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Regadenoson

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ABSTRACT

Single-photon emission computerized tomography for myocardial perfusion imaging (MPI) is a non-invasive technique. MPI is performed by subjecting the patient to exercise or by using a pharmacological stress agent. Regadenoson is a selective A_{2A} adenosine receptor agonist used when MPI with exercise is contraindicated. It binds to the A_{2A} receptor and stimulates adenylate cyclase, resulting in increased cAMP, which phosphorylates protein kinase A thereby opening the ATP-dependant potassium channels leading to hyperpolarization in the coronary vascular smooth muscle. After a single bolus dose of regadenoson 400 µg, a peak plasma concentration (C_{max}) of 13.6 ng/mL is attained in 1–4 min, with a terminal half-life of 2 h. It has a quick onset, short duration sufficient enough for hyperemic response, with comparable efficacy to adenosine, but with fewer side-effects. The adverse effects of this drug are dyspnea, headache, flushing, chest pain and atrioventricular block. Regadenoson is used for MPI in patients with co-morbid conditions like mild-to-moderate reactive airway disease, obstructive lung disease and renal impairment.

KEY WORDS: Regadenoson, A_{2A} adenosine receptor agonist, myocardial perfusion imaging

Introduction

Coronary artery disease (CAD) is the most common form of heart disease diagnosed by invasive and non-invasive techniques. One of the non-invasive techniques is myocardial perfusion imaging (MPI), using single-photon emission computerized tomography (SPECT), magnetic resonance imaging (MRI) and positron emission tomography (PET).[1,2] MPI evaluates coronary perfusion at rest and during stress using radionuclide agents or perfusion tracers such as technetium-99m (Tc-99m) and, thus, identifies areas of reduced perfusion and restriction in coronary blood flow (CBF), which helps in diagnosis and prognosis.[3] Serial MPIs can monitor disease progression, detect post-revascularization restenosis and efficacy of therapy.[3] In CAD, the CBF is reduced to the regions of the myocardium supplied by diseased arteries, and hence MPI studies use either physical exercise or pharmacological stress agents (PSA) to induce maximum myocardial hyperemia.[4] Exercise MPI is contraindicated in patients with large abdominal aortic aneurysm, left bundle branch block, peripheral vascular disease and neurological and orthopedic problems. In such instances, stress MPI is done using PSAs like adenosine, dipyridamole and dobutamine.[3,5]

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Adenosine and dipyridamole are non-selective activators of adenosine A_1, A_{2A}, A_{2B} and A_3 receptors that result in undesirable side-effects such as chest pain, flushing, dyspnea, bronchospasm, atrioventricular (AV) block and hypotension.[2,3] Dobutamine produces chest pain and arrhythmias. The above drugs are to be administered by special infusion devices continuously based on body weight.[3] To overcome these adverse effects and practical problems, a new adenosine analog, regadenoson, a selective A_{2A} adenosine receptor agonist, has been approved by the FDA in April 2008 for use in MPI studies.[6] This article reviews the clinical pharmacology, therapeutic indications, adverse effects and clinical efficacy of regadenoson.

Chemistry

The structural modification of adenosine has yielded several new molecules that are more stable in plasma, are lipophilic and have selective A_{2A} agonistic activity.[4] The chemical nature of regadenoson is adenosine, 2-[4-(methylamino) carbonyl]-1*H*-pyrazol-1-yl]-monohydrate. The 4-substituted pyrazole (regadenoson) confers high selectivity to the A_{2A} receptor. N-pyrazole class provides more affinity for the A_{2A} receptor than the C-pyrazole class.[7] Its structure is as shown in Figure 1.

Pharmacodynamics

Exercise-induced increase in CBF is dependent

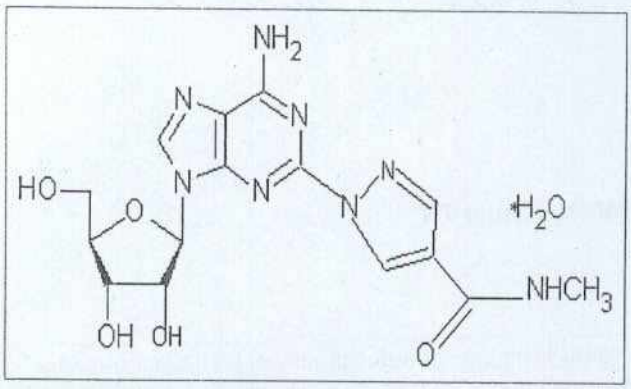

Figure 1: Structure of regadenoson

on endothelium-mediated vasodilatation, whereas the vasodilator stress agents act directly and increase the coronary microcirculation.[8]

Regadenoson has a low affinity for the A_{2A} adenosine receptor, with less than 10-fold lower affinity for the A_1 adenosine receptor and weak affinity for the A_{2B} and A_3 adenosine receptors.[1] A_{2A} receptors are stimulatory G protein (Gs); binding of regadenoson to A_{2A} activates adenyl cyclase thus increasing cyclic adenosine 5′-monophosphate (cAMP) with subsequent phosphorylation of protein kinase A (PKA), which opens K_{ATP} channels (ATP-dependant potassium current) producing membrane hyperpolarization.[9-11]

A_{2A} adenosine receptors are located on the surface of arterial vascular smooth muscle cells, activation of which dilates the coronary vessels resulting in increased CBF.

A maximum of 3.4 fold increase in CBF occurs in a dose-dependant manner due to a large A_{2A} receptor reserve, despite having a lower affinity for the receptor. When only 25% of the A_{2A} receptors are bound by regadenoson, maximal vasodilatation up to 90% is seen.[1,2,12-15] Regadenoson-produced dilatation in the arteries is in the order of coronary >> brain > forelimb > pulmonary artery.[16]

Increase in CBF occurs within 0.5–2.3 min, with a two-fold increase at 8.5 min (range: 0.1–31 min), which is ample time for the administration and distribution of radiopharmaceutical.[1] This increase in blood flow has been observed in normal coronary arteries, with little or no increase in stenotic arteries. Myocardial uptake of the radionuclide agent [Technetium-99m (Tc-99m)] is directly proportional to CBF, and its uptake is lower in myocardial regions supplied by stenotic arteries. But, MPI studies have greater intensity in areas perfused by normal arteries, which helps in identifying the ischemic area.

Regadenoson is feasible with low-level exercise, well tolerated with improved quality of images in MPI. Low-level exercise for 4 min will induce a sympathetic response that can reduce the occurrence of hypotension and enhance the quality of image by greater distribution of blood (radiotracer) to the heart as compared with the gut and liver, thereby alienating the inferior wall of the myocardium from the intestines.[17,18]

Hemodynamic actions

In clinical studies, the majority of patients had an increased heart rate up to 21 beats/min and a decrease in blood pressure of 24 (systolic) and 15 (diastolic) mmHg, respectively, within 45 min of regadenoson administration, but had returned to normal within 150 min.[13,19] Aminophylline blocks adenosine receptors; therefore, 100 mg of the drug attenuated the increase in CBF, but not tachycardia caused by 400 μg of regadenoson.[13] The mechanism of regadenoson-mediated tachycardia was investigated in a rat heart model, wherein pre-treatment with a β-blocker, selective A_{2A} antagonist and ganglion blockers reduced the tachycardia. Further, it was observed that regadenoson caused more than two-fold increase in serum norepinephrine and epinephrine levels. These results suggest that sinus tachycardia is mainly due to the direct sympathetic stimulation rather than being baroreceptor mediated.[20] This increase in heart rate by regadenoson was significantly blunted in diabetic compared with non-diabetic patients, possibly due to sympathetic denervation in diabetic patients, supporting the above sympathoexcitation mechanism.[21]

Pharmacokinetics

Regadenoson is administered as an intravenous bolus dose of 400 μg. The maximum plasma concentration (C_{max}) of 13.6 ng/mL was attained in 1–4 min in the dose range of 0.3–20 μg/kg in healthy subjects; age, gender, clearance, half-life and volume of distribution were independent of the dose given, and hence it was administered as a fixed bolus dose.[1,6,22] The comparison between regadenoson and adenosine is shown in Table 1.

It has been shown to have quick distribution, with a volume of distribution (Vd) of 78.7 L.[1,6] Nearly 20–30% of regadenoson is protein bound.[16] The maximal tolerated dose (MTD) was 20 μg/kg while the C_{max} at this dose ranged from 69 to 134 ng/mL.[16]

Metabolism and Excretion

In vitro studies with human and animal liver microsomes have not detected any metabolites of regadenoson, indicating that the drug was not metabolized in the liver.[1,6,22] It follows triphasic elimination; the initial phase t½ was 2–4 min, which coincided with pharmacodynamic action, followed by an intermediate phase with a mean t½ of 30 min that coincided with the loss of pharmacodynamic effect. The terminal elimination phase (t½) was ≈ 2 hrs.[1,6] Regadenoson is not a substrate for either adenosine deaminase or cell nucleoside transporter; therefore, it is not rapidly metabolized in plasma like adenosine.[13] About 57% (range 19–77%) of the regadenoson is excreted unchanged in the urine, and the remaining in bile.[1,5,16,23,24] The average plasma renal clearance was 450 mL/min, indicating the role of renal tubular secretion in its elimination.[1,23] Clearance increases with body weight.[6]

Table 1: Comparison between regadenoson and adenosine[1,4-6,23,33]

Parameter	Regadenoson	Adenosine
Potency	10-times more potent than adenosine	Less potent
Receptor selectivity	Selective A_{2A} adenosine receptor agonist with low affinity for A_1 and A_{2B} receptors	Non-selective agonist including A_{2A} receptor
Administration	Non-weight based, single-dose, rapid IV bolus that requires no IV admixture or infusion pump or continuous administration	Bolus weight-based 4–6-min IV infusion
Dose	400 μg	140 μg/kg/min
Duration of infusion	10-s bolus	4–6 min
Radiotracer injection	30 s after bolus	Third minute of infusion
Time to peak plasma concentration, T_{max}	33 s	30 s
Metabolism	No hepatic metabolism	Deaminated to inosine by adenosine deaminase
Elimination	57% appears in urine unchanged	Cellular uptake
Half-life	1st phase: 2-4 min 2nd phase: 30 min 3rd phase: 2 h	<10 s
Duration of action	2.3 min#	6 s*
Coronary blood flow	Increased to >2-times baseline in 30 s and decreased to <2-times baseline in 10 min	Maximum response at 2–3 min after infusion onset; return to baseline within 1–2 min following cessation of infusion
Heart rate	Faster and greater peak increase in HR versus adenosine	Less faster and greater peak increase in HR
Heart rate >100 beats per min	22%	13%
Systolic blood pressure <90 mmHg (↓ >35 mmHg)	2% (7%)	3% (8%)
Diastolic blood pressure <50 mmHg (↓ >25 mmHg)	2% (4%)	4% (5%)
Coronary hyperemia	2–5 min longer than adenosine	Less as compared with regadenoson
Adverse effects	Less bronchoconstriction, AV blocks, hypotension	Bronchoconstriction, AV blocks, hypotension
Risk of seizures	Yes	No

AV: atrioventricular; IV: intravenous. *Single bolus. #Duration of action is defined as duration of coronary blood flow maintained >2.5-times of baseline; HR - Heart rate

In renal impairment (CrCl < 30 mL/min), regadenoson renal clearance was decreased and elimination half-life increased as compared with healthy subjects (CrCl ≥ 80 mL/min), but no adverse consequences were reported.[4,19] Hence, no dose adjustment is needed in these patients.

Special Population

Pharmacokinetic parameters remained unchanged with advancing age, gender and race.[5] Regadenoson should be used in pregnant women only if the potential benefit to the patient justifies the risk to the fetus (category C). Breast feeding should be stopped for 10 hrs following drug administration as the drug gets cleared in 10 h. In a study, 56% of the study population was ≥65 years, and adverse events were same as in patients <65 years, but a higher incidence of hypotension was observed in patients ≥75 years of age. Safety and effectiveness in neonates, infants, children and adolescents <18 years of age has not been established.[5]

Indications and Usage

1. Regadenoson is a pharmacologic stress agent (PSA) indicated for radionuclide MPI in patients unable to undergo adequate exercise stress for diagnosing CAD[1,5]
2. It is also used as PSA in MPI studies indicated in post-cardiac transplantation, chronic kidney disease, non-dialysis patients and PET imaging[25-27]
3. Real-time myocardial contrast echocardiography (RTCME) is a non-invasive method for the detection of CAD where regadenoson can be used without radionuclide, thereby obviating radiation exposure.[28]

Dosage and Administration

The hyperemic response to regadenoson doses of 400 μg and 500 μg were similar in magnitude and duration, with mean peak CBF velocity maintained at >2.5-times that of baseline for 2.3 and 2.4 min, respectively. More patients in the 500 μg group reported flushing, dyspnea and dizziness, although the differences were not statistically significant.[13,29] Hence, the recommended intravenous dose of 400 μg (5 mL) is administered as a rapid injection within 10 s into a peripheral vein and immediately flushed with 5 mL saline. Then, radionuclide MPI agent (technetium-99m sestamibi) is injected directly into the same catheter within 10–20 s

after the saline flush.[5] The dose of regadenoson need not be adjusted based on the weight and renal functions; therefore, it can be supplied in prefilled syringes (strength 0.4 mg/5 mL).[30]

*The other radionuclides' used are technetium-99m (^{99m}Tc) compounds (tetrofosmin, teboroxime), thallium-201 (^{201}Tl), iodine-123 (^{123}I)-labeled fatty acids, gallium citrate-67 (^{67}Ga), ^{123}I metaiodobenzylguanidine and Rubidium-82 (Rb-82 for PET MPI).[27,31]

Adverse Effects

Most adverse reactions have been mild and self-limiting.[5] The majority occur soon after administration and resolve within 15 min, except headache, which subsided within 30 min.[1] The most common reactions were dyspnea, headache and flushing. Less-common reactions were chest discomfort, dizziness, chest pain, nausea, abdominal discomfort, dysgeusia and flushing.[32] Rhythm or conduction abnormalities were seen in 26% versus 30% of the subjects receiving regadenoson versus adenosine. First-degree and second-degree AV blocks were 3% versus 7% and 0.1% versus 1%.[30] During post-marketing surveillance, the most frequently reported reactions were nausea, vomiting and diarrhea.[32] The other adverse effects reported include tremors, syncope, seizures, transient ischemic attacks, worsening of migraine, complete heart block with asystole (in persons with normal sinus rhythm), QTc prolongation, ST segment depression, hypersensitivity reactions and musculoskeletal pain.[17,18,28,33-36] Clinically significant increase in blood pressure was seen in hypertensives undergoing MPI with low-level exercise, which could have been due to sympathetic stimulation.[35,17]

Seizures have been reported within 2–5 min of regadenoson administration in patients on treatment or without prior history of seizures.[33] Stimulation of A_{2A} receptors in striatum, nucleus accumbens, cortex and tuberculum olfactorium can lead to increased glutaminergic excitotoxicity, as well as inhibition of A_1-mediated neuroprotection, which can exacerbate seizures from the cortex and limbic systems.[33,37] Regadenoson-induced seizures can be controlled with benzodiazepines.[33]

Treatment of overdose

For regadenoson overdose or severe persistent adverse effects like systolic blood pressure <80 mmHg, second degree or complete heart block, wheezing, severe chest pain associated with ST depression, intravenous aminophylline is effective at a dose of 50–250 mg over 30–60 s.[17,24]

Precautions

Regadenoson can depress the SA and AV nodes (A_1 receptor) and hence it should not be used in patients with sinus bradycardia and sick sinus syndrome.[6]

- The risk of serious hypotension may be higher in patients with autonomic neuropathy and pre-existing hypotension[1]
- Regadenoson may cause bronchoconstriction and respiratory compromise in chronic obstructive pulmonary disease (COPD) or asthma because of its affinity to A_{2B} and A_3 receptor, and appropriate bronchodilator therapy should be kept on standby[6]
- Anti-ischemic cardiac medications (including β-blockers, nitrates and calcium antagonists) should be withheld for at least 48 h prior to performing a diagnostic imaging test.[24]

Drug Interactions

- Methylxanthines (caffeine and theophylline) are non-specific adenosine receptor antagonists and may interfere with the vasodilatory activity of regadenoson.[10,12] They attenuate the duration but not the peak increase in CBF. Xanthines (coffee, green tea, colas and chocolate) should be avoided for at least 12 h prior to regadenoson administration[5,22]
- Dipyridamole may potentiate the vasodilatory effects of regadenoson, and should be withheld for at least 2 days prior to regadenoson administration[6]
- n-acetyl cysteine, an inhibitor of adenosine deaminase, restores the oxidant–antioxidant balance in idiopathic pulmonary fibrosis, longterm enzyme inhibition and upregulation of adenosine receptors (including A_{2A}). Thus, when regadenoson is administered to these patients, it can lead to complete heart block with asystole in patients with previous sinus rhythm.[34]

Clinical studies

The aim of the Adenoscan (adenosine) Versus Regadenoson Comparative Evaluation for Myocardial Perfusion Imaging (ADVANCE MPI) 1 and 2 trials was to demonstrate the non-inferiority of regadenoson in comparison with adenosine by examining the concordance of images detecting myocardial perfusion defects. ADVANCE MPI 1 and 2 were methodologically identical, double-blind, randomized, active-comparator, multicentric, phase III trials.[24,25] The findings of the study are shown in Table 2 under efficacy studies.

Conclusions

The clinical efficacy of regadenoson during pharmacologic stress testing for MPI was similar to adenosine and produced sufficient hyperemic response but with fewer side-effects. It can be administered as a single bolus dose of 400 μg, having quick onset and short duration of action. Dose adjustment based on body weight or renal functions is not necessary. It simplifies drug delivery as specific infusion equipment is not required. It offers patients a quicker and easier procedure with mild side-effects. The drug can be safely used in patients with mild-to-moderate reactive airway disease and obstructive lung disease. Thus, it is a safe alternative to adenosine for SPECT MPI. The other A_{2A} agonists in phase III clinical trials are binodenoson and apadenoson.[3] Regadenoson can also be used to measure coronary hemodynamics in the cardiac catheterization with the flow-Doppler catheter. Stress MPI may also be performed with cardiac resonance and contrast echocardiography.

Table 2: Clinical studies

Authors	Study population	Study design	Intervention group	Comparator group	Outcome
Efficacy studies					
Iskandrian *et al.*[38], advance MPI 2	Coronary artery disease, n=784; both males and females, with mean age of 64 years in both groups	Multi-centric phase III, non-inferiority RCT, DB	1st imaging study, both groups received adenosine 140 µg/kg/min IV infusion for 6 min followed by		1. Regadenoson is non-inferior to adenosine for use in SPECT myocardial perfusion imaging in assessing reversible perfusion defects
			Regadenoson 400 µg IV bolus over <10 s. N=495	Adenosine 140 µg/kg/min IV infusion for 6 min. n=260	2. Safety and tolerability comparable to adenosine
Cerqueira *et al.*[39]	Total n=2,015. The efficacy analysis set included 1871 patients. The mean age was 66 and 65 years in the regadenoson and adenosine groups, respectively	Multi-centric phase III, non-inferiority RCT, DB, P	1st imaging study, both groups received adenosine 140 µg/kg/min IV infusion for 6 min followed by		1. Agreement rate for images were 63% and 62% in the regadenoson and adenosine groups, respectively
			Regadenoson 400 µg IV bolus over <10 s, N=1240	Adenosine 140 µg/kg/min IV infusion for 6 min, N=631	2. Regadenoson is as efficacious as adenosine and is better tolerated regardless of age, gender, BMI and diabetes
Safety studies					
Thomas *et al.*[40] RegCOPD trial	Chronic obstructive pulmonary disease (COPD) moderate (n=38) and severe COPD (n=11)	RCT, DB, placebo-controlled crossover trial	Regadenoson 400 µg IV bolus over <10 s	Placebo	Mean decline in FEV_1 was 0.11±0.02 L and 0.12±0.02 L (P=0.55) in patients on regadenoson and placebo, respectively, and new-onset wheezing was observed in 12% and 6% patients, respectively (P=0.33)
					Regadenoson was safe in patients with moderate and severe COPD
Leaker *et al.*[41]	n=48, asthma patients with a positive adenosine monophosphate challenge test	RCT, DB, placebo-controlled crossover trial, mild (n=24), moderate (n=24) asthma	Regadenoson 400 µg IV bolus over <10 s	Placebo	No difference in FEV_1 between regadenoson and placebo. Regadenoson was safe and well tolerated
Thomas *et al.* RegEx trail[17]	Coronary artery disease, n=60; both males and females, with mean age of 70 and 69 years in RegEx and PlcEx groups, respectively	Multi-centric RCT, DB, placebo-controlled pilot study	1st imaging study, both groups received adenosine 140 mcg/kg/min IV infusion in supine position (AdenoSup) for 6 min followed by		1. Adverse effects were less in the RegEx group 77% as compared with adenosine 95%. PlcEx had the least, with 33%
			Regadenoson (RegEx) 400 µg IV bolus over <10 s with low-level exercise (4 min), n=39	Placebo (PlcEx) with low-level exercise (4 min), n=21	2. Heart rate and dyspnea was higher in the RegEx group as compared with the PlcEx and AdenoSup groups without increase in blood pressure
					3. Second-degree AV block was seen with AdenoSup
					Regadenoson with low-level exercise was feasible and well tolerated
Pharmacokinetic studies					
Gordi *et al.*[22]	Thirty-six healthy, male volunteers aged 18–50 years	RCT, DB, placebo-controlled crossover study	Single IV bolus doses of regadenoson that ranged from 0.1 to 30.0 µg/kg	—	In the dose range of 0.3–20 µg/kg in healthy subjects, age, gender, clearance, half-life and volume of distribution were independent of the dose given, and hence it is given as fixed bolus dose. Maximum tolerated doses of regadenoson were 10 µg/kg in the standing position and 20 µg/kg in the supine position. Adverse events like hypotension and tachycardia were more prevalent at regadenoson doses >3 µg/kg
Hendel *et al.* dose ranging study[29]	Coronary artery disease, n=36; both males and females, with mean age of 67.3 years in both groups	Multi-centric, non-RCT, open-label phase II placebo controlled	1st imaging study, both groups received adenosine 140 mcg/kg/min IV infusion (2–46 days) followed by		1. ↑HR and ↓SBP, DBP was observed and incidence of flushing, dyspnea and dizziness was higher with the 500 µg dose
			Regadenoson 400 µg IV bolus over <10 s, n=18	Regadenoson 500 µg IV bolus over <10 s, n=18	Regadenoson 400 µg is equally effective as 500 mcg and better tolerated

(*Contd...*)

Table 2: (Contd...)

Authors	Study population	Study design	Intervention group	Comparator group	Outcome
			Pharmacokinetic studies		
Gordi *et al.*[19]	*N*=16, with impaired renal function	Patient undergoing MPI studies with different creatinine clearance values (range: 15–132 mL/min)	Single IV bolus dose of 400 μg regadenoson	–	Elimination half-life was prolonged with decreasing renal function. Maximum plasma concentration, number or severity of adverse events did not differ significantly between the subjects. Dose adjustments were not necessary with reduced renal function
			Pharmacodynamic study		
Lieu *et al.*[13]	*N*=34, coronary catheterization for coronary artery disease	Open-label phase II study	Single IV bolus dose of regadenoson (10, 30, 100, 300, 400 or 500 μg) infused over 10 s	–	Vasodilatory effect with regadenoson doses of 400 and 500 μg were similar in magnitude and duration. 400 μg was better tolerated than 500 μg
			Hemodynamic study		
Hage *et al.*[21]	643 patients with a history of DM (65.4±0.4 years, 32% women) and 1357 patients without DM (65.5±0.3 years, 29% women)	Phase III, RCT, P, DB	Regadenoson 400 μg IV bolus over <10 s	Adenosine 140 μg/kg/min IV infusion for 6 min	Compared with non-DM, the DM group had higher HR at baseline (68.4 vs. 65.2 beats/min, $P<0.00$) and smaller HR response after adenosine or regadenoson administration (29.4% vs. 36.1%, $P<0.001$)
			Caffeine study		
Gaemperli *et al.*[15]	*n*=41, healthy volunteers (15 female) aged 18 years or older, non-smokers and regular coffee drinkers	Phase II, RCT, DB, placebo-controlled, crossover study	Regadenoson 400 μg IV bolus over <10 s 200 mg caffeine capsule (a dose corresponding to 2 cups of coffee on Day 1 and placebo on Day 2)	Regadenoson 400 μg IV. Placebo on Day 1 and 200 mg caffeine capsule (corresponding to 2 cups of coffee) on Day 2	Regadenoson causes coronary hyperemia with and without prior caffeine ingestion in healthy volunteers, and moderate caffeine consumption may not interfere with regadenoson stress MPI. Caffeine attenuated the severity of side-effects and improved the tolerability of regadenoson

n, number of patients; RCT, randomized controlled trial; DB, double blind; P, placebo; MPI, myocardial perfusion imaging; DM, diabetes mellitus; IV, intravenous; RegEx, regadenoson with low-level exercise; Adenosup, adenosine; PlcEx, placebo with low-level exercise; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure

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