Diagnostic and Prognostic Value of Dipyridamole Echocardiography in Patients With Suspected Coronary Artery Disease

Comparison With Exercise Electrocardiography

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Background  Before any new diagnostic test is accepted in clinical practice, such a test should be compared with established diagnostic tools in an appropriately large series of patients encompassing the complete spectrum of challenges to which the test is exposed. The aim of the present study was to assess the relative diagnostic and prognostic accuracies of high-dose dipyridamole echocardiography (two-dimensional echocardiographic monitoring during dipyridamole infusion up to 0.84 mg/kg over 10 hours) versus maximal symptom-limited bicycle exercise ECG test in patients with angina.

Methods and Results  We studied 429 consecutive in-hospital patients who met the following inclusion criteria: history of chest pain, off antianginal therapy for at least 2 days (1 week for β-blockers), no previous myocardial infarction and/or obvious regional left ventricular dysynergy of contraction (akinesis or dyskinesis) at baseline, and acceptable acoustic window under resting conditions. All patients underwent dipyridamole echocardiography and exercise ECG—on different days and in random order—within 1 week of coronary angiography (which was performed independent of test results) and were followed up for 37.8 ± 14 months (range, 1 to 73 months). Criteria of positivity were for dipyridamole echocardiography, a transient regional dysynergy absent in the baseline examination; for exercise ECG, an ST-segment shift of ≥0.1 mV from baseline; and for coronary angiography, a luminal reduction of ≥75% in at least one major coronary vessel (50% for left main). There were 183 patients without and 246 with coronary artery disease. 132 had one-, 70 had two-, and 44 had three- and/or left main vessel disease. The specificity was higher for dipyridamole echocardiography than for exercise ECG (90% versus 51%, P < .001). The overall sensitivity of dipyridamole echocardiography was similar to that of exercise ECG (75% versus 74%, P = NS), with no significant differences in the subset with one- (67% versus 69%, P = NS), two- (79% versus 77%, P = NS), or three- (93% versus 86%, P = NS) vessel disease. During the follow-up, there were 20 deaths, 13 nonfatal myocardial infarctions, and 126 revascularization procedures. In the univariate analysis, dipyridamole resulted in higher χ² values than did exercise stress testing. A Cox forward stepwise survival analysis identified the dipyridamole time as the most powerful prognostic predictor of death (χ² = 19.4, P < .0001) of all invasive and noninvasive parameters. The dipyridamole time also provided independent and additional prognostic information when it was adjusted for age, diabetes, resting ECG, and exercise stress test according to a modified, interactive stepwise procedure. This is true when death only, death and myocardial infarction, and death, myocardial infarction, and revascularization procedures were considered end points.

Conclusions  In patients with no previous myocardial infarction and good resting left ventricular function, compared with exercise ECG, dipyridamole echocardiography has a similar sensitivity and a higher specificity for the noninvasive detection of angiographically assessed coronary artery disease. Dipyridamole echocardiography also provides information in addition to that provided by exercise ECG for predicting death, infarction, and all events when the presence as well as the timing, severity, and extension of dipyridamole-induced wall motion abnormalities are considered. (Circulation. 1994;89:1160-1173.)

Key Words  • dipyridamole • echocardiography • ischemia

Stress echocardiography is being increasingly proposed as a new tool for the diagnosis of coronary artery disease. The low cost, noninvasiveness, and availability of echocardiography make it particularly suitable—as a cardiac imaging modality—to be combined with stressful interventions. In particular, dipyridamole echocardiography is gaining popularity as an exercise-independent method of diagnosing coronary artery disease. In the initial experience, high-dose dipyridamole echocardiography has been shown to be relatively inexpensive, feasible, safe, fast, and highly accurate for the diagnosis of angiographically assessed coronary artery disease as well as for prognostic stratification. The diagnostic value of dipyridamole-induced transient dyssynergy has also been confirmed by other imaging techniques, such as radionuclide ventriculography and magnetic resonance, which are less dependent than two-dimensional echocardiography on operator experience and patient acoustic window, although they are certainly characterized by a lower temporal resolution. Although a considerable amount of information was obtained from this relatively new diagnostic test, much more is needed before it can become an accepted option in clinical practice. According to Feinstein, a new test is somewhat similar to a new drug, and the initial phase I and II studies in selected populations should be followed by phase III large-scale studies, in which the test is compared with

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established diagnostic tools in an appropriately large series of consecutive patients who encompass the complete spectrum of challenges to which the test is exposed. Exercise ECG remains the cornerstone of noninvasive diagnosis of coronary artery disease. However, recent developments in dipyridamole echocardiography have posed important practical questions for the clinician. What is the true relative feasibility, diagnostic accuracy, and prognostic power of exercise ECG and dipyridamole echocardiography in an unselected population of consecutive patients with suspected coronary artery disease? Should dipyridamole echocardiography supersede exercise ECG? Is there a role for these tests in combination? What is the prognostic value of noninvasive and invasive tests when their contribution is analyzed considering the logical progression of the information as it becomes available to the physician, with clinical data first, noninvasive test data second, and angiographic data last?

A rational approach to answering these specific questions as well as to providing the necessary "phase III" information for dipyridamole echocardiography requires a systematic comparison of the two tests in a large population of consecutive patients who are submitted to coronary angiography independent of the test results. We therefore performed the two tests in a consecutive in-hospital patient population who were admitted for suspected coronary artery disease, had no previous myocardial infarction, and were not receiving therapy at the time of testing. All patients were also followed up to evaluate the relative prognostic accuracy of the two tests in predicting death.

Methods

One thousand forty-nine consecutive in-patients, without previous bypass surgery, who were admitted to our coronary clinic between 1986 and June 1991 for coronary angiographic evaluation because of chest discomfort, were initially considered. Exclusion criteria were unequivocal history of previous myocardial infarction or ECG evidence of previous transmural myocardial infarction (337 patients), unstable angina (95 patients), need to continue antianginal (65 patients) or xanthine (1 patient) medication, inability to exercise adequately (physical handicap or blood pressure of ≥180/110 mm Hg) or presence of ECG alterations preventing interpretation of the ECG (left bundle branch block or digitalis) (61 patients), technically poor acoustic window at baseline (34 patients), and presence of an obvious regional dyskinesis (akinesis or dyskinesis) detected by two-dimensional echocardiography under resting conditions (27 patients).

The remaining 429 patients (122 women and 307 men; mean age, 55±8.5 years) were considered suitable candidates for exercise ECG and dipyridamole echocardiography, which were performed—on different days and in random order—within 1 week of coronary angiography. Each test was examined by observers who were blind to the results of the other test and of coronary angiography. One hundred thirty-eight patients with ECG abnormalities at rest that were different from those listed in the exclusion criteria were included in the study (ST-T abnormalities, 84 patients; right bundle branch block, 18 patients; voltage criteria of hypertrophy, 36 patients). Baseline characteristics of patients are reported in Table 1. Diabetes was defined by either antidiabetic therapy or a fasting plasma glucose level of >140 mg/dL in more than one determination, hypertension by blood pressure of ≥160 mm Hg for systolic or ≥95 mm Hg for diastolic in more than one determination or by treatment with antihypertensive drugs, hypercholesterolemia when the plasma cholesterol level was >240 mg/dL, and obesity when the weight was ≥20% over the ideal weight by height, age, and sex.

Historical data, presence of risk factors, and results of all noninvasive and invasive examinations performed during admission were prospectively entered, at the time of discharge from hospital, into a database (Hewlett Packard 92069A7 DATA BASE MANAGEMENT SYSTEM), modified in our institute. Of the 429 patients of this study, 99 were included in a previously published study.

Exercise ECG

All patients performed a multistage upright bicycle ergometer test, with an initial workload of 25 W and subsequent
TABLE 2. Results of Dipyridamole Echocardiography and Exercise ECG (1-mm ST depression)

<table>
<thead>
<tr>
<th></th>
<th>Patients Without CAD (n=183)</th>
<th>Patients With CAD (n=246)</th>
<th>Total (n=429)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RPP, mm Hg · bpm (mean±SD)</td>
<td>26 605±5114</td>
<td>23 784±6192</td>
<td>24 987±6068</td>
</tr>
<tr>
<td>Workload, max W (mean±SD)</td>
<td>105.2±30.07</td>
<td>95.8±33.8</td>
<td>99.8±32.8</td>
</tr>
<tr>
<td>Time, min (mean±SD)</td>
<td>8.40±2.45</td>
<td>7.67±2.70</td>
<td>8.0±2.6</td>
</tr>
<tr>
<td>Positive</td>
<td>89</td>
<td>48</td>
<td>183</td>
</tr>
<tr>
<td>Positive and time of ≤6</td>
<td>26</td>
<td>14</td>
<td>69</td>
</tr>
<tr>
<td>Positive and RPP of ≤20 000</td>
<td>10</td>
<td>5</td>
<td>64</td>
</tr>
<tr>
<td>Chest pain</td>
<td>61</td>
<td>50</td>
<td>124</td>
</tr>
<tr>
<td>Dipyridamole echocardiography</td>
<td></td>
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<tr>
<td>WMSI (mean±SD)</td>
<td>1.04±0.11</td>
<td>1.32±0.27</td>
<td>1.20±0.25</td>
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<tr>
<td>Time (mean±SD)</td>
<td>16.18±2.64</td>
<td>9.96±5.01</td>
<td>12.62±5.18</td>
</tr>
<tr>
<td>Positive</td>
<td>19</td>
<td>10</td>
<td>184</td>
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<tr>
<td>Positive test with time of ≤8</td>
<td>11</td>
<td>6</td>
<td>117</td>
</tr>
<tr>
<td>Positive test with WMSI of &gt;1.4</td>
<td>3</td>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>ECG changes</td>
<td>12</td>
<td>6</td>
<td>151</td>
</tr>
<tr>
<td>Chest pain</td>
<td>16</td>
<td>8</td>
<td>149</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; bpm, beats per minute; IHD, ischemic heart disease; WMSI, wall motion score index; and RPP, rate-pressure product.

Increments of 25 W every 2 minutes. A 12-lead ECG and blood pressure determination were performed at baseline and every minute thereafter. Criteria for interrupting the test were severe chest pain, diagnostic ST-segment shift, fatigue, excessive blood pressure rise (systolic blood pressure of >240 mm Hg, diastolic blood pressure of >120 mm Hg), limiting dyspnea, or maximal predicted heart rate in the absence of ischemia.

ECG tracings were considered diagnostic for myocardial ischemia when a horizontal or downsloping ST-segment shift of at least 0.1 mV, 0.08 second after the J point, in three consecutive beats, could be detected. However, sensitivity and specificity are not as high as 0.15 mV and for 0.1 mV ST-segment depression. In patients with resting ST-T abnormalities, 1-mm depression from baseline was considered significant. In the case of right bundle branch block, exercise-induced ST-segment shift was considered significant when it also occurred in leads V5 and/or V6.

ECG tracings were analyzed visually by an experienced cardiologist who was blind to angiographic and dipyridamole echocardiography findings. The maximum rate-pressure product (heart rate multiplied by systolic blood pressure) and exercise time (in minutes), assessed either at peak exercise (in negative tests) or at the peak of electrocardiographically determined ischemia (in positive tests), were also evaluated. Twelve patients with equivocal ST-T changes were counted as normal.

Dipyridamole Echocardiography

Two-dimensional echocardiographic and 12-lead ECG monitoring were performed in combination with a dipyridamole infusion of 0.56 mg/kg over 4 minutes followed by 4 minutes of no dose and then 0.28 mg/kg in 2 minutes. The cumulative dose was 0.84 mg/kg over 10 minutes. Aminophylline (240 mg), which promptly reverses the effects of dipyridamole, was readily available. During the procedure, blood pressure and ECG were recorded each minute. The ECG criteria for ischemia during this test were the same as during the exercise stress test. Two-dimensional echocardiograms were obtained continuously during and up to 10 minutes after dipyridamole administration. Commercially available wide-angle phased-array imaging systems (Hewlett Packard 77020, Toshiba Sonolayer FFA270A, or ESAOTE Biomedica SIM 7000; 2.5- and 3.5-MHz transducers) were used. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the test, new areas of abnormal wall motion were identified in multiple views whenever possible. The videotapes were analyzed by the cardiologist-echocardiographer performing the test, who was blind to the clinical and angiographic data. A wall motion score index was derived for rest and peak dipyridamole echocardiograms in each patient. The left ventricle was divided into 11 segments according to segmentation already adopted in the EPIC multicenter trial subproject on residual ischemia. The 11 left ventricular segments considered for analysis were apex, proximal and distal anterior septum, proximal and distal inferior septum, proximal and distal anterior wall, proximal and distal lateral wall, and proximal and distal inferior wall.

Segmental wall motion was graded as normal, normal motion at rest with normal/increased wall motion (hyperkinesis) after dipyridamole (score, 1); hypokinetic, marked reduction in endocardial motion (score, 2); akinetiic, virtual absence of inward motion (score, 3); or dyskinetic, paradoxical wall motion away from the left ventricular center in systole (score, 4). The wall motion score index was derived by summation of individual segment scores divided by the number of interpreted segments. Inadequately visualized segments were not scored. In positive tests, the dipyridamole time, ie, minutes from the beginning of drug infusion to the development of the stress-induced dyskinesis, was also evaluated. In negative tests, the dipyridamole time was
TABLE 3. Sensitivity, Specificity, and Accuracy of Dipyridamole Echocardiography and Exercise ECG

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<td></td>
<td>EET</td>
<td>CI</td>
<td>DET</td>
<td>CI</td>
<td>EET</td>
<td>CI</td>
<td>EET</td>
<td>CI</td>
<td>EET</td>
<td>CI</td>
<td>EET</td>
<td>CI</td>
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<tr>
<td>Any vessel disease</td>
<td>74</td>
<td>67.0-79.0</td>
<td>75</td>
<td>70.2-81.1</td>
<td>0.01</td>
<td>NS</td>
<td>51</td>
<td>44.0-59.0</td>
<td>90</td>
<td>85.0-93.8</td>
<td>59.75</td>
<td>&lt;.0005</td>
<td>64.6</td>
<td>81.1</td>
<td>33.83</td>
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<td>One-vessel disease</td>
<td>69</td>
<td>60.0-76.0</td>
<td>67</td>
<td>58.0-75.6</td>
<td>0.20</td>
<td>NS</td>
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<td>65.6-86.3</td>
<td>79</td>
<td>67.1-87.5</td>
<td>0.05</td>
<td>NS</td>
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<td>Three- or left main</td>
<td>86</td>
<td>72.6-94.8</td>
<td>93</td>
<td>81.3-98.6</td>
<td>3.00</td>
<td>NS</td>
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<tr>
<td>vessel disease</td>
<td>75%</td>
<td>48</td>
<td>29.4-67.5</td>
<td>24</td>
<td>10.3-43.5</td>
<td>3.72</td>
<td>NS</td>
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<tr>
<td>90%</td>
<td>67</td>
<td>54.0-77.8</td>
<td>79</td>
<td>67.0-87.9</td>
<td>3.20</td>
<td>NS</td>
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<tr>
<td>100%</td>
<td>89</td>
<td>74.6-97.0</td>
<td>78</td>
<td>61.8-90.2</td>
<td>1.60</td>
<td>NS</td>
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<tr>
<td>Isolated LAD</td>
<td>70</td>
<td>59.2-80.0</td>
<td>67</td>
<td>55.3-76.8</td>
<td>0.36</td>
<td>NS</td>
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<tr>
<td>Isolated LCx</td>
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<td>51.9-95.7</td>
<td>73</td>
<td>44.9-92.2</td>
<td>1.00</td>
<td>NS</td>
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<tr>
<td>Isolated RCA</td>
<td>61</td>
<td>43.5-76.9</td>
<td>64</td>
<td>46.2-79.2</td>
<td>0.05</td>
<td>NS</td>
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<tr>
<td>Any vessel disease in</td>
<td>75</td>
<td>68.0-81.0</td>
<td>76</td>
<td>68.0-85.0</td>
<td>0.08</td>
<td>NS</td>
<td>56</td>
<td>45.0-66.0</td>
<td>84</td>
<td>73.0-89.0</td>
<td>20.51</td>
<td>&lt;.0005</td>
<td>68.7</td>
<td>78.8</td>
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<tr>
<td>men</td>
<td>75</td>
<td>68.0-81.0</td>
<td>76</td>
<td>68.0-85.0</td>
<td>0.08</td>
<td>NS</td>
<td>56</td>
<td>45.0-66.0</td>
<td>84</td>
<td>73.0-89.0</td>
<td>20.51</td>
<td>&lt;.0005</td>
<td>68.7</td>
<td>78.8</td>
<td>10.56</td>
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<td>54.5-83.9</td>
<td>68</td>
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<td>0.06</td>
<td>NS</td>
<td>46</td>
<td>34.6-57.1</td>
<td>96</td>
<td>89.6-99.2</td>
<td>41.00</td>
<td>&lt;.0005</td>
<td>54.1</td>
<td>86.9</td>
<td>27.59</td>
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<td>women</td>
<td>71</td>
<td>54.5-83.9</td>
<td>68</td>
<td>51.9-81.9</td>
<td>0.06</td>
<td>NS</td>
<td>46</td>
<td>34.6-57.1</td>
<td>96</td>
<td>89.6-99.2</td>
<td>41.00</td>
<td>&lt;.0005</td>
<td>54.1</td>
<td>86.9</td>
<td>27.59</td>
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<td>Any vessel disease in</td>
<td>83</td>
<td>72.7-91.2</td>
<td>76</td>
<td>65.8-85.2</td>
<td>0.01</td>
<td>NS</td>
<td>49</td>
<td>35.6-65.7</td>
<td>88</td>
<td>76.3-94.9</td>
<td>12.46</td>
<td>&lt;.0005</td>
<td>68.8</td>
<td>81.2</td>
<td>6.48</td>
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<tr>
<td>men with normal</td>
<td>83</td>
<td>72.7-91.2</td>
<td>76</td>
<td>65.8-85.2</td>
<td>0.01</td>
<td>NS</td>
<td>49</td>
<td>35.6-65.7</td>
<td>88</td>
<td>76.3-94.9</td>
<td>12.46</td>
<td>&lt;.0005</td>
<td>68.8</td>
<td>81.2</td>
<td>6.48</td>
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<td>resting ECG</td>
<td>67</td>
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<td>76</td>
<td>67.9-83.2</td>
<td>4.8</td>
<td>&lt;.05</td>
<td>62.5</td>
<td>50.3-73.6</td>
<td>86</td>
<td>75.9-93.1</td>
<td>12.56</td>
<td>&lt;.0005</td>
<td>65.7</td>
<td>79.5</td>
<td>12.56</td>
</tr>
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</table>

EET indicates exercise ECG; DET, dipyridamole echocardiography; CI, 95% confidence interval; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

arbitrarily assumed to be 17 minutes (when aminophylline is given). All stress echocardiography procedures were performed according to a protocol approved by the Committee of the Scientific Council at the Institute of Clinical Physiology, National Council of Research.

Angiographic Study

Patients underwent biplane left ventriculography and selective right and left coronary arteriography, using either the Judkins or the Sones technique. Multiple views of each coronary artery were obtained, including craniocaudal views. A vessel was considered to have significant obstruction if its diameter was narrowed by ≥75% with respect to the prestenotic tract (50% for left main). Two independent observers, who were blind to the results of the exercise ECG and dipyridamole echocardiography, visually analyzed coronary angiograms. When there was disagreement about the degree of stenosis, a third observer reviewed the study, and the judgment was binding.

Follow-up

After discharge from hospital, patients were seen in our outpatient clinic every 6 months. The follow-up of patients who did not attend the scheduled appointments was obtained by written questionnaires or telephone interviews with the patient, close relatives, or the referring physician. Data were analyzed considering the following end points: death only, death and nonfatal myocardial infarction, and death, nonfatal myocardial infarction, and revascularization procedures.

When death and myocardial infarction were considered end points, 120 patients referred for coronary revascularization during a period of 5 years were censored at the time of revascularization (a conservative approach resulting in underestimation of the event rate).
**Statistical Analysis**

Values are given as mean±SD. For both exercise ECG and dipyridamole echocardiography, sensitivity, specificity, and accuracy in detecting angiographically assessed coronary artery disease were calculated according to standard definitions. When appropriate, the confidence interval (CI) was given. Differences between the results of exercise ECG and dipyridamole echocardiography were compared by using the McNemar test.

The individual effect of certain variables on event-free survival was evaluated with the use of the Cox regression model (BMDP 2t., Department of Biomathematics, University of California at Los Angeles, revised 1987).

Two different analyses were carried out with the Cox procedure. The first analysis was performed according to the unmodified forward selection stepwise procedure. In this case, the variables were entered in the model on the basis of a computed significance probability; accordingly, the variable that has the most significant relation to dependent outcome is selected first for inclusion in the model, and a solution to the functional form of the equation is computed. At the second and subsequent steps, the set of variables remaining at each point is evaluated, and the most significant is included if it improves the prediction of the outcome (dependent variable), but in this case this probability is conditional on the presence of the variable already selected. The algorithm ceases to select variables when there is no further significant improvement in the prediction of the whole model.

We also analyzed the data according to a modified stepwise procedure, where the significant individual variables were included in the model in the same order in which they are actually considered by the cardiologist (historical and clinical data first, ECG variables second, dipyridamole echocardiographic variable third, and angiographic variables last). At each step, a variable was required to have a significance of 0.1 to be entered into the model.

Variables selected for examination were age (continuous values), sex, risk factors (hypertension, smoking, hypercholesterolemia, diabetes, obesity, familiarity [no/yes for all]), type of angina at history (stratified in typical/atypical and in four
Fig 2. Kaplan-Meier infarction-free survival curves of 429 study patients stratified according to exercise stress testing (EET) (top) and dipyridamole echocardiography (DET) (bottom) results. DET <1.4 wall motion score index indicates positive DET with wall motion score index of ≤1.4; DET >1.4 wall motion score index, positive DET with wall motion score index of >1.4; EET >20 000 RPP, positive EET at rate-pressure product of >20 000; EET ≤20 000 RPP, positive EET at rate-pressure product of ≤20 000.

classes according to the Canadian classification), presence of ECG abnormalities in basal conditions (no/yes), and number of coronary vessels narrowed ≥75% (no vessels; one-, two-, or three-vessel disease; or left main disease). For exercise stress ECG results, the variables selected were ST-T changes during the test (negative, positive 1 mm, or positive 1.5 mm), rate-pressure product (continuous values), time (continuous values), ECG positivity stratified in five levels according to the maximum rate-pressure product (negative, positive tests with only 1-mm ST depression and rate-pressure product >20 000, positive tests with only 1-mm ST depression and rate-pressure product ≤20 000, positive tests with 1.5-mm ST depression and rate-pressure product >20 000, or positive tests with 1.5-mm ST depression and rate-pressure product ≤20 000), and the duration of exercise (negative, positive at 1 mm with exercise time of >6 minutes, positive at 1 mm with exercise time of ≤6 minutes, positive at 1.5 mm with exercise time of ≤6 minutes, or positive at 1.5 mm with exercise time of ≤6), and chest pain (no/yes). For dipyridamole echocardiography, the selected variables were echocardiographic positivity during dipyridamole echocardiography (negative, positive at high dose, or positive at low dose), dipyridamole time stratified from 1 to 17 minutes, wall motion score index at peak dipyridamole (continuous values), chest pain during the test (no/yes), and ST-T changes during the test (no/yes).

A value of $P<.05$ was considered statistically significant.

Results

Results of dipyridamole echocardiography and exercise ECG are reported in Table 2.

Feasibility and Safety

No major side effects occurred during either exercise ECG or dipyridamole echocardiography in any patient. In all patients, the quality of echocardiograms was unchanged during dipyridamole echocardiography and therefore suitable for analysis. However, in three patients, the higher dose could not be administered be-
cause of limiting side effects occurring during the lower dose: excessive tachycardia with palpitations (one patient) and hypotension and symptomatic bradycardia (two patients). The test results of these three patients, who therefore completed a “submaximal” dipyridamole echocardiography test, were included into the analysis.

Diagnostic Accuracy for Angiographically Assessed Coronary Artery Disease

There were 183 patients with no significant coronary artery disease and 246 with coronary artery disease: 132 had one-, 70 had two-, and 44 had three-vessel disease. When 0.1-mV ST-segment shift was chosen as a cutoff between negative and positive exercise stress testing, dipyridamole echocardiography had a superior specificity (90% versus 51%, \( P<.001 \)), whereas the two tests showed a similar sensitivity for the detection of angiographically assessed coronary artery disease (dipyridamole echocardiography, 75%; exercise ECG, 74%; \( P=NS \)). Of the 72 patients with coronary artery disease and negative exercise ECG, 18 (25%) did not reach 85% of target heart rate, predicted on the basis of age and sex. Excluding from the analysis patients with submaximal testing, the sensitivity of exercise ECG increased to 80%. The specificity of exercise was substantially lower than that of dipyridamole in both men and women (\( P<.001 \)), in patients with abnormalities of the resting ECG, and in patients with normal resting ECG (\( P<.001 \)) (Table 3). The sensitivity was comparable in the different subsets of patients with one-, two-, and three-vessel disease (Table 3). In patients with one-vessel disease, the sensitivity was similar in patients with isolated left anterior descending, left circumflex, and right coronary artery disease (Table 3). In patients with one-vessel disease, dipyridamole echocardiography sensitivity was similar to that of exer-
cise ECG for patients with 75% stenosis, 90% stenosis, and 100% occlusion (Table 3). When 0.15-mV ST-segment shift was taken as a cutoff between negative and positive exercise stress testing, the sensitivity of exercise stress decreased to 71% (CI, 66 to 77.4), whereas the specificity increased to 59% (CI, 47.8 to 62).

**Prognostic Data**

Patients were followed up for a period ranging from 1 to 73 months (mean, 37.8 ± 14 months). During the follow-up, there were 20 deaths (15 cardiac and 5 noncardiac), 13 myocardial infarctions, and 12 revascularization procedures (percutaneous transluminal coronary angioplasty [60] and coronary artery bypass surgery [66]). The 5-year cumulative incidence rate of revascularization procedures was 36%. Survival, survival without infarction, and survival without events are reported in the curves of Figs 1, 2, and 3 according to the results of exercise ECG and dipyridamole echocardiography, respectively. It should be noted that both exercise and dipyridamole test alone allowed good stratification. In particular, no deaths occurred in the patients with negative exercise ECG and rate-pressure product of > 20,000, whereas the death rate at 3 years was 16.4% in the patients with positive exercise stress testing at a rate-pressure product of < 20,000. Survival according to coronary angiography results is reported in Fig. 4.

The variables reported in Table 4 were found to be univariate predictors of death; the dipyridamole time was the most powerful parameter. When a forward stepwise regression procedure was performed, the dipyridamole time, presence of diabetes mellitus, positivity of exercise at low rate-pressure product, and resting ECG were found to be independent and additional predictors of subsequent death (Table 5). When variables were entered into the model according to an interactive, clinically realistic approach, after considering age and diabetes as well as resting and exercise ECG, dipyridamole echocardiography added significant prognostic information (Table 6). At that point, coronary angiography did not show significant additional prognostic power.

Also, when survival without infarction and survival without events were considered, dipyridamole echocardiography added prognostic information after taking account of clinical and exercise ECG data. The univariate and multivariate predictors of survival without infarction and survival without events are shown in Tables 7 through 10.

**Discussion**

In patients with normal resting function, dipyridamole echocardiography has a similar sensitivity and a higher specificity compared with exercise ECG for the noninvasive detection of angiographically assessed coronary artery disease. The sensitivity of both tests increases in more severe and/or extensive forms of coronary artery disease. Dipyridamole echocardiography also has a higher prognostic value than exercise ECG for predicting death, myocardial infarction, and revascularization procedures when the presence as well as the severity and extension of dipyridamole-induced wall motion abnormality are considered. If clinical and exercise ECG data are considered first, according to a clinically realistic model of prognostication, dipyridamole echocardiography results add significantly to the prognostic stratification. These findings confirm and expand previous research showing the high diagnostic accuracy and prognostic value of dipyridamole echocardiography as first reported by our group 16 and later confirmed by several laboratories evaluating the test in various patient subsets, ranging from stable angina,6-8 early after infarction,9-12,13 angioplasty14 or bypass surgery,10 or risk stratification for elective vascular surgery.13 However, a few unique features of the present study are worth mentioning and relate to the methodology used and criteria for patient selection.

**Stress Echocardiographic Methodology**

The echocardiographic methodology of the present study differs in two important aspects from that used in previous reports from our laboratory.2,11
TABLE 5. Significant Predictors of Death According to a Forward Procedure

<table>
<thead>
<tr>
<th></th>
<th>$\chi^2$</th>
<th>$P$</th>
<th>Risk Ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DET/time</td>
<td>19.437</td>
<td>.000</td>
<td>1.1477</td>
<td>1.0288-1.2804</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.734</td>
<td>.005</td>
<td>3.3236</td>
<td>1.2812-8.6676</td>
</tr>
<tr>
<td>EET/ECG + RPP</td>
<td>6.095</td>
<td>.014</td>
<td>1.7550</td>
<td>1.0877-2.8319</td>
</tr>
<tr>
<td>Resting ECG</td>
<td>3.830</td>
<td>.050</td>
<td>2.3328</td>
<td>0.9597-5.6710</td>
</tr>
<tr>
<td>Age</td>
<td>2.935</td>
<td>.087</td>
<td>1.0470</td>
<td>1.0000-1.1054</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DET, dipyridamole echocardiography; EET, exercise ECG; and RPP, rate-pressure product.

First, the studies were not performed and interpreted by two independent observers; rather, the cardiologist-echocardiographer performing the test also interpreted the study. This considerably reduced the time required for evaluating the test results, without any detectable loss in accuracy. The five members of the echocardiographic laboratory staff shared the responsibility of performing and interpreting the test. No detectable differences in diagnostic performance among the observers could be noted, which is consistent with the established notion that accuracy of stress echocardiography is observer dependent but fairly constant in experienced hands.\(^3\) We had already shown that the interobserver and intraobserver reproducibility is very high (>90%) between experienced observers\(^3\) and, therefore, that the routine use of separate multiple readings is not cost effective. Nevertheless, in the more realistic conditions of the present study, which are more likely to reproduce those found in a busy echocardiographic laboratory,\(^2\) the diagnostic accuracy of dipyridamole echocardiography proved to be very high and not significantly lower than that reported in initial studies on smaller patient series that were evaluated under more controlled conditions.

Second, in addition to the presence of the dyssnergy, the analysis of echocardiographic data included an assessment of the timing as well as of the wall motion score index, evaluated both under resting conditions and at peak dipyridamole. This allowed us to evaluate the prognostic correlates of the main echocardiographic parameters potentially capable of quantifying the induced ischemia.\(^2\) We previously showed the high reproducibility of dipyridamole time,\(^2\) which is directly correlated to exercise time\(^2\) and inversely correlated to the severity of coronary stenosis\(^2\) and to the impairment in flow reserve.\(^3\)

**Patient Selection**

Some features of our patient population should be considered. It has been said that any new diagnostic tool is usually tested, at least initially, in a very select patient population—representing "the welllest of the well and the sickest of the sick," in whom the diagnostic test performance is likely to be better than that in a "real" population.\(^2\) However, in the present study, we selected a consecutive series of patients admitted for diagnostic work-up. In this way, our population probably reflects the continuous spectrum of the disease, and the performance of the test is as close as possible to that found in the real world. This may be why the sensitivity and specificity of both tests are a little lower than those previously reported. In particular, in our population, we recorded an extremely low specificity of exercise ECG, which might appear to be in disagreement with extensive experience with this test.\(^3\) This finding might have multiple explanations linked to exercise ECG test data analysis, to angiographic data analysis, and, perhaps most important in our opinion, to patient selection. Regarding exercise ECG data analysis, we restricted positivity criteria to classic ECG criteria, without considering the combination of several other variables, such as heart rate, work load, and so on, that might increase the overall diagnostic power of exercise testing.\(^3\) Regarding angiographic assessment, we set the cutoff for significant stenosis at 75% with visual assessment, which means that some patients with "subcritical" stenoses actually might have had "critical" stenoses by quantitative analysis. Patient selection may be another major factor of poor specificity for several reasons. In our study population, there was a relatively high proportion of women and of patients with abnormal baseline ECGs; however, the restriction of analysis either to men or to patients with normal resting ECGs increases specificity only to a limited extent. Of greater importance might have been the presence of a high proportion of patients with microvascular disease or angina of vasospastic origin, in whom—even in the presence of entirely normal coronary arteries—stress-induced ST-segment changes are frequently seen during exercise.\(^3\) Previous studies from our institution have shown that

TABLE 6. Significant Predictors of Death According to an Interactive Procedure

<table>
<thead>
<tr>
<th></th>
<th>$\chi^2$</th>
<th>$P$</th>
<th>Risk Ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.373</td>
<td>.004</td>
<td>1.0470</td>
<td>1.0000-1.1054</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.120</td>
<td>.013</td>
<td>3.3326</td>
<td>1.2812-8.6676</td>
</tr>
<tr>
<td>Resting ECG</td>
<td>2.660</td>
<td>.103</td>
<td>2.3328</td>
<td>0.9597-5.6710</td>
</tr>
<tr>
<td>EET/ECG + RPP</td>
<td>15.899</td>
<td>.000</td>
<td>1.7554</td>
<td>1.0877-2.8319</td>
</tr>
<tr>
<td>DET/time</td>
<td>6.980</td>
<td>.008</td>
<td>1.1477</td>
<td>1.0288-1.2804</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EET, exercise ECG; and DET, dipyridamole echocardiography.
these patients represent a sizeable portion of patients with normal resting function undergoing coronary angiography for a chest pain syndrome. Obviously, in this population, the specificity of exercise ECG is unusually low. On the other hand, these patients are more likely to be referred for coronary angiography than are patients with no coronary artery disease and negative stress testing, especially considering the high rate of false-positives found in this subset with perfusion imaging techniques.

Moreover, sensitivity was found to be lower when exercise stress testing was compared with a “better” test. The main advantages of this prospective technique derive from its capacity to show a complete spectrum of consecutive challenges to which both tests were exposed. We believe, therefore, that the indexes of diagnostic accuracy reported in this article are likely to mirror exactly how the tests perform under clinical conditions. Another important point is that our population was not receiving therapy. It is known that antianginal therapy may prevent ischemia, in its ECG/echocardiographic manifestations evoked by either exercise or dipyridamole testing. Furthermore, our patients had no previous myocardial infarction. Because the inclusion of patients with previous myocardial infarction is known to inflate test sensitivity and the diagnosis of coronary artery disease is not at issue in patients with myocardial infarction, the inclusion of such patients in investigations purporting to predict coronary disease is inappropriate. The selection of patients from those referred for coronary angiography because of chest pain can explain why the clinical history of angina is not so important in this patient population, whereas it usually is in the general population.

Study Limitations

The gold standard used for comparison of noninvasive test results was the angiographically assessed coronary artery disease. It is known that angiographic stenosis is not necessarily related to the degree of impairment in regional coronary flow reserve. Furthermore, the visual assessment suffers from relatively high intraobserver and interobserver variability. Although a subjective visual estimate of “percent stenosis” lacks accuracy and repeatability and does not provide accurate insight into the hemodynamic impact of a lesion, the simplicity of the percent stenosis estimate and the force of tradition favor its continued use: in most cardiological centers, the visual assessment of coronary stenosis remains the definitive gold standard.

A second limitation is inherent to the sensitivity-specificity approach that we used; this approach requires a dichotomous response for both test results and coronary artery disease when all, in fact, show a continuous spectrum of severity. Therefore, in the present study, we also evaluated a few parameters of severity of exercise testing (peak rate-pressure product and exercise time) and of dipyridamole echocardiography response (wall motion score index, dipyridamole time), which proved to be effective in prognostic stratification. Furthermore, for exercise stress testing, we considered stratification into five subgroups, taking into account both different levels of ECG positivity and different levels of rate-pressure product or exercise time; this stratification was found to be more effective in prognostic stratification than presence of ST-segment changes, rate-pressure product, and exercise time considered separately. The stronger predictive power of dipyridamole time in comparison with wall motion score index for the prediction of death might be
TABLE 7. Univariate Predictors of Death and Nonfatal Myocardial Infarction

<table>
<thead>
<tr>
<th>Predictive Factor</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of vessels narrowed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75%</td>
<td>13.09</td>
<td>.0003</td>
</tr>
<tr>
<td>DET/WMSI</td>
<td>12.94</td>
<td>.0003</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12.27</td>
<td>.0005</td>
</tr>
<tr>
<td>DET/time</td>
<td>12.10</td>
<td>.0005</td>
</tr>
<tr>
<td>DET/echo positivity</td>
<td>10.93</td>
<td>.0009</td>
</tr>
<tr>
<td>EET/ECG positivity and RPP</td>
<td>10.88</td>
<td>.0010</td>
</tr>
<tr>
<td>EET/RPP</td>
<td>9.74</td>
<td>.0018</td>
</tr>
<tr>
<td>EET/ECG positivity and time</td>
<td>9.41</td>
<td>.0022</td>
</tr>
<tr>
<td>EET/ECG positivity</td>
<td>8.26</td>
<td>.0041</td>
</tr>
<tr>
<td>Sex</td>
<td>7.63</td>
<td>.0057</td>
</tr>
<tr>
<td>DET/ECG positivity</td>
<td>6.69</td>
<td>.0097</td>
</tr>
<tr>
<td>Age</td>
<td>5.84</td>
<td>.0157</td>
</tr>
<tr>
<td>EET/time</td>
<td>4.62</td>
<td>.0316</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>3.24</td>
<td>.0717</td>
</tr>
<tr>
<td>DET/pain</td>
<td>2.79</td>
<td>.0946</td>
</tr>
<tr>
<td>Canadian angina class</td>
<td>2.40</td>
<td>.1213</td>
</tr>
</tbody>
</table>

DET indicates dipyridamole echocardiography; WMSI, wall motion score index; echo, echocardiography; EET, exercise ECG; RPP, rate-pressure product; and IHD, ischemic heart disease. n = 429.

The result, at least in part, of the test protocol that we used. According to our approach, the development of a new wall motion abnormality is an absolute end point of the test, chosen to prevent potential complications from severe or prolonged ischemia. The wall motion score index may have been more meaningful if a more aggressive protocol were used, implying full-dose administration in all patients. On the other hand, when dipyridamole results were entered into the Cox model, the most significant variable was chosen; both dipyridamole time and wall motion score index are indexes of the severity of test positivity, and their χ² value had very close values in the univariate analysis. The selection of one index in the multivariate analysis implied the exclusion of the other one.

A limitation of the study is the low number of reliable events (only 20 deaths). Death is an unusual event in patients with suspected coronary artery disease; when an unequivocally reliable hard event (death) is chosen, the multivariate analysis gives unstable results. For this reason, the literature is inflated by studies in which the assessment of the outcome is based on soft events, such as revascularization procedures and recurrence of angina. The former is a consequence of the test rather than an indicator of an adverse prognosis; the latter is also dependent on the psychological profile of each patient. Myocardial infarction may also be an unreliable event, when patients are contacted by telephone calls or questionnaires, because about 25% of infarcts occur asymptptomatically.37 For this reason, we analyzed data considering as end points the following: death only, death and nonfatal myocardial infarction, and death, nonfatal myocardial infarction, and revascularization procedures.

Statistical Approach

When a Cox regression model is used to identify independent prognostic variables, the most commonly used selection algorithm is the forward selection stepwise procedure. It was used in the majority of articles reporting the prognostic value of thallium myocardial scintigraphy and exercise radionuclide ventriculography.38-41 With this procedure, variables are included in or removed from the model according to a computed significance probability, from the highest to the lowest. Moreover, the prognostic value of each variable, found to be an independent predictor, is conditional on that of variables already selected. When we analyzed our data according to a forward stepwise procedure, the information we have is that age does not add prognostic information to that provided by dipyridamole time, diabetes mellitus, exercise stress testing, and resting ECG. Moreover, exercise stress testing provides prognostic information even when it was adjusted for dipyridamole time and diabetes.

However, what a cardiologist wants to know from a new test is whether it adds prognostic information to that provided by clinical data and more simple, feasible, and widespread tests, such as exercise ECG. In only few studies, the data were analyzed according to a realistic clinical sequence.52-43 According to this analysis, neither radionuclide ventriculography nor thallium scintigraphy52-43 provided additional prognostic information to that provided by clinical data and exercise test results in patients with normal resting ECGs. We also used a modified interactive stepwise procedure, in which the significant univariate variables were included in the model in the natural sequence in which clinical information and noninvasive tests are considered in the course of patient evaluation. The information we have according to this analysis is that dipyridamole time provides pros-

TABLE 8. Significant Predictors of Death and Nonfatal Infarction According to an Interactive Procedure

<table>
<thead>
<tr>
<th>Predictive Factor</th>
<th>χ²</th>
<th>P</th>
<th>Risk Ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5.840</td>
<td>.016</td>
<td>1.0311</td>
<td>0.9885-1.0755</td>
</tr>
<tr>
<td>Sex</td>
<td>6.712</td>
<td>.010</td>
<td>2.7986</td>
<td>0.8356-9.3730</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9.753</td>
<td>.002</td>
<td>3.1508</td>
<td>1.4669-6.7666</td>
</tr>
<tr>
<td>EET/ECG positivity and RPP</td>
<td>6.449</td>
<td>.011</td>
<td>1.2774</td>
<td>0.9710-1.6804</td>
</tr>
<tr>
<td>DET/WMSI</td>
<td>3.538</td>
<td>.060</td>
<td>3.5883</td>
<td>1.0000-13.0087</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EET, exercise ECG; RPP, rate-pressure product; DET, dipyridamole echocardiography; and WMSI, wall motion score index.
TABLE 9. Univariate Predictors of All Events

<table>
<thead>
<tr>
<th>Predictor</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>DET/echo positivity</td>
<td>95.58</td>
<td>.0000</td>
</tr>
<tr>
<td>DET/time</td>
<td>86.67</td>
<td>.0000</td>
</tr>
<tr>
<td>No. of vessels narrowed ( \geq 75% )</td>
<td>80.23</td>
<td>.0000</td>
</tr>
<tr>
<td>DET/WMSI</td>
<td>71.81</td>
<td>.0000</td>
</tr>
<tr>
<td>EET/ECG positivity and RPP</td>
<td>35.28</td>
<td>.0000</td>
</tr>
<tr>
<td>EET/ECG positivity and time</td>
<td>29.55</td>
<td>.0000</td>
</tr>
<tr>
<td>DET/ECG positivity</td>
<td>29.09</td>
<td>.0000</td>
</tr>
<tr>
<td>Sex</td>
<td>25.88</td>
<td>.0000</td>
</tr>
<tr>
<td>EET/ECG positivity</td>
<td>24.97</td>
<td>.0000</td>
</tr>
<tr>
<td>Canadian angina class</td>
<td>20.56</td>
<td>.0000</td>
</tr>
<tr>
<td>EET/RPP</td>
<td>19.12</td>
<td>.0000</td>
</tr>
<tr>
<td>DET/pain</td>
<td>18.94</td>
<td>.0000</td>
</tr>
<tr>
<td>Atypical/typical pain</td>
<td>13.20</td>
<td>.0003</td>
</tr>
<tr>
<td>Age</td>
<td>7.76</td>
<td>.0054</td>
</tr>
<tr>
<td>EET/time</td>
<td>5.53</td>
<td>.0187</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.95</td>
<td>.0470</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.88</td>
<td>.0895</td>
</tr>
</tbody>
</table>

DET indicates dipyridamole echocardiography; echo, echocardiography; WMSI, wall motion score index; EET, exercise ECG; and RPP, rate-pressure product.

n=429.

tic information even when it was adjusted for age, diabetes, resting ECG, and exercise stress testing.

The apparent disagreement between the estimation of risk ratio and the \( \chi^2 \) values in the multivariate analysis can be explained by the different stratification of each variable: dipyridamole test can have values from 1 to 17, and the risk ratio represents the increase in risk for every increment of 1 (17 steps); exercise stress testing is stratified into five subgroups (as reported in “Methods”), and in this case the risk ratio represents the increase in risk from one subgroup to the following one (five steps); and finally, diabetes is considered a binary variable (no/yes), and in this case the risk ratio represents the increased risk resulting from having versus not having diabetes.

Clinical Implications

In patients with chest pain of unknown origin, representing true diagnostic dilemmas, dipyridamole echocardiography shows an excellent specificity and an acceptable sensitivity and is especially good in more severe and/or extensive angiographically assessed coronary artery disease. In comparison with exercise ECG, dipyridamole echocardiography exhibited a similar sensitivity and a much higher specificity. Obviously, exercise ECG offers unique information on cardiovascular efficiency, which is not available by pharmacological testing.\(^{19,44}\)

Conversely, echocardiography provides information on the site and extent of myocardial ischemia as well as data on ejection fraction, left ventricular hypertrophy, and valve function under resting conditions, which can be of paramount value to the clinician.\(^1\) In view of the relatively low cost, short imaging time, widespread availability of two-dimensional echocardiography, short learning curve for stress echocardiography, and prognostic information provided by the test, a potential role for dipyridamole echocardiography can be envisaged as a complement to exercise ECG in the difficult task of predicting coronary anatomy in the patient with chest pain and no previous myocardial infarction and/or resting dyssynergy.

The information obtained with dipyridamole echocardiography might be considered grossly comparable—in terms of diagnostic accuracy—to that obtained with other forms of stress echocardiography, such as exercise echocardiography or dobutamine echocardiography, as shown by experimental\(^{46-51}\) and clinical\(^{46-51}\) studies. It is important to emphasize that the diagnostic information derived from a given test can be combined with a second test only if the results of the two tests are relatively independent of one another.\(^52\) Such an independence derives from the independence of the pathophysiological processes leading to test positivity. In studies published to date, patients with false-positive ST-segment responses to exercise usually have normal echocardiographic scans with dipyridamole.\(^4\) Furthermore, dipyridamole can provoke echocardiographically detectable myocardial ischemia only in the presence of hemodynamically significant epicardial coronary stenosis, whereas exercise can provoke ischemia through a vasodilatory mechanism.\(^5\)

It therefore can be reasonably concluded that these two tests, which assess abnormalities in myocardial electrophysiology and cardiovascular efficiency (exercise ECG) and location and severity of ischemia (dipyridamole echocardiography), might be used in combination. This analysis should not be construed as an argument favoring the routine use of a combination of exercise ECG and dipyridamole echocardiography. In the usual patient with the diagnostic dilemma of a chest pain syndrome, systematic application of the two tests may be unfeasible as well as unwise. In terms of pure

TABLE 10. Significant Predictors of All Events According to an Interactive Procedure

<table>
<thead>
<tr>
<th>Predictor</th>
<th>( \chi^2 )</th>
<th>( P )</th>
<th>Risk Ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>7.756</td>
<td>.005</td>
<td>1.0095</td>
<td>1.0000-1.0291</td>
</tr>
<tr>
<td>Sex</td>
<td>23.763</td>
<td>.000</td>
<td>1.6821</td>
<td>1.0199-2.7745</td>
</tr>
<tr>
<td>Canadian angina class</td>
<td>12.730</td>
<td>.000</td>
<td>1.5611</td>
<td>1.1823-2.0613</td>
</tr>
<tr>
<td>EET/ECG positivity and RPP</td>
<td>31.238</td>
<td>.000</td>
<td>1.1829</td>
<td>1.0502-1.3324</td>
</tr>
<tr>
<td>DET/WMSI</td>
<td>30.614</td>
<td>.000</td>
<td>2.9658</td>
<td>1.4648-6.0045</td>
</tr>
<tr>
<td>No. of vessels narrowed ( \geq 75% )</td>
<td>15.524</td>
<td>.000</td>
<td>2.9658</td>
<td>1.1864-1.6367</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EET, exercise ECG; RPP, rate-pressure product; DET, dipyridamole echocardiography; WMSI, wall motion score index.
diagnostic performance, dipyridamole echocardiography did significantly better than exercise ECG. However, one must consider that exercise ECG is by far a less expensive, and more widespread and “routine” procedure than dipyridamole echocardiography, which requires a two-dimensional echocardiograph and personnel with specific expertise in stress echocardiography. Therefore, a rational approach may still be to use exercise ECG as a first-line test and to reserve dipyridamole echocardiography for patients with either a positive at high intermediate workload or a nondiagnostic (with exercise-induced chest pain or submaximal workload achieved during stress) exercise ECG. Also, a markedly positive ECG (with a low workload) is an indication to coronary angiography, without additional testing. Dipyridamole echocardiography is especially indicated in the presence of conditions further reducing the reliability of exercise-induced ECG changes, such as female gender or hypertension, that do not influence the diagnostic performance of dipyridamole echocardiography. Once dipyridamole echocardiography is performed, the response should be evaluated according to the type of positivity, which may provide important stratification of the ischemic response. This strategy of testing appears to be reasonable in our cost-conscious era in which we face the major challenge of maintaining the highest diagnostic standards in the presence of a substantial decrease in resources. However, it remains to be prospectively validated in another series of patients. The results of this study and others indicate that the functional consequences, elicited by stress testing, of any given anatomic configuration may have more of an impact on outcome than the mere number of vessels with stenosis when ventricular function is intact.

In conclusion, dipyridamole echocardiography has a similar sensitivity and a higher specificity compared with exercise ECG in patients with normal resting function. Dipyridamole echocardiography does not offer only a binary, black-or-white response but rather complex stratification of the ischemic response with an array of shades of gray, including the extent, severity, and timing of the transient dysynergy. The severity of the stress-induced ischemia is even more important than its presence in identifying the coronary anatomy and prognostic outlook of a patient.

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