Adverse effects associated with regadenoson myocardial perfusion imaging

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INTRODUCTION

Single-photon emission computed tomography myocardial perfusion imaging (MPI) is one of the most widely used non-invasive methods for assessing patients with known or suspected coronary artery disease (CAD).[1] Exercise is the preferred stressor, however, in cases of patients who either cannot exercise adequately or there are contraindications to exercise, vasodilating agents can be used instead. Of these, regadenoson is the only FDA-approved A2A adenosine receptors selective agonist; due to its selectivity and ease of use, it is the stressing agent of choice in the United States and its use is increasing in other countries. After binding to A2A receptors on smooth muscle cells, regadenoson leads to vasodilatation, predominantly of the coronary bed and secondarily of the periphery. The majority of the administered dose is renally excreted (58% of the administered dose)[2] and its clearance is prolonged in individuals with impaired renal function.[3]

In addition to its ease of administration (single bolus of 200 mcg given intravenously, IV), when compared to adenosine, regadenoson has been shown to be non-inferior for identifying perfusion defects[4] and providing prognostic data.[5–10] Furthermore, it is better tolerated as evidenced by a lower summed score of chest pain, dyspnea, and flushing reported by the patients[4] and has a comparable safety profile.[4] Despite its advantages, there still are certain undesirable effects associated with the use of regadenoson, the incidence of which is overall low. Nevertheless, it is clinically important to not only recognize these undesirable effects, but also to manage them appropriately.

In this issue of the *Journal*, Agrawal et al. describe two patients who underwent regadenoson MPI and experienced chest pain during the test.[11] In the first patient, treatment with oral nitroglycerin worsened symptoms, led to the development of hypotension and evolution of electrocardiographic (ECG) changes with initially persistent ST-segment depression followed by ST elevation. Resting MPI and coronary angiography revealed severe multi-vessel CAD. The second patient complained of chest pain after receiving regadenoson along with evidence of ST-segment depression. Both the symptoms, as well as the ECG changes resolved following administration of IV aminophylline and the patient was able to complete his stress test. Similarly to the first case, severe multi-vessel CAD was evident on MPI and coronary angiography. The two case examples of differential response to nitroglycerin vs aminophylline serve to stress the importance of recognizing adverse effects seen with regadenoson MPI and the proper management strategies that should be used. The authors conclude that in patients with severe underlying CAD, development of chest pain and ECG changes after regadenoson most likely represents coronary steal. In such cases, nitroglycerin has the risk of causing further steal and clinical deterioration, as opposed to

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aminophylline which may offer benefit by ameliorating the extent of steal and resolving patient symptoms.[11]

CARDIOVASCULAR ADVERSE EFFECTS

The differential management and immediate clinical response of these two cases exemplify the importance of knowledge of the potential side effects associated with use of regadenoson and what the optimal antidote is. In the landmark ADVANCE-MPI trial, chest pain and shortness of breath were among the most frequently reported side effects of regadenoson (29% and 28%, respectively).[4] Episodes of fatal and non-fatal myocardial ischemia and infarction have also been reported in association with regadenoson[12–14] and as of June 2017, there were 70 cases of myocardial infarction and/or acute myocardial infarctions and 28 deaths were reported to the FDA via its adverse event reporting system (FAERS).[15] There have been so far no identifiable risk factors to accurately predict and risk stratify patients for development of the above-mentioned adverse effects.[16] The underlying mechanism mediating the development of chest pain and myocardial ischemia following administration of regadenoson remains unclear. It has been hypothesized that regadenoson-induced vasodilation of coronary collaterals and subsequent coronary steal may account for this (i.e., enhanced blood flow from the subendocardium to the subepicardium in a coronary territory supplied by a stenosed vessel). Another plausible explanation could be the development of hypotension and tachycardia that may accompany regadenoson. The pathogenesis of these is also not well understood, but it is believed that an exaggerated vasovagal reaction (Bezold–Jarisch reflex) in conjunction with vagal stimulation (an A2A receptor-mediated mechanism) in the *area postrema* (located at the floor of the fourth ventricle) might mediate this,[17] especially in cases preceded by nausea and vomiting.[18] An alternate explanation could be the A2A-mediated activation of the sympathetic afferent nerves leading to enhanced sympathetic activity and reflex vagal stimulation.[19–21] This may prove particularly risky, especially in the subgroup of patients unable to tolerate hypotension, such as the elderly, those with a history of stroke, significant left ventricular outflow tract obstruction, or severe ischemic left ventricular dysfunction and in those undergoing hybrid regadenoson–exercise stress since hypotension may be exacerbated with upright posture. Finally, regadenoson itself may stimulate production of endogenous adenosine further potentiating the following effects: (a) coronary transmural steal phenomenon, (b) adenosine-related vasodilatation which may in turn result in diminished flow through collaterals and arterioles and a drop in perfusion pressure, and (c) a reduction in distal perfusion pressure due to increased flow across a stenosed vessel. These may be of particular concern in patients with known significant multi-vessel CAD with restricted coronary flow reserve.

The above adverse effects, albeit rare, deserve immediate medical attention and when observed, need to be treated appropriately, as administration of the wrong therapeutic agent may lead to further clinical deterioration. The occurrence of chest pain in a patient undergoing regadenoson MPI, with or without further evidence of myocardial ischemia, namely development of hypotension and/or ECG changes, needs to be differentiated as either being a non-specific symptom vs originating from imbalance between myocardial oxygen demand and supply and thus representing true angina. The timing of occurrence of the pain is of critical importance, as evidenced by the two case reports by Agarwal et al.[11] Myocardial ischemia that develops in close proximity to regadenoson administration will respond better to aminophylline as opposed to nitroglycerin. The latter may in fact potentiate regadenoson-induced steal, coronary vasodilation, and reduced perfusion pressure of the coronary bed, the cumulative effect of which may result in worsening myocardial ischemia, or even development of infarction, and rapid deterioration of the patient. This is in contrast to myocardial ischemia occurring independently of regadenoson administration (or after a significant delay from its administration) which may benefit from nitroglycerin. Although the duration of coronary dilation in response to regadenoson may be prolonged, significant hyperemia (> twofold increase over baseline) usually lasts less than 10 minutes.[19] Therefore, it is likely that coronary steal would occur during this window although this has not been systematically evaluated to our knowledge.

The two most common cardiovascular side effects following administration of regadenoson include modest reductions in systolic and diastolic blood pressure (average of 13 and 8 mmHg, respectively) and modest increase in heart rate (average increase of 25 ± 11 bpm) as documented in the ADVANCE-MPI trials.[4] Based on animal experiments, it is now clear that regadenoson-mediated tachycardia results from either direct sympathetic stimulation or withdrawal of vagal tone[17,20,21] and is not a baroreflex-mediated epiphenomenon secondary to peripheral vasodilation as once thought. The heart rate response (HRR) to regadenoson is a prognostically important, non-perfusion-derived MPI index[22] and can be calculated as the percent difference in heart rate from baseline with lower values reflecting worse prognosis. Values greater than 30% are thought normal, whereas less than 15% abnormal or blunted.[23] Older age, male gender, reduced left ventricular systolic function,

perfusion defects, and history of obesity, diabetes mellitus, and chronic kidney disease have all been shown to correlate with a decreased HRR to regadenoson.[22–28]

Given its selectivity for the A2A receptors, A1 receptor-mediated cardiac undesirable effects, namely sinoatrial nodal dysfunction and atrioventricular (AV) block occur less frequently with regadenoson compared to adenosine. This was confirmed in the ADVANCE-MPI trials, where 2.8% of patients developed first-degree AV block and only one patient had Wenckebach second-degree AV block and there were no instances of complete heart block or asystole.[4] Despite this initial observation, there have since been isolated case reports and small case series describing the occurrence of de novo advanced heart block and asystole following regadenoson and requiring immediate management and stabilization.[29–35] As of June 2017, a total of 56 cases of third-degree heart block and 26 cases of sinus arrest associated with regadenoson stress testing were reported via FAERS.[15] In a recent meta-analysis, the incidence of overall and high-grade AV block—defined as second- and third-degree AV block—related to the administration of regadenoson at the dose given during MPI was low (less than 0.5%) and observed much less frequently with regadenoson compared to adenosine (incidence of de novo overall AV block with adenosine was 8.58%; 95% CI 5.55% to 12.21% vs. regadenoson which was 0.30%; 95% CI 0.04% to 0.82%, $P < 0.001$, OR 30.6; 95% CI 11.0 to 85.3; incidence of high-grade AV block for adenosine was 5.21%; 95% CI 2.81%–8.30% vs regadenoson which was 0.05%; 95% CI < 0.001%–0.19%, $P < 0.001$, OR 77.2; 95% CI 20.3 to 293.0) (Figure 1).[36] It remains unclear why certain patients develop sinoatrial and AV node dysfunction following use of regadenoson. Similarly to the development of chest pain and myocardial ischemia, conduction disturbances in response to regadenoson, have also been postulated to result from neural-mediated pathways, namely (a) a prominent vasovagal reaction and (b) pronounced sympathetic activity and reflex vagal stimulation. Another mechanism, also overlapping with the pathogenesis of myocardial ischemia is the regadenoson-mediated increased production of endogenous adenosine. This may be more evident in the subgroup of patients with severe underlying CAD or extensive collateral circulation. In this subset of patients, regadenoson may lead to coronary steal or a sudden drop in systemic blood pressure, followed by ischemia, which may in turn lead to overproduction of adenosine and activation of the A1 receptors in the sinoatrial and AV nodes and suppressed conduction. Current ASNC guidelines caution against using regadenoson in patients with known sinoatrial and/or second- or third-degree AV block without a functioning pacemaker. Profound sinus bradycardia and Mobitz type 1 second-degree AV block (Wenckebach block) are listed as relative contraindications.

Other less frequent cardiovascular side effects following regadenoson include ventricular and supraventricular tachycardias, such as atrial fibrillation and flutter.[37] Prolongation of the QT interval might also occur as a result of regadenoson-induced tachycardia and shortening of the R–R interval without appropriate shortening of the QT interval.[20,38] This type of QT prolongation has not been associated with torsades de pointes or sudden cardiac death. Table 1 lists the cardiovascular side effects that may follow use of regadenoson and their respective treatment.

NON-CARDIOVASCULAR ADVERSE EFFECTS

Given its high selectivity for the A2A receptors, regadenoson was initially anticipated to have been free of pulmonary-related side effects due to A2B and A3 receptor activation. Initial large-scale trials using regadenoson either excluded patients with known bronchospastic/bronchorestrictive lung disease or only allowed for inclusion of a small fraction of patients with known COPD or asthma (range 6%-16%).[4,35,39,40] Following initial post-marketing reports of wheezing, dyspnea, and respiratory arrest,[16] the use of regadenoson in patients with COPD and/or asthma was examined in randomized, double-blinded, cross-over, placebo-controlled trials that included patients with moderate-severe COPD (RegCOPD) and mild-moderate asthma (RegAsthma).[41,42] These showed that use of regadenoson in the above patient subgroups was well tolerated without significant changes in respiratory rate, FVC, FEV1, new-onset wheezing, or bronchoconstriction and oxygen saturation compared to placebo.[41,42] Of note, dyspnea was reported in 61% of patients in the regadenoson group vs 0% in the placebo group, this however, was not confirmed by objective measurements. None of the patients in these studies required treatment with bronchodilators or oxygen.[41,42] The above findings have been confirmed by larger studies showing a safe and favorable pulmonary profile of regadenoson.[43] Adding low level exercise to regadenoson has been proposed as one way to attempt to decrease the development of pulmonary side effects and improve tolerability in patients with COPD and/or asthma.[35,44] Data are still limited and definitive conclusions cannot be drawn.[45] The most critical component of combination stress testing is careful selection of the patients that may benefit.[45] The ones included in the studies had relatively stable COPD/asthma, their asthma severity being at the most moderate, without recent exacerbations and only

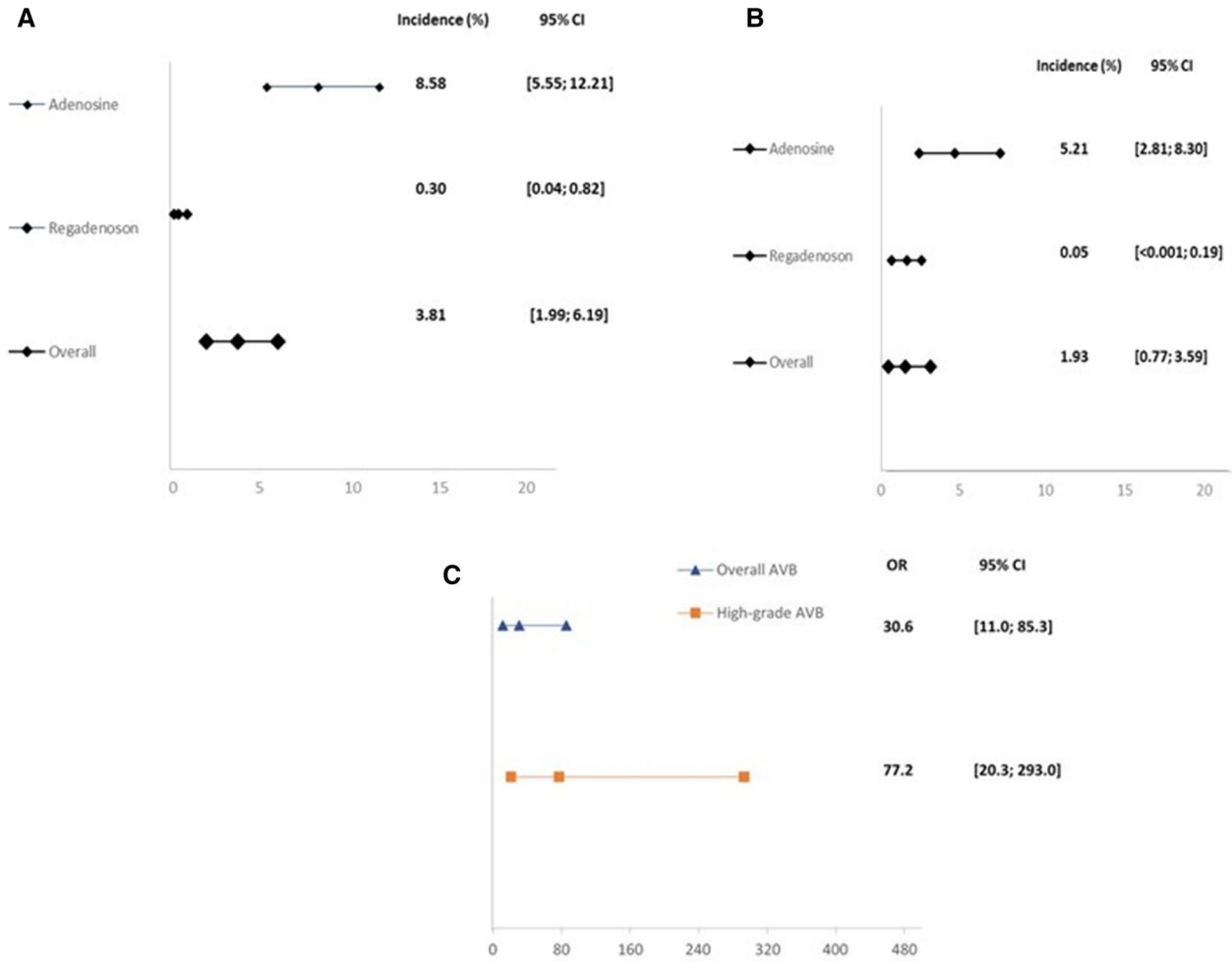

Figure 1. **A** Incidence of overall AVB following administration of adenosine vs regadenoson, as reported in the literature. **B** Incidence of high-grade AVB following administration of adenosine vs. regadenoson, as reported in the literature. **C** Odds ratio for overall and high-grade AVB associated with administration of adenosine and regadenoson stress SPECT-MPI. Forest plots for **A** and **B** and data for odds ratio obtained and modified from the meta-analysis by Andrikopoulou et al.[36] High-grade AVB defined as any occurrence of second- and/or third-degree AVB. *AVB*, atrioventricular block; *SPECT-MPI*, single-photon emission computed tomography myocardial perfusion imaging.

seldom used their rescue inhalers. More randomized trials are needed to accurately define the safety of regadenoson in patients with pulmonary disease.[45] Regadenoson should be avoided in patients with severe COPD or asthma with active bronchoconstriction (i.e., actively wheezing in the stress laboratory). In these cases, alternative stressors and/or modalities should be used, such as dobutamine MPI, or stress echocardiography. In patients with known severe pulmonary disease but who are not having active wheezing consideration should be given to administering supplemental oxygen through a mask or nasal cannula and having nebulizers and inhalers at hand, in case they are needed, or prophylactically giving bronchodilators prior to regadenoson.

Gastrointestinal side effects, namely nausea, diarrhea, and abdominal discomfort have been reported in about 2%-8% of patients following regadenoson.[4,35,39,40] These adverse effects occur more frequently in patients with advanced renal disease.[39,40] With the exception of diarrhea, these are short-lived, and can be easily managed conservatively.

One of the most dreadful complications associated with the use of regadenoson, albeit rare, is new-onset or recurrent convulsive seizures.[16,37,46,47] As of 2017, a total of 55 cases of convulsions and 11 cases of seizure-like and partial seizures were reported to the FDA,[15] though the exact de novo occurrence of seizures with regadenoson MPI is unknown. The pathogenetic mechanism is not yet delineated; It is thought that activation

Table 1. Select side effects related to regadenoson administration during vasodilator myocardial stress SPECT-MPI and their respective preferred treatment

Cardiovascular side effects	Aminophylline	Other treatment	Comments
Acute myocardial infarction	Indicated	Guideline-based treatment with antiplatelets, anticoagulants, beta blockers, coronary arteriogram	
Myocardial ischemia	Indicated		Consider aminophylline for cases of myocardial ischemia related to regadenoson-induced steal
Complete heart block	Indicated	Temporary pacemaker in cases of symptomatic and/or persistent complete heart block	
Sinus arrest	Indicated	Temporary pacemaker in cases of symptomatic and/or prolonged sinus arrest	
Hypotension	Indicated	Intravenous fluids when indicated	Consider aminophylline for cases of more than moderate reduction ($\geq$ 20 mmHg)
Tachycardia	Indicated		Consider aminophylline for cases of severe and/or persistent tachycardia
Bradycardia	Indicated		Consider aminophylline for cases of symptomatic and/or persistent bradycardia
SVT/Atrial fibrillation/Atrial flutter	Indicated	Consider guideline-based treatment with beta blockers, calcium channel blockers	For unstable cases, may need to cardiovert
Ventricular fibrillation	Indicated	ACLS-based treatment including defibrillation	
Severe bronchoconstriction	Indicated	Supportive treatment with oxygen and bronchodilators	In severe respiratory distress/failure, or extreme cases of respiratory arrest, will need to intubate
Seizures/convulsions	Not indicated	Benzodiazepines	Aminophylline is contraindicated

SPECT-MPI, single-photon emission computed tomography myocardial perfusion imaging; *SVT*, supraventricular tachycardia

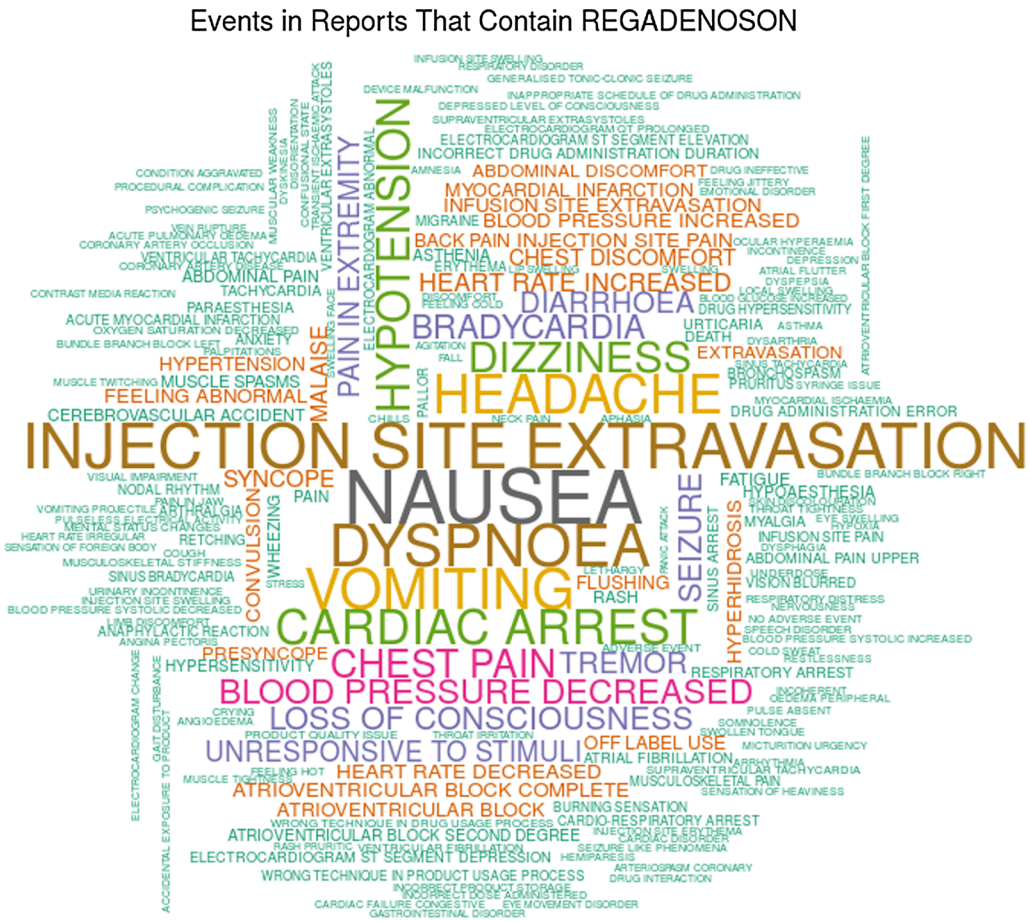

Figure 2. Side effects following administration of regadenoson that have been reported to the FDA/FAERS. Size of the word corresponds to the frequency of reports submitted to the FDA. Figure adopted from and available at the official FAERS website. https://openfda.shinyapps.io/dash/ (accessed on 1/11/2018).

of the A2A receptors in the central nervous system, primarily at the nucleus accumbens, striatum, and tuberculum olfactorium, and to a lesser extent the cortex and hippocampus, results in inhibition of the A1 neuroprotective effects and instead activates glutamatergic excitatory pathways, ultimately leading to potentiation of cortical and limbic seizures.[48–51] The development of seizures was described in a small case series of three patients receiving regadenoson.[46] In two of them, those were episodes of recurrent seizures (both patients were chronically treated with anticonvulsive medications and they had been stable for years). In the third patient, these were new-onset seizures.[46] In all three patients, seizures were noted within 2–5 minutes of regadenoson administration and in all three, episodes began as secondary and quickly converted to secondary generalized with verbal unresponsiveness.[46] Aminophylline is not a good option for treating regadenoson-induced seizures not only because it is not effective in this setting but also since it may even perpetuate the seizures.[46] Benzodiazepines are the treatment of choice. Further treatment may include other anticonvulsive therapies. Risk stratifying patients for the development of seizures following regadenoson is not yet feasible, though a known history of seizures is definitely a risk factor. Special attention should be given when obtaining the patients' medical history with respect to prior seizures. High level of caution is recommended even if the patient has been relatively free of seizures and consideration of alternate stressors and/or modalities is warranted in patients who have been having active seizures. Benzodiazepines must be at hand. Current ASNC guidelines list seizure disorder as a relative contraindication for regadenoson administration.[37]

Non-specific side effects, such as myalgias, tremors, and hypersensitivity reactions have all been reported following regadenoson, but they are all short-lived and usually self-terminate.[37] An up-to-date list of all adverse

effects reported following injection with regadenoson in patients undergoing vasodilator stress testing can be found in the website of FDA[15] (Figure 2). The most serious side effects associated with the administration of regadenoson for MPI along with their recommended management are listed in Table 1.

CONCLUSION

As the population ages, use of vasodilators with MPI instead of exercise will continue to rise. A2A selective agonists, such as regadenoson, are easier to use and associated with better safety and tolerability profiles than non-selective agents such as adenosine and dipyridamole. Despite its advantage and its diagnostic and prognostic value, clinicians should be aware of the side effects associated with regadenoson. The vast majority of these side effects are short-lived, benign, and spontaneously terminate. On rare occasions, however, more serious cardiovascular and neurological adverse events may develop, namely symptomatic myocardial ischemia, infarction, high-grade AV block, asystole, and seizures. Such events can be avoided with careful risk stratification and selection of patients prior to administering regadenoson and personalizing the potential risks and benefits for each patient individually. Clinicians should be aware of the preferred method of managing possible side effects and know when aminophylline is safe to be administered.

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