JACC Vol. 26, No. 4
October 1995:908–13

Stress Echocardiographic Results Predict Risk of Reinfarction Early After Uncomplicated Acute Myocardial Infarction: Large-Scale Multicenter Study

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Objectives. **This study sought to assess the value of dipyridamole echocardiography in predicting reinfarction in patients evaluated early after uncomplicated acute myocardial infarction.**

Background. **The identification of future nonfatal reinfarction seems an elusive target for physiologic testing. However, a large sample population is needed to detect minor differences in phenomena with a low event rate.**

Methods. **We assessed the value of dipyridamole echocardiography in predicting reinfarction in 1,080 patients (mean [±SD] age 56 ± 9 years; 926 men, 154 women) evaluated early (10 ± 5 days) after uncomplicated acute myocardial infarction and followed up for 14 ± 10 months.**

Results. **Submaximal studies due to limiting side effects occurred in 14 patients (1.3%); these test results were included in the analysis. Results of dipyridamole echocardiography were positive in 475 patients (44%). During follow-up, there were 50 reinfarctions: 45 nonfatal, 5 fatal (followed by cardiac death ≤4 days after reinfarction). Reinfarction (either nonfatal or fatal) occurred in 30 patients with positive and 20 with negative results (6.3% vs. 3.3%, $p < 0.01$). Nonfatal reinfarction occurred in 25 patients with positive and 20 with negative results (5% vs. 3.3%, $p < 0.05$). Reinfarction was fatal in 5 of 30 patients with positive and in none of 20 with negative results (16.6% vs. 0%, $p = 0.07$). The relative risk of reinfarction was 1.9.**

Conclusions. **Dipyridamole echocardiographic positivity identifies patients evaluated early after uncomplicated acute myocardial infarction at higher risk of reinfarction, especially fatal reinfarction.**

(J Am Coll Cardiol 1995;26:908–13)

The term coronary risk defines the probability of developing acute ischemic events that adversely affect prognosis. It is generally true that in many patients such risk is proportional to severity of coronary atherosclerosis and inducible ischemia during stress testing. The hypothesis has been tested, confirmed and reconfirmed (1,2) that the larger, and more severe, the reversible perfusion defect or transient wall motion abnormality during stress, the greater the likelihood of a future cardiac event. Nevertheless, the results of stress testing can predict different types of coronary risk varying accuracy. For instance, in patients with uncomplicated acute infarction, the results of stress echocardiography are very efficient in predicting recurrence of angina (relative risk of 3) and cardiac death (relative risk of 4), but it remains unclear whether they can predict reinfarction (3,4). Several studies (5,6) of risk stratification report the inability of electrocardiographic (ECG) stress testing to predict reinfarction. These clinical data are consistent with the present understanding of the pathophysiologic mechanisms of reinfarction (7–9). In recent years, plaque composition and vulnerability (type of lesion) rather than degree of stenosis (size of lesion) have emerged as crucial factors leading to sudden rupture of the plaque surface, usually with thrombosis superimposed, which underlies the great majority of myocardial infarctions (10,11). To consider this concept truly proved, one should use noninvasive stress tests yielding results that are closely related to the extent and severity of coronary artery disease, with a stronger power than

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Manuscript received October 21, 1994; revised manuscript received May 9, 1995, accepted May 25, 1995.

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0735-1097/95/$9.50
0735-1097(95)00293-D

Table 1. Rest and Dipyridamole Stress Findings for 1,080 Study Patients

Age (yr)	56 ± 9
Male/female	926/154
Q wave infarction	812 (75%)
Non-Q wave infarction	268 (25%)
Thrombolytic therapy	610 (56%)
WMSI at rest	1.4 ± 0.3
Positive DET results	475 (44%)
WMSI at peak dipyridamole	1.6 ± 0.3
Low dose positive DET results	222 (20%)
High dose positive DET results	253 (23%)
ECG changes during DET	319 (29%)
Chest pain during DET	172 (16%)

Data presented are mean value ± SD or number (%) of patients. DET = dipyridamole echocardiography; ECG = electrocardiographic; WMSI = wall motion score index.

exercise ECG (12). In addition, a very large sample population is required to detect minor differences in phenomena with a low event rate, such as myocardial reinfarction (13).

To assess the capability of pharmacologic stress echocardiography to predict fatal or nonfatal reinfarction, we analyzed data from 1,080 patients enrolled in the Echo Persantine International Cooperative (EPIC) study, who were evaluated early after a first uncomplicated acute myocardial infarction by dipyridamole echocardiography and followed-up for a mean (±SD) of 14 ± 10 months.

Methods

Patients. Our study included 1,080 patients (926 men, 154 women; mean [±SD] age 56 ± 9 years, range 23 to 85) with clinically uncomplicated acute myocardial infarction enrolled in the EPIC study, a subproject on residual ischemia (3). The prognostic value of dipyridamole echocardiography in a patient population unselected for age was previously assessed in a subset of 925 patients (3) as well as in an elderly cohort (4). All patients entering the present analysis fulfilled the following inclusion criteria: recent uncomplicated myocardial infarction (i.e., without continuing myocardial ischemia, left ventricular failure, shock or important cardiac arrhythmias); technically acceptable echocardiographic study at baseline; absence of absolute contraindications to dipyridamole echocardiography (i.e., severe bronchopneumopathic disease requiring chronic phylline therapy); and enrollment in a follow-up program. Demographic and clinical characteristics and baseline and stress results for the study patients are reported in Table 1. All patients underwent dipyridamole echocardiography 10 ± 5 days after (range 2 to 30) a first uncomplicated myocardial infarction. According to individual needs and physician choice, 843 patients were evaluated without and 237 with antianginal medications (nitrates, calcium antagonists or beta-adrenergic blocking agents alone or in combination).

Dipyridamole echocardiography. Two-dimensional echocardiographic and 12-lead ECG monitoring were performed in combination with a dipyridamole infusion of 0.56 mg/kg body weight over 4 min followed by 4 min of observation, then 0.28 mg/kg over 2 min (14). The cumulative dose was therefore 0.84 mg/kg over 10 min. Aminophylline (240 mg), which promptly reverses the effects of dipyridamole, was readily at hand. During the procedure, blood pressure and the ECG were recorded each minute. The test was considered positive for ECG criteria when an ST segment shift >0.1 mV from baseline occurring 0.08 s after J point. Two-dimensional echocardiograms were obtained continuously during and up to 10 min after dipyridamole administration. Commercially available imaging systems were used. At baseline studies as well as during stress, all standard echocardiographic views were obtained whenever possible. During the test, new areas of abnormal wall motion were identified in multiple views whenever possible. The videotapes were analyzed by a cardiologist–echocardiographer who had no knowledge of the clinical and angiographic data. A wall motion score index was derived for rest and peak dipyridamole echocardiograms for each patient. The left ventricle was divided into 11 segments as follows: apex; proximal and distal anterior septum; proximal and distal inferior septum; proximal and distal anterior wall; proximal and distal lateral wall; proximal and distal inferior wall (3). The wall motion score index was derived by summation of individual segment scores divided by the number of interpreted segments.

Segmental wall motion was graded from 1 to 4 as follows: 1 = *normal* (normal motion at rest, with normal/increased wall motion [hyperkinesia] after dipyridamole); 2 = *hypokinetic* (marked reduction in endocardial motion); 3 = *akinetic* (virtual absence of inward motion); 4 = *dyskinetic* (paradoxic wall motion away from the left ventricular center in systole). Test results were considered positive when the wall motion score increased by one grade or more at peak stress (e.g., a normal segment becoming hypokinetic, akinetic or dyskinetic, or a hypokinetic segment becoming akinetic or dyskinetic). However, akinesia becoming dyskinesia was not considered a positive result because the change could be due to passive stretching phenomena rather than "active" ischemia. Inadequately visualized segments were not scored. For positive test results, the dipyridamole time (i.e., time in minutes from the beginning of drug infusion to the development of stress-induced dyssynergy) was also evaluated. For negative test results, the dipyridamole time was arbitrarily assumed to be 17 min (when aminophylline was given).

Quality control of stress echocardiographic readings. It is well known that the diagnostic performance of stress echocardiography is significantly related to the level of expertise of the cardiologist–echocardiographer performing the test because evaluation of regional wall motion is subjective and qualitative (3,4). Therefore, quality control of diagnostic performance at the different centers was of critical importance in acquiring meaningful information for the data bank. A prerequisite for inclusion of the centers was a threshold of at least 100 previously performed tests because previous studies (3) suggest that this level of training is necessary to achieve a satisfactory

diagnostic performance in stress echocardiography. In the study centers, two criteria had to be satisfied to meet quality control requirements.

The first criterion was tested on videotape with 20 dipyridamole echocardiography studies prepared at the coordinating center (Institute of Clinical Physiology, Pisa). For all 20 studies, the reading of two experienced independent observers was concordant as to presence and site of dyssynergy, and the stress results were in full agreement with the presence and site of coronary stenoses during coronary angiography. The unanimous reading by the two observers was arbitrarily assumed to be the reference standard against which to evaluate the reading of each participating center. The reader from each center interpreted the videotape in blinded manner, with no access either to clinical and angiographic data or to the interpretation of other observers. It was assumed a priori that the minimal threshold of concordance to meet the first criterion for quality control had to be ≥90%.

The second criterion consisted of sampling 20 consecutive studies from each contributing center. These 20 studies were examined in a blinded manner by an experienced cardiologist–echocardiographer at the coordinating center whose reading was arbitrarily assumed to be the reference standard. It was assumed a priori that the minimal threshold of concordance to meet the second criterion of quality control had to be ≥80%. The lower concordance cutoff compared with the first criterion is due to the fact that the second set of tapes was not selected on the basis of the superior quality but was randomly sampled from each center in a consecutive fashion. All 11 study centers met the minimal requirements for quality control.

Follow-up data. Follow-up data were obtained from at least one of four sources: 1) review of the patient's hospital record; 2) personal communication with the patient's physician and review of the patient's chart; 3) a telephone interview with the patient conducted by trained personnel; or 4) a staff physician visiting the patients at regular intervals in the outpatient clinic. By inclusion criteria, follow-up data were obtained in all patients. The outcome event was infarction (both nonfatal and fatal). Myocardial infarction was documented by a consistent history, ECG changes and cardiac enzyme level elevations and confirmed by hospital chart or hospital discharge letter review. Sudden cardiac death occurring out of hospital and unobserved was not considered to be associated with infarction.

Statistical analysis. Results are expressed as mean value ± SD. Continuous variables were compared by Student *t* test (two-tailed). Statistical analysis of discrete variables was performed with the chi-square test; the Fisher exact test was used when appropriate. Relative risk ratios were calculated according to standard definition (15). Kaplan-Meier life-table estimates of infarction-free survival were used, and differences were tested with the Mantel-Haenszel statistic. A p value <0.05 was considered statistically significant.

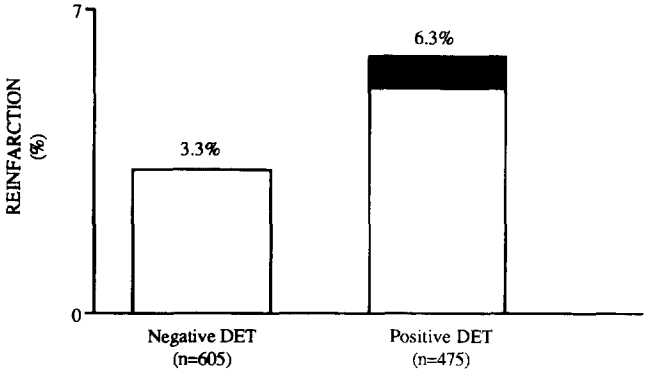

Figure 1. Histogram showing the incidence of reinfarction in patients with negative and those with positive results of dipyridamole echocardiography (DET). The intergroup difference is significant ($p < 0.01$). **Hatched bar** = fatal reinfarction; **open bars** = nonfatal reinfarction.

Results

Dipyridamole echocardiography. For all patients, echocardiograms were considered interpretable during dipyridamole echocardiography, and therefore suitable for analysis. No major cardiac side effect (e.g., infarction, death, prolonged cardiac asystole or sustained ventricular tachycardia) occurred during dipyridamole echocardiography. In 14 patients (1.3%), the higher dypyridamole dose could not be administered because of limiting side effects that occurred either during or 4 min after the lower dose (hypotension and symptomatic bradycardia in 9, brief cardiac asystole in 1, headache in 2, excessive tachycardia with palpitations in 2). The test results for these 14 patients, who therefore completed "submaximal" dipyridamole echocardiography were included in the analysis. Results of dipyridamole echocardiography were positive in 475 (44%) patients; in 222 (20%) positive results occurred after the low dipyridamole dose (Table 1). At the time of testing, 237 patients were taking antianginal therapy (99 of 605 with negative results, 138 of 475 with positive results (16% vs. 29%, $p < 0.001$). Left ventricular function at rest, as assessed by the wall motion score index, was similar in patients with positive and negative results (1.40 ± 0.30 vs. 1.41 ± 0.30, p = NS).

Follow-up data. The mean follow-up period was 14 ± 10 months. The duration of follow-up was similar in patients with positive and negative findings on dipyridamole echocardiography (13 ± 9 vs. 15 ± 10 months, respectively, p = NS). During the follow-up period, there were 50 myocardial infarctions, of which 5 were fatal (i.e., followed by in-hospital death within 4 days of reinfarction), and 45 were nonfatal.

Correlation between dipyridamole echocardiography and follow-up data. Myocardial reinfarction occurred in 20 of 605 patients with negative results (3.3%) but was fatal in none. Myocardial reinfarction also occurred in 30 of 475 patients with positive results (6.3%, $p < 0.01$ vs. negative results) and was fatal in 5 (Fig. 1). Patients with and without reinfarction at follow-up were similar in age, gender distribution, rest wall motion score index (Table 2). Coronary angiography was performed in 352 of 475 patients with positive and in 296 of the

Table 2. Rest and Stress Findings in Patients With or Without Reinfarction During the Follow-Up Period

	Pts With Reinfarction (n = 50)	Pts Without Reinfarction (n = 1,030)
Age (yr)	57 ± 8	56 ± 9
Male/female	41/9	885/145
Rest WMSI	1.4 ± 0.3	1.4 ± 0.3
Peak stress WMSI	1.7 ± 0.3	1.6 ± 0.3

All differences are nonsignificant. Data presented are mean value ± SD or number of patients (Pts). WMSI = wall motion score index.

605 with negative results (74% vs. 49%, respectively, $p < 0.001$). Revascularization (bypass surgery in 105, angioplasty in 84) was performed in 137 of 475 patients with positive and 52 of 605 patients with negative results (28% vs. 8%, $p < 0.0001$). The incidence of cardiac death was higher in patients with positive than in those with negative results (5.6% vs. 2.3%, $p < 0.02$). The relative risk ratio (i.e., the relative occurrence of cardiac events in patients with abnormal test results compared with that in those with normal test results) was 1.9 for fatal and 1.6 for nonfatal reinfarction. Reinfarction was fatal in 5 of 30 patients with positive results and in none of 20 with negative results (16.6% vs. 0%, $p = 0.07$). By Kaplan-Meier analysis, the 12-month infarction-free survival rate was 96.6% in patients with negative and 92.2% in patients with positive results (chi-square 9.6, $p < 0.005$).

Discussion

Reinfarction (especially fatal reinfarction) occurs more frequently in patients with positive than in those with negative stress echocardiographic results. These data have important pathophysiologic and clinical implications.

Risk stratification for reinfarction by stress echocardiography: correlation with angiographic data. In theory, a physiologic approach, such as one that uses stress testing, cannot predict such phenomena as fissuration, embolization, ulceration and thrombosis, which are largely unrelated to the hemodynamic severity of the plaque. The most frequent situation that gives rise to infarction is occlusion of a previously noncritical (and therefore "stress lucent") stenosis. Previous angiographic studies (16–18) suggest that in two of three infarctions, the culprit lesions had only mild to moderate stenosis in a substantial number of patients at first evaluation. However, one of three myocardial infarctions occur at a previously critical stenosis, resulting in an angiographic and clinical event (16,17). Therefore, overall risk stratification for reinfarction (either fatal or nonfatal) might be linked to this 33% event rate resulting from occlusion of severely narrowed arteries. The ischemic potential of such arteries, which are more likely to progress to occlusion (19), can be detected by noninvasive evaluation (20,21). In addition, independent of plaque severity, plaque morphology of the complex type (suggestive of ulceration or thrombus, or both) is more likely to result in occlusion (22) and is associated with a more than fourfold increased risk of myocardial infarction for any percent stenosis (23). It has been recently demonstrated (24) that regardless of stenosis severity, complex coronary lesion morphology is associated with a higher dipyridamole stress echocardiographic sensitivity (24), again emphasizing the potential of physiologic testing to identify lesions more prone to occlusion.

Stress echocardiography and risk of reinfarction: a fatal attraction? The relative risk of infarction in patients with positive results is significant but low; however, it becomes higher when fatal reinfarction is considered. A correlation exists between stress echocardiographic results and angiographically assessed coronary artery disease. The more severe or extensive the coronary artery disease present in patients with positive stress echocardiographic results, the more compensatory phenomena, either the coronary circulation through collateral vessels or ventricular function through compensatory remote hyperkinesia (linked to hyperemia of nonoccluded vessels), will be hindered, especially in the presence of acute coronary occlusion (25). This interpretation is in keeping with angiographic data (26) showing that in the presence of preexisting, more severe and extensive coronary artery disease, a new occlusion is also more likely to result in a fatal infarction.

Study limitations. In our study there was no centralized reading of stress echocardiograms. Results of all dipyridamole echocardiography were interpreted in the peripheral center and were directly entered into the data bank. This system not only substantially spared human and technologic resources, but was also the logical prerequisite for a large-scale study that aimed to represent the overall performance of the test rather than the results of a few superspecialized centers. Because the assessment of echocardiograms is qualitative and subjective, variability in reading echocardiograms might have modulated the results of individual centers. However, the reliability of the results obtained was substantiated by the high interobserver agreement in stress echocardiographic readings among experienced observers (27) as well as by the successful quality control of stress echocardiographic tapes, as shown by the consistent interpretations given by all peripheral readers.

It is well known that patients identified as "high risk" on the basis of abnormalities in specialized tests tend to receive treatments likely to improve their prognosis (3). This may have occurred in our cohort because previous data suggested the usefulness of dipyridamole echocardiography in stratifying prognosis in such patients. In our study, patients with positive results had more coronary angiographic studies and more revascularization procedures than patients with negative results, possibly blunting the reported differences in infarction rate that would have been observed without such interventions.

Information on medical therapy during the follow-up period was not included in our data base. Different drug therapies (such as aspirin or beta-blockers) may have asymmetrically affected the infarction rate in the two study groups.

Finally, although the number of patients enrolled was very large, only five patients had a documented fatal infarction, and hard conclusions about this small number cannot be drawn.

Comparison with previous studies. Our results are consistent with previous studies (3,20,28) showing that stress echocardiography, particularly dipyridamole stress echocardiography, effectively predicts cardiac death. However, data from published reports (3,20,28) are much more inconclusive with regard to infarct prediction by stress testing. Exercise electrocardiography has repeatedly shown no capability to predict reinfarction. In earlier studies (29), patients with ST segment depression appeared to have a poorer prognosis (29), but in most recent studies (30–38) this is much less evident. However, the correlation between coronary anatomy and results of exercise electrocardiography is weak at best, especially in patients with myocardial infarction (12). In addition, patients classified as high risk on the basis of abnormalities detected by specialized noninvasive tests may be selected to undergo treatment such as coronary revascularization, which is likely to improve their prognosis (39).

Nuclear medicine provides greater accuracy in detecting coronary artery disease, but very limited data are available with regard to its prognostic power in patients early after acute myocardial infarction. Due to the low incidence of reinfarction, no separate analysis for this event is provided in reports describing the effectiveness of risk stratification using exercise–thallium (40) or dipyridamole–thallium (41,42). Limited data are also available with regard to the value of stress echocardiography in predicting reinfarction (43–45). Even studies that include hundreds of patients are statistically underpowered when the expected relative risk ratio is in the range of 2 and the index event characterized by very low incidence (~4%/year in patients with uncomplicated myocardial infarction) (3). Our analysis of published reports indicates that despite the pathophysiologic and clinical importance of reinfarction, the capability of present specialized stress modalities to predict this event remains unconfirmed.

Conclusions. The results of the present study, as well as those of previous studies (3,4), indicate that although dipyridamole stress echocardiography seems to be effective in predicting risk of reinfarction, it is more effective in predicting the recurrence of angina (relative risk of 3) and cardiac death (relative risk of 4). However, the risk of reinfarction is less well predicted, with a relative risk of 2 associated with positive results. This is consistent with the concept that both stenosis severity and plaque type are important and that stress test results "see" stenosis severity and, to a certain extent, morphology but are "blind" to plaque type (46,47). The best prediction is achieved for fatal reinfarction: 16.6% in the group with positive results and 0% in the group with negative results. Whether this stratification capability applies to other forms of pharmacologic stress echocardiographic testing, such as dobutamine, whose large-scale validation is currently in progress (48), remains to be assessed in future studies.

We are grateful to Claudia Taddei for secretarial help and to Antonio Caselli, PhD for review of the English.

References

1. Gunnar RM, Bourdillon PDW, Dixon DW, et al. Guidelines for the early management of patients with acute myocardial infarction: a report of the ACC/AHA task force on assessment of diagnostic and therapeutic cardiovascular procedures (subcommittee to develop guidelines for management of patients with acute myocardial infarction). J Am Coll Cardiol 1990;16: 249–92.
2. Zaret BL. Beyond prognostic epiphenomenology. J Nucl Cardiol 1994;1: 223–4.
3. Picano E, Landi P, Bolognese L, Chiarandà G, et al. Prognostic value of dipyridamole-echocardiography early after uncomplicated myocardial infarction: a large scale multicenter trial. Am J Med 1993;11:608–18.
4. Camerieri A, Picano E, Landi P, Michelassi C, Pingitore A, Minardi G, Gandolfo N, Seveso G, Chiarella F, Bolognese L, Chiarandà G, et al. The prognostic value of dipyridamole echocardiography test early after myocardial infarction in elderly patients. J Am Coll Cardiol 1993;22:1809–15.
5. Chang J, Atwood JE, Froelicher V. Prognostic impact of myocardial ischemia. J Am Coll Cardiol 1994;23:225–8.
6. Deedwania PC. Does myocardial ischemia portend poor prognosis? J Am Coll Cardiol 1994;23:229–32.
7. Gorlin R, Fuster V, Ambrose JA. Anatomic-physiologic links between acute coronary syndromes. Circulation 1986;74:6–9.
8. Ambrose JA. Plaque disruption and the acute coronary syndromes of unstable angina and myocardial infarction: if the substrate is similar, why is the clinical presentation different? J Am Coll Cardiol 1992;19:1653–8.
9. MacIsaac A, Thomas JD, Topol EJ. Toward the quiescent coronary plaque. J Am Coll Cardiol 1993;2:1228–41.
10. Fuster V, Badimon JJ, Badimon L. Clinical-pathological correlations of coronary disease progression and regression. Circulation 1992;86 Suppl III:III-1–11.
11. Falk E. Why do plaques rupture? Circulation 1992;86: Supp III:III-30–42.
12. ESC Working Group on Exercise Physiology, Physiopathology and Electrocardiography. Guidelines for cardiac exercise testing. Eur Heart J 1993;14: 969–88.
13. Snedecor GW, Cochran WG. Statistical Methods. 8th ed. Ames (IA): Iowa State University Press, 1989:55–7.
14. Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. High dose dipyridamole echocardiography test in effort angina pectoris. J Am Coll Cardiol 1986;8:848–54.
15. Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards: a statement for Health professionals from the American Heart Association. Special report. Circulation 1990;82:2286–322.
16. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56–62.
17. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988;78:1157–66.
18. Brown BG, Gallery CA, Badger RS, et al. Incomplete lysis of thrombus in the moderate underlying atherosclerotic lesion during intracoronary infusion of streptokinase for acute myocardial infarction: quantitative angiographic observations. Circulation 1986;73:653–61.
19. Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. Circulation 1994;89:959–68.
20. Severi S, Picano E, Michelassi C, et al. Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease: comparison with exercise electrocardiography. Circulation 1994;89: 1160–73.
21. Picano E, Parodi O, Lattanzi F, et al. Assessment of anatomic and physiologic severity of single vessel coronary artery lesions by dipyridamole echocardiography: comparison with positron emission tomography and quantitative arteriography. Circulation 1994;89:753–61.
22. Haft JI, Al-Zarka AM. Comparison of the natural history of irregular and smooth coronary lesions: insights into the pathogenesis, progression, and prognosis of coronary atherosclerosis. Am Heart J 1993;126:551.
23. Ellis S, Alderman EL, Cain K, Wright A, Bourassa M, Fisher L, and the participants of the Coronary Artery Surgery Study (CASS). Morphology of the anterior descending coronary territory lesions as a predictor of anterior

myocardial infarction: a CASS registry study. J Am Coll Cardiol 1989;13: 1481–91.

24. Lu C, Picano E, Pingitore A, et al. Complex artery coronary lesion morphology influences results of stress echocardiography. Circulation 1995; 91:1669–75.
25. Gregg DE. The natural history of coronary collateral development. Circ Res 1974;35:335–7.
26. Harris PJ, Lee KL, Harrell FE Jr, Behar VS, Rosati RA. Outcome in medically treated coronary artery disease. Ischemic events: nonfatal infarction and death. Circulation 1980;62:718–26.
27. Picano E, Lattanzi F, Orlandini A, Marini C, L'Abbate A. Stress echocardiography and the human factor: the importance of being expert. J Am Coll Cardiol 1991;17:666–9.
28. Picano E, Severi S, Michelassi C, et al. Prognostic importance of dipyridamole-echocardiography test in coronary artery disease. Circulation 1989;80: 450–9.
29. Theroux P, Waters D, Halphen C, Debaisieaux JC, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. N Engl J Med 1979;301:341–5.
30. Piccalò G, Pirelli S, Massa D, Cipriani M, Sarullo FM, De Vita C. Value of negative predischarge exercise testing in identifying patients at low risk after acute myocardial infarction treated by systemic thrombolysis. Am J Cardiol 1992;70:31–3.
31. Leroy E, McFadden EP, Lablanche JM, Bauters C, Quandalle P, Bertrand ME. Prognostic significance of silent myocardial ischemia during maximal exercise testing after a first acute myocardial infarction. Eur Heart J 1993;14:1471–5.
32. Mickley H, Pless P, Nielsen JR, Møller M. Residual myocardial ischemia in first non-Q versus Q wave infarction: maximal exercise testing and ambulatory ST-segment monitoring. Eur Heart J 1993;14:18–25.
33. Krone RJ, Gillespie JA, Weld FM, Miller P, Moss AJ, and the Multicenter Postinfarction Research Group. Low-level exercise testing after myocardial infarction: usefulness in enhancing clinical risk stratification. Circulation 1985;71:80–9.
34. Nielsen J, Mickley H, Damsgaard EM, Frøland A. Predischarge maximal exercise test identifies risk for cardiac death in patients with acute myocardial infarction. Am J Cardiol 1990;65:149–153.
35. Fioretti P, Brower RW, Simoons ML, et al. Prediction of mortality during the first year after acute myocardial infarction from clinical variables and stress test at hospital discharge. Am J Cardiol 1985;55:1313–18.
36. Madsen EB, Gilpin E, Ahnve S, Henning H, Ross J. Prediction of functional capacity and use of exercise testing for predicting risk after acute myocardial infarction. Am J Cardiol 1985;56:839–45.
37. Mickley H, Pless P, Nielsen JR, Berning J, Møller M. Transient myocardial ischemia after a first acute myocardial infarction and its relation to clinical characteristics, predischarge exercise testing and cardiac events at one-year follow-up. Am J Cardiol 1993;71:139–44.
38. Volpi A, De Vita C, Franzosi MG, et al. Predictors of nonfatal reinfarction in survivors of myocardial infarction after thrombolysis. Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) data base. J Am Coll Cardiol 1994;24:608–15.
39. DeBusk RF. Specialized testing after recent acute myocardial infarction. Ann Intern Med 1989;110:470–81.
40. Gibson RS, Watson DD, Craddock GB, et al. Prediction of cardiac events after uncomplicated myocardial infarction: a prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. Circulation 1983;2:321–36.
41. Leppo JA, O'Brien J, Rothendler JA, Getchell JD, Lee VW. Dipyridamole-thallium 201 scintigraphy in the prediction of future cardiac events after acute myocardial infarction. N Engl J Med 1984;310:1014–8.
42. Gimple LW, Hutter AM, Guiney TE, Boucher CA. Prognostic utility of predischarge dipyridamole-thallium imaging compared to predischarge submaximal exercise electrocardiography and maximal exercise thallium imaging after uncomplicated acute myocardial infarction. Am J Cardiol 1989;64: 1243–8.
43. Ryan T, Armstrong WF, O'Donnel JA, Feingenbaum H. Risk stratification after acute myocardial infarction by means of exercise two-dimensional echocardiography. Am Heart J 1987;114:1305–16.
44. Krivokapich J, Child JS, Gerber RS, Lem V, Moser D. Prognostic usefulness of positive or negative exercise stress echocardiography for predicting coronary events in ensuing twelve months. Am J Cardiol 1993;71:646–51.
45. Applegate RJ, Dell'Italia LJ, Crawford MH. Usefulness of two-dimensional echocardiography during low-level exercise testing early after uncomplicated acute myocardial infarction. Am J Cardiol 1987;60:10–4.
46. Picano E. Stress echocardiography: from pathophysiological toy to clinical tool. Circulation 1992;85:1604–12.
47. Picano E. Stress echocardiography. 2nd ed. Heidelberg: Springer-Verlag, 1994.
48. Picano E, Mathias W Jr, Pingitore A, Bigi R, Previtali M, on behalf of the EPIC study group. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, large scale, multicenter trial. Lancet 1994; 344:1190–2.