Safety of dipyridamole testing in 73,806 patients: The Multicenter Dipyridamole Safety Study

Jean Lette, MD, James L. Tatum, MD, Sheila Fraser, CA, D. Douglas Miller, MD, David D. Waters, MD, Gary Heller, MD, Eric B. Stanton, MD, Hee Seung Bom, MD, Jeffrey Leppo, MD, and Stanley Nattel, MD, for the Multicenter Dipyridamole Safety Study Investigators

Background. **Dipyridamole imaging is widely used as an alternative to exercise testing to identify and risk stratify patients with coronary artery disease. Safety data on intravenous dipyridamole stress testing has been derived largely from individual institutional data.**

Methods and Results. **Data were collected retrospectively by 85 coinvestigators from 73,806 patients who underwent intravenous dipyridamole stress imaging in 59 hospitals and 19 countries to determine the incidence of major adverse reactions during testing. The dose of dipyridamole infused was 0.56 mg/kg in 64,740 patients, 0.74 mg/kg in 6551 patients, and 0.84 mg/kg in 2515 patients. Combined major adverse events among the entire 73,806 patients included seven cardiac deaths (0.95 per 10,000), 13 nonfatal myocardial infarctions (1.76 per 10,000), six nonfatal sustained ventricular arrhythmias (0.81 per 10,000) (ventricular tachycardia in two and ventricular fibrillation in four), nine transient cerebral ischemic attacks (1.22 per 10,000), (with speech or motor deficit), one stroke, and nine severe bronchospasms (1.22 per 10,000) (one intubation and eight near intubations). In addition to the safety data, detailed demographic, peripheral hemodynamic, side effect, and concomitant drug data were examined in a subgroup of 3751 patients. End points from subsets of patients were compared with those of the group as a whole. Multivariate analysis revealed that dipyridamole-induced chest pain was more common in patients less than 70 years old ($p = 0.0017$), those with a history of coronary revascularization ($p = 0.002$), or patients taking aspirin ($p = 0.0001$). Minor noncardiac side effects were less frequent among the elderly ($p = 0.0053$) and more frequent in women ($p = 0.0001$) and patients taking maintenance aspirin ($p = 0.0034$). When a patient was judged on the basis of the adequacy of hemodynamic response to be a dipyridamole "nonresponder" (< 10 mm Hg drop in systolic blood pressure and 10 beats/min increase in heart rate), the only significant predictor was angiotensin-converting enzyme inhibitor intake ($p = 0.0025$). Inferoposterior hypoperfusion was significantly more frequent in patients with dipyridamole-induced hypotension: 57% (44/77) ($p < 0.0001$) of those who had hypotension and 89% (8/9) ($p = 0.0076$) who had severe symptomatic bradyarrhythmias displayed inferoposterior defects on thallium scanning. Caffeine levels were determined in 391 consecutive patients: levels greater than 5 mg/L were observed in only eight patients (2%), suggesting that methylxanthine levels sufficient to alter the hemodynamic response to dipyridamole resulting in suboptimal hyperemic stress are unlikely when patients take nothing by mouth after midnight.**

Conclusion. **The risk of serious dipyridamole-induced side effects is very low and is comparable to that reported for exercise testing in a similar patient population. (J NUCL CARDIOL 1995;2:3-17.)**

Key Words: dipyridamole · stress testing · radionuclide imaging · coronary heart disease · coronary hyperemia/vasodilation · asthma

From Maisonneuve Hospital and the Montreal Heart Institute, Montreal, Quebec, Canada, the Medical College of Virginia, Richmond, Va., St. Louis University Medical Center, St. Louis, Mo., Hartford Hospital, Hartford, Conn., St. Joseph's Hospital, Hamilton, Ontario, Canada, the Chonnam University Hospital, Kwangju, Korea, and the University of Massachusetts Medical Center, Worcester, Mass.

Supported by an educational grant from DuPont Pharma, Billerica, Mass.

Submitted for publication Aug. 15, 1994; revision accepted Oct. 3, 1994.

Reprint requests: Jean Lette, MD, Montreal Heart Institute, 5000 Belanger St. E., Montreal, Quebec, Canada H1T-IC8.

1071-3581/95/$3.00 + 0 **43/1/60982**

Pharmacologic coronary vasodilation stress produced by intravenous dipyridamole, when used in conjunction with myocardial perfusion imaging, provides a clinically useful alternative to exercise testing in patients who are unable to achieve an acceptable level of dynamic cardiac stress. The heterogeneous regional distribution of coronary blood flow produced by dipyridamole hyperemia yields myocardial perfusion images similar to those obtained with exercise testing, allowing for both the accurate detection of underlying coronary stenoses and the risk stratification of patients with suspected and known coronary heart disease.[1-9]

The risk of severe complications including myocardial infarction, death, and stroke has been previously reported to be low.[10,11] Recent anecdotal case reports[12-23] have generated concern that the complication rate may be increasing as the test is used more widely, prompting some clinicians to seek alternative methods of pharmacologic stress testing. The principal goal of this study was to define the incidence of severe complications of dipyridamole stress testing in a large and clinically heterogeneous cohort of patients.

A secondary goal of this study was to determine the covariables associated with variation in heart rate, blood pressure, minor noncardiac side effects, chest pain, and S-T segment changes, which have been reported previously,[23-30] in a subgroup of 3715 patients for whom detailed hemodynamic, clinical electrocardiographic, and drug data were available. The efficacy of aminophylline as a dipyridamole antidote was evaluated in 92 patients with hyperemia-induced S-T segment changes. Caffeine blood levels also were measured in 391 unselected patients who had been instructed to take nothing by mouth (including coffee and tea) after midnight to assess patient compliance with physician instructions.

MATERIAL AND METHODS

Multicenter Survey of 73,806 Patients. Seventy-five sites were surveyed to determine their capacity to provide required information on the number of dipyridamole tests performed, the interval during which they were performed, the dose regimen used, and the number of severe complications encountered. Severe complications to be ascertained were cardiac death, nonfatal myocardial infarction, sustained ventricular tachycardia, ventricular fibrillation, transient ischemic attacks (speech or motor defect), stroke, noncardiac death, severe bronchospasm (with intubation, near intubation, or hospitalization), and severe or unusual reactions to dipyridamole or aminophylline. The exact number of tests performed was compiled at each site with either individual patient records, patient data bases, or pharmacy records. Because reporting of severe reactions was dependent on physician recollection, a number of measures were taken to ensure that reporting was reliable: only severe adverse effects were considered and, for all cases of adverse effects reported, the site investigator was required to review the medical chart and complete a detailed questionnaire pertaining to the sequence of events leading to the complication, as well as the patient's medical history and subsequent investigation.

Any center that was either unable to identify all patients who sustained adverse effects or who did not complete the detailed complication reports was excluded from the study. These techniques contributed to the high level of ascertainment for complications. Interestingly, the complication rates reported exceeded those in some previous large-scale reports of pharmacologic stress testing. In addition, the variability of complication rates between sites was low, indicating that the level of reporting was similar. Of the 75 sites, 16 were not able to comply with the aforementioned requirements, usually because of lack of resources to compile the data and not because of a higher complication rate. Unstable angina requiring hospitalization and coronary revascularization and acute pulmonary edema were uncommon and were not included as study end points because of the difficulty in defining these conditions objectively.

Substudy of 3715 Patients

Patient population. This phase of the study consisted of 3715 consecutive patients referred for dipyridamole myocardial perfusion imaging at the Medical College of Virginia between 1986 and 1992. Patients were referred for dipyridamole stress testing based on the clinical determination that they would not reach an adequate level of exercise on the treadmill, most commonly because of physical limitations or negative chronotropic drugs.

Each patient was interviewed and medical records were reviewed before the patient signed an informed, written consent to participate in the dipyridamole testing protocol, as approved by the Institutional Review Board on the Conduct of Human Research. Data from the patient interview, available medical records, and subsequent record searches were entered into a database that included the parameters listed in Tables 1 and 2. Theophylline derivatives (except pentoxiphylline) were discontinued 48 hours before testing. Patients otherwise took nothing by mouth after midnight for all other drugs, including coffee, tea, and other caffeine-containing drinks (thus discontinued 8 to 12 hours before testing).

Dipyridamole testing protocol. Dipyridamole was infused during 4 minutes in the supine position with a dose of 0.56 mg/kg to a maximum of 60 mg. The heart rate, blood pressure, and a 12-lead electrocardiogram (ECG) were recorded before and every minute after the onset of dipyridamole infusion for a total of 10 minutes. In addition, three electrocardiographic leads were monitored continuously. ^{201}Tl was injected at 7 minutes (2.5 to 3.5 mCi). The early set of single-photon emission computed tomographic (SPECT) images was acquired after the 10-minute period of monitoring. Redistribution imaging was performed 3 to 4

hours later. SPECT imaging was performed with a standard 180-degree semicircular arc starting from the 45-degree right anterior oblique position.

Side effects. Side effects were recorded continuously during the 10-minute observation period. Patients were informed as to the potential side effects at the time they provided informed consent (30 to 60 minutes before testing). The presence of side effects was not solicited actively at the time of or after the infusion of dipyridamole but was simply questioned in general terms, with side effects recorded as volunteered by the patient.

Electrocardiographic interpretation. All ECGs were interpreted by a blinded observer. The baseline electrocardiogram was used for comparison.

Study End Points

Change in heart rate. The maximal increase in heart rate during the 10-minute observation period compared with the baseline supine heart rate was the first end point.

Change in systolic blood pressure. The maximal decrease in systolic blood pressure during the 10-minute observation period compared with the baseline value was another endpoint.

Nonresponders. Two different definitions of "nonresponder" were considered. Heart rate nonresponder included patients whose heart rate increased by less than 10 beats/min during the test. Heart rate and blood pressure nonresponders were those patients whose heart rate increased by less than 10 beat/min and whose systolic blood pressure decreased by less than 10 mm Hg during the test.

Hypotension. In view of the controversy surrounding the definition of hypotension in the medical literature, we used three different classifications for the purpose of data analysis (Table 3): a systolic blood pressure of 90 mm Hg or less, a greater than 20% drop in systolic blood pressure, or a greater than 50 mm Hg drop in mean arterial pressure. Patients with symptomatic hypotension had either dizziness, lightheadedness, or syncope.

Chest pain. Dipyridamole-induced chest pain included symptoms of chest discomfort, arm pain, or neck tightness.

Criteria for positive electrocardiographic changes. The electrocardiographic response to dipyridamole was considered positive if there was 1 or more mm of additional (compared with baseline) horizontal or downsloping S-T segment depression. Electrocardiographic changes were deemed to have resolved if the ECG no longer met the criteria for positivity (≥ 1 mm of additional horizontal or downsloping S-T segment depression during the period of observation, for a total of 10 minutes).

Aminophylline-Electrocardiographic Substudy. In this substudy, 92 consecutive patients with criteria for a positive electrocardiographic response were evaluated as to the response of intravenous aminophylline. Forty-seven patients received aminophylline and 45 did not. A profile of these patients is shown in Table 4.

Caffeine Substudy. Caffeine blood levels were measured by high-pressure liquid chromatography in an unselected population of 391 patients referred for dipyridamole testing, who were told to take nothing by mouth (including coffee) after midnight.

Statistical Analysis of Data from the Subgroup. All data from the subgroup study were maintained in a relational data base (Ingres; Relational Technology, Alameda, Calif.). Statistical analysis was performed with the SAS software system for data analysis (SAS Institute Inc., Cary, N.C.). Mean and SD determinations are reported for continuous variables and simple frequency distributions for discrete measurements. Intergroup univariate comparisons used the t test procedure for impaired continuous variables. For discrete variables, the χ^2 analysis was used. In each case the significance level was set at $p < 0.05$. Multivariate analysis was performed by logistic regression applied to the independent variables listed in Tables 1 and 2 in a stepwise fashion. Models were designed to examine four dependent testing outcomes: angina-like chest pain, minor side effects, heart rate nonresponders, and heart rate and blood pressure nonresponders (Table 5). A significance level of $p < 0.05$ was set for inclusion of the variable in the model.

RESULTS

Multicenter Survey of 73,806 Patients. Data were collected retrospectively by 85 coinvestigators from 59 hospitals in 19 countries. The dose of dipyridamole infused was 0.56 mg/kg in 64,740 patients, 0.74 mg/kg in 6551 patients, and 0.84 mg/kg in 2515 patients, for a total of 73,806 patients.

The variability in the complication rate from one center to another is low, suggesting that the detection and reporting of events were accomplished with a similar degree of accuracy. All patients who had complications were identified and their medical charts reviewed.

Nonfatal Myocardial Infarctions. There were 13 nonfatal myocardial infarctions, including 7 non-Q-wave infarctions and 6 Q-wave infarctions. The patients were 61 ± 9.3 years old at the time of the event. Of the 13 patients, 23% (3/13) had had a recent (<3 weeks) infarction (3, 12, and 13 days before testing), 23% (3/13) had a history of spontaneous angina at rest less than 48 hours (2, 10, and 36 hours) before the test, 31% (4/13) had diabetes, and 62% (8/13) had a history of hypertension. None of these patients had hypotension during dipyridamole infusion.

There were two patterns of presentation of dipyridamole-induced nonfatal myocardial infarction. In 62% (8/13) of patients, chest pain or ischemic S-T segment changes were followed rapidly by signs of infarction despite aminophylline injection. The delay between the onset of the infusion and the appearance of ischemia was less than 10 minutes in six of eight patients and 30 and 60 minutes in the remaining two.

Table 1. Substudy clinical parameters

Group	*n* (%)	Δ SBP (mm Hg) (mean ± SD) [*p* value]	Δ HR (beats/min) (mean ± SD) [*p* value]
Total	3715 (100)	14.07 ± 14.83	17.11 ± 11.26
Male patients	1484 (39.95)	14.94 ± 14.25	15.62 ± 10.72 [0.0001]
Age ≥ 70 yr	1007 (27.11)	17 ± 15.9 [0.0001]	15.5 ± 10.37 [0.0001]
Weight ≥ 93 kg	544 (14.64)	10.09 ± 11.94 [0.0001]	18.38 ± 11.13 [0.0043]
Insulin-dependent diabetics	267 (7.2)	14.91 ± 15.74 [0.373]	13.88 ± 10.14 [0.0001]
Hypertension	414 (11.14)	14.53 ± 16.72 [0.546]	17.67 ± 11.47 [0.29]
After CABG or PTCA	222 (5.98)	14.39 ± 14.85 [0.737]	15.03 ± 10.7 [0.003]
Kidney transplantation	106 (2.85)	15.31 ± 16.06 [0.428]	14.59 ± 8.84 [0.004]
Hepatic failure‡	58 (1.56)	9.43 ± 12.51 [0.006]	16.97 ± 12.41 [0.929]

SBP, Systolic blood pressure; *HR*, heart rate; *MSE*, minor noncardiac side effects; *CABG*, coronary artery bypass grafting; *PTCA*, percutaneous transluminal coronary angiography.
*Increment in heart rate less than 10 beats/min.
†Increment in heart rate less than 10 beats/min and drop in systolic blood pressure less than 10 mm Hg.
‡Pre-liver transplantation workup.

Table 2. Substudy concurrent medical therapy

Group	*n* (%)	Δ SBP (mm Hg) (mean ± SD) [*p* value]	Δ HR (beats/min) (mean ± SD) [*p* value]
Total	3715 (100)	14.07 ± 14.83	17.11 ± 11.26
Antihypertensives	243 (6.54)	14.21 ± 17.62 [0.895]	16.84 ± 10.37 [0.678]
Antiarrhythmics	54 (1.45)	15.19 ± 11.46 [0.485]	13.09 ± 8.76 [0.0013]
Diuretics	595 (16.02)	13.37 ± 13.61 [0.169]	14.48 ± 10.39 [0.0001]
Dipyridamole	89 (2.40)	14.87 ± 13.14 [0.597]	16.45 ± 11.27 [0.571]
Pentoxiphylline	45 (1.21)	18.66 ± 17.63 [0.086]	13.93 ± 8.87 [0.02]
Immunosuppressants	90 (2.42)	14.35 ± 16 [0.878]	14.62 ± 10.79 [0.03]
Digoxin	176 (4.74)	14.61 ± 12.99 [0.591]	13.77 ± 10.44 [0.0001]
Aspirin	572 (15.40)	12.14 ± 15.66 [0.0012]	16.67 ± 10.24 [0.276]
ACE inhibitors	307 (8.26)	13.57 ± 15.57 [0.54]	14.06 ± 9.37 [0.0001]
Calcium antagonists	533 (14.35)	13.15 ± 15.01 [0.117]	16.32 ± 11.18 [0.079]
β-Blockers	178 (4.79)	13.2 ± 14.49 [0.404]	16.3 ± 8.97 [0.223]

For abbreviations see Table 1.
*Increment in heart rate less than 10 beats/min.
†Increment in heart rate less than 10 beats/min. and drop in systolic blood pressure less than 10 mm Hg.

In 38% (5/13) of patients, dipyridamole-induced chest pain or ischemic S-T segment changes resolved completely after aminophylline injection, only to recur later and progress to myocardial infarction. The delay from the onset of the infusion to the initial episode of transient ischemia in the five patients was 3, 4, 7, 12, and 48 minutes. Recurrent ischemia followed by signs of infarction appeared, respectively, 15, 33, 50, 240, and 248 minutes from the onset of infusion. We would expect delayed and asymptomatic (without immediate electrocardiographic changes) infarctions to be underreported in our study.

Sustained Ventricular Arrhythmia (Table 6). Dipyridamole-induced sustained ventricular arrhythmias were reported in six patients, ventricular tachycardia in four, and fibrillation in two. All patients required emergency cardioversion. Only 50% (3/6) of patients had clinical or electrocardiographic signs of ischemia before the onset of the arrhythmia. All patients had a history of myocardial infarction and severe baseline left ventricular dysfunction. None of the patients had significant dipyridamole-induced hypotension before the onset of the arrhythmia and none gave a history of spontaneous resting angina

MSE (*n*/%) [*p* value]	Chest pain (*n*/%) [*p* value]	Nonresponder HR* (*n*/%) [*p* value]	Nonresponder HR + BP† (*n*/%) [*p* value]
357/9.61	362/9.74	794/21.37	83/2.23
86/5.80 [0.001]	87/5.86 [0.0001]	362/24.39 [<0.0001]	27/1.82 [0.189]
73/7.25 [0.003]	74/7.35 [0.003]	241/23.93 [0.02]	18/1.79 [0.261]
57/10.48 [0.457]	54/9.93 [0.877]	90/16.54 [0.003]	13/2.39 [0.791]
35/13.11 [0.045]	28/10.49 [0.679]	88/32.96 [<0.0001]	10/3.75 [0.078]
35/8.45 [0.397]	48/11.59 [0.178]	90/21.74 [0.847]	10/2.42 [0.791]
17/7.66 [0.299]	33/14.86 [0.009]	50/22.52 [0.694]	4/1.80 [0.646]
11/10.09 [0.790]	5/4.59 [0.076]	23/21.7 [0.937]	2/1.9 [0.815]
4/6.90 [0.477]	3/5.17 [0.235]	14/24.14 [0.607]	2/3.45 [0.521]

MSE (*n*/%) [*p* value]	Chest pain (*n*/%) [*p* value]	Nonresponder HR* (*n*/%) [*p* value]	Nonresponder HR + BP† (*n*/%) [*p* value]
357/9.61	362/9.74	794/21.37	83/2.23
26/10.70 [0.551]	28/11.52 [0.334]	52/21.40 [0.992]	6/2.47 [0.798]
4/7.41 [0.578]	8/14.81 [0.208]	16/29.63 [0.137]	0/0 [0.265]
53/8.91 [0.516]	61/10.25 [0.660]	169/28.40 [<0.0001]	22/3.70 [0.007]
7/7.9 [0.366]	9/10.1 [0.882]	19/21.35 [0.963]	3/3.37 [0.442]
6/13.3 [0.429]	5/11.1 [0.779]	13/28.89 [0.253]	1/2.22 [0.984]
6/6.7 [0.350]	5/5.6 [0.182]	24/26.67 [0.194]	2/2.22 [0.985]
15/8.52 [0.611]	22/12.50 [0.210]	60/34.09 [<0.0001]	7/3.98 [0.104]
75/13.11 [0.002]	89/15.56 [<0.0001]	119/20.80 [0.710]	14/2.45 [0.684]
25/8.14 [<0.357]	32/10.42 [0.683]	91/29.64 [<0.0001]	15/4.89 [0.001]
63/11.82 [0.068]	80/22 [<0.0001]	121/22.7 [0.454]	15/2.80 [0.319]
21/11.8 [0.324]	24/13.5 [0.092]	25/14 [0.013]	6/3.37 [0.291]

within 48 hours of the test. Only one patient had a history of malignant ventricular arrhythmia and underwent implantation of an automatic cardiac defibrillator with a known malfunction. Electrophysiologic testing was subsequently performed in three patients: results were negative in two patients and positive in one. The latter patient subsequently underwent uneventful dipyridamole testing with maintenance doses of sotalol.

Cardiac Death (Table 7). Seven patients died of cardiac complications after dipyridamole testing. The events leading to death were progressive hypotension in three patients, intractable pulmonary edema in two, and refractory ventricular fibrillation in two, despite prompt administration of aminophylline in each case.

All patients who died had a history of myocardial infarction and 57% (4/7) had a history of congestive heart failure. One patient had a history of prolonged chest pain the night before the test.

Acute Severe Bronchospasm (Table 8). There were nine cases of severe bronchospasm requiring either intubation, near intubation, or hospitalization. The final diagnoses were acute pulmonary edema in one patient and probable anaphylactic reaction in another. Of the remaining seven patients, 71% (5/7) had either severe labile asthma (1/5) or severe chronic obstructive pulmonary disease (COPD) with a history

Table 3. Hypotension

Definition	Symptomatic (*n*/%)*	Asymptomatic (*n*/%)
Dipyridamole-induced systolic BP <90 mm Hg	4/0.1	73/2
>20% drop in systolic BP	13/0.4	378/11
>50 mm drop in mean pressure	0	4/0.11

BP, Blood pressure.
*Symptoms include dizziness, lightheadedness, or syncope.

Table 4. Aminophylline-electrocardiographic substudy: all patients

	Aminophylline (n = 47)	No aminophylline (n = 45)	p Value
Age (yr)	64.3 ± 1.6	69.6 ± 1.7	0.03
No. of mean (%)	12 (25.5)	17 (37.8)	NS
Time ECG positive	7.4 ± 0.2	7.2 ± 0.2	NS
No. with symptoms (%)*			
Chest pain	36 (76.6)	10 (22.2)	0.001
Headache	4 (8.5)	3 (6.7)	NS
Dizziness	3 (6.4)	1 (2.2)	NS
Flushing	2 (4.2)	0 (0.0)	NS
Nausea	7 (14.9)	1 (2.2)	0.03
Hypotension	3 (6.4)	1 (2.2)	NS
Dyspnea	10 (21.3)	2 (4.4)	0.02
RPP			
Baseline	11,777 ± 471	12,202 ± 481	NS
7 Min	14,665 ± 583	14,089 ± 596	NS
10 Min	15,176 ± 593	14,222 ± 607	NS
No. with ECG resolution (%)	28 (60.0)	3 (6.7)	0.001
Duration of ECG change	2.6 ± 0.5	5 ± 0.9	0.05

NS, Not significant; *ECG*, electrocardiogram; *RPP*, rate pressure product.
*Before administration of aminophylline.

of acute respiratory failure (4/5); 71% (5/7) of patients were receiving maintenance oral prednisone therapy.

Cerebrovascular Events. There were nine transient cerebral ischemic attacks (TIAs) with transient motor or speech defect and one stroke. The mean age was 64.1 years (range 33 to 84 years). The event was hemispheric in six patients (left-sided in four and right-sided in two), bulbar in two, and indeterminate in one; signs of cerebrovascular ischemia lasted less than 30 minutes in seven patients and 24 hours in the remaining two. None of the patients had hypotension (systolic blood pressure ≤90 mm Hg) before the event. A carotid artery Doppler study was performed in five patients with TIAs: two had significant underlying stenoses and three did not. The patient who had a stroke had a history of left hemispheric TIA and a 90% stenosis of both internal carotid arteries on carotid Doppler ultrasonography. A minimal residual defect remained 2 months later.

Risk of High- Versus Low-Dose Testing. The number of patients who received the low (0.56 mg/kg)-, intermediate (0.70 mg/kg)-, and high (0.84 mg/kg)-dose regimens was, respectively, 12, 0, and 1 for myocardial infarction; 6, 1, and 0 for cardiac death; 3, 1, and 2 for sustained ventricular arrhythmia; 9, 0, and 0 for TIAs; 8, 1, and 0 for severe bronchospasm; and 1, 0, and 0 for stroke.

Other Complications

Noncardiac death. One patient died during cardiac imaging about 10 minutes after the onset of dipyridamole imaging. An autopsy revealed massive pulmonary embolism. The test had been performed for the investigation of atypical chest pain of recent onset.

Seizures. Three patients had seizures during

Table 5. Logistic regression analysis

Predictor (end point)	Standard error	*p* Value	Odds ratio
Chest pain			
Aspirin	0.13	0.0001	1.945
Prior CABG or PTCA	0.186	0.0002	2.0
Age ≥ 70 yr	0.135	0.0017	0.653
Male sex	0.125	0.0001	0.45
Constant	0.077	0.0001	0.133
Minor noncardiac side effects			
Male sex	0.1255	0.0001	0.463
Aspirin	0.1385	0.0034	1.499
Age ≥ 70 yr	0.135	0.0053	0.686
Constant	0.075	0.0001	0.1412
Heart rate and blood pressure nonresponders			
ACE inhibitors	0.29	0.0025	2.409
Constant	0.12	0.0001	0.020
Heart rate nonresponders			
Weight ≥ 93 kg	0.1253	0.0025	0.6849
Diuretics	0.1068	0.0009	1.428
Digoxin	0.1685	0.0020	1.683
β-Blockers	0.2213	0.0038	0.527
Insulin	0.1245	0.0001	1.808
Renal failure	0.2221	0.312	1.612
Age ≥ 70 yr	0.09	0.0294	1.216
Male sex	0.081	0.0001	1.402
Constant	0.07	0.0001	0.201

CABG, Coronary artery bypass grafting; *PTCA*, percutaneous transluminal coronary angioplasty.

dipyridamole infusion: two were known to have epilepsy and had not taken their medication the morning of the test (one patient underwent uneventful repeat testing while receiving anticonvulsant medication). A detailed neurologic investigation of a third patient was entirely negative.

Severe reactions to dipyridamole ($n = 3$) or aminophylline ($n = 1$) were uncommon. Reactions to dipyridamole included severe chills ($n = 2$) and one death from probable anaphylaxis (bronchospasm and hypotension followed by death). One patient had tachycardia and hypotension (reversed with intravenous fluids) after aminophylline injection.

Symptomatic bradyarrhythmias (sinus bradycardia or heart block) were uncommon ($n = 7$; 1/10,000) but probably underreported because they were classified as "other severe complications" in the report form and patients' charts were not reviewed individually in the large-scale study. We believed that the substudy of 3715 patients would be more reliable to determine the risk of bradyarrhythmias, because it involved better-controlled electrocardiographic monitoring.

Substudy of 3715 Patients (Tables 1 and 2)

Sex. The subset of male patients had a significantly diminished heart rate response to dipyridamole infusion and were more likely to be classified as heart rate nonresponders (24% of men) ($p = 0.0001$).

Age. Elderly patients (≥ 70 years) had a more significant decrease in mean systolic blood pressure ($p = 0.0001$) and a less significant increase in heart rate during drug infusion ($p = 0.0001$). These hemodynamic changes were associated with a lesser incidence of minor side effects (7.3%) ($p = 0.003$) and a greater incidence of chest pain (7.4%) ($p = 0.003$). Of interest, 24% of the elderly population were judged to be heart rate nonresponders ($p = 0.02$).

Body weight. Patients of greater body weight demonstrated a significantly smaller change in mean systolic blood pressure ($p = 0.0001$) but a significantly greater increase in mean heart rate after dipyridamole infusion ($p = 0.0043$). A relatively small percentage of these patients, who received the largest doses of dipyridamole (maximum 60 mg, which corresponds to 93 kg on a milligram-per-killigram basis), were heart rate nonresponders (16.5%) ($p = 0.003$).

Diabetes mellitus treated with insulin. The diabetic population had a decreased heart rate response to dipyridamole infusion ($p = 0.0001$), with

Table 6. Sustained ventricular arrhythmia

Patient	Arrhythmia	Dose (mg)	Delay (min)*	DIP-induced ischemia	Age (yr)	Sex	LVEF (%)	Coronary angiogram	Known V arrhythmia	Comments
1	V Tach	44	60	No	75	M	19	N/A	No	
2	V Tach	55	30	No	53	M	30	3VD	Yes	Implantable automatic cardiac defibrillator with known malfunction
3	V Fib	38	10	CP	75	F	35	2VD	No	Sudden death 1 yr later
4	V Fib	73	45	CP, ↓ ST	56	M	27	3VD	No	Negative EPS, follow-up: Asx 2 yr after CABG
5	V Fib	43	8	No	66	M	†	2VD	No	Negative EPS
6	V Fib	52	19	↓ ST	68	M	31	1VD	No	Positive EPS, repeat DIP testing under sotacor uneventful

DIP, Dipyridamole; *LVEF*, left ventricular ejection fraction; *V*, ventricular; *V Tach*, ventricular tachycardia; *N/A*, test not performed; *VD*, vessel disease; *V Fib*, ventricular fibrillation; *CP*, chest pain; *EPS*, electrophysiologic study; *Asx*, asymptomatic; *CABG*, coronary artery bypass grafting.
*Delayed from the onset of dipyridamole infusion.
†Significant left ventricular dysfunction (anterior and posterior akinesis).

Table 7. Cardiac death

Patient	Dose (mg)	Delay (min)	Description of event	Age (yr)	Sex	Recent ischemia*	Severity of pretest angina	Previous MI	CHF	Comments
1	55	5	Chest pain ↓ ST → shock	48	M	N	3	1	N	
2	50	34	Pulmonary edema → cardiac arrest	46	M	N	0	1	1	Autopsy: severe 3VD, recent infarction
3	44	8	Chest pain → pulmonary edema → cardiac arrest	57	M	N	0	1	1	
4	41	17	Chest pain → V Fib → cardioversion → irreversible V Fib 30 min later	55	M	N	1	1	1	
5	25	2	MI → shock	70	M	1	3	1	1	Died after 4 wk in ICU (on ventilator and intraaortic balloon)
6	32	34	Irreversible V Tach → V Fib	62	M	N	0	1	N	Autopsy: recent MI
7	45	4	Irreversible hypotension → shock	70	M	1	4	1	N	Prolonged chest pain night before test

Only one patient (no. 6) had a recent (10 day) myocardial infarction.
MI, Myocardial infarction; *CHF*, history of congestive heart failure; *VD*, vessel disease; *V Fib*, ventricular fibrillation; *ICU*, intensive care unit; *V Tach*, ventricular tachycardia.
*Spontaneous angina less than 48 hours before test.

31% of this population being classified as heart rate nonresponders.

Organ transplantation. The subset of patients undergoing evaluation for kidney transplantation, 17% of whom were suffering from diabetes, also demonstrated a diminished chronotropic response to dipyridamole infusion ($p = 0.004$). By contrast, patients with hepatic failure (pre-liver transplantation

Table 8. Acute severe bronchospasm

Patient	Dose (mg)	Delay (min)*	Duration of wheezing (min)	Age (yr)	Sex	Pulmonary history	Medication
1	72	5	240	63	F	Admission for COPD and asthma (prior ARF, continuous O_2 at home)	β_2, Th, Pred
2	30	4	10	51	M	COPD, emphysema (prior intubation for ARF)	β_2, Pred
3	43	6	20	55	M	COPD, emphysema	β_2, Atr, Pred
4†	20	2	60	68	F	Asthma during childhood	None
5	40	6	20	50	M	COPD, asthma (prior intubation for ARF)	β_2, Atr, Becl, Th, Pred
6	50	2 and 90	180	55	F	Asthma (severe labile)	β_2, Becl, Th
7‡	40	45	45	61	F	Prior admissions for pulmonary edema, CHF	Th
8	40	4	180	67	M	COPD, emphysema (prior intubation for ARF)	β_2, Atr, Pred
9	34	4	45	69	F	Asthma (moderate)	β_2, Becl

COPD, Chronic obstructive pulmonary disease; *ARF*, acute respiratory failure; *β_2*, β_2-agonist; *Th*, theophylline; *Pred*, prednisone; *Atr*, atrovent; *Becl*, beclovent; *CHF*, congestive heart failure.
*Delay from onset of dipyridamole infusion.
†Final diagnosis: anaphylaxis.
‡Final diagnosis: acute pulmonary edema (on chest x-ray film).

workup) had a normal chronotropic response but significantly smaller decreases in systolic blood pressure during drug infusion ($p = 0.006$).

Hypertension. Of interest, hypertensive patients did not demonstrate significant differences in peripheral hemodynamic response from the mean response of the total population. These patients were no more likely to have hypertension during drug infusion.

Previous coronary revascularization. The subgroup of patients who had undergone prior coronary bypass graft surgery or percutaneous transluminal coronary angioplasty demonstrated a smaller change in heart rate during dipyridamole infusion ($p = 0.003$). Despite this, a significantly greater percentage of the population who had undergone prior coronary revascularization (14.9%) had chest pain during dipyridamole infusion ($p = 0.009$).

Concomitant drug therapy. Diabetic patients taking insulin had more noncardiac side effects (13.1%; $p = 0.045$), and patients taking aspirin had more minor side effects (13.1%; $p = 0.002$) and chest pain (15.6%; $p = 0.0001$) during drug stress. Previous administration of dipyridamole ($n = 89$) or pentoxiphylline ($n = 45$) was not associated with a higher nonresponse rate. The number of heart rate nonresponders was significantly higher among patients taking diuretics (28.4%; $p < 0.0001$), digoxin (34%; $p < 0.0001$), and angiotensin-converting enzyme (ACE) inhibitors (30%; $p < 0.0001$).

Interestingly, among all clinical parameters and drugs recorded, only digoxin (4%; $p = 0.007$) and ACE inhibitors (4.9%; $p = 0.01$) were associated with a higher rate of both heart rate and blood pressure nonresponse.

Multiple Analysis (Table 5). When logistic regression (maximal likelihood ratio method) was applied to the independent variables, the predictors were (1) for chest pain; aspirin intake ($p = 0.0001$), female sex ($p = 0.0001$), prior coronary revascularization ($p = 0.0002$), and age less than 70 years ($p = 0.0017$); (2) for minor noncardiac side effects: female sex ($p = 0.0001$), aspirin intake ($p = 0.0034$), and age less than 70 years ($p = 0.0053$); (3) for heart rate and blood pressure nonresponders: ACE inhibitor intake ($p = 0.0025$); (4) for heart rate nonre-

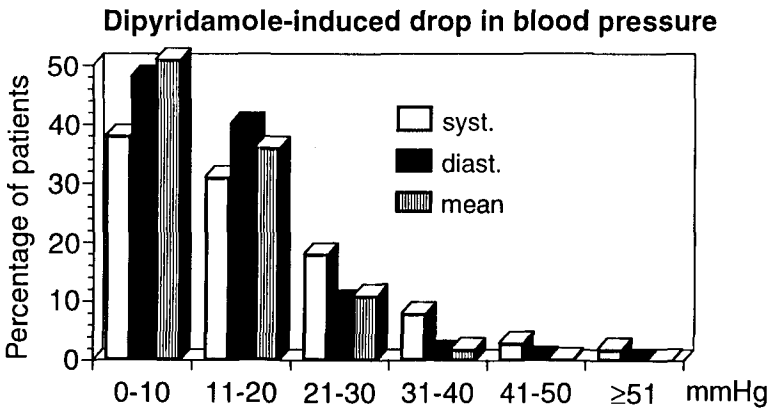

Figure 1. Spectrum of dipyridamole-induced drop in systolic *(syst.)*, diastolic *(diast.)*, and mean blood pressure.

sponders: weight of 93 kg or greater ($p = 0.0025$), diuretics ($p = 0.0009$), digoxin ($p = 0.002$) or insulin intake ($p = 0.0001$), absence of β-blocker intake ($p = 0.0038$), kidney transplantation ($p = 0.029$), and male sex ($p = 0.0001$).

Characteristics of Patients with Dipyridamole-Induced Hypotension (Figure 1, Table 3). Asymptomatic episodes of significant hypotension (as high as 11% depending on the definition of hypotension) were more common than symptomatic episodes (to 0.4%). A significant drop in systolic blood pressure to less than 90 mm Hg was observed in 77 patients. In 10 of 77 patients the hypotension appeared to be caused by a bradyarrhythmia, with a heart rate of less than 60 beats/min. The result of the ^{201}Tl-labeled SPECT myocardial perfusion study was normal in 22 patients (29%) and displayed inferoposterior defects in 44 (57%): the defects were fixed in 14 of 44 patients and partially or completely reversible in 30 of 44. There were perfusion defects in all three coronary territories in five patients (6.5%). Inferoposterior defects (44/77) were more common than anterior defects (18/77) ($p < 0.0001$).

Of the 10 patients with both bradycardia (heart rate <60 beats/min; sinus bradycardia in all cases) and hypotension (systolic blood pressure <90 mm Hg), one patient had a pacemaker set at a rate of less than 60 beats/min and all nine remaining patients had underlying perfusion defects (inferoposterior in seven of nine, apical in one of nine, and in all three coronary territories in one of nine patients). Inferoposterior defects (8/9) were more common than anterior defects (2/9) ($p = 0.0076$).

Aminophylline-Electrocardiographic Substudy (Table 4). The two groups (aminophylline and no aminophylline) were not significantly different with regard to sex, time at which the ECG became positive, and rate pressure products (baseline, 7 minutes, and 10 minutes) (Table 4). The patients receiving aminophylline were younger than the patients not receiving aminophylline (64 vs 70 years; $p < 0.03$). The group receiving aminophylline had more symptoms, most commonly chest pain (77% vs 22%) but also nausea, dyspnea, and hypotension. The electrocardiographic evidence of ischemia resolved within the 10-minute observation period in 28 (60%) of the 47 patients given aminophylline but resolved in only three (7%) of the 45 patients in the group not treated with aminophylline ($p < 0.001$) (Table 4). The time required for the ECG to become negative in patients receiving aminophylline was 2.6 ± -0.5 minutes, whereas without aminophylline electrocardiographic resolution required 5.0 ± -0.9 minutes ($p < 0.05$).

Caffeine Substudy. The caffeine blood level was 0 mg/L in 252 patients, 0.5 mg/L in 54 patients, 1 mg/L in 46 patients, 2 mg/L in 31 patients, 5 mg/L in three patients, and 10 mg/L in five patients. The sample of patients with blood levels above 5 mg/L ($n = 8$; 2%) was too small to provide reliable statistics on the correlation between caffeine and peripheral hemodynamic effects.

Severe Complications. Among the 3715 patients, there was one nonfatal myocardial infarction, one transient cerebral ischemic attack, one noncardiac death from anaphylaxis to dipyridamole, and one case of severe bronchospasm that responded to aminophylline. There were no episodes of pulmonary edema, no cardiac deaths, no malignant ventricular arrhythmias, and no strokes. Four patients had severe symptomatic sinus bradycardia with secondary hypotension. There were no cases of transient heart

block. None of the patients required immediate hospitalization for unstable angina or emergency coronary revascularization.

DISCUSSION

Response to Dipyridamole in Patient Subsets

Age. Elderly patients (≥ 70 years) had a more significant drop in systolic blood pressure and a less significant increase in heart rate during the infusion protocol. Although this hemodynamic response is at variance with an earlier publication of data from 93 patients in which 79 were greater than 65 years of age,[31] our findings are consistent with a more recent study of 129 patients in which the eldest group demonstrated a more profound drop in systolic blood pressure.[32] Our study confirms that dipyridamole testing can be carried out safely in elderly patients.

Insulin-dependent diabetes. The diabetic population is known to be at risk for autonomic nervous system dysfunction, which may account for the high rate of heart rate nonresponders (31%).

Concomitant drug therapy. The higher rate of nonresponders in patients taking digoxin, diuretics, and ACE inhibitors may be related to vagal potentiation by digoxin or a decreased baroreflex function associated with congestive heart failure and hypertension, for which these drugs are commonly prescribed.[33,34]

Minor side effects. We report a lower incidence of chest pain (362/3715; 10%) and minor noncardiac side effects (357/3715; 10%) compared with previous studies.[4,10,23,35] Although this may reflect a selection bias in favor of less sick patients, we suspect that the data reported in previous studies were obtained after actively soliciting reports of side effects from patients during the infusion. We limited our intervention to describing potential side effects before the test and asking patients to report them at the time of the infusion.

Hypotension with and without bradycardia. A wide range of pathophysiologic pathways can lead to dipyridamole-induced hypotension. When there is associated tachycardia, systemic arteriolar hypersensitivity to dipyridamole or transient left ventricular dysfunction is the most likely mechanism.[1,36,37] Possible mechanisms for dipyridamole-induced bradyarrhythmias and secondary hypotension include transient inferoposterior wall ischemia with reflex sinus bradycardia or atrioventricular nodal block or peripheral arteriolar vasodilation (Bezold-Jarish reflex), transient exacerbation of a preexisting sick sinus syndrome, or an inhibitory effect of dipyridamole on the sinoatrial or atrioventricular node.[15,38,39] Our findings suggest that inferoposterior ischemia plays a major role: 89% (8/9) ($p = 0.0076$) of patients who had severe symptomatic bradycardia and 57% (44/77) ($p < 0.0001$) of patients with dipyridamole-induced hypotension displayed inferoposterior perfusion defects on ^{201}Tl scanning. Transient left ventricular dysfunction may have occurred in 6% (5/77) of patients with perfusion defects in all three coronary territories.

Efficacy of aminophylline. Although anginal pain is not a reliable indicator of ischemia in association with dipyridamole infusion,[23,27,40] S-T segment depression is highly specific although relatively insensitive.[26,28-30] For this reason, we chose electrocardiographic changes as an objective marker of ischemia and an end point to assess the efficacy of aminophylline in reversing the effects of dipyridamole. In our study, during the 10-minute observation period, only 3% of electrocardiographic changes resolved within the 10-minute observation period in patients who did not receive aminophylline, compared with 60% of those who did ($p = 0.001$). Our findings confirm previous reports that aminophylline promptly reverses dipyridamole-induced ischemia.[36,41,42]

Caffeine substudy. Several investigators have expressed concern that consumption of caffeine before intravenous dipyridamole may block adenosine vasodilation, producing false-negative pharmacologic stress test results.[43-46] Prior studies have shown that caffeine blood levels on the order of 10 mg/L[46] can produce erroneous results in patients with known coronary disease, although experimental data suggest an effect at lower levels.[43] The caffeine substudy was carried out to assess the frequency of significant caffeine blood levels in an unselected population of patients who are instructed to take nothing by mouth after midnight. In our group of 391 patients, only eight (2%) had levels above 5 mg/L. This suggests that in routine clinical practice, caffeine levels sufficient to alter the hemodynamic response resulting in false-negative study results are infrequent.

Severe myocardial ischemia during dipyridamole testing. Dipyridamole-induced unstable angina and transient pulmonary congestion/edema were not included in the large-scale study because of the problem of interobserver variability in defining these end points. Both our substudy of 3715 patients and previous reports[10,39] indicate that these are both uncommon and treatable conditions.

Comparison with exercise stress testing. Although exercise testing is generally considered to be safe, it carries a risk 60-fold to 100-fold higher than that of daily physical activity in patients with coronary disease. According to the guidelines of the American Heart Association, one can expect about 74 infarctions and deaths during exercise testing in 73,806 patients.[47] The cardiac event rate (13 nonfatal myocardial infarctions and 7 cardiac deaths = 20/73,806), which we report after dipyridamole infusion, therefore compares favorably with that of exercise testing, despite the selection bias in favor of sicker patients referred for dipyridamole imaging. Potential causes for underdiagnosis of myocardial infarctions in our study, such as delayed complications or silent infarctions, would apply equally to exercise testing.

Dipyridamole-induced bronchospasm. We describe nine cases of severe wheezing during dipyridamole testing. However, it is apparent that the wheezing was attributable to pulmonary edema in one patient, probably a manifestation of dipyridamole allergy in another (with a history of childhood asthma), and completely unpredictable in a third patient with emphysema in whom pretest respiratory function testing had not demonstrated any significant bronchospastic component. All of the six remaining patients had asthma or COPD with a significant bronchospastic component. Indeed, of the six patients, three had previously undergone intubation for acute respiratory failure, one had known severe labile asthma, and four required maintenance prednisone therapy.

Although severe bronchospasm has been reported previously,[23,48-50] the risk appears low, but we do not know precisely how many of the 73,806 patients had known asthma or COPD at the time of the test and therefore cannot quantify the risk on the basis of our large-scale study. In the substudy of 3715 patients, there were three (one severe) cases of bronchospasm among 62 patients with known asthma or COPD (based on a history of intake of bronchodilators).

Based on our data, we suggest that clinicians consider an alternative mode of stress testing in patients with a history of acute respiratory failure or severe or labile asthma and those taking maintenance doses of oral prednisone for pulmonary disease. Dobutamine infusion is a safe and simple alternative to dipyridamole in patients with severe bronchospastic disease.[51]

Cerebrovascular disease. The issue of dipyridamole testing in patients with cerebrovascular disease is controversial, mainly because recommendations have been made on the basis of anecdotal case reports.[22,52] In our study there was only one stroke among 73,806 patients. There were nine (1/8,000) TIAs with a motor or speech defect. Of the five patients who underwent Doppler ultrasonography, only two had underlying carotid stenoses, and none of the patients were hypotensive during the test. We suspect that the TIAs represent a transient effect of dipyridamole on cerebral autoregulation and microcirculation.[53-57] The theoretic risk of dipyridamole-induced hypotension followed by stroke in patients with carotid stenoses does not appear to be high in clinical practice. Severe nondiagnosed coronary disease is a major cause of death in patients with cerebrovascular disease, so the risk of not performing the test should be considered in evaluating the risk-benefit relationship.[58] A study (the Dipyridamole Cerebrovascular Disease Study)[52] is presently underway to attempt to determine the risk/benefit ratio of dipyridamole testing in patients with known cerebrovascular disease. Preliminary results suggest that the risk is very low; there was only one TIA among 400 patients with known cerebrovascular disease.

Risk of low- versus high-dose testing. Our study confirms previous reports to the effect that intermediate- and high-dose testing does not carry a greater risk than low-dose testing.[39] Because high-dose testing usually consists of administering the low (0.56 mg/kg)-dose regimen during 4 minutes followed by a supplementary dose only if the patient tolerates the initial dose well, the safety of the high-dose regimen probably indicates that patients who are destined to have a severe reaction will do so during the low-dose test.

Conclusion. The risk of serious dipyridamole-induced side effects is very low and is comparable to that reported for exercise testing in a similar patient population.

References

1. Picano E, Simonetti I, Carpeggiani C, et al. Regional and global biventricular function during dipyridamole stress testing. Am J Cardiol 1989;63:429-32.
2. Lam JYT, Chaitman BR, Glaenzer M, et al. Safety and diagnostic accuracy of dipyridamole-thallium imaging in the elderly. J Am Coll Cardiol 1988;11:585-9.
3. Taillefer R, Lette J, Phaneuf D-C, Léveillé J, Lemire F, Essiambre R. Thallium-201 myocardial imaging during pharmacologic coronary vasodilation: comparison of oral and intravenous administration of dipyridamole. J Am Coll Cardiol 1986;8:76-83.
4. Iskandrian AS, Verani MS, Heo J. Pharmacologic stress testing: mechanism of action, hemodynamic responses, and results in detection of coronary artery disease. J Nucl Cardiol 1994;1:94-111.
5. Albro PC, Gould KL, Westcott RJ, Hamilton GW, Ritchie JL, Williams DL. Noninvasive assessment of coronary stenosis by

myocardial imaging during pharmacologic coronary vasodilation III clinical trial. Am J Cardiol 1978;42:751-60.
6. Depuey EG, Guertler-Krawczynska E, D'Amato PH, Patterson RE. Thallium-201 single photon emission computed tomography with intravenous dipyridamole to diagnose coronary artery disease. Coron Artery Dis 1990;1:75-82.
7. Demangeat JL, Constantinesco A, Mossard JM, Chambron J, Voegtlin R. Evaluation of myocardial perfusion and left ventricular function by 201T1 scintigraphy after dipyridamole. Eur J Nucl Med 1981;6:491-503.
8. Sone T, Kobayashi T, Mizutani K, Yamamoto M, Watanabe T. A study on the noninvasive evaluation of coronary vasodilating drugs with thallium-201 myocardial images. Jpn Heart J 1981;22:763-71.
9. Brown KA, Rimmer J, Haisch C. Noninvasive cardiac risk stratification of diabetic and nondiabetic uremic renal allograft candidates using dipyridamole-thallium-201 imaging and radionuclide ventriculography. Am J Cardiol 1989;64:1017-21.
10. Ranhosky A, Kempthorne-Rawson J. Intravenous Dipyridamole Thallium Imaging Study Group. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. Circulation 1990;81:1205-9.
11. Bayliss J, Pearson M, Sutton GC. Ventricular dysrhythmias following intravenous dipyridamole during "stress" myocardial imaging. Br J Radiol 1983;56:686.
12. Egloff P, Douard H, Barat JL, Broustet JP. Trouble du rythme ventriculaire grave d'origine ischémique au cours d'une scintigraphie au dipyridamole. Arch Mal Coeur 1991;84:861-3.
13. Arrigo F, Patane S, Quattrocchi G. Arrhythmias during dipyridamole test: report of 3 cases. Int J Cardiol 1992;37: 415-7.
14. Kwai AH, Jacobson AF, McIntyre KM, Williams WH, Tow DE. Persistent chest pain following oral dipyridamole for thallium 201 myocardial imaging. Eur J Nucl Med 1990;16:745-6.
15. Pennell DJ, Underwood SR, Ell PJ. Symptomatic bradycardia complicating the use of intravenous dipyridamole for thallium-201 myocardial perfusion imaging. Int J Cardiol 1990;27:272-4.
16. Marwick TH, Hollman J. Acute myocardial infarction associated with intravenous dipyridamole for rubidium-82 PET imaging. Clin Cardiol 1990;13:230-1.
17. Biddle P, Lanspa TJ, Mohiuddin SM, Malesker MA, Hilleman DE. Myocardial infarction after dipyridamole-assisted thallium-201 imaging. DICP 1989;23:665-7.
18. Eagle KA, Boucher CA. Intravenous dipyridamole infusion causes severe bronchospasm in asthmatic patients. Chest 1989;95:258-9.
19. Friedman HZ, Goldberg SF, Hauser AM, O'Neill WW. Death with dipyridamole-thallium imaging (letter). Ann Intern Med 1988;109:990-1.
20. Blumenthal MS, McCauley CS. Cardiac arrest during dipyridamole imaging. Chest 1988;93:1103-4.
21. Lewen MK, Labovitz AJ, Kern MJ, Chaitman BR. Prolonged myocardial ischemia after intravenous dipyridamole thallium imaging. Chest 1987;92:1102-4.
22. Whiting JH Jr, Datz FL, Gabor FV, Jones SR, Morton KA. Cerebrovascular accident associated with dipyridamole thallium-201 myocardial imaging: case report. J Nucl Med 1993; 34:128-30.
23. Lette C, Cerino M, Laverdière M, Tremblay J, Prenovault J. Severe bronchospasm followed by respiratory arrest during thallium-dipyridamole imaging. Chest 1989;95:1345-7.
24. Kahn D, Argenyi EA, Berbaum K, Rezai K. The incidence of serious hemodynamic changes in physically limited patients following oral dipyridamole challenge before thallium-201 scintigraphy. Clin Nucl Med 1990;15:678-82.
25. Sylven C, Beerman B, Jonzon B, Brandt R. Angina pectoris–like pain provoked by intravenous adenosine in healthy volunteers. Br Med J 1986;293:227-30.
26. Zhu YY, Lee W, Botvinick E, et al. The clinical and pathophysiologic implications of pain, ST abnormalities, and scintigraphic changes induced during dipyridamole infusion: their relationships to the peripheral hemodynamic response. Am Heart J 1988;116:1071-80.
27. Takeishi Y, Tono-oka I, Meguro M, et al. The relationship between chest pain during thallium-201 scintigraphy with dipyridamole and myocardial ischemia. Jpn Circ J 1991;55:465-72.
28. Villanueva FS, Smith WH, Watson DD, Beller GA. ST-segment depression during dipyridamole infusion, and its clinical, scintigraphic and hemodynamic correlates. Am J Cardiol 1992;69:445-8.
29. John RM, Taggart PI, Sutton PM, Costa DC, Ell PJ, Swanton H. Vasodilator myocardial perfusion imaging: demonstration of local electrophysiological changes of ischaemia. Br Heart J 1992;68:21-30.
30. Laarman GJ, Verzijlbergen JK, Ascoop CA. Ischemic ST-segment changes after dipyridamole infusion. Int J Cardiol 1987;14:384-6.
31. Gerson MC, Moore EN, Ellis K. Systemic effects and safety of intravenous dipyridamole in elderly patients with suspected coronary artery disease. Am J Cardiol 1987;60:1399-401.
32. Irace L, Aiello C, Perna B, Russo PE, Ruggierro B, Citro R. Systemic effects of intravenous dipyridamole in patients in various age groups. Minerva Cardioangiol 1990;38:293-7.
33. Ziegler MG, Ruiz-Ramon P, Shapiro MH. Abnormal stress responses in patients with diseases affecting the sympathetic nervous system. Psychosom Med 1993;55:339-46.
34. Creager MA, Creager SJ. Arterial baroreflex regulation of blood pressure in patients with congestive heart failure. J Am Coll Cardiol 1994;23:401-5.
35. Laarman G, Niemeyer MG, van der Wall EE, et al. Dipyridamole thallium testing: noncardiac side effects, cardiac effects, electrocardiographic changes and hemodynamic changes after dipyridamole infusion with and without exercise. Int J Cardiol 1988;20:231-8.
36. Klein HO, Ninio R, Eliyahu S, et al. Effects of dipyridamole test on left ventricular function in coronary artery disease. Am J Cardiol 1992;69:482-8.
37. Granato JE, Watson DD, Belardinelli L, Cannon JM, Beller GA. Effects of dipyridamole and aminophylline on hemodynamics, regional myocardial blood flow and thallium-201 washout in the setting of a critical coronary stenosis. J Am Coll Cardiol 1990;16:1760-70.
38. Sun JW, Yuan F, Xu J, Meng FY. Adenosine's role in the genesis of bradyarrhythmias induced by acute myocardial hypoxia. Chin Med J (Engl) 1992;105:883-95.
39. Picano E, Marini C, Pirelli S, et al, on behalf of the Echo-Persantine International Cooperative Study Group. Safety of intravenous high-dose dipyridamole echocardiography. Am J Cardiol 1992;70:252-8.
40. Pearlman JD, Boucher CA. Diagnostic value for coronary artery disease of chest pain during dipyridamole-thallium stress testing. Am J Cardiol 1988;61:43-5.
41. Kern MJ, Wolford T, Donohue TJ, et al. Quantitative demonstration of dipyridamole-induced coronary steal and alteration by angioplasty in man: analysis by simultaneous, continuous dual Doppler spectral flow velocity. Cathet Cardiovasc Diagn 1993;29:329-34.
42. Wang T, Mentzer RM Jr, Van Wylen DG. Interstitial adenosine with dipyridamole: effect of adenosine receptor

blockade and adenosine deaminase. Am J Physiol 1992;263: H552-8.
43. Smits P, Lenders JW, Thien T. Caffeine and theophylline attenuate adenosine-induced vasodilatation in humans. Clin Pharmacol Ther 1990;48:410-8.
44. Smits P, Straatman C, Pijpers E, Thien T. Dose-dependent inhibition of the hemodynamic response to dipyridamole by caffeine. Clin Pharmacol Ther 1991;50:529-37.
45. Smits P, Corsten FH, Aengevaeren WR, Wackers FJ, Thien T. False-negative dipyridamole-thallium-201 myocardial imaging after caffeine infusion. J Nucl Med 1991;32:1538-41.
46. Smits P, Aengevaeren WR, Corstens FH, Thien T. Caffeine reduces dipyridamole-induced myocardial ischemia. J Nucl Med 1989;30:1723-6.
47. Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards: a statement for health professionals from the American Heart Association. Circulation 1990;82: 2286-322.
48. Houben JJ. The role of dipyridamole in bronchospasm (letter). Chest 1990;98:253-5.
49. Heikela A, Haavisto M, Grannas R. Pulmonary uptake of PGE_2 is inhibited by dipyridamole in rat isolated lungs. Prostaglandins 1982;23:147-56.
50. Lette J, Cerino M, Laverdière M, Tremblay J, Prenovault J. Dipyridamole-induced bronchospasm (letter). Chest 1990;98: 253-5.
51. Pennell DJ, Underwood SR, Ell PJ. Safety of dobutamine stress for thallium myocardial perfusion tomography in patients with asthma. Am J Cardiol 1993;71:1346-50.
52. Lette J. Dipyridamole testing in cerebrovascular patients (letter). J Nucl Med 1993;34:1389-90.
53. Ko KR, Ngai AC, Winn HR. Role of adenosine in regulation of regional cerebral blood flow in sensory cortex. Am J Physiol 1990;259:H1703-8.
54. Heistad DD, Marcus ML, Gourley JK, Busija DW. Effect of adenosine and dipyridamole on cerebral blood flow. Am J Physiol 1981;240:H775-80.
55. Kassell NF, Boarini DJ, Olin JJ, Sprowell JA. Cerebral and systemic circulatory effects of arterial hypotension induced by adenosine. J Neurosurg 1983;58:69-76.
56. Boarini DJ, Kassell NF, Olin JJ, Sprowell JA. The effect of intravenous dipyridamole on the cerebral and systemic circulations of the dog. Stroke 1982;13:842-7.
57. Puiroud S, Pinard E, Seylaz J. Dynamic cerebral and systemic circulatory effects of adenosine, theophylline and dipyridamole. Brain Res 1988;453:287-98.
58. Hobson RW II, Weiss DG, Fields WS, et al, and the Veterans Affairs Cooperative Study Group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993;328:221-7.
59. Miller DD, Labovitz AJ. Dipyridamole and adenosine vasodilator stress for myocardial imaging: vive la différence! J Am Coll Cardiol 1994;23:390-2.
60. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS, and the Investigators of the Multicenter Adenoscan Trial. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial registry. J Am Coll Cardiol 1994;23:384-9.
61. Pennell DJ, Mavrogeni S, Anagnostopoulos C, Ell PJ, Underwood SR. Thallium myocardial perfusion tomography using intravenous dipyridamole combined with maximal exercise stress. Nucl Med Commun 1993;14:939-45.
62. Pennell DJ, Forbat SM, Karwatowski SP, Mavrogeni S, Underwood SR. Adenosine with exercise for thallium-201 cardiac imaging [Abstract]. Nucl Med Commun 1993;14:262.

APPENDIX: THE MULTICENTER DIPYRIDAMOLE SAFETY STUDY*

Principal Investigators: Jean Lette, MD, and James L. Tatum, MD

Administrative Coordinator: Sheila Fraser, CA

Editorial and Scientific Advisory Committee: Jean Lette, MD, James L. Tatum, MD, Sheila Fraser, CA, D. Douglas Miller, MD, David D. Waters, MD, Gary Heller, MD, Eric B. Stanton, MD, Hee Seung Bom, MD, Jeffrey Leppo, MD, and Stanley Nattel, MD, for the Multicenter Dipyridamole Safety Study Investigators

List of Investigators: Agatha A. van der Schaaf, MD, Sir Charles Gairdner Hospital, Perth, Australia; Jacques Melin, MD, Cliniques Universitaires St-Luc, Brussels, Belgium; Protasio L. da Luz, MD, Aguinaldo Pereira de Moraes, MD, Claudio Meneghetti, MD, and Antonio Mansur, MD, Instituto do Coração, São Paulo, Brazil; Eric B. Stanton, MD, St. Joseph's Hospital, Hamilton, Ontario, Canada; Ronald Graveline, MD, Cité de la Santé de Laval, Laval, Quebec, Canada; Gilbert A. Hurwitz, MD, Victoria Hospital, London, Ontario, Canada; Jerry Stern, MD, Jewish General Hospital, Montreal, Quebec, Canada; Jean-Paul Soucy, MD, Notre-Dame Hospital, Montreal, Quebec, Canada; Michel Picard, MD, and Lucie Carrier, MD, Pierre Boucher Hospital, Montreal, Quebec, Canada; Jean Lette, MD, Michel Cerino, MD, Daniel McNamara, MD, Marie-Claire Eybalin, MD, and André Levasseur, MD, Maisonneuve Hospital, Montreal, Quebec, Canada; Raymond Taillefer, MD, Hôtel-Dieu de Montréal Hospital, Montreal, Quebec, Canada; Jean Lette, MD, Michel Cerino, MD, André Arsenault, MD, and Jean Grégoire, MD, Montreal Heart Institute, Montreal, Quebec, Canada; Michel Picard, MD, St. Luc Hospital, Montreal, Quebec, Canada; Terrence D. Ruddy, MD, Ross A. Davies, MD, and Sharon Ann Kearns, RN, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; Jean Guimond, MD, Hôpital Laval, Quebec, Quebec, Canada; Jean Verreault, MD, Centre Hospitalier St. Vincent-de-Paul, Sherbrooke, Quebec, Canada; Guy Bisson, MD, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada; Sylvain Houle, MD, Toronto General Hospital, Toronto, Ontario, Canada; Norman Laurin, MD, Centre Hospitalier Saint-Joseph, Trois-Rivières, Quebec, Canada; Quoc Tuan Ton That, MD, Centre Hospitalier de Valleyfield, Valleyfield, Quebec, Canada; Maria Kiess, MD, and Bob Brown, RN, St. Paul's Hospital, Vancouver, British Columbia, Canada; Chengmo Zhu, MD, Rui Jin Hospital, Shanghai, Peoples Republic of China; Avijit Lahiri, MD, Northwick Park Hospital, Harrow, England; Dudley Pennell, MD, Royal Brompton Hospital, London, England; Kari S. Virtanen, MD, Helsinki University Central Hospital, Helsinki, Finland; Olivier Mundler, MD, Michèle Duet, MD, Bruno Berolatti, MD, and Michel Fauchet, MD, Hôpital

*From the Maisonneuve Hospital and the Montreal Heart Institute, Montreal, Quebec, Canada.

Lariboisière, Paris, France; Christoph A. Nienaber, MD, University Hospital Eppendorf, Hamburg, Germany; Constantinos Athanasopoulos, MD, Dimitrios Fasitsas, MD, Nikolaos Vassilopoulos, MD, and Elias Karayannis, MD, Cardiological Center of Athens, Athens, Greece; Teresio Varetto, MD, Ospedale Regionale di Aosta, Aosta, Italy; Giuseppe Medolago, MD, and Antonio Piti, MD, Ospedale Riuniti di Bergamo, Bergamo, Italy; Giancarlo Carini, MD, Graziana Labanti, MD, and Anna-Maria Lusa, MD, Ospedale Bellaria, Bologna, Italy; Salvatore Pirelli, MD, Ospedale Niguarda, Milano, Italy; Teresio Varetto, MD, Ospedale Molinette, Torino, Italy; Michele Galli, MD, Fondazione Clinica del Lavoro, Veruno, Italy; Nagara Tamaki, MD, Kyoto University Faculty of Medicine, Kyoto, Japan; Tsunehiko Nishimura, MD, National Cardiovascular Center, Osaka, Japan; Fumitaka Ohsuzu, MD, National Defense Medical College, Saitama, Japan; Osamu Okazaki, MD, Nakano National Chest Hospital, Tokyo, Japan; Jaetae Lee, MD, Kyungpook University Hospital, Taegu, Korea; Hee Seung Bom, MD, Chonnam University Hospital, Kwangju, Korea; J. Fred Verzylbergen, MD, St. Antonius Hospital, Nieuwegein, The Netherlands; Bob Dugal, MD, Ostfold Central Hospital, Fredrisktad, Norway; Hans-Jacob Nerdrum, MD, Akershus Central Hospital, Nordbyhagen, Norway; Luis Providência, MD, PhD, João Morais, MD, and Moreira da Silva, MD, University Hospital, Coimbra, Portugal; Sergei Novikov, MD, and Evgenie Ostroumov, MD, USSR Cardiology Research Center, Moscow, Russia; Matthias E. Pfisterer, MD, University Hospital Basel, Basel, Switzerland; Elizabeth G. Krawczynska, MD, Crawford Long Hospital, Atlanta, Ga.; Elizabeth G. Krawczynska, MD, Grady Hospital, Atlanta, Ga.; Elizabeth G. Krawczynska, MD, Emory University Hospital, Atlanta, Ga.; James E. Udelson, MD, Tufts University School of Medicine, Boston, Mass.; Gary V. Heller, MD, Memorial Hospital, Pawtucket, R.I.; E. Gordon DePuey, MD, St. Luke's/Roosevelt Hospital Center, New York, N.Y.; Judith H. Murphy, MD, Likoff Cardiovascular Institute, Philadelphia, Pa.; James L. Tatum, MD, Medical College of Virginia, Richmond, Va.; Frederick L. Weiland, MD, Roseville Community Hospital, Roseville, Calif.; Elias H. Botvinick, MD, James R. Lucas, MD, Poonam Agarwal, MD, YuYing Zhu, MD, and Michael W. Dae, MD, UC San Francisco Medical Center, San Francisco, Calif.; D. Douglas Miller, MD, Bernard R. Chaitman, MD, Liwa T. Younis, MD, and Sheila Byers, RN, St. Louis University Medical Center, St. Louis, Mo.

Cynthia Crawford-Green, Howard University Hospital, Washington, D.C.; and Jeffrey A. Leppo, MD, University of Massachusetts Medical Center, Worcester, Mass.

Study Consultants: Denis Gossard, MD, Jeanne Teitelbaum, MD, Alain Beaupré, MD, Bernard Thibault, MD, Raymond Dandavino, MD, Marc Houde, MD, and Jacques-Friborg, MD, Maisonneuve Hospital, Montreal, Quebec, Canada, and Bernard Thibault, MD, Montreal Heart Institute, Montreal, Quebec, Canada.