Early Dipyridamole $^{99m}$Tc-Sestamibi Single Photon Emission Computed Tomographic Imaging 2 to 4 Days After Acute Myocardial Infarction Predicts In-Hospital and Postdischarge Cardiac Events

Comparison With Submaximal Exercise Imaging

Kenneth A. Brown, MD; Gary V. Heller, MD, PhD; Ronald S. Landin, MD; Leslee J. Shaw, PhD; George A. Beller, MD; Michael J. Pasquale, MD; Stephen B. Haber, PhD

**Background**—Because of its brief hemodynamic effects and minor effect on determinants of myocardial oxygen demand, vasodilator stress myocardial perfusion imaging (MPI) can be applied very early after acute myocardial infarction (AMI) for risk stratification, allowing management decisions to be made earlier and thus potentially shortening hospitalization stays, reducing costs, and preventing early cardiac events. This multicenter randomized trial compared the prognostic value of early dipyridamole MPI and standard predischarge submaximal exercise MPI in patients who presented with AMI.

**Methods and Results**—Patients who presented with their first AMI (n=451) were randomized in a 3:1 ratio to undergo either both an early (day 2 to 4) dipyridamole $^{99m}$Tc-sestamibi MPI study and a predischarge (day 6 to 12) submaximal exercise $^{99m}$Tc-sestamibi MPI study or only the predischarge study. Multivariate predictors of in-hospital cardiac events included nuclear imaging summed stress and summed reversibility scores and peak creatine kinase. For postdischarge cardiac events, multivariate predictors in patients undergoing dipyridamole MPI included only the summed stress, reversibility, and rest imaging scores and anterior MI. For a given summed stress score, the interaction of reversibility score further improved the predictive value. Dipyridamole MPI showed better risk stratification than submaximal exercise MPI.

**Conclusions**—Dipyridamole MPI very early after MI predicts early and late cardiac events, with superior prognostic value compared with submaximal exercise imaging. The extent and severity of the stress defect and reversibility of the defect were the most important predictors of cardiac death and recurrent MI. This technique can allow management decisions to be made earlier with regard to AMI patients and could have important economic impact if applied widely.

(Reprinted from Circulation 1999;100:2060-2066.)

Key Words: prognosis ■ myocardial infarction ■ perfusion ■ imaging ■ vasodilation ■ stress ■ coronary artery disease

Noninvasive risk stratification after uncomplicated acute myocardial infarction (AMI) has been shown to be useful in guiding future patient management. Typically, this has involved low-level exercise testing 5 to 7 days after admission, with or without myocardial perfusion imaging (MPI). However, important cardiac events may occur before this testing time, and the end points of ST-segment depression and angina have a low sensitivity for identifying patients at risk for cardiac death or myocardial infarction (MI).7 Also, additional invasive procedures or hospital discharge is deferred for nearly a week, which prolongs hospitalization and increases costs. If the same or better prognostic information could be obtained at day 2 to 4, earlier management decisions could be made, which would reduce costs and potentially prevent early cardiac events.

See p 2040

Vasodilator stress in conjunction with MPI may have particular advantages for early risk stratification after MI. Data suggest it is more sensitive for coronary artery disease...
than submaximal exercise imaging.\(^8\) Vasodilator stress produces modest and brief hemodynamic changes and can be applied safely in conjunction with MPI 2 to 4 days after AMI.\(^9,10\) Limited data (50 patients) also suggest that very early postinfarction dipyridamole MPI predicts in-hospital and late cardiac events.\(^9\) The present multicenter study was undertaken to more definitively determine the prognostic value of dipyridamole \(^{99m}\)Tc-sestamibi MPI performed 2 to 4 days after infarction compared with standard predischarge submaximal exercise \(^{99m}\)Tc-sestamibi MPI performed 6 to 12 days after infarction.

**Methods**

**Study Design**

This multicenter (22 sites; see Appendix) randomized, controlled trial evaluated stable patients recovering from uncomplicated first AMI. Eligible patients were randomized to a dipyridamole or submaximal exercise group in a 3:1 ratio. Patients assigned to the dipyridamole group underwent intravenous dipyridamole \(^{99m}\)Tc-sestamibi single photon emission computed tomographic (SPECT) MPI 48 to 96 hours after MI, followed by submaximal exercise \(^{99m}\)Tc-sestamibi MPI 6 to 12 days after MI. Patients randomized to the submaximal exercise group underwent submaximal exercise MPI 6 to 12 days after infarction without early dipyridamole stress to allow assessment of any excess risk associated with administration of intravenous dipyridamole.\(^9\) A 3:1 randomization was used as a compromise between obtaining an adequate number of patients to assess such risk and maximizing the number of patients who would undergo dipyridamole imaging for prognosis.

**Patient Population**

Patients were excluded if they had chest pain beyond the initial 24 hours, cardiogenic shock, class III or IV heart failure, coronary revascularization within 6 weeks before randomization, cardiomyopathy, contraindications to dipyridamole or theophylline, inability to perform low-level exercise, or coexisting diseases that would affect lifespan. The study was approved by the institutional review committee at each center; subjects gave informed consent.

**Electrocardiographic Classification of MI**

Standard 12-lead ECGs were obtained on the day of admission and 2 to 4 days later and were interpreted by 2 investigators blinded to other patient data. MI was classified as Q-wave or non–Q-wave by standard criteria. Infarct location was classified as anterior (leads V\(_1\) through V\(_6\), I, and aVL), inferior (II, III, and aVF), posterior (V\(_7\) through V\(_12\)), or indeterminate.

**Myocardial Perfusion Imaging**

A same-day rest-stress imaging protocol was used. Rest and stress images were obtained \(\approx\)1 hour after injection of 7.5 and 22.5 mCi \(^{99m}\)Tc-sestamibi, respectively. Dipyridamole (0.56 mg/kg) was infused intravenously a mean of 3.3±0.7 days after onset of MI. \(^{99m}\)Tc-sestamibi was injected 7 minutes after initiation of the dipyridamole infusion; no exercise was performed. Submaximal exercise was performed 6 to 12 days after MI (mean 7.4±3.9 days) according to a modified Bruce protocol. Exercise end points included completion of Bruce stage II or 75% of maximum predicted heart rate, whichever came first. The exercise test was discontinued early if any of the following signs occurred: progressive moderate chest pain, dyspnea, fatigue, claudication, 10 mm Hg fall in systolic blood pressure, marked (0.3 mV) ST-segment depression, or development of ventricular tachycardia. \(^{99m}\)Tc-sestamibi was injected at peak stress, and exercise continued for 60 to 90 seconds after injection. An ECG response was considered ischemic if \(\approx\)0.1 mV of horizontal or downsloping ST-segment depression occurred compared with baseline. ECG responses were classified as indeterminate for patients with left bundle-branch block, severe ST-segment abnormalities, Wolf-Parkinson-White syndrome, or paced rhythms or if the patient was taking digoxin. SPECT images were obtained with a high-resolution collimator in a 64×64 matrix across 180° with 64 projections of 25 seconds each. Gated imaging was not performed for this study.

All unprocessed data were submitted to a core laboratory (Hartford Hospital) for processing. A low-pass Butterworth filter was used for reconstruction. A 17-segment qualitative analysis was used for regional tracer uptake (Figure 1). All analysis was performed as a blinded consensus of 3 investigators (K.A.B., G.V.H., and R.S.L.). Segmental uptake was graded by use of a 5-point scoring system where 0 is normal, 1 is mild reduction in activity, 2 is moderate reduction, 3 is severe reduction, and 4 is absence of activity). The summed stress score (SSS) and summed rest score (SRS) were determined by the sum of scores for each of the 17 segments on stress and rest images, respectively. A summed difference (reversibility) score (SDS) was determined by the sum of the difference between the SSS and SRS for each segment. SSS and SRS were categorized as low (0 through 4), intermediate (5 through 8), or high.

**TABLE 1. Clinical and Outcome Characteristics of Patients Undergoing Dipyridamole \(^{99m}\)Tc-Sestamibi 2–4 Days and/or Submaximal Exercise \(^{99m}\)Tc-Sestamibi 6–12 Days After First MI**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>57±12</th>
<th>57±12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>91 (32)</td>
<td>96 (31)</td>
</tr>
<tr>
<td>Cardiac risk factors, n (%)</td>
<td>Diabetes</td>
<td>56 (20)</td>
</tr>
<tr>
<td></td>
<td>Family history</td>
<td>173 (61)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>165 (58)</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>210 (74)</td>
</tr>
<tr>
<td></td>
<td>ECG infarct location, n (%)</td>
<td>Anterior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indeterminate</td>
</tr>
<tr>
<td></td>
<td>Q-wave MI</td>
<td>174 (60)</td>
</tr>
<tr>
<td>Enzymatic results, n</td>
<td>CK-MB, %</td>
<td>4±1</td>
</tr>
<tr>
<td></td>
<td>CK, IU</td>
<td>1894±1688</td>
</tr>
<tr>
<td></td>
<td>Thrombolytic therapy, n (%)</td>
<td>159 (56)</td>
</tr>
<tr>
<td></td>
<td>Total length of stay, d</td>
<td>8±4</td>
</tr>
<tr>
<td></td>
<td>Arteriography, n (%)</td>
<td>187 (66)</td>
</tr>
<tr>
<td>Outcomes, n (%)</td>
<td>In-hospital</td>
<td>Cardiac death or reinfarction</td>
</tr>
<tr>
<td></td>
<td>PTCA/CABG</td>
<td>24 (8.5)</td>
</tr>
<tr>
<td></td>
<td>Postdischarge</td>
<td>Death or MI</td>
</tr>
</tbody>
</table>
SDS was categorized as low (0 through 2), intermediate (3 through 7), or high (>7).

Clinical Access to Imaging Data

By protocol, the imaging data from the early dipyridamole MPI study were not available to treating physicians. However, the predischarge submaximal exercise MPI results were available, and management decisions were made at the discretion of the treating physician.

Clinical Follow-Up

All patients were followed up throughout their hospitalization and by telephone interview 3, 6, 12, 18, and 24 months after discharge (mean 1.9 ± 0.2 years). Significant changes in cardiovascular status were confirmed by examination of the patient’s hospital records and written follow-up from the principal investigator from each center.

Clinical, hemodynamic, and nuclear variables (Table 1) for in-hospital cardiac events were evaluated with logistic regression analysis, and variables with P < 0.20 on the univariate assessment were entered into the multivariate model. Variables were entered into the modeling process to mirror the clinical scenario: clinical variables, followed by early in-hospital measures, then nuclear test variables. Cox proportional hazards analysis was used for postdischarge cardiac events, and univariate estimators (P < 0.20) were entered into a multivariate model in steps: clinical variables, in-hospital measures, and nuclear test variables. The multivariate model was developed with consideration of model overfitting procedures that allow assessment of 1 variable for every 5 to 10 outcomes observed.

To control for confounding risk markers, we developed a risk-adjusted multivariate model that adjusted for other important clinical estimators of outcome and evaluated any first-order interaction

<table>
<thead>
<tr>
<th>TABLE 3. Univariate and Multivariate Logistic Regression Predictors of In-Hospital Cardiac Events in Patients Undergoing Dipyridamole 99mTc-Sestamibi Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictor</td>
</tr>
<tr>
<td>Clinical history</td>
</tr>
<tr>
<td>Stress test results</td>
</tr>
<tr>
<td>Nuclear results</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease.
TABLE 5. Multivariate Predictors of Postdischarge Cardiac Death or Recurrent MI in Patients Undergoing Dipyridamole $^{99m}$Tc-Sestamibi Imaging

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\chi^2$</th>
<th>P</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior MI</td>
<td>3.8</td>
<td>0.05</td>
<td>1.6 (1.1–2.3)</td>
</tr>
<tr>
<td>Nuclear results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS</td>
<td>4.83</td>
<td>0.02</td>
<td>2.4 (1.2–5.2)</td>
</tr>
<tr>
<td>SSS</td>
<td>4.68</td>
<td>0.03</td>
<td>1.71 (1.2–3.7)</td>
</tr>
<tr>
<td>SRS</td>
<td>4.58</td>
<td>0.032</td>
<td>1.4 (1.1–2.8)</td>
</tr>
</tbody>
</table>

Figure 2. Annual cardiac death or recurrent MI rate as a function of SSS, SDS, and SRS for dipyridamole (DP) and submaximal exercise (EX) $^{99m}$Tc-sestamibi SPECT imaging. Event rate increased as scores increased. The ability to predict cardiac events was better for dipyridamole studies than for exercise studies for each summed score (P value depicted). All event rates are derived from risk-adjusted Cox survival curves. Intermed indicates intermediate.

Figure 3. Annual cardiac death or MI rate as a function of SSS and thrombolytic therapy. The predictive value of SSS was greater for patients receiving thrombolysis (P=0.02).

Figure 4. Annual cardiac death or MI rate as a function of SDS for a given SSS. For each SSS subgroup, cardiac event risk increased as SDS increased. The effect of SDS was greatest in the intermediate (Intermed) SSS group.

Variables judged to influence the interpretation of the predictive value of the nuclear scan. The prognostic value of predischarge submaximal exercise imaging was evaluated as described above for dipyridamole $^{99m}$Tc-sestamibi imaging.

**Results**

**Patient Characteristics**

A total of 451 patients were enrolled in the study, 339 of whom were randomized to the dipyridamole plus submaximal exercise group and 112 to the submaximal exercise–only group. Of the 339 patients randomized to dipyridamole stress imaging, 284 patients received the infusion during the 48- to 96-hour time frame (mean 3.3 ± 0.7 days). Fifty-five patients did not undergo dipyridamole stress because of clinical indications such as recurrent chest pain, heart failure, or cardiac death. Of the 284 patients who underwent early dipyridamole stress imaging, 226 went on to have submaximal exercise $^{99m}$Tc-sestamibi imaging; 58 patients were excluded because of clinical indications. Of the 112 patients randomized to undergo only submaximal exercise, 83 underwent submaximal exercise MPI. Patients were excluded from either group at the discretion of the treating physicians. For analysis of prognostic value, all patients who underwent submaximal exercise $^{99m}$Tc-sestamibi imaging were evaluated, including the 226 patients who had undergone dipyridamole stress imaging. Table 1 shows the clinical, stress test, MPI, and outcome characteristics of each group. There were no significant differences for any of the patient variables between those randomized to dipyridamole and those randomized to submaximal exercise stress alone.

**Hemodynamic Effects**

Hemodynamic responses to dipyridamole and submaximal exercise are shown in Table 2. Changes in heart rate, blood pressure, and rate-pressure product were all significantly less during dipyridamole infusion than with submaximal exercise (P<0.05). There were no adverse events attributable to the early dipyridamole infusion.

**Nuclear Imaging Results**

Results of early dipyridamole and submaximal exercise MPI are shown in Table 2. The frequency of small/mild stress defects (SSS 0 to 4) was greater in patients who underwent submaximal exercise stress (74%) than in those who underwent dipyridamole stress (58%; P<0.01). There was no significant difference between the groups in the distribution of rest or reversibility scores.

**In-Hospital Cardiac Events and Predictors**

During in-hospital follow-up (8±4 days after infarction), cardiac events occurred in 29 patients: cardiac death in 2, recurrent nonfatal MI in 3, and coronary revascularization after antecedent ischemic symptoms in 24. The significant univariate predictors of in-hospital cardiac events included...
SSS, SDS, and a family history of coronary disease but no dipyridamole stress end points, such as angina or ECG changes (Table 3). SSS, SDS, and peak creatine kinase (CK) were also found to be multivariate predictors of events (Table 3). Compared with clinical data, the incremental addition of nuclear imaging data significantly increased the overall multivariate predictive model $\chi^2$ from 4.0 to 20.2 ($P < 0.05$).

**Postdischarge Follow-Up**

Of 284 patients in the dipyridamole group, 29 had in-hospital cardiac events, 24 had revascularization within 90 days of hospital discharge, and 1 patient was lost to follow-up. Posthospitalization follow-up was obtained for the remaining 230 dipyridamole patients. For 309 patients who underwent submaximal exercise, 24 had coronary revascularization within 90 days of hospital discharge and 2 were lost to follow-up, which left a cohort of 283 submaximal exercise patients with follow-up. Cardiac events are shown in Table 1. Death or recurrent MI occurred in 37 patients in the dipyridamole group and in 31 patients in the submaximal exercise group.

**Predictive Value of Early Dipyridamole 99mTc-Sestamibi Imaging for Postdischarge Cardiac Events**

Univariate predictors of postdischarge cardiac death or recurrent MI are shown in Table 4. Among clinical variables, significant predictors included age, diabetes, smoking, peak CK, peak CK-MB, anterior infarct location, and Q-wave infarction. No dipyridamole stress variable had significant predictive value. Among nuclear imaging variables, both SDS and SSS were significant predictors.

Multivariate predictors of postdischarge cardiac death or infarction included only anterior location of MI and each of the nuclear imaging variables (SDS, SSS and SRS) (Table 5).

The reversibility index, SDS, had the greatest relative risk for cardiac events. Nuclear imaging data significantly ($P < 0.05$) improved the overall predictive model $\chi^2$ when added to clinical data: global $\chi^2$ increased from 6.1 ($P = 0.05$) to 20.2 ($P = 0.0002$). Cardiac event rates derived from the risk-adjusted Cox survival curve as a function of SSS, SDS, and SRS are depicted in Figure 2. The annual event rate ranged from 2% in patients with a low SSS or SDS to ~12% in patients with a high SSS or SDS ($P < 0.05$). The ability to separate low- and high-risk subgroups by use of SSS was significantly better for patients who received thrombolysis than for those who did not ($P = 0.02$) (Figure 3).

**Interaction of SSS and SDS**

Patients in all SSS groups could be further risk stratified by use of the degree and extent of reversibility (Figure 4). In the low and intermediate SSS groups, the annual cardiac event rate was very low (0%) in patients with low SDS. However, the event rate in the intermediate SSS group increased to 6% and 17% in patients with intermediate and high SDS, respectively. In patients with the highest SSS totals, the cardiac event rate remained high even when the degree and extent of reversibility were small.

**Predictive Value of Predischarge Submaximal Exercise 99mTc-Sestamibi Imaging for Postdischarge Cardiac Events**

Univariate predictors of postdischarge cardiac death or recurrent MI are shown in Table 6. Significant clinical predictors included age, diabetes, smoking, peak CK, peak CK-MB, anterior MI, Q-wave MI, and thrombolytic therapy. Significant stress test variables included peak heart rate, peak systolic blood pressure, and exercise-induced chest pain. Only SSS was a borderline significant nuclear imaging variable ($P = 0.09$). The submaximal exercise ECG had no significant predictive value for cardiac events (Figure 5).

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Multivariate predictors of postdischarge cardiac death or recurrent MI are shown in Table 7. The only significant predictor was SSS ($P<0.02$). Peak CK had a borderline predictive value ($P=0.08$). The annual Kaplan-Meier cardiac event rates as a function of SSS, SDS, and SRS are shown in Figure 2. Nuclear imaging data significantly ($P<0.01$) improved the global $\chi^2$ of the predictive model when all data were forced into the model, increasing the $\chi^2$ from 7.3 ($P=0.03$) to 17.2 ($P=0.007$).

Comparison of Dipyridamole Stress and Submaximal Exercise MPI

The ability to stratify patients according to risk, separating low- from high-risk patients, was significantly better with dipyridamole imaging than with submaximal exercise imaging for SSS ($P<0.05$), SDS ($P<0.001$), and SRS ($P<0.05$) (Figure 2). This was manifested as greater differences for event rates among low, intermediate, and high-risk groups defined by the extent and severity of the stress perfusion defect (SSS), reversibility (SDS), and rest perfusion (SRS) defect (Figure 2).

Discussion

The present study demonstrates that dipyridamole $^{99m}$Tc-sestamibi SPECT imaging has powerful prognostic value when performed as early as 2 days after an uncomplicated acute MI, which confirms an earlier pilot study. Our data are consistent with a larger body of literature that shows that peridischARGE (day 5 to 21) stress nuclear imaging predicts early and late cardiac events after AMI. The present study is a multicenter affirmation that noninvasive risk stratification can be performed very early after MI without loss of predictive value compared with traditional predischarge exercise imaging, thereby potentially shortening hospitalization stays by allowing earlier management decisions to be made regarding whether invasive or interventional procedures are necessary. Earlier imaging information not only may reduce costs but may also potentially prevent early cardiac events by directing early intervention.

Nuclear Imaging Predictors of Cardiac Events

We found that the size and severity of both the stress defect and reversibility of the defect observed with dipyridamole $^{99m}$Tc-sestamibi imaging had significant univariate and multivariate predictive value for in-hospital and late cardiac events. These imaging variables have been shown to have strong predictive value in many prior studies involving a wide spectrum of coronary heart disease.

Our study suggests that the degree and extent of reversibility (SDS) provide complimentary prognostic information to the stress defect score. Regardless of the total stress defect score, the risk of cardiac events was related to the extent and degree of reversibility. This effect was greatest in the intermediate SSS group (Figure 4). The overall annual cardiac event rate was 5% in this group but decreased to 0% in patients with a low SDS and increased to 17% in patients with a high SDS. Even in patients with small stress defects (low SSS), the annual rate of cardiac events rose from 0% to 5% as the reversibility index increased. The least effect was seen in the group with the largest and most severe stress defects (high SSS), in whom the cardiac event rate remained relatively high even with a low SDS, which confirms previous data showing a high event rate in patients with extensive infarction.

Patients Receiving Thrombolysis

Our study confirms several recent studies demonstrating that stress nuclear MPI retains its predictive value in AMI patients receiving thrombolysis. Our finding is in contrast to earlier reports that suggested that $^{201}$Tl imaging was not useful in such patients, perhaps because these latter studies were retrospective and potentially biased because imaging data were available to treating physicians.

Comparison of Dipyridamole Versus Submaximal Exercise Nuclear Imaging

We found that the ability to separate low- and high-risk patients was greater with dipyridamole MPI than with submaximal exercise MPI (Figure 2). This could reflect a greater sensitivity for detecting myocardial ischemia, especially outside the infarct zone. Of note, the frequency of large and medium defects in our study was greater for patients who underwent dipyridamole stress than for those who underwent only submaximal exercise MPI, despite similar resting imaging scores (Table 2).

Limitations of the Study

Our study cohort was selected to include only patients with uncomplicated first MI. Thus, it is unclear how our data would apply to patients with prior MI. In general, however, risk stratification is most valuable in intermediate-risk subgroups. Thus, early vasodilator MPI would be expected to be most valuable in patients with prior MI who do not have extensive areas of infarction and who have uncomplicated early hospital courses.

Conclusions and Clinical Implications

Our study confirms earlier data suggesting that risk stratification by use of vasodilator stress nuclear MPI can be performed safely and can provide powerful prognostic data as early as 2 days after MI, a time frame generally not suitable for exercise or $\beta$-adrenergic stress. Not only was there no loss in predictive power compared with submaximal exercise nuclear imaging performed later in the hospitalization, but prognostic value was actually superior when dipyridamole stress was used. With the current increasing pressures to reduce hospital costs, the ability of risk stratification with dipyridamole $^{99m}$Tc-sestamibi imaging to allow management decisions regarding discharge versus intervention to be made at day 2 rather than day 5 to 7 could have important economic impact if applied widely. In addition, some in-hospital cardiac events may be prevented, which would further reduce costs. Thus, patients identified to be at low risk for cardiac events by dipyridamole $^{99m}$Tc-sestamibi imaging could be considered for early discharge, whereas patients at high risk could be referred for early catheterization and possible revascularization.
Acknowledgments

This study was supported by a research grant from Dupont Pharmaceuticals Company, North Billerica, Mass. The authors thank Jeanne Kennedy for expert assistance in manuscript preparation, Paul Widner for guidance in the study design, and Debra Messinger for help in the imaging core laboratory.

Appendix

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References

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Circulation. 1999;100:2060-2066
doi: 10.1161/01.CIR.100.20.2060

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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