Stress Testing

Prognostic Value of Pharmacological Stress Echocardiography in Patients With Known or Suspected Coronary Artery Disease

A Prospective, Large-Scale, Multicenter, Head-to-Head Comparison Between Dipyridamole and Dobutamine Test

Alessandro Pingitore, MD, Eugenio Picano, MD, PitiD, Albert Varga, MD, Guido Gigli, MD, Lauro Cortigiani, MD, Mario Previtali, MD, Giovanni Minardi, MD, Massimo Quarta Colosso, MD, Jorge Lowenstein, MD, Wilson Mathias, Jr., MD, Patrizia Landi, BSc on behalf of the Echo-Persantine International Cooperative (EPIC) and Echo-Dobutamine International Cooperative (EDIC) Study Groups

Pisa, Italy

OBJECTIVES The study compared the prognostic value of dipyridamole and dobutamine stress echocardiography in patients with known or suspected coronary artery disease.

BACKGROUND Extensive information is available on the relative diagnostic accuracy of the two tests assessed in a head-to-head fashion, whereas comparative data on their prognostic yield are largely preliminary to date.

METHODS Dipyridamole (up to 0.84 mg/kg over 10 min) atropine (up to 1 mg over 4 min) (DIP) and dobutamine (up to 40 μg/kg/min)-atropine (1 mg over 4 min) (DOB) stress tests were performed in 460 patients with known or suspected coronary artery disease. Patients were followed up for 38 ± 21 months.

RESULTS The DIP was negative in 253 and positive in 207 patients. The DOB was negative in 242 and positive in 218 patients. During the follow-up, there were 80 cardiac events. For all cardiac events, the negative and positive predictive value were 83% and 17% for DOB, 84% and 19% for DIP, respectively (p < NS). Considering only cardiac death, by univariate analysis Wall-Motion Score Index (WMSI) at DIP peak dose (chi-square 13.80, p = 0.0002) was the strongest predictor, followed by WMSI DOB (χ² = 8.02, p < 0.004) and WMSI at rest (χ² = 6.85, p < 0.008). By stepwise analysis, WMSI at DIP peak dose was the most important predictor (RR [relative risk] 7.4, p < 0.0001).

CONCLUSIONS In patients at low-to-moderate risk of cardiac events, pharmacological stress echocardiography with either dobutamine or dipyridamole allows effective and grossly comparable, risk stratification on the basis of the presence, severity and extension of the induced ischemia. (J Am Coll Cardiol 1999;34:1769–77) © 1999 by the American College of Cardiology

According to the recent guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) pharmacological stress echocardiography with either dobutamine or dipyridamole is a class 1 indication (of documented effectiveness and usefulness) for the diagnosis of coronary artery disease and for the prognostic stratification of patients with known coronary artery disease (1). The American Society of Echocardiography has also recommended pharmacological stress echocardiography with either dobutamine or dipyridamole as the preferred modality in patients who cannot exercise (2). The choice of one pharmacological test over the other as the preferred imaging echocardiographic modality may depend upon local drug cost, test safety, and information provided in terms of diagnostic accuracy and prognostic stratification (3). Extensive information is available on the relative diagnostic accuracy of the two tests assessed in a head-to-head fashion (4–13), whereas comparative data on their prognostic yield are largely preliminary to date (13,14), encompassing only two studies (13,14) totaling 184 patients. These studies showed a similar prognostic value of the two tests, but suffered some limitations: “state of the art” protocols (high dose with atropine coadministration) were not used; soft events, such as revascularization procedures, had to be...
undergo two stress tests was obtained from all patients.

and beta blockers in 16 cases). Verbal informed consent to cases (nitrates and calcium antagonists in 17 and nitrates beta-adrenergic blocking in 13, and combined therapy in 33 which consisted of nitrates in 21, calcium antagonists in 15, underwent both testing under identical antianginal therapy, eight patients were off therapy at the time of testing; 82 patients performed dobutamine first. Three hundred-fifty of 206 patients performed dipyridamole first and 254 different days, in random order, and within 15 days. A total formed dipyridamole and dobutamine stress testing on months) myocardial infarction; 155 had angina pectoris and cated myocardial infarction; 108 had a previous (....

METHODS

Patients. From the EPIC and EDIC data bank, 538 patients (510 men, mean age 60 ± 12 years) who had performed both dipyridamole-atropine (DIP) and dobutamine-atropine (DOB) stress echocardiography were initially selected. Of these, 37 patients were excluded because the two tests were performed within a time interval >15 days; 18 patients performed the two tests under different therapeutic conditions and an additional 23 pa-

cluded as meaningful end points owing to the very low incidence of hard events; patient population was strictly selected and enrolled in single centers, possibly not representing the full spectrum of patients arriving to the stress echocardiography laboratory. The purpose of this study was to compare, head-to-head, the prognostic value of dipyridamole and dobutamine stress echocardiography in patients with known or suspected coronary artery disease in a large-scale, multicenter, observational and prospective study design on the basis of evidence collected by 14 different echocardiographic laboratories. All laboratories had an established experience in stress echocardiography, met the quality-control requirements for stress echocardiographic interpretation before starting patient enrollment, and belonged to the stress echocardiographic network of the EPIC (Echo Persantine International Cooperative) and EDIC (Echo Dobutamine International Cooperative) studies.

Stress echocardiographic protocols. DOBUTAMINE-ATROPINE. Dobutamine was infused in 3-min dose increments, starting from 5 µg/kg/min and increased to 10, 20, 30, and 40 µg/kg/min (10,15). When no end point was reached, atropine (in four divided doses of 0.25 mg up to a maximum of 1 mg) was added to the continuing 40 µg/kg/min dobutamine infusion.

DIPYRIDAMOLE-ATROPINE. Dipyridamole was infused intravenously at a dose of 0.56 mg/kg body weight over 4 min, followed by 4 min of no dose and then, if the test was still negative, 0.28 mg/kg over 2 min. When no end point was reached at 3 min after the end of dipyridamole infusion, atropine (in four divided doses of 0.25 mg up to a maximum of 1 mg) was given (16).

Echocardiographic analysis. Two-dimensional echocar-
diographic monitoring was performed throughout and up to 10 min after stopping the drug infusion. Two-dimensional images were recorded at baseline and at the end of each step. Regional wall-motion analysis was evaluated at baseline and at peak stress with a semiquantitative assessment of a Wall-Motion Score Index (WMSI), with the 16-segment model of the left ventricle, each segment ranging from 1 = normal/hyperkinetic to 4 = dyskinetic, according to recommend-

ations of the American Society of Echocardiography (17). The WMSI was derived by dividing the sum of individual segment scores by the number of interpretable segments (17). Test positivity was defined as the occurrence of at least one of the following conditions: 1) new dyssyn-

ergia in a region with normal rest function (i.e., normoki-

nesia becoming hypokinesia, akinesia or dyskinesia); 2) worsening of rest dyssynergia (i.e., hypokinesia becoming akinesia or dyskinesia). Resting akinesia becoming dyskinesia was not considered a criterion of positivity, because this can result from passive stretching phenomena rather than from active ischemia (18). The extension and severity of induced ischemia was expressed as a Delta WMSI: a variation between the resting WMSI and peak WMSI without considering functional recovery of basally asynergic segments.

Furthermore, the extension of induced ischemia was also expressed as the number of ischemic segments at peak stress. Nonechocardiographic test end points were the following (10): peak atropine dose; 85% of target heart rate; achievement of conventional end points (such as severe chest pain and/or diagnostic ST segment changes). The test was also stopped, in the absence of diagnostic end points, for one of the following reasons of submaximal, nondiagnostic test (10): intolerable symptoms; limiting asymptomatic side effects, consisting of a) hypertension (systolic blood pressure >220 mm Hg; diastolic blood pressure >120 mm Hg); b) hypotension (relative or absolute): >30 mm Hg fall of blood pressure; c) supraventricular arrhythmias; supraventricular tachycardia or atrial fibrillation; d) ventricular arrhythmias: ventricular tachycardia; frequent, polymorphous premature ventricular beats.

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIP = dipyridamole-atropine</td>
</tr>
<tr>
<td>DOB = dobutamine-atropine</td>
</tr>
</tbody>
</table>
| EDIC = Echo Dobutamine Inter-
  national Cooperative         |
| EPIC = Echo Persantine Inter-
  national Cooperative         |
| RR = relative risk           |
| WMSI = Wall-Motion Score In-
  dex |
Quality control of stress echocardiographic readings. Quality control of the diagnostic performance in the different centers was of critical importance in acquiring meaningful information into the data bank. In the enrolled centers, the quality control was performed based upon two criteria, each one having to be met to fulfill the quality-control requirements (19).

The first criterion was tested on a videotape with 20 stress echocardiographic studies prepared in the coordinating center (Institute of Clinical Physiology in Pisa, Italy). In all these 20 studies the reading of two experienced independent observers was concordant as to presence and site of dysynchrony, and the stress results were in full agreement with presence and site of coronary stenoses during coronary angiography. The unanimous reading of the two observers was arbitrarily assumed to be the “gold standard” against which to evaluate the reading of each participating center. The reader from each center interpreted the videotape in a blinded fashion, with no access either to clinical and angiographic data or to the interpretation given by other observers. It was assumed a priori that the minimum threshold of concordance to pass this part of the quality control had to be 90%. The second criterion consisted in random-sampling 20 consecutive studies from each contributing center. These 20 studies were examined in a blinded fashion by an experienced cardiologist-echocardiographer of the coordinating center and whose reading was arbitrarily assumed to be the “gold standard.” It was assumed a priori that the minimum threshold of concordance to pass the quality control had to be 80%. The lower concordance cutoff in comparison with the first type of reading was due to the fact that this second set of tapes was not selected on the basis of the superior quality but randomly sampled from each center in a consecutive fashion. All 14 enrolled centers met the minimum requirements of quality control.

Follow-up data. The follow-up data were obtained from at least one of four sources: review of the patient’s hospital record; personal communication with the patient’s physician and review of the patient’s chart; a telephone interview with the patient conducted by trained personnel; a staff physician visiting the patients at regular intervals in the outpatient clinic (19). Events were defined as cardiac-related deaths, nonfatal myocardial infarction, and revascularization procedures. For patients who died in the hospital or at home, the cause of death was elucidated from the medical record, from the family, and from the local physician who signed the death certificate. The definition of cardiac-related death required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. In case of death out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. Myocardial infarction was defined as a cardiac event requiring hospital admission to the hospital, with development of new electrocardiograph (ECG) changes and cardiac enzyme-level increases. Revascularization procedures were considered only when they had been performed three months after the tests. Test results were available to the referring physician who was responsible for the decision to submit a patient to a revascularization procedure. As always, this decision was made after considering all the clinical, echocardiographical, and angiographic variables.

Statistical analysis. Values are expressed as mean ± standard deviation. The individual effect of certain variables on event-free survival was evaluated with the use of the Cox regression model (BMDP 2L, Department of Biomathematics, University of California at Los Angeles, revised 1987). The 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 was 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 entire model. Selected variables were the following: age, sex, history of angina, previous myocardial infarction, concomitant antianginal therapy, recent acute uncomplicated myocardial infarction, previous angioplasty (history of PTCA; percutaneous transluminal coronary angioplasty), previous coronary artery bypass graft (CABG) surgery (history of CABG), WMSI at rest (resting WMSI), dipyridamole and dobutamine-atropine stress echocardiography positivity, WMSI at peak dobutamine (DOB WMSI) and at peak dipyridamole (DIP WMSI), Delta-WMSI of DIP and DOB (Delta DIP and Delta DOB WMSI), number of ischemic segments during DIP, number of ischemic segments during DOB, dipyridamole and dobutamine time (i.e., test duration to time of echocardiographically detected ischemia).

Continuous variables were compared by the paired two-sample $t$ test. Proportions were compared by the chi-square statistic; the Fisher exact test was used when appropriate. Kaplan-Meier survival curves event-free of cardiac death were used to summarize the follow-up experience in these patients and to clarify presentation. Differences of survival curves were tested with the log-rank statistic. A $p$ value below 0.05 was considered statistically significant. Receiver-operating characteristics analysis was used to determine the optimal cutoff value for prediction of cardiac death with respect to the DIP and DOB WMSI and the number of ischemic segments during both tests. The best cutoff value
was defined as the point with the highest sum of sensitivity and specificity.

RESULTS

Feasibility and tolerability of DIP and DOB. One patient had sustained ventricular tachycardia during DOB testing. Additional minor but limiting side effects occurred in 36 DOB and 13 DIP patients, yielding an overall feasibility of 92% and 97%, respectively (p < 0.005). The test results of these patients were included in the analysis as negative tests.

Stress echocardiographic findings. The resting WMSI was 1.37 ± 0.38 for the overall population. The DIP test was negative in 253 and positive in 207 patients. Of the positive tests, 73 were positive at low dose (≥8 min), 90 at high dose (>8 min up to 12 min), and 44 during or after atropine infusion. The DOB test was negative in 242 and positive in 218 patients. Of the positive tests, 99 were positive at low dose and 92 at high dose, yielding a feasibility of 92% and 97%, respectively (p < 0.005). The positive value was 96% for DOB and 97% for DIP (p = NS). Among the subset with positive DIP, eight events occurred in the 44 patients with atropine, 15 in the 90 patients with high dose and 16 in the 73 patients with low dose positivity (18% vs. 16.6% vs. 22%, p = NS). Considering DOB, events occurred in 42 of the 242 patients with negative and in 38 of the 218 patients with positive test (16% vs. 19%, p = NS). Among the subset with positive DOB, six events occurred in the 27 patients with atropine, 16 in the 92 with high dose and 16 in the 99 patients with low dose positivity (22% vs. 17% vs. 16%, p = NS). The relationship between all cardiac events and different stress-test responses is shown in Table 1.

For all cardiac events, the negative predictive value was 83% for DOB and 84% for DIP (p = NS), and the positive predictive value was 17% for DOB and 19% for DIP (p = NS). Considering only cardiac death, there were 12 events in patients with positive and 6 events in those with negative DIP (5.7% vs. 2.3%, p = NS). Considering DOB, 10 cardiac deaths were in patients with positive and 8 in those with negative DOB (4.5% vs. 3.3%, p = NS). By univariate analysis, DIP WMSI (chi-square 13.80, p < 0.0002) was the strongest predictor. The other independent predictors are shown in Table 2. By stepwise analysis, DIP WMSI was the most important predictor followed by previous angioplasty; see Table 3. For cardiac death, the negative predictive value was 96% for DOB and 97% for DIP (p = NS), and the positive predictive value was 5% for DOB and 6% for DIP (p = NS). Figures 1 and 2 show the Kaplan–Meier survival curves according to the DIP and DOB results, respectively. With DIP, the survival decreased progressively, going from negativity to atropine, higher dose and low dose positivity—the more pronounced step down being observed with low dose positivity. With DOB, a similar pattern was observed for low and higher dose positivity, whereas atropine positivity (which was only observed in 27 patients) was associated with a trend to a better survival than DOB.
Table 2. Univariate Predictors of Cardiac Events

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cardiac Death HR (95% CI)</th>
<th>Cardiac Death AMI HR (95% CI)</th>
<th>Cardiac Death Revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting WMSI</td>
<td>4.3 (1.5–11.9)</td>
<td>2.6 (1.6–4.9)</td>
<td>1.8 (1.0–3.1)</td>
</tr>
<tr>
<td>WMSI DIP</td>
<td>7.1 (2.6–19.5)</td>
<td>5.2 (1.3–21.6)</td>
<td>1.8 (1.0–3.0)</td>
</tr>
<tr>
<td>WMSI DOB</td>
<td>3.3 (2.8–11.5)</td>
<td>2.2 (1.1–4.3)</td>
<td>1.9 (1.7–3.1)</td>
</tr>
<tr>
<td>DIP±</td>
<td>2.9 (1.1–7.7)</td>
<td>2.3 (1.2–4.5)</td>
<td>1.2 (0.8–1.9)</td>
</tr>
<tr>
<td>DOB±</td>
<td>1.5 (0.6–4.0)</td>
<td>0.9 (0.4–2.2)</td>
<td>1.1 (0.7–1.7)</td>
</tr>
<tr>
<td>Delta WMSI DIP</td>
<td>2.6 (1.4–5.6)</td>
<td>4.9 (1.2–19.1)</td>
<td>2.2 (0.6–8.0)</td>
</tr>
<tr>
<td>Delta WMSI DOB</td>
<td>1.2 (0.1–3.8)</td>
<td>1.6 (0.3–7.5)</td>
<td>2.1 (0.8–1.4)</td>
</tr>
<tr>
<td>DOB Time</td>
<td>0.6 (0.3–0.9)</td>
<td>0.9 (0.6–1.1)</td>
<td>1.1 (0.8–1.3)</td>
</tr>
<tr>
<td>DIP Time</td>
<td>1.6 (1.1–2.3)</td>
<td>1.4 (1.1–1.9)</td>
<td>1.1 (0.9–1.4)</td>
</tr>
<tr>
<td>Ischemic segments DIP</td>
<td>1.2 (0.8–1.8)</td>
<td>1.7 (1.1–2.7)</td>
<td>1.1 (0.5–2.8)</td>
</tr>
<tr>
<td>Ischemic segments DOB</td>
<td>1.2 (0.8–1.8)</td>
<td>0.9 (0.5–1.3)</td>
<td>1.1 (0.8–1.4)</td>
</tr>
<tr>
<td>Gender</td>
<td>1.0 (0.3–3.5)</td>
<td>2.1 (0.6–7.1)</td>
<td>1.7 (0.8–3.4)</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (0.3–1.1)</td>
<td>0.9 (0.9–1.0)</td>
<td>1 (0.9–1.3)</td>
</tr>
<tr>
<td>History of angina</td>
<td>1.1 (0.7–2.3)</td>
<td>0.7 (0.4–1.4)</td>
<td>0.6 (0.4–1.0)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.0 (0.2–4.4)</td>
<td>2.3 (1.1–4.9)</td>
<td>0.9 (0.4–1.9)</td>
</tr>
<tr>
<td>Recent MI</td>
<td>1.5 (1.1–2.6)</td>
<td>0.9 (0.4–1.8)</td>
<td>1.4 (0.9–2.3)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.4 (0.6–3.9)</td>
<td>1.1 (0.5–2.1)</td>
<td>1.1 (0.6–1.6)</td>
</tr>
<tr>
<td>History of PTCA</td>
<td>4.8 (2.4–22.2)</td>
<td>2.3 (0.7–7.6)</td>
<td>0.9 (0.3–3.1)</td>
</tr>
<tr>
<td>History of CABG</td>
<td>1.9 (0.4–8.5)</td>
<td>1.1 (0.2–4.9)</td>
<td>1.2 (0.5–2.8)</td>
</tr>
<tr>
<td>Antianginal therapy</td>
<td>1.1 (0.4–2.6)</td>
<td>1.8 (0.8–3.8)</td>
<td>1.2 (0.7–2.2)</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; DOB = dobutamine-atropine stress echocardiography; DIP = dipyridamole-atropine stress echocardiography; MI = myocardial infarction; CABG = coronary artery bypass graft; WMSI = Wall-Motion Score Index; PTCA = percutaneous transluminal coronary angioplasty.

Table 3. Stepwise Predictor of Cardiac Events

<table>
<thead>
<tr>
<th>Variables</th>
<th>Chi-Square</th>
<th>p Value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stepwise predictors of cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMSI DIP</td>
<td>14.62</td>
<td>0.0001</td>
<td>7.4</td>
<td>2.70–20.5</td>
</tr>
<tr>
<td>History of PTCA</td>
<td>5.31</td>
<td>0.02</td>
<td>5.8</td>
<td>1.6–20.4</td>
</tr>
<tr>
<td>Stepwise predictors of cardiac death and MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIP±</td>
<td>6.55</td>
<td>0.01</td>
<td>2.3</td>
<td>1.2–4.5</td>
</tr>
<tr>
<td>Stepwise predictors of cardiac death, MI, and revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMSI DOB</td>
<td>7.5</td>
<td>0.005</td>
<td>1.9</td>
<td>1.2–3.1</td>
</tr>
</tbody>
</table>

DIP = dipyridamole-atropine stress echocardiography; DOB = dobutamine-atropine stress echocardiography; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

negativity (observed in 218 patients). Figures 3 and 4 show the Kaplan-Meier survival curves stratified according to the results of rest-stress WMSI variation during DIP and DOB testing, respectively. With both stress, the survival was progressively worse for larger variations in WMSI.

DISCUSSION

In patients at low-to-moderate risk of cardiac events, pharmacological stress echocardiography with either dobutamine or dipyridamole allows an effective risk stratification on the basis of the presence, timing, severity, and extension of the induced ischemia. In particular, the extension and severity of induced left ventricular dysfunction are the most important predictors of cardiac related death among the parameters describing the stress echocardiographic response. When stratifying the positive response according to timing severity and extension of ischemia, patients with a positive test at low dose and/or with a high Delta WMSI (>0.37) were at higher risk of cardiac death than were those with a positive test at high dose and/or with a low Delta WMSI (≤0.37). These data are in agreement with previous stress echocardiographic studies (19,20) and are consistent with the linear relationship described between WMSI at peak stress and extension and severity of underlying coronary artery disease (21), which is a well-known angiographic predictor of unfavorable prognosis (22). Both DIP and
DOB had a comparable prognostic value, with a marginal—albeit statistically significant when cardiac death is considered—edge in favor of DIP. This may be due to a higher number of diagnostic studies obtained with DIP than with DOB in our series, in keeping with previous reports (7,9–11).

In addition, when compared to dobutamine, dipyridamole stress echocardiography positivity more frequently occurs with prognostically unfavorable angiographic patterns, such as plaque morphology of the complex type (23–25) or in the presence of coronary occlusion and coronary collateral circulation (24,26). Finally, positivity of DOB—with negativity of DIP—is more often found in patients with normal coronary arteries and in patients with single-vessel disease of mild-to-moderate severity (12,25), which define prognostically benign subsets.

Comparison with previous studies. The results of this study confirm the data of two recent studies by Minardi et al. (13) and Schröeder et al. (14) showing a similar prognostic value of dipyridamole and dobutamine assessed in a head-to-head comparison. However, these studies were performed in a small sample size and needed the use of soft cardiac events, such as revascularization procedures, to document the prognostic power of the two tests. Our results confirm and expand these previous observations. In fact, in the present study, we assessed the prognostic yield of dipyridamole and dobutamine in a large patient population, with more than three years’ follow-up. This sample size allowed us to document the prognostic value also using only cardiac-related death as the end point in a subset of patients at low-to-moderate risk for cardiac events (i.e., patients in stable clinical conditions with relatively well-preserved left ventricular function). In this subset of patients, the predictive value of any diagnostic test is usually low, and this may be the reason for the modest, but significant, value of the relative risk of WMSI at peak stress in comparison to other

Figure 1. Kaplan–Meier survival curves event free of cardiac death in patients with negative and positive DIP. Survival is worse in patients with positive DIP. In patients with positive DIP, progressive worse survival is identified with positivity after atropine, high dose and low dose. DIP + low dose vs. DIP negative, p < 0.0001. Cardiac death (n = 18); follow-up 38 ± 21 months.

Figure 2. Kaplan–Meier survival curves event free of cardiac death in patients with negative and positive DOB. In patients with positive DOB, progressive worse survival is identified with positivity after high dose and low dose, whereas patients with positivity after atropine have a survival comparable to, or even better than, patients with DOB negativity (p = NS among all groups). Cardiac death (n = 18); follow-up 38 ± 21 months.
studies that enrolled patients at higher risk for cardiac events (22–29).

**Study limitations.** The prognostic yield of myocardial viability was not assessed in this study. However, as documented in patients with recent myocardial infarction, recognition of myocardial viability during dobutamine is prognostically important only for predicting unstable angina, but not cardiac-related death. Viability, recognized with echocardiographic methods, predicts cardiac death only in patients with severe left ventricular dysfunction (28), who were excluded from the present study. Even in those patients, the prognostic value of viability is outperformed by ischemia, which is the major determinant of cardiac death, especially if its severity is titrated through the WMSI (20,28–30).

In addition, the number of events in the study was limited: only 18 cardiac deaths (3.9% of the total population), despite the high number of enrolled patients (n = 460) and the long duration of the follow-up (38 months on average). Our population was clearly at low risk for cardiac events, consisting of clinically stable patients, with preserved left ventricular function, undergoing two stresses in a few days. Any stress test for coronary artery disease looks much better when faced with more extensive forms of disease, with high incidence of events, and much less well in patients with milder forms of disease, with low incidence of events (31).

Conversely, the literature is inflated by studies in which the assessment of the outcome is based on soft and pathophysiologically heterogeneous events, such as revascularization procedures, unstable angina, nonfatal reinfarction, and cardiac death, in a population at high cardiac risk. However, the goal of the present study was not to establish, in absolute terms, the prognostic impact of the two tests in a well-selected population, but rather to assess their relative prognostic value in a garden variety of patients representing the entire spectrum of population usually referred to the echocardiography laboratory.

Moreover, our study was observational, not randomized, and the decision of medical treatment over coronary revascularization was made by the referring physician on the basis

**Figure 3.** Kaplan-Meier survival curves event free of cardiac death in patients stratified according to the results of rest-stress WMSI variation during DIP (Delta DIP WMSI). The survival is progressively worse for larger variations on WMSI. Delta DIP WMSI > .37 vs. DIP negative, p < 0.0001; Delta DIP WMSI >.37 vs. DIP ≤ .37, p < 0.004. Cardiac death (n = 18); follow-up 38 ± 21 months.

**Figure 4.** Kaplan-Meier survival curves event free of cardiac death in patients stratified according to the results of rest-stress WMSI variation during DOB (Delta DOB WMSI). The survival is progressively worse for larger variations on WMSI. Delta DOB WMSI > .37 vs. DOB negative, p < 0.005. Cardiac death (n = 18); follow-up 38 ± 21 months.
of clinical, anatomical and stress echocardiographic findings. This might have contributed to diluting the positive predictive value of the stress test for hard end points as the beneficial effects of ischemia-guided coronary revascularization procedures are well known (29). However, most of our patients with negative stress echocardiogram had no revascularization procedures: thereby, the extremely high negative predictive value of the two tests is likely to reflect largely a natural history follow-up. Our data also emphasize that what is best for diagnosis is not necessarily ideal for prognostic stratification: atropine coadministration, especially with dobutamine, did not efficiently stratify patients with a higher risk in comparison to those with negative results. When prognostic stratification is the main target, more conservative protocols are probably warranted.

**Clinical implications.** Pharmacological stress echocardiographic tests with dipyridamole and dobutamine are feasible and safe. Both tests are able to predict cardiac death, confirming—even in a population at low cardiac risk—the prognostic power already documented in several subgroups of patients (19,27–29), when the positive response is stratified on the basis of timing, severity, and extension of induced ischemia. The prognostic power of the two tests is substantially similar, with a slight advantage for dipyridamole. From a practical point of view, both tests should be implemented—to be used as equally suitable alternatives in the individual patient—for an optimization of diagnostic and prognostic performance of a stress echocardiography laboratory. There are three main reasons for this policy: 1) Each patient being referred for stress evaluation may suffer from relative or absolute contraindications to either stress modality, or may undergo a therapy clearly lowering the diagnostic potential of a given stress; 2) both dipyridamole and dobutamine have excellent overall tolerability and feasibility, as shown by large-scale multicenter experience (32,33). Nevertheless, submaximal nondiagnostic tests do occur in some patients because of side effects; therefore, these patients may be referred to the other stress test; 3) for the detection of minor, less extensive and severe forms of coronary artery disease, a combined pharmacological stress procedure may be needed at least when diagnosis, rather than prognosis, is the mission of testing (34). It is important that all stress echocardiographic laboratories become familiar with both stress procedures for a flexible and versatile diagnostic approach that may allow tailoring the best stress test to individual patient needs (3).

Reprint requests and correspondence: Dr. Alessandro Pingitore, CNR, (Consiglio Nazionale Ricerche), Institute of Clinical Physiology, Via Savi 8, 56100 Pisa, Italy. E-mail: pingi@tfc.pi.cnr.it.

**REFERENCES**


