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Safety Profile of Adenosine Stress Perfusion Imaging: Results From the Adenoscan Multicenter Trial Registry

MANUEL D. CERQUEIRA, MD, FACC, MARIO S. VERANI, MD, FACC,*
MARKUS SCHWAIGER, MD, FACC,† JAEKYEONG HEO, MD,‡
ABDULMASSIH S. ISKANDRIAN, MD, FACC‡ AND
THE INVESTIGATORS OF THE MULTICENTER ADENOSCAN TRIAL§
Seattle, Washington; Houston, Texas; Philadelphia, Pennsylvania; Ann Arbor, Michigan

Objectives. The purpose of this study was to determine the safety of adenosine infusion at 140 μg/kg per min in conjunction with radionuclide imaging in 9,256 consecutive patients.

Background. Adenosine produces maximal myocardial hyperemia directly with a rapid onset of action. In addition, when used in conjunction with radionuclide perfusion imaging, it has proven efficacy for the diagnosis of coronary artery disease in patients unable to exercise. Because the ultrashort half-life (<10 s) allows dose titration and rapid reversal of side effects, it may be safer than other available pharmacologic agents.

Methods. Patients were prospectively entered at 21 clinical sites. Information on safety and adverse events during and immediately after adenosine infusion was maintained in the Adenoscan Multicenter Trial Registry.

Results. The infusion protocol was completed in 80% of patients, required dose reduction in 13% and was terminated early in 7%. Interpretable imaging studies were obtained in 98.7% of patients, and 0.8% of patients received aminophylline. Minor and well tolerated side effects were reported in 81.1% of patients. There were no deaths, one myocardial infarction, seven episodes of severe bronchospasm and one episode of pulmonary edema. Transient atrioventricular (AV) node block occurred in 706 patients (first-degree in 256, second-degree in 378 and third-degree in 72) and resolved spontaneously in most patients (n = 508) without alteration in the adenosine infusion. There were no sustained episodes of AV block. Patients >70 years of age had an increased risk of developing AV block (age <70, 7.05% vs. ≥70, 9.44%, p = 0.001, relative risk 1.37).

Conclusions. Adenosine infusion is safe. Vasodilator and negative dromotropic side effects are generally well tolerated. Serious side effects are relatively rare, and they reverse with termination of adenosine infusion. Interpretable radionuclide studies were obtained in 98.7% of patients and aminophylline reversal was seldom required.

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Pharmacologically induced coronary artery hyperemia is being used with increasing frequency in conjunction with radionuclide perfusion imaging for the detection of coronary stenoses and risk stratification in patients with suspected or known coronary artery disease who are unable to perform adequate levels of exercise. Extensive data on efficacy and safety have been acquired with oral and intravenous dipyridamole (1–7), which increases coronary blood flow (8) by allowing extracellular accumulation of endogenously produced adenosine. Direct intravenous infusion of adenosine has also been shown to increase coronary blood flow (9,10). Additionally, in combination with thallium-201 perfusion imaging, it has a sensitivity and specificity for detecting coronary artery disease comparable to that obtained with exercise thallium-201 scintigraphy (11–21). Adenosine produces maximal myocardial hyperemia directly, has a rapid onset of action and an ultrashort half-life (<10 s) that allows dose titration and rapid reversal of side effects (22).

The Adenoscan Multicenter Trial Registry was a prospective, open label phase III trial using fixed dose, continuous intravenous infusion of adenosine in patients referred for clinically indicated diagnostic radionuclide perfusion imaging who were unable to perform exercise stress. From this registry, we report on the frequency of early adverse events (during and immediately after adenosine infusion), their severity and the response required in 9,256 consecutive patients. In 1,067 patients, we also recorded delayed or recurrent adverse events during the immediate 24-h period after infusion.

From the Departments of Radiology and Medicine, University of Washington School of Medicine and Department of Veterans Affairs Medical Center, Seattle, Washington; *Section of Cardiology, Department of Internal Medicine, Baylor College of Medicine and The Methodist Hospital, Houston, Texas; †Division of Nuclear Medicine and Cardiology, Department of Internal Medicine, University of Michigan, University of Michigan Medical Center, Ann Arbor, Michigan; and ‡‡The Philadelphia Heart Institute, Presbyterian Medical Center, Philadelphia, Pennsylvania. §A complete list of participating centers and principal investigators appears in the Appendix. This study was supported in part by Medco Research, Inc., Los Angeles, California.

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Address for correspondence: Dr. Manuel D. Cerqueira, Department of Veterans Affairs Medical Center (115), 1660 South Columbian Way, Seattle, Washington 98108.

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Methods

Between January 4, 1989 and March 13, 1992, a total of 9,256 consecutive patients were prospectively enrolled. All patients gave informed consent and the protocol was approved by the institutional review board on human research at each participating center. A complete cardiovascular history was obtained and recorded for each patient on enrollment. Patients were entered at 21 clinical sites. All information on safety and adverse events during and immediately after adenosine infusion was prospectively recorded on standardized forms and maintained in a central registry. Cohorts from this registry have been included in prior reports (11–18).

Patient selection. Patients with known or suspected coronary artery disease referred for clinically indicated radionuclide perfusion imaging who were unable to perform exercise stress were eligible for enrollment. Excluded were patients with hypotension (systolic blood pressure <80 mm Hg), asthma, decompensated or chronic obstructive pulmonary disease that did not allow termination of bronchodilator therapy, caffeine ingestion within 24 h, severe aortic stenosis, unstable angina or acute myocardial infarction within 24 h of the study. Each patient was monitored and questioned before, during and immediately after termination of adenosine infusion, specifically for the occurrence of the following adverse events: shortness of breath or dyspnea, atrioventricular (AV) block, hypotension, arrhythmias, chest pain, ST segment depression on the electrocardiogram (ECG), flushing, gastrointestinal discomfort, headache, light-headedness, nervousness and nausea. All adverse events were graded on the basis of clinical severity by the physician investigators as mild, moderate or severe and recorded on standardized forms. Each event was also rated as unrelated or as definitely, probably, possibly related to adenosine infusion. Episodes of first, second or third degree AV block were designated as mild, moderate or severe, respectively. Finally, the response to each reaction was coded as tolerated without dosage adjustment, tolerated with dosage adjustment, required termination of adenosine infusion or required reversal with aminophylline. Aminophylline administration was a clinical decision made by individual physicians.

Adenosine infusion protocol. Adenosine (Adenoscan, Medco Research, Inc.) was infused at 140 μg/kg per min through a peripheral venous catheter, using an accurate infusion pump over 6 min (total dose 0.84 mg/kg body weight) as shown in Figure 1. After 3 min of infusion, the radionuclide perfusion tracer was administered intravenously in the contralateral arm in most patients and the infusion continued for an additional 3 min. Patients with poorly tolerated side effects had the adenosine dose decreased or the infusion terminated, depending on the severity of the effects. The rate of dose reduction and the decision to terminate were determined by individual physicians on the basis of perceived clinical risk. Whenever possible, the radioisotope was injected and the adenosine infusion maintained for at least an additional minute. Persistent symptoms, despite termination of the infusion, were managed by physicians as clinically indicated with aminophylline (an adenosine receptor antagonist administered at 75 mg over 1 min to a maximal dose of 225 mg). Nitroglycerin could be administered to patients with persistent chest pain not responding to aminophylline.

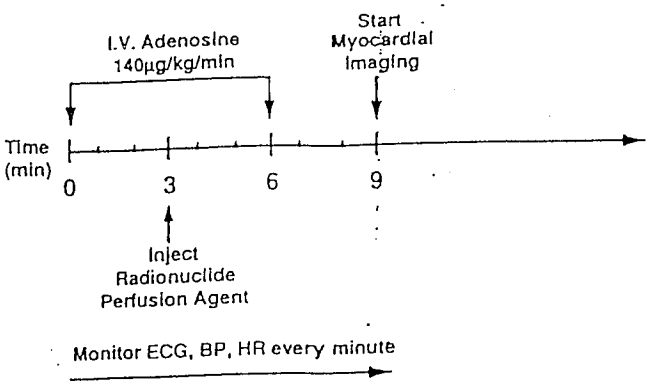

Figure 1. Adenosine infusion protocol for pharmacologic stress in conjunction with radionuclide perfusion imaging. Perfusion agents were administered earlier than 3 min in the presence of ischemia or intolerable side effects and the infusion was continued for an additional minute to maintain maximal coronary blood flow. Infusion requires a highly accurate pump system. BP = blood pressure; ECG = electrocardiogram; HR = heart rate; I.V. = intravenous.

Thallium-201 was the perfusion agent used in the majority of patients (89.7%), but 4.2% received technetium-99m sestamibi, 3.7% received nitrogen-13 ammonia or rubidium-82 and 2.3% received other agents. The ECG was monitored continuously and blood pressure and heart rate were measured at baseline and every minute during the adenosine infusion and for a minimum of 5 min after it was terminated.

Delayed adverse events. At five medical centers, 1,067 consecutive patients undergoing thallium imaging were prospectively evaluated over 24 h after the termination of adenosine infusion to characterize safety beyond the immediate imaging period. In-patients were questioned directly and their charts reviewed. Outpatients were contacted by telephone interview. Adverse events were classified by investigators as delayed (reported during 24 h of follow-up but not reported during the infusion) or recurrent (reported during the infusion and recurring during the 24-h follow-up period). Delayed or recurrent events were further clinically graded as benign (mild or moderate in severity and with spontaneous resolution) or potentially significant (severe and without spontaneous resolution).

Statistical analysis. All values are expressed as the mean value ± 1 SD. Patient percentages are expressed relative to the number of patients who had available data for the specific variable. Differences between groups and hemodynamic changes over time were determined by *t* test comparison or analysis of variance (ANOVA) for repeated mea-

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Table 1. Patient Characteristics

Age (yr)	
Mean ± SD	65.0 ± 11.6
>65	55%
Gender (%)	
Male	54
Female	46
Race (%)	
White	85.4
Black	11.9
Other	2.8
Risk factors (%)	
Hypertension	56.6
Cardiomyopathy	5.5
CAD	
Proved	49.3
Suspected	50.7
CHF	14.1
Prior MI	23.1
Prior CABG	17.3

CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction.

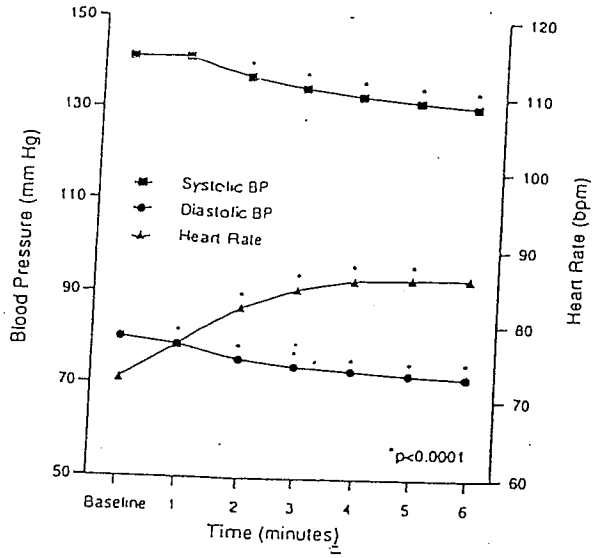

Figure 2. Changes in systolic and diastolic blood pressure (BP) and heart rate in patients who completed the full adenosine infusion protocol (n = 6,921) at 140 μg/kg per min over 6 min. *p < 0.0001 in comparison with prior time interval. bpm = beats per minute.

sures. A p value < 0.05 was considered significant. When multiple comparisons were performed, the Bonferroni correction was used to determine the p value required for statistical significance. The relation between the occurrence of AV block and various clinical and hemodynamic variables was explored using univariate and multivariate analysis. For univariate analysis, discrete variables were compared by *t* tests and continuous variables by chi-square analysis. Variables with p < 0.05 by univariate analysis were entered into the stepwise logistic regression analysis.

Results

Patient characteristics. Table 1 lists the characteristics of the patients enrolled in this protocol. In general, these characteristics are typical of patients referred for diagnostic radionuclide perfusion imaging who are unable to perform exercise stress.

Hemodynamic response. Figure 2 shows the heart rate and blood pressure response at baseline and during the 6 min of adenosine infusion in patients completing the 6-min infusion. The typical hemodynamic response was a modest reduction in systolic and diastolic blood pressure with a compensatory increase in heart rate. Severe hypotension or paradoxic hypertension was infrequent in these patients, as well as in those who had a dose reduction or termination. Heart rate increased significantly during each minute of infusion except between the 5th and 6th min. Systolic and diastolic blood pressure decreased during each minute of infusion except that systolic blood pressure remained unchanged between baseline and minute 1. The following baseline to maximal changes were recorded: heart rate increased from 72.6 ± 13.7 to 86.3 ± 27.3 beats/min, systolic blood pressure decreased from 140.9 ± 24.3 to 131.4 ± 27.3 mm Hg and diastolic blood pressure decreased from 79.9 ± 11.9 to 71.9 ± 14.2 mm Hg.

Protocol completion. As shown in Figure 3, the 6-min 140-μg/kg per min adenosine infusion protocol was completed in 7,226 patients (80%), required dose reduction in 1,165 patients (13%) and was terminated early in 664 patients (7%). Aminophylline was given to 71 patients (0.8%). Despite adenosine dose reduction or early termination, radioisotope was injected and the infusion continued for an additional period in 98.7% of patients. In some patients, the occurrence of significant ECG changes or chest pain was the reason for the early termination or dose reduction.

Figure 3. The 6-min high dose adenosine infusion protocol was completed in 7,226 patients (80%). The short half-life of adenosine allowed dose reduction in 1,165 patients (13%) who experienced intolerable side effects.

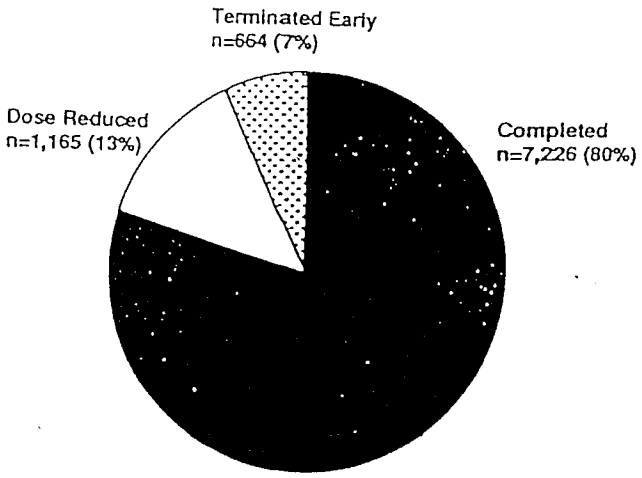

Table 2. Frequency of Adverse Events (>2%) During Adenosine Infusion (n = 9,256)

	No.	%
Flushing	3,377	36.5
SOB/dyspnea	3,260	35.2
Chest pain	3,207	34.6
GI discomfort	1,352	14.6
Headache	1,318	14.2
TNJ discomfort	1,078	11.6
Light-headedness	783	8.5
AV block	706	7.6
ST-T changes	531	5.7
Arrhythmia	309	3.3
UE discomfort	213	2.3

AV = atrioventricular; GI = gastrointestinal; SOB = shortness of breath; TNJ = throat, neck, jaw; UE = upper extremity.

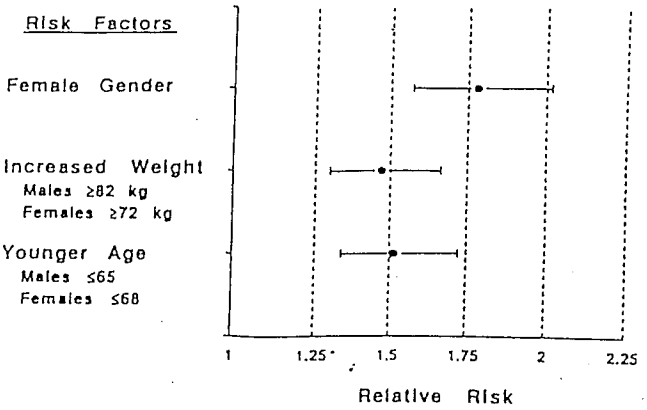

Figure 4. The relative risk of having any side effects during adenosine infusion as determined by stepwise logistic regression analysis was modestly increased in women, patients whose body weight was higher than the median body weight and those whose age was less than the median age.

Adverse events. There were no deaths in 9,256 patient studies. A total of 17,191 adverse events were reported by 7,507 patients (81.1%); no adverse events were reported by 1,749 patients (18.9%). Patients without adverse events had fewer hemodynamic changes than did patients reporting events. The occurrence of individual adverse events are presented in Table 2 for those events with >2% frequency. Of the adverse reactions, 78.4% were clinically graded by investigators as mild, 9.6% as moderate and 4.7% as severe. The relation between reported events and adenosine infusion was graded as related in the majority (definitely related in 85% and probably related in 9.6%).

Cardiovascular or other potentially significant clinical events included: hypotension in 163 (1.8%), bradycardia in 23 (0.2%), bronchospasm in 12 (0.1%, of which seven episodes were classified as severe), hypertension in 5 (0.05%), myocardial infarction in 1 (0%) and pulmonary edema in 1 (0%). The single patient who developed myocardial infarction had undergone percutaneous transluminal coronary angioplasty of the left anterior descending artery 3 days before adenosine scintigraphy. During angioplasty, a severe circumferential dissection was noted and chest pain was experienced but not reported by the patient in the ensuing 72 h.

As shown in Figure 4 from the stepwise logistic regression analysis final model, the relative risk of having any adverse event regardless of severity was increased in women (odds ratio 1.78), patients with body weight above the median (odds ratio 1.47) and patients younger than the median age (odds ratio 1.52).

Atrioventricular block. Atrioventricular block of any type occurred in 706 (7.6%) of all patients studied. Of these, 256 had first degree block, 378 had second degree block and only 72 patients (0.78% of all patients enrolled) experienced third degree AV block. Five hundred eight episodes of AV block self-terminated without requiring interventions and 133 resolved with a reduction of the dose. Only 57 patients had adenosine administration terminated because of AV block. Six patients with AV block received aminophylline, but in all cases, the episodes had already self-terminated. There were no differences in the occurrence of ischemia (perfusion defects or ischemic ECG changes) between patients with and without AV block. Thus, these episodes of AV node block probably represent a direct adenosine effect on the conduction system rather than a manifestation of ischemia.

Univariate analysis of baseline clinical and ECG characteristics, medications (including beta-adrenergic and calcium blockers) and patient age, entered as a continuous variable, identified only age as a predictor of AV block. Separate analyses were also performed entering age as a discrete variable, starting at age ≤50 or >50 years and increasing by 5-year intervals to age 75 years. The best separation by age occurred for patients <70 years (63% of all patients tested) versus patients ≥70 years (37%) (AV block incidence of 7.05% vs. 9.44%, $p < 0.001$). When this age dichotomy was entered into the logistic regression analysis model, the relative risk for AV node block was modestly increased (odds ratio 1.37, 95% confidence intervals of 1.17 to 1.61). Beta- and calcium channel blockers and conduction system abnormalities on the baseline ECG were not predictors of AV node block.

Delayed or recurrent adverse events. In the 1,067 patients monitored for 24 h, there were 142 delayed events and 107 recurrent events reported for a total of 23%. Of the 142 delayed events, 21 events in 17 patients were considered potentially significant and included headache (n = 6), gastrointestinal discomfort (n = 3), extremity discomfort (n = 3), hypotension (n = 2), chest pain (n = 2), paresthesia (n = 1), asthenia (n = 1), bradycardia (n = 1), light-headedness/dizziness (n = 1) and inability to walk (n = 1). The majority of these events resolved spontaneously or with minimal intervention and were judged by physicians to be unrelated or not clearly due to the adenosine infusion.

Discussion

These results show that adenosine infusion in conjunction with radionuclide perfusion imaging is safe in comparison with dipyridamole infusion or exercise stress testing. There were no deaths in 9,256 patients and serious side effects were rare and reversed with termination of the infusion. Aminophylline reversal was seldom required. Although there was a statistically significant increased risk for total side effects in women, younger patients and those above the median body weight, the relative risk ratios are low and do not allow clinical prediction for adverse events in an individual patient. Delayed or recurrent adverse reactions in the 24 h after infusion were infrequent and generally considered unrelated to the adenosine infusion.

Comparison with dipyridamole. Safety and adverse reactions in conjunction with dipyridamole-induced hyperemia have been reported in two large series of patients (5,6). Chahosky et al. (5) retrospectively acquired safety data in 11 patients receiving standard dose dipyridamole infusion and reported two deaths and four myocardial infarctions. Picano et al. (6) prospectively acquired similar information in 9,122 patients receiving high dose dipyridamole with echocardiography and reported one death and two myocardial infarctions. Using continuous, high dose adenosine infusion, we observed no deaths and one myocardial infarction. The myocardial infarction occurred in a patient who had a severe coronary artery dissection during angioplasty with subsequent chest pain and who retrospectively was not a good candidate for adenosine pharmacologic testing because of his unstable condition.

Because of the short half-life of adenosine, side effects reverse on termination or a decrease in the rate of the infusion. Aminophylline, an adenosine receptor antagonist, is used infrequently. Only 71 patients (0.8%) in our registry received aminophylline as opposed to 11.6% in the report by Chahosky et al. (5) and its routine use in all patients by Picano et al. (6). In 20% of our patients receiving adenosine, adverse events were treated by simply decreasing the dose. Such dose titration is not possible with dipyridamole, which has a long half-life (>30 min) that does not allow dose adjustment and requires aminophylline to reverse side effects. The administration of aminophylline may itself cause adverse events. Picano et al. (6) reported clinically significant side effects due to aminophylline reversal in 17 patients: 13 episodes of ST segment elevation associated with echocardiographic wall motion abnormalities in patients with variant angina, 3 episodes of hypotension/bradycardia and 1 episode of atrial fibrillation. Although minor side effects are more frequent with adenosine, they are well tolerated and resolve with termination of the infusion.

Considering that patients undergoing pharmacologic stress testing are generally older and more debilitated than those undergoing exercise stress, these results suggest that both dipyridamole and adenosine are safe and that severe cardiac events are rare using either agent. Adenosine offers the following advantages: rapid onset of action, proven potency as a direct coronary vasodilator, the ability to rapidly modulate its pharmacologic effects through dose adjustment, short half-life and a low incidence of aminophylline administration for reversal.

Incidence of adverse events by age, gender and body weight. During intravenous dipyridamole infusion, a higher frequency of total side effects has been reported in women relative to men and in obese patients (7,23). We report similar findings with the use of adenosine. Younger patients were more likely to report adverse events than were older patients. The reason for this age difference is not obvious and may be related to differences in perception, adenosine receptor sensitivity or adenosine metabolism.

Atrioventricular block. This occurred in 7.6% of patients but terminated spontaneously in most, and there were no prolonged episodes in any patient. The increase in relative risk in patients ≥70 years (9.44%) versus patients <70 years (7.05%) does not allow prediction of risk in an individual patient. Patients taking beta- or calcium channel blockers were not at increased risk.

The observation that perfusion defects and ischemic ECG changes did not predict AV block suggests that the block was a transient and direct pharmacologic effect of adenosine on the AV node. This is well known and underlies the current indication of adenosine as an effective drug for treatment of supraventricular tachycardia (22). Special care must be taken to infuse adenosine at a constant rate during its use with radionuclide perfusion imaging. It is optimally infused by using an accurate and preferably computerized pump system that allows the infusion rate to be decreased without being completely stopped. Stopping the infusion completely before reducing the dose results in a rapid reversal of the hyperemia and it may take 1 to 2 min to reach maximal hyperemia at the new dose. Rapid injection and flushing of the radiopharmaceutical agent through the intravenous tubing being used for the adenosine infusion should be avoided because this bolus effect will cause high blood levels and increase the risk of AV node block. The transient effects of adenosine on the conduction system are reported to be unresponsive to atropine.

Delayed or recurrent adverse events. The occurrence of delayed or recurrent side effects in the 24 h after adenosine infusion was low and in most cases considered unrelated to the prior adenosine infusion. Because adenosine is an endogenous substance with a plasma half-life of <10 s, it is difficult to attribute delayed or recurrent adverse events to its use. It is more likely that the reported events were related to the patients' ongoing medical problems, changes in medications or changes in management.

Conclusions. These prospective findings in a large group of patients establish the overall safety of adenosine pharmacologic hyperemia in conjunction with radionuclide perfusion imaging.

Addendum

Since completion of enrollment of the 9,256 patients presented in this report, approximately 1,800 additional patients have been enrolled and there was one reported death after a total patient enrollment of 11,000.

Appendix

Study Participants

The following clinical centers and principal investigators participated in the Adenoscan Multicenter Trial Registry:

Naomi P. Alazraki, MD, Emory University Medical Center, Atlanta. *L. Chapman Bean, MD*, Arizona Heart Institute, Phoenix, Arizona: *elardinelli, MD*, University of Florida, Gainesville, Florida: *Malcom u, MD*, Mayo Clinic, Rochester, Minnesota: *Daniel S. Berman, MD*, dars-Sinai Medical Center, Los Angeles, California: *Elias H. Botvinick, MD*, University of California, San Francisco, California: *Jorge Cheirif, MD*, Veterans Administration Medical Center, Houston, Texas: *Christopher L. Hr n, MD*, Temple University Hospital, Philadelphia, Pennsylvania: *Gary er, MD, PhD*, Memorial Hospital, Pawtucket, Rhode Island: *Abdul- S. Iskandrian, MD*, Philadelphia Heart Institute, Philadelphia, Pennsylvania: *Donald L. Johnston, MD*, Mayo Clinic, Rochester, Minnesota: *ffrey A. Leppo, MD*, University of Massachusetts Medical Center, Worcester, Massachusetts: *Jamshid Maddahi, MD*, St. Joseph Medical Center, Burbank, California: *Lloyd S. Parker, MD*, St. Joseph Medical Center, Burbank, California: *Syed Mohiuddin, MD*, Creighton Cardiac Center, Omaha, Nebraska: *Joel S. Raichlen, MD*, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania: *Gregg J. Reis, MD*, Beth Israel Hospital, Boston, Massachusetts: *Heinrich R. Schelbert, MD, PhD*, UCLA School of Medicine, Los Angeles, California: *Markus Schwaiger, MD*, University of Michigan Medical Center, Ann Arbor, Michigan: *A. Allen Seals, MD*, University of Florida, Jacksonville, Florida: *Jerry Stolzenberg, MD*, Miami Heart Institute, Miami Beach, Florida: *Mario S. Verani, MD*, Baylor College of Medicine and The Methodist Hospital, Houston, Texas: *Kim Allan Williams, MD*, University of Chicago Physicians Group, Chicago, Illinois.

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