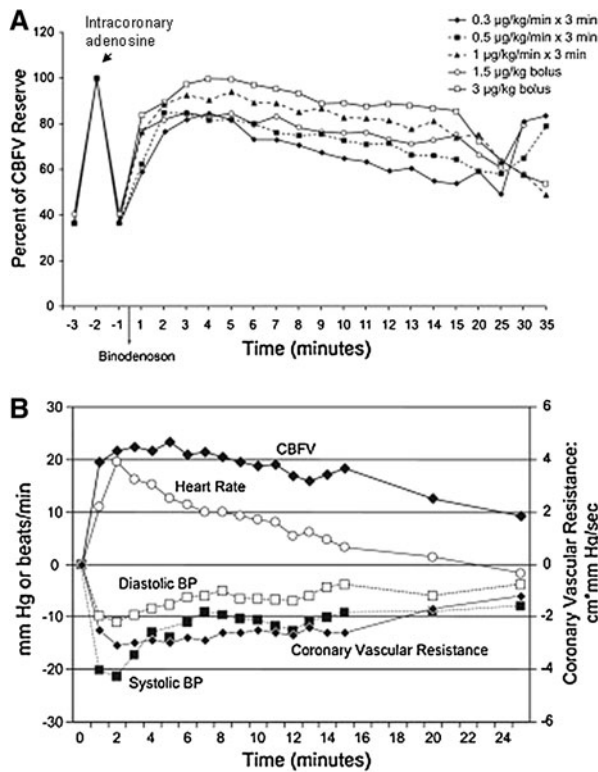


Figure 11. A Mean CBF velocity (CBFV) responses as % of adenosine CBFV for 5 binodenoson doses compared to intracoronary adenosine. B The time course effects of binodenoson 1.5 µg/kg IV bolus on CBF velocity, BP and coronary vascular resistance (modified from Glover et al²¹).

decrease in BP compared to adenosine.²⁸ The recovery of HR and BP was slower with regadenoson compared to adenosine.²⁸

Binodenoson caused dose-dependent changes in BP and HR.²⁵ The 1.5 µg/kg dose caused an increase in HR from 75 ± 14 to 97 ± 15 bpm, and a decrease in SBP and DBP from 133 ± 23 to 103 ± 20 mm Hg and 72 ± 8 to 55 ± 10 mm Hg, respectively.²⁵ The 3.0 µg/kg dose caused an increase in HR from 75 ± 15 to 108 ± 11 bpm, and a decrease in SBP and DBP from 126 ± 21 to 103 ± 17 mm Hg and 74 ± 11 to 59 ± 10 mm Hg, respectively.²⁵ The BP and HR returned to baseline levels within 15 minutes.²⁵ In the initial multicenter trial of binodenoson vs adenosine, there were no significant differences between the 1.5 µg/kg binodenoson dose and adenosine in SBP and DBP drops compared to adenosine (Table 4).³¹ However, the 1.5 µg/kg binodenoson dose caused a higher increase in HR compared to adenosine.³¹

Apadenoson caused a dose-dependent decrease in BP and increase in HR. The respective SBP and HR changed by -8.6% ± 11.6% and 21.9% ± 15.5% with the 1.0 µg/kg dose and by -14 ± 10.6% and 29.9 ± 18.5% with the 2.0 µg/kg dose.²⁶

EFFECT OF OTHER DRUGS

Administration of 100 mg of IV aminophylline 1 minute after the 400 µg regadenoson bolus reduced the duration of >2-fold increase in peak flow velocity from 6.9 to 0.6 minutes with no effect on the HR increase (Figure 10B).¹¹ In a double-blind, randomized, placebo controlled crossover study, 20 subjects received caffeine/placebo and 21 subjects received placebo/caffeine (200 mg capsules) during ¹⁵O H₂O positron emission tomography (PET).³² MBF was measured 2 hours after receiving caffeine or placebo capsules at

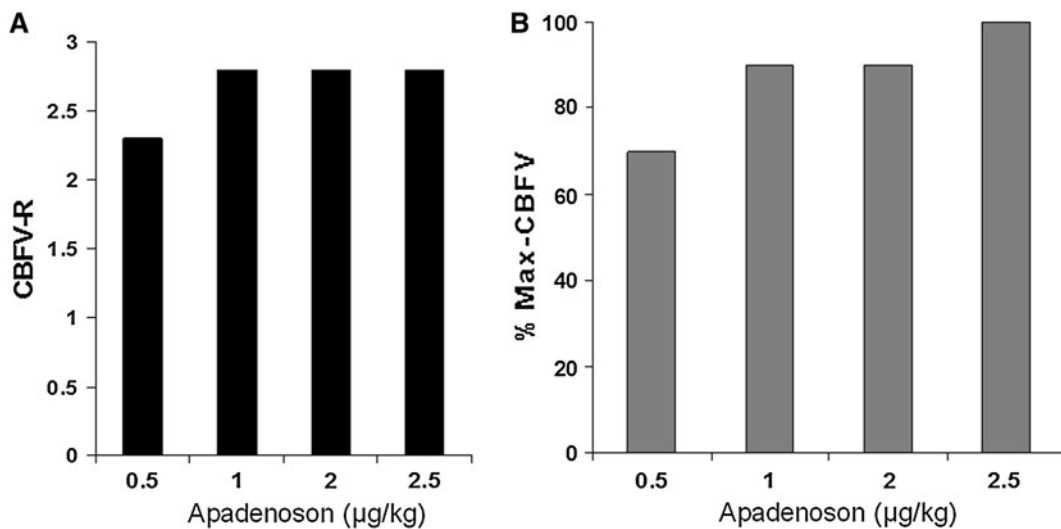


Figure 12. A CBF velocity reserve of various apadenoson doses in human subjects studied by a flow wire. B Percentage of CBF velocity reserve of various apadenoson doses to adenosine (from Kern et al²⁶).

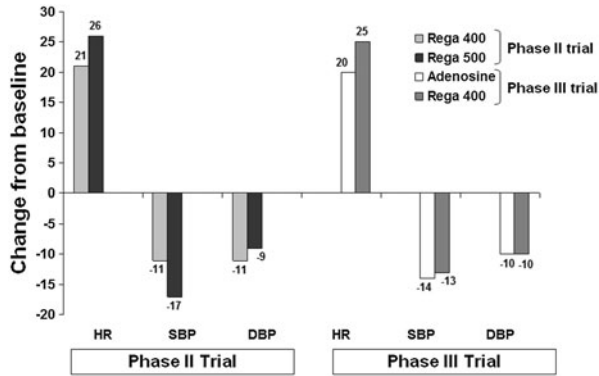


Figure 13. The effects of 400 and 500 μg regadenoson and adenosine on heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) in the phase II and III regadenoson trials^{27,28}.

rest and after administration of a 400 μg IV bolus of regadenoson.³² The regadenoson-mediated CFR was not significantly different after caffeine (2.75 ± 0.16) or placebo (2.97 ± 0.16) although caffeine blunted the regadenoson-mediated HR increase and did not have an effect on the BP.³²

STRESS MPI

In the phase II multicenter trial, 36 patients with ischemia on adenosine (140 $\mu\text{g}/\text{kg}/\text{minute}$ infusion over 6 minutes) 99m-Tc sestamibi SPECT had regadenoson (400 or 500 μg IV bolus) 99m-Tc sestamibi SPECT within 2-46 days from the adenosine study.²⁷ The agreement rates of the 400 and 500 μg regadenoson doses for the visual presence of ischemia were 89% and 76%, respectively, compared with adenosine SPECT.²⁷ The agreement rates between adenosine and regadenoson were 57% for the visual analysis and 69% for the quantitative analysis.²⁷ The 400 μg regadenoson dose was subsequently adopted as the dose used in the phase III trial.

The phase III (ADVANCE MPI 2 Trial), multicenter, international, double-blinded trial studied 784 patients who underwent an initial qualifying adenosine SPECT study followed by a 2:1 randomization to regadenoson (400 μg rapid IV bolus) or adenosine (140 $\mu\text{g}/\text{kg}/\text{minute}$ infusion over 6 minutes) SPECT.²⁸ The average agreement rate was 0.64 ± 0.04 for the adenosine-adenosine SPECT images and 0.63 ± 0.03 for the regadenoson-adenosine SPECT images which were above the pre-specified non-inferiority margin.²⁸ The agreement rates for adenosine-regadenoson and adenosine-adenosine groups were $>90\%$ by quantitative analysis.²⁸ The image quality was good or excellent in 88% of regadenoson studies and in 90% of adenosine

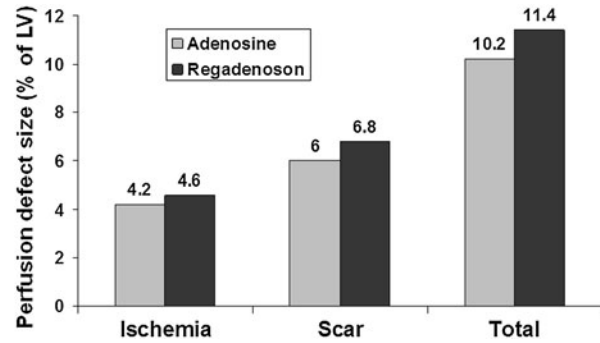


Figure 14. Quantitative evaluation of perfusion defect size (% of left ventricle) for adenosine and regadenoson in the ADVANCE MPI 2 Trial³³.

studies.²⁸ Quantitative analysis from the ADVANCE MPI 2 Trial showed no differences between total and ischemic perfusion defect extent and severity between regadenoson and adenosine SPECT images (Figure 14).³³ Linear regression analysis showed excellent correlation between adenosine and regadenoson for ischemic ($r = 0.95$, $P < .001$) and total ($r = 0.97$, $P < .001$) perfusion SPECT defects.³³ The agreement rates of adenosine and regadenoson images were similar within age, gender, BMI, and DM subgroups.³⁴ The image quality was similar within the subgroups for adenosine and regadenoson except for men who had a better image quality compared to women.³⁴

In a multicenter, randomized, single-blind, 2-arm crossover trial, 240 patients underwent 2 SPECT studies in random order, one after stress with adenosine and one with binodenoson, using IV boluses of 0.5, 1, or 1.5 $\mu\text{g}/\text{kg}$ over 30 seconds or a 0.5 $\mu\text{g}/\text{kg}/\text{minute}$ infusion over 3 minutes.³¹ Exact categorical agreement in the severity and extent of ischemic defects between the different binodenoson doses and adenosine ranged from 79% to 87% with kappa values from 0.69 to 0.85.³¹ All doses showed good general correlation though the 1.5 $\mu\text{g}/\text{kg}$ dose showed the closest correlation.³¹ The results of the phase III VISION 302 trial of Binodenoson have been published in abstract form. The study involved 2 double-blind, double-dummy MPI procedures in random order within 7 days. One was with a 1.5 $\mu\text{g}/\text{kg}$ binodenoson bolus along with a 6-minute placebo infusion and one with a placebo bolus along with 140 $\mu\text{g}/\text{kg}/\text{minute}$ of adenosine infused over 6 minutes. The study included 402 patients in the binodenoson arm and 404 patients in the adenosine arm. The mean paired summed difference scores (SDS) of binodenoson vs adenosine images was -0.09 (CI -0.44 to 0.27) was well within the pre-specified 1.5 SDS units for noninferiority. The concordance between the 2 stressors was 61% and complete discordance was 3%.

Table 4. Side effects of binodenoson (1.5 µg/kg) and adenosine³¹

	Adenosine N = 226 (%)	Binodenoson N = 55 (%)	P value
Side effects			
Chest pain	138 (61)	24 (45)	
Flushing	128 (57)	18 (34)	
Dyspnea	130 (58)	22 (42)	
Any subjective side effect	207 (92)	38 (72)	<.021
Intensity of side effect	8.8	5.0	<.01
AV block	7 (3)	0 (0)	
Bronchospasm	0	0	
Hypotension	0	0	
HR > 125 bpm	1 (0.4)	2 (4)	
Any objective side effect	8 (4)	2 (4)	
SBP change	-22.3 ± 15.9	-22.0 ± 17.2	
DBP change	-13.9 ± 9.2	-12.2 ± 7.0	
HR change	23.1 ± 11.8	30.9 ± 13.0	<.05

SAFETY AND ADVERSE EFFECTS

In the phase II trial of regadenoson, 72% of subjects had mild and self-limiting side effects that resolved spontaneously within 10 minutes.²⁷ The 400 µg group had a lower rate of side effects (61% vs 83% in the 500 µg group) and less pronounced hemodynamic changes (Figure 13).²⁷ No subject had bronchospasm, second or third degree AV block, myocardial infarction or death.²⁷ In the phase III trial, regadenoson was better tolerated than adenosine and the summed symptom score (chest pain, flushing and dyspnea) was significantly lower after regadenoson compared to adenosine.²⁸ The various side effects observed in the phase III trial are summarized in Table 5. Abdominal pain with or without nausea or vomiting, diarrhea, fecal incontinence, myalgias, musculoskeletal pain, tremor, and hypersensitivity have been reported in the post-marketing experience. Transient QTc prolongation has also been reported shortly after Lexiscan administration though without any clinical significance.

The frequency of side effects was lower with binodenoson compared to adenosine in the initial multicenter trial (Table 4).³¹ The severity of the symptoms as assessed by visual analog scores for the intensity of subjective adverse events was less with binodenoson.³¹ There were no AV blocks or hypotension with binodenoson. There were no significant differences in systolic and diastolic BP drops between the different binodenoson doses and adenosine.³¹ In the phase III trial, the incidence of second or third degree AV block was 0% for binodenoson and 3% for adenosine ($P = .004$). Compared to adenosine, binodenoson had lower frequencies of flushing (50% vs 32%; $P < .05$), chest pain

(61% vs 38%; $P < .05$), and dyspnea (51% vs 42%; $P < .05$). Patient-rated intensities of these events were significantly lower during binodenoson than adenosine and more patients preferred binodenoson over adenosine. Changes in BP were comparable between the two stressors though maximal changes in HR were higher with binodenoson compared to adenosine (25.3 vs 22.5 bpm, $P < .001$).

Despite the selectivity for the A2A receptor, side effects still occurred albeit they were briefer and less severe though the more serious side effects such as significant hypotension, AV blocks, and bronchospasm were not observed. The reason for the persistence of side effects could be that the doses of regadenoson used in clinical studies might be causing regadenoson to be less selective for the A2A receptor.⁴ The Integrated ADVANCE MPI Trial assessed the effects of age, gender, obesity, and DM on the safety of regadenoson and adenosine MPI.³⁴ Regadenoson was associated with a lower incidence of chest pain, flushing, and throat, neck, or jaw pain, a higher incidence of headache and gastrointestinal discomfort and a lower combined symptom score in nearly all subgroups.³⁴ Women felt less comfortable than men with both stress agents.³⁴

STRESS MPI IN SPECIAL PATIENT POPULATIONS

Patients with Lung Disorders

Patients with asthma or chronic obstructive pulmonary disease (COPD) are at an increased risk of adenosine-induced bronchospasm via activation of the

Table 5. Side effects of adenosine and regadenoson in the phase III trial²⁸

	Adenosine N = 267 (%)	Regadenoson N = 517 (%)	P value
Side effects			
Chest pain	34 (13)	41 (8)	.04
Chest discomfort	42 (16)	57 (11)	.07
Angina pectoris	22 (8)	40 (8)	.78
Flushing	63 (24)	86 (17)	.02
Dyspnea	49 (18)	128 (25)	.05
Nausea	12 (4)	29 (6)	.61
Abdominal discomfort	5 (2)	32 (6)	<.01
Headache	42 (16)	148 (29)	<.001
Dizziness	9 (3)	35 (7)	.05
Feeling hot	17 (6)	19 (4)	.1
Any severe side effect	18 (7)	25 (5)	.32
Any side effect	210 (79)	409 (79)	.93
Objective scores			
Summed symptom score	1.1 ± 0.08	0.9 ± 0.05	.013
Tolerability score	2.6 ± 0.06	2.3 ± 0.05	<.001
Other side effects			
Second degree AV block	3 (1.1)	0 (0)	.043
ST-T changes	42 (17)	80 (17)	NS
Major events			
Death	0 (0)	0 (0)	NS
MI	0 (0)	0 (0)	NS
Bronchospasm	0 (0)	0 (0)	NS

A2B and A3 adenosine receptors.³⁵ The safety of regadenoson was studied in a randomized, double-blind, placebo-controlled crossover trial that enrolled 48 patients with mild to moderate asthma and a positive adenosine monophosphate challenge test.³⁵ Patients were randomized to regadenoson/placebo or placebo/regadenoson in a 1:1 ratio where each patient received 400 µg of regadenoson and a matching placebo on 2 separate treatment days separated by a 1 to 14 days washout period.³⁵ All patients abstained from the use of bronchodilators for at least 6 hours prior to the study. There was no significant difference in the mean forced expiratory volume in 1 second (FEV1) at any time point between regadenoson and placebo (Figure 15A).³⁵ The mean ratio of the (FEV1) at each tested time point relative to the baseline FEV1 was significantly higher after treatment with regadenoson compared with placebo from 10 to 60 minutes after treatment (Figure 15B).³⁵ Bronchoconstrictive reactions (>15% reduction of FEV1 within 2 hours compared to baseline) occurred in the moderate asthma group and were similar in the regadenoson and placebo groups (4.3% vs 4.2%, *P* = NS), were clinically silent and did not require any therapy.³⁵ Dyspnea occurred in 34% of patients after

regadenoson and in none of the patients after placebo. The occurrence of dyspnea was not associated with a decrease in FEV1 (Figure 15C) and none of the patients in either groups had <92% oxygen desaturation.³⁵

In another randomized, double-blind, placebo-controlled crossover trial, the safety of regadenoson was evaluated in 49 patients with moderate to severe chronic obstructive pulmonary disease (COPD).³⁶ Short-acting bronchodilators were withheld for at least 8 hours before treatment. There were no differences between regadenoson and placebo on repeated (measured at pre-specified time intervals up to 2 hours post-regadenoson or placebo administration) follow up FEV1, forced vital capacity, respiratory rate, pulmonary examinations, and oxygen saturation (Figure 15D, E).³⁶ The mean maximum decline in FEV1 was 0.11 ± 0.02 L and 0.12 ± 0.02 L (*P* = .55) in the regadenoson and placebo groups, respectively.³⁶ New-onset wheezing was noted in 6% and 12% of the regadenoson and placebo groups, respectively (*P* = .33).³⁶ Bronchoconstrictive reactions were clinically silent and occurred in 12.2% and 6.1% of the regadenoson and placebo groups, respectively (*P* = .31). Dyspnea was reported in 61% of patients in the regadenoson group and in 0% of patients in the

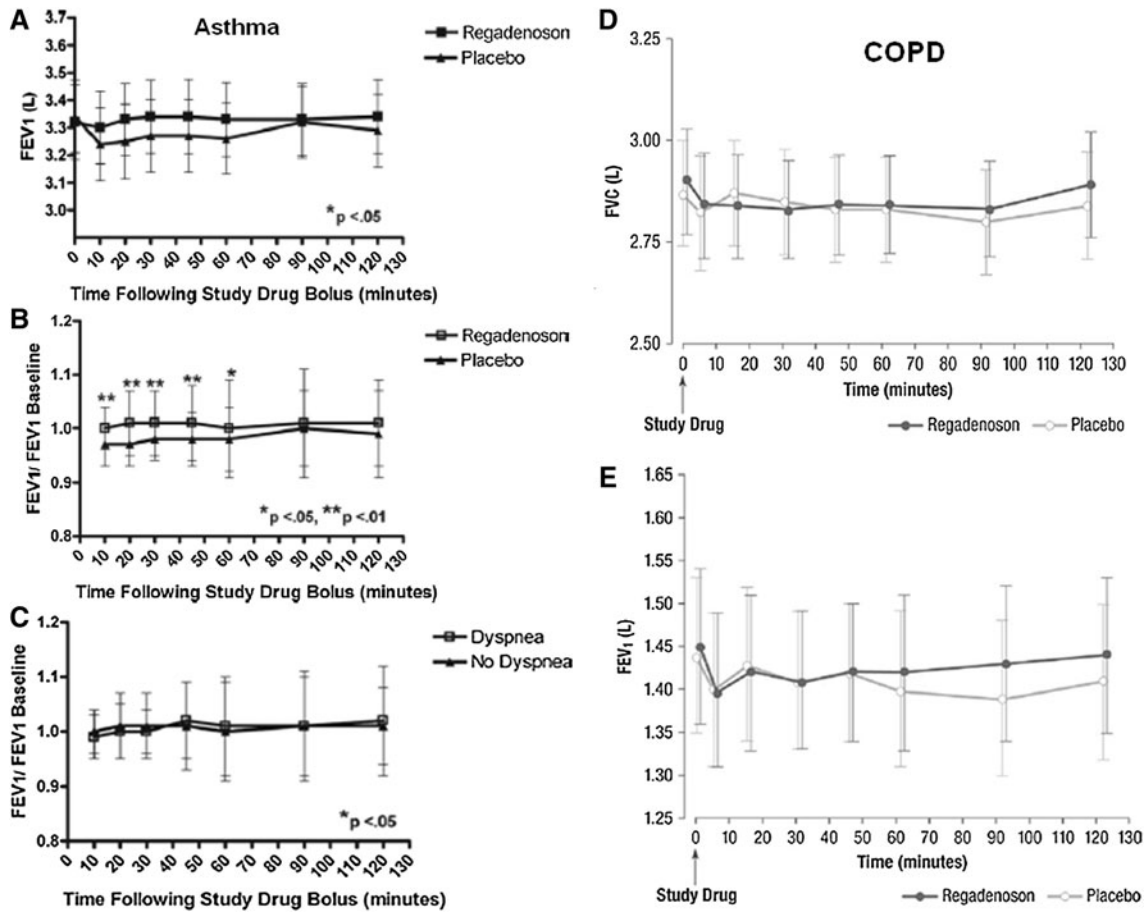


Figure 15. Time points for the effects of placebo and regadenoson on FEV1 (A), FEV1/FEV1 baseline (B) and the effect of dyspnea on FEV1 (C) in patients with asthma. Time effects for effects of placebo and regadenoson on FVC (D) and FEV1 (E) in patients with COPD^{35,36}.

placebo group and was not related to decline in FEV1 or other objective findings. No patient required treatment with bronchodilators or oxygen.³⁶

In a dose-escalating, single-blinded phase and a placebo-controlled, double-blinded phase study, binodenoson was administered to 87 adults with documented mild, intermittent, asthma.³⁷ In the single-blinded phase, 3 sequential cohorts of 8 subjects received intravenous binodenoson (0.5, 1.0, and 1.5 µg/kg). In the double-blinded phase, the subjects were randomly assigned to either binodenoson 1.5 µg/kg (n = 41) or placebo (n = 22).³⁷ The most common adverse events were tachycardia, dizziness, and flushing. Binodenoson was well tolerated and caused no clinically significant bronchoconstriction defined as decrease in FEV1 of ≥20% from baseline or significant changes in the pulmonary function parameters (FEV1, forced vital capacity, pulse oximetry, and forced expiratory flow during the middle 50% of the forced vital capacity).³⁷

Patients with Renal Disease

The safety of regadenoson that is renally excreted was studied in 277 consecutive patients with end stage renal disease (ESRD) who underwent regadenoson SPECT for clinical indications and were compared to a cohort of 134 patients with normal renal function.³⁸ The patients with ESRD were younger than the controls. The ESRD patients had similar rates of abnormal myocardial perfusion imaging (19% vs 18% compared to controls, *P* = NS) and lower left ventricular ejection fractions (57% ± 12% vs 64% ± 12% compared to controls, *P* < .001). The changes in HR and systolic BP from peak stress to baseline were 20 ± 12 beats/minute vs 22 ± 13 beats/minute and -11 ± 24 mm Hg vs -12 ± 23 mm Hg in the ESRD and control groups, respectively (*P* = NS for both). Side effects were reported in very few patients in either group during the stress test and no patient had serious adverse events in either group.³⁸ Thus, regadenoson was well tolerated in patients with ESRD.

Patients with Liver Disease

In one study, 168 consecutive patients with end stage liver disease (ESLD) who underwent regadenoson MPI were compared to a control group of 168 patients from the same time period with no liver disease and with comparable MPI results.³⁹ Patients with ESLD were younger (58 ± 7 vs 62 ± 12 years, $P = .0002$).³⁹ The MPI images were normal in 96% of patients in each group.³⁹ The LVEF was higher in the ESLD group compared to the control group ($72\% \pm 10\%$ vs $66\% \pm 11\%$, $P = .0001$). Compared to the control group, the ESLD group had a lower increase in the HR in response to regadenoson (16 ± 11 vs 23 ± 16 bpm, $P = .0001$), but similar changes in SBP (-9 ± 12 vs -11 ± 14 mm Hg) and DBP (-6 ± 8 vs -7 ± 10 mm Hg) and similar incidence of regadenoson side effects.³⁹ There were no deaths or medication-related adverse events that required hospitalization in either group within 30 days index study.³⁹

Regadenoson in Combination with Exercise MPI

Regadenoson with low level exercise in patients undergoing MPI was evaluated in a randomized, double-blind, placebo, and active controlled study.⁴⁰ Patients who underwent standard adenosine MPI for clinical indications were randomized in a 2:1 manner to low-level exercise with bolus intravenous injection of regadenoson ($n = 39$) or placebo ($n = 21$).⁴⁰ Adverse events occurred in 95%, 77%, and 33% of patients receiving adenosine alone, regadenoson with exercise, and placebo with exercise, respectively. Peak HR was 13 bpm greater following regadenoson with exercise compared to placebo exercise ($P = .006$).⁴⁰ Change in mean SBP from baseline, change from baseline to nadir SBP, and percentage of patients with a decline in SBP by ≥ 20 mm Hg were not significantly different between regadenoson with exercise and placebo with exercise.⁴⁰ The mean heart-to-liver and heart-to-gut ratios were improved with regadenoson with exercise compared to adenosine alone.⁴⁰ Compared to adenosine, 70% of patients felt that regadenoson with exercise was better based on a tolerability questionnaire.⁴⁰ One drawback of this study is that there was no regadenoson only arm for comparison.

In another study, 1,263 patients underwent regadenoson stress MPI (596 with low-level exercise).⁴¹ Regadenoson with exercise compared to regadenoson alone was associated with significantly lower rates of shortness of breath (23% vs 32%), dizziness (12% vs 19%), palpitations (6.7% vs 37%), and nausea (1.2% vs 3.3%).⁴¹ Chest pain (33% vs 37%), headache (0.7% vs 2.1%), and transient AV blocks (0.34% vs 0.15%) were

not significantly different between the regadenoson with exercise and the regadenoson alone groups, respectively.⁴¹ The regadenoson with exercise group compared to the regadenoson alone group had significantly more frequent drop in SBP by >10 mm Hg (56% vs 47%) and >30 mm Hg (12% vs 7%) and a higher peak HR (104 ± 19 vs 91 ± 17 bpm).⁴¹ One drawback of the study is that the same patients were not compared with and without exercise.

SUMMARY

Regadenoson was FDA approved in April 2008. Its use as a stressor is gaining more acceptance and adoption instead of adenosine or dipyridamole given its ease of administration and better tolerability. The other A2A receptor agonists are still in various stages of development. Despite their selectivity to the A2A receptor, side effects related to activation of the other adenosine receptors continue to occur albeit at a lower frequency and with less severity and duration compared to the selective adenosine agonists. The search for the ideal selective adenosine agonist is not over yet.

References

1. Orlandi C. Pharmacology of coronary vasodilation: A brief review. *J Nucl Cardiol* 1996;3:S27-30.
2. Kaul S. The role of capillaries in determining coronary blood flow reserve: Implications for stress-induced reversible perfusion defects. *J Nucl Cardiol* 2001;8:694-700.
3. Wacker CM, Bauer WR. Myocardial microcirculation in humans—new approaches using MRI. *Herz* 2003;28:74-81.
4. Zoghbi GJ, Iskandrian AE. Pharmacological stress testing. In: Garcia EV, Iskandrian AE, editors. *Nuclear cardiac imaging: Principles and applications*. New York: Oxford University Press; 2008. p. 293-315.
5. Gemignani AS, Abbott BG. The emerging role of the selective A2A agonist in pharmacologic stress testing. *J Nucl Cardiol* 2010;17:494-7.
6. Olah ME, Stiles GL. Adenosine receptor subtypes: Characterization and therapeutic regulation. *Annu Rev Pharmacol Toxicol* 1995;35:581-606.
7. Hendel RC, Jamil T, Glover DK. Pharmacologic stress testing: New methods and new agents. *J Nucl Cardiol* 2003;10:197-204.
8. Sato A, Terata K, Miura H, Toyama K, Loberiza FR Jr, Hatoum OA, et al. Mechanism of vasodilation to adenosine in coronary arterioles from patients with heart disease. *Am J Physiol Heart Circ Physiol* 2005;288:H1633-40.
9. Muller CE, Jacobson KA. Recent developments in adenosine receptor ligands and their potential as novel drugs. *Biochim Biophys Acta* 2010;1808:1290-308.
10. Al Jaroudi W, Iskandrian AE. Regadenoson: A new myocardial stress agent. *J Am Coll Cardiol* 2009;54:1123-30.
11. Lieu HD, Shryock JC, von Mering GO, Gordi T, Blackburn B, Olmsted AW, 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.

12. Gordi T, Frohna P, Sun HL, Wolff A, Belardinelli L, Lieu H. A population pharmacokinetic/pharmacodynamic analysis of regadenoson, an adenosine A_{2A}-receptor agonist, in healthy male volunteers. *Clin Pharmacokinet* 2006;45:1201-12.
13. Gordi T, Blackburn B, Lieu H. Regadenoson pharmacokinetics and tolerability in subjects with impaired renal function. *J Clin Pharmacol* 2007;47:825-33.
14. Barrett RJ, Lamson MJ, Johnson J, Smith WB. Pharmacokinetics and safety of binodenoson after intravenous dose escalation in healthy volunteers. *J Nucl Cardiol* 2005;12:166-71.
15. Glover DK, Ruiz M, Takehana K, Petruzella FD, Riou LM, Rieger JM, et al. Pharmacological stress myocardial perfusion imaging with the potent and selective A(2A) adenosine receptor agonists ATL193 and ATL146e administered by either intravenous infusion or bolus injection. *Circulation* 2001;104:1181-7.
16. Gao Z, Li Z, Baker SP, Lasley RD, Meyer S, Elzein E, et al. Novel short-acting A_{2A} adenosine receptor agonists for coronary vasodilation: Inverse relationship between affinity and duration of action of A_{2A} agonists. *J Pharmacol Exp Ther* 2001;298:209-18.
17. Cerqueira MD. The future of pharmacologic stress: Selective A_{2A} adenosine receptor agonists. *Am J Cardiol* 2004;94:33D-40D. discussion 40D-42D.
18. Trochu JN, Zhao G, Post H, Xu X, Belardinelli L, Belloni FL, et al. Selective A_{2A} adenosine receptor agonist as a coronary vasodilator in conscious dogs: Potential for use in myocardial perfusion imaging. *J Cardiovasc Pharmacol* 2003;41:132-9.
19. Zhao G, Linke A, Xu X, Ochoa M, Belloni F, Belardinelli L, et al. Comparative profile of vasodilation by CVT-3146, a novel A_{2A} receptor agonist, and adenosine in conscious dogs. *J Pharmacol Exp Ther* 2003;307:182-9.
20. Mekkaoui C, Jadbabaie F, Dione DP, Meoli DF, Purushothaman K, Belardinelli L, et al. Effects of adenosine and a selective A_{2A} adenosine receptor agonist on hemodynamic and thallium-201 and technetium-99m-sestaMIBI biodistribution and kinetics. *JACC Cardiovasc Imaging* 2009;2:1198-208.
21. Glover DK, Ruiz M, Yang JY, Koplán BA, Allen TR, Smith WH, et al. Pharmacological stress thallium scintigraphy with 2-cyclohexylmethylidenehydrazinoadenosine (WRC-0470). A novel, short-acting adenosine A_{2A} receptor agonist. *Circulation* 1996;94:1726-32.
22. Dhalla AK, Wong MY, Wang WQ, Biaggioni I, Belardinelli L. Tachycardia caused by A_{2A} adenosine receptor agonists is mediated by direct sympathoexcitation in awake rats. *J Pharmacol Exp Ther* 2006;316:695-702.
23. Zhao G, Serpillon S, Shryock J, Messina E, Xu X, Ochoa M, et al. Regadenoson, a novel pharmacologic stress agent for use in myocardial perfusion imaging, does not have a direct effect on the QT interval in conscious dogs. *J Cardiovasc Pharmacol* 2008;52:467-73.
24. Zhao G, Messina E, Xu X, Ochoa M, Sun HL, Leung K, et al. Caffeine attenuates the duration of coronary vasodilation and changes in hemodynamics induced by regadenoson (CVT-3146), a novel adenosine A_{2A} receptor agonist. *J Cardiovasc Pharmacol* 2007;49:369-75.
25. Hodgson JM, Dib N, Kern MJ, Bach RG, Barrett RJ. Coronary circulation responses to binodenoson, a selective adenosine A_{2A} receptor agonist. *Am J Cardiol* 2007;99:1507-12.
26. Kern MJ, Hodgson JM, Dib N, Mittleman RS, Crane PD. Effects of apadenoson, a selective adenosine A_{2A} receptor agonist for myocardial perfusion imaging, on coronary blood flow velocity in conscious patients. *Circulation* 2006;114:582. (Abstract).
27. Hendel RC, Bateman TM, Cerqueira MD, Iskandrian AE, Leppo JA, Blackburn B, et al. Initial clinical experience with regadenoson, a novel selective A_{2A} agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. *J Am Coll Cardiol* 2005;46:2069-75.
28. Iskandrian AE, Bateman TM, Belardinelli L, Blackburn B, Cerqueira MD, Hendel RC, 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.
29. Hage FG, Heo J, Franks B, Belardinelli L, Blackburn B, Wang W, et al. Differences in heart rate response to adenosine and regadenoson in patients with and without diabetes mellitus. *Am Heart J* 2009;157:771-6.
30. Hage FG, Perry G, Heo J, Iskandrian AE. Blunting of the heart rate response to adenosine and regadenoson in relation to hyperglycemia and the metabolic syndrome. *Am J Cardiol* 2010;105:839-43.
31. Udelson JE, Heller GV, Wackers FJ, Chai A, Hinchman D, Coleman PS, et al. Randomized, controlled dose-ranging study of the selective adenosine A_{2A} receptor agonist binodenoson for pharmacological stress as an adjunct to myocardial perfusion imaging. *Circulation* 2004;109:457-64.
32. Gaemperli O, Schepis T, Koepfli P, Siegrist PT, Fleischman S, Nguyen P, et al. Interaction of caffeine with regadenoson-induced hyperemic myocardial blood flow as measured by positron emission tomography: A randomized, double-blind, placebo-controlled crossover trial. *J Am Coll Cardiol* 2008;51:328-9.
33. Mahmarian JJ, Cerqueira MD, Iskandrian AE, Bateman TM, Thomas GS, Hendel RC, et al. Regadenoson induces comparable left ventricular perfusion defects as adenosine: A quantitative analysis from the ADVANCE MPI 2 trial. *JACC Cardiovasc Imaging* 2009;2:959-68.
34. Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE. 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. *JACC Cardiovasc Imaging* 2008;1:307-16.
35. Leaker BR, O'Connor B, Hansel TT, Barnes PJ, Meng L, Mathur VS, et al. Safety of regadenoson, an adenosine A_{2A} receptor agonist for myocardial perfusion imaging, in mild asthma and moderate asthma patients: A randomized, double-blind, placebo-controlled trial. *J Nucl Cardiol* 2008;15:329-36.
36. Thomas GS, Tammelin BR, Schiffman GL, Marquez R, Rice DL, Milikien D, et al. Safety of regadenoson, a selective adenosine A_{2A} agonist, in patients with chronic obstructive pulmonary disease: A randomized, double-blind, placebo-controlled trial (RegCOPD trial). *J Nucl Cardiol* 2008;15:319-28.
37. Murray JJ, Weiler JM, Schwartz LB, Busse WW, Katial RK, Lockey RF, et al. Safety of binodenoson, a selective adenosine A_{2A} receptor agonist vasodilator pharmacological stress agent, in healthy subjects with mild intermittent asthma. *Circ Cardiovasc Imaging* 2009;2:492-8.
38. Aljaroudi W, Hermann D, Hage F, Heo J, Iskandrian AE. Safety of regadenoson in patients with end-stage renal disease. *Am J Cardiol* 2009;105:133-5.
39. Aljaroudi W, Iqbal F, Koneru J, Bhambhani P, Heo J, Iskandrian AE. Safety of regadenoson in patients with end-stage liver disease. *J Nucl Cardiol* 2011;18:90-5.
40. Thomas GS, Thompson RC, Miyamoto MI, Ip TK, Rice DL, Milikien D, et al. The RegEx trial: A randomized, double-blind, placebo- and active-controlled pilot study combining regadenoson, a selective A(2A) adenosine agonist, with low-level exercise, in patients undergoing myocardial perfusion imaging. *J Nucl Cardiol* 2009;16:63-72.
41. Kwon DH, Cerqueira MD, Young R, Houghtaling P, Lieber E, Menon V, et al. Lessons from regadenoson and low-level treadmill/regadenoson myocardial perfusion imaging: Initial clinical experience in 1263 patients. *J Nucl Cardiol* 2010;17:853-7.