Prognostic Value of Early Exercise Testing After Coronary Stent Implantation

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The clinical value of early exercise stress testing (EST) after coronary stenting to predict long-term clinical outcomes is unknown. Of 1,000 unselected patients who underwent coronary stenting, 446 random patients underwent early EST the day after intervention. Clinical long-term outcomes (41 ± 20 months) were correlated with normal (n = 314 [70%]) or positive (n = 102 [23%]) EST results. Patients with inconclusive test results (n = 30 [7%]) were excluded from the analysis. Overall mortality was significantly higher in patients with positive EST results (9.3% vs 3.9%, p = 0.04). Major adverse cardiac events and cardiac mortality also tended to be higher in patients with positive stress test results (45.4% vs 35.4%, p = 0.08, and 4.1% vs 1.1%, p = 0.05, respectively). Patients with the combination of positive stress test results and incomplete revascularization appeared to be the group at highest risk for major adverse cardiac events (47.1% vs 33.3% for patients with normal stress test results and complete revascularization, p = NS). Negative stress test results reduced (odds ratio 0.329, 95% confidence interval 0.120 to 0.905, p = 0.031) and a lower ejection fraction increased (odds ratio 0.942, 95% confidence interval 0.897 to 0.989, p = 0.017) the risk for death. In conclusion, an early stress test after coronary stenting provides important prognostic information. Positive stress test results, especially in combination with incomplete revascularization, are associated with higher mortality, a trend toward more repeat revascularization procedures, and higher risk for major adverse cardiac events. **(Am J Cardiol 2008;101:807–811)**

The relevance of early symptom-limited exercise stress testing (EST) after coronary intervention with stent implantation with respect to long-term prognosis has not been established. After the demonstration that early EST after coronary stenting is safe and not associated with increased risk for adverse cardiac events or complications at the access site,[1] we assessed its prognostic value on long-term clinical outcomes.

Methods and Results

A total of 1,000 patients were randomized to early symptom-limited EST the first day after coronary bare-metal stenting or no stress testing. The patient selection has been described in more detail previously.[1] Of 498 patients randomized to the stress test, 446 patients were physically able to perform the entire stress test. In 52 patients, the test had to be discontinued prematurely or could not be initiated because of co-morbidities. The results of EST were classified into 3 groups: (1) positive (either clinically or electrically), n = 102 (23%); (2) normal (clinically and electrically), n = 314 (70%); and (3) inconclusive (complete left bundle branch block, insufficient double product), n = 30 (7%). Group 3 was excluded from the analysis, and only the groups with positive and normal EST results were analyzed.

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Complete clinical follow-up of patients with either positive or normal EST results (n = 416) was achieved in 92% of patients (n = 382), with a mean duration of follow-up of 41 ± 20 months (Figure 1).

Pathologic EST results were defined as typical chest pain during or within the first 5 minutes after the end of the stress test or horizontal or down-sloping ST-segment depression ≥1 mm or elevation for ≥60 to 80 ms after the end of the QRS complex. EST results were classified as conclusive if the rate–pressure product was >20,000 or ≥85% of the calculated maximal workload was achieved. Major adverse cardiac events (MACEs) were defined as death, myocardial infarction, or repeat revascularization (repeat percutaneous coronary intervention or coronary bypass grafting). The status of completeness of revascularization was grouped according to angiographic measurements. A patient with no stenosis >50% was classified as completely revascularized. In case of positive stress test results, the decision on reintervention was left to the discretion of the operator on an individual patient basis. In a clinically stable situation, a staged approach with reintervention several weeks later was the preferred strategy. Clinical follow-up was obtained either by clinical reevaluation or by telephone interview using a questionnaire. The local ethics committee approved the follow-up query, and all patients included in the analysis gave written informed consent for the follow-up evaluation.

Continuous data are expressed as mean ± SD unless otherwise mentioned. Continuous variables were compared using Student's *t* test or analysis of variance as appropriate. Categorical variables were compared using the chi-square test. Survival estimates were computed using the Kaplan-Meier method and compared using a log-rank test. A

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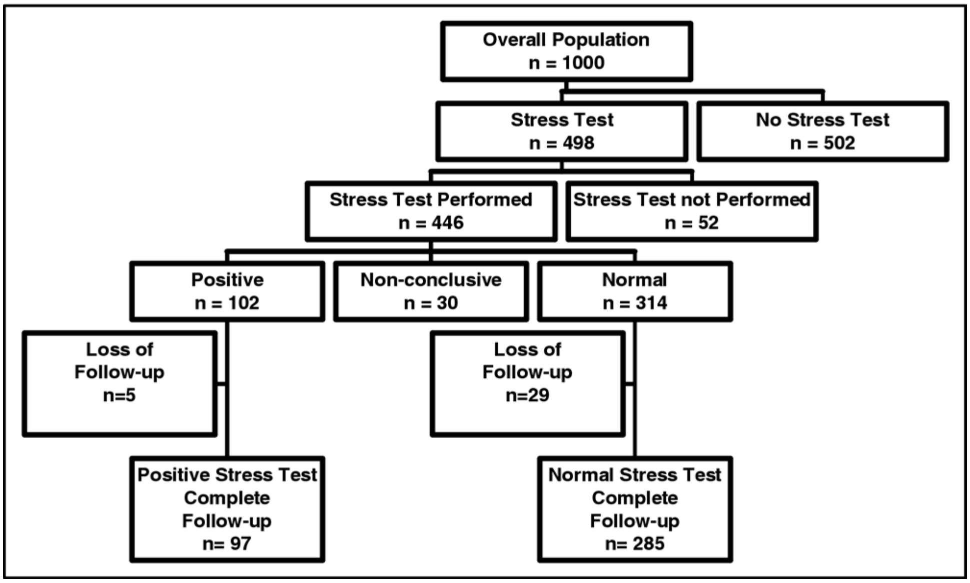

Figure 1. Flow chart of the study design.

Table 1
Baseline characteristics

Variable	EST Results	
	Positive (n = 97)	Normal (n = 285)
Age (yrs)	63 ± 10	61 ± 10
Women	13 (16%)	54 (19%)
Diabetes mellitus	24 (25%)	51 (18%)
Hypertension	60 (62%)	154 (54%)
Dyslipidemia*	60 (62%)	160 (56%)
Current smoking	38 (39%)	117 (41%)
Indication for percutaneous coronary intervention		
Elective	80 (82%)	225 (79%)
Acute coronary syndromes	17 (18%)	60 (21%)
No. of coronary arteries narrowed		
1	30 (31%)	120 (42%)
2	40 (41%)	100 (35%)
3	27 (28%)	65 (23%)

Data are expressed as mean ± SD or as number (percentage).

* Total cholesterol ≥5.2 mmol/L or treatment with a lipid-lowering drug.

Table 2
Procedural characteristics

Variable	EST Results	
	Positive (n = 97)	Normal (n = 285)
Left ventricular ejection fraction (%)	67 ± 8	64 ± 10
Multivessel coronary intervention	20 (21%)	66 (23%)
Multivessel coronary stenting	6 (6%)	31 (11%)
Treated coronary artery		
Left anterior descending	36 (37%)	128 (45%)
Left circumflex	27 (28%)	57 (20%)
Right coronary artery	30 (31%)	88 (31%)
Bypass graft/left main	4 (4%)	11 (4%)
No. of stents/patient	1.4 ± 1.2	1.4 ± 0.7
Stent diameter (mm)	3.0 ± 0.4	3.1 ± 0.4
Total stent length (mm)	17 ± 10	19 ± 12
Suboptimal result	12 (12%)	8 (9%)
Incomplete revascularization	53 (55%)	128 (45%)
Antiplatelet treatment		
Glycoprotein IIb/IIIa inhibitors	10 (10%)	34 (12%)
Ticlopidine	32 (33%)	74 (26%)
Clopidogrel	65 (67%)	211 (74%)

Data are expressed as mean ± SD or as number (percentage).

2-tailed p value <0.05 was considered significant. Logistic regression analysis was performed, and variables with p values <0.15 in the univariate model (multivessel percutaneous coronary intervention, EST results, METs, double product, maximal heart rate, and the ejection fraction) were entered in the multivariate model. All statistical analyses were performed using SPSS version 10.0.5 (SPSS, Inc., Chicago, Illinois).

The baseline data and procedural characteristics of patients with positive and normal EST results were comparable (Tables 1 and 2, respectively). After coronary stenting, patients received a thienopyridine, either ticlopidine (500-mg loading dose followed by 250 mg twice daily for 2 to 4 weeks) or clopidogrel (300-mg loading dose followed by 75 mg/day for ≥1 month), in addition to acetylsalicylic acid. In approximately 10% of patients, the final result was suboptimal, defined as residual dissection or residual stenosis >20%.

The results of EST (using the modified Bruce protocol) are listed in Table 3. All patients included in the analysis reached a rate–pressure product >20,000 and/or ≥85% of the calculated maximal working capacity.

Medication intake after a mean follow-up period of 41±20 months was similar for the 2 groups (Table 4).

Figure 2 depicts MACEs stratified according to the results of EST. Overall mortality was significantly higher in patients with positive EST results (Figures 2 and 3), largely driven by a higher rate of cardiac death. The overall MACE rate was high in the 2 groups after a follow-up period of >3 years and amounted to 45.4% and 35.4%, respectively. This

Table 3
Exercise stress testing

Variable	EST Results		p Value
	Positive (n = 97)	Normal (n = 285)	
METs	9.8 ± 2.0	9.9 ± 2.5	NS
Maximal heart rate (beats/min)	136 ± 18	129 ± 21	0.005
Systolic blood pressure × maximal heart rate	24,941 ± 5,629	23,617 ± 5,899	0.052
Working capacity (%)	109 ± 21	107 ± 23	NS

Data are expressed as mean ± SD.

Table 4
Medications at follow-up

Variable	EST Results	
	Positive (n = 97)	Normal (n = 285)
Acetylsalicylic acid	82 (85%)	248 (87%)
Thienopyridine	9 (9%)	28 (10%)
Statin	75 (77%)	217 (76%)
β blocker	63 (56%)	162 (57%)
ACE inhibitor or ARB	44 (45%)	134 (47%)
Calcium antagonist	20 (21%)	77 (27%)

ACE = angiotensin=converting-enzyme; ARB = angiotensin receptor blocker.

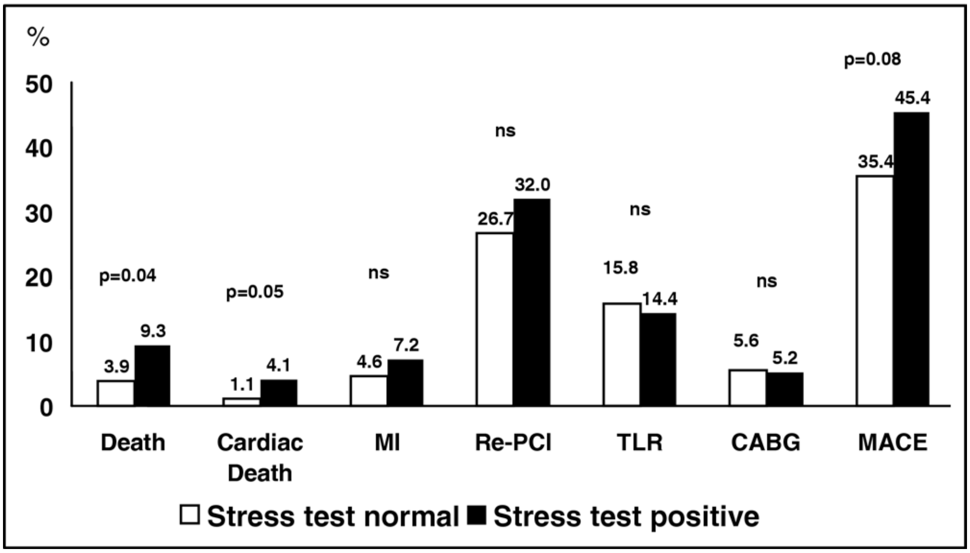

Figure 2. MACEs allocated to results of EST. CABG = coronary artery bypass grafting; MI = myocardial infarction; RE-PCI = repeat percutaneous coronary intervention; TLR = target lesion revascularization.

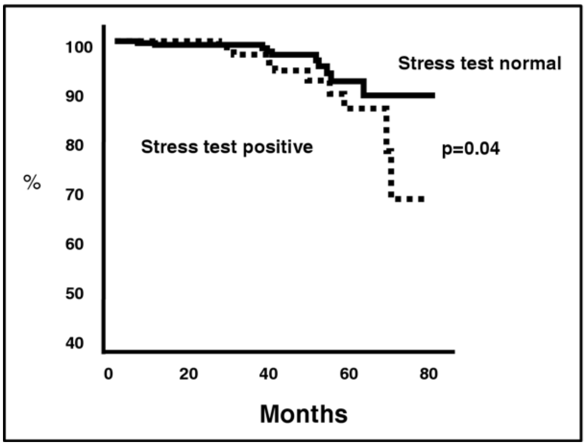

Figure 3. Kaplan-Meier survival curve of the 2 groups.

difference did not reach statistical significance (p = 0.08) but showed a strong trend in favor of the group with normal EST results, with a lower need for repeat revascularization procedures.

To further evaluate prognosis according to revascularization status, the patient cohort was divided into 4 subgroups: normal EST results and complete revascularization (n = 159), normal EST results and incomplete revascularization (n = 126), positive EST results and complete revascularization (n = 46), and positive EST results and incomplete revascularization (n = 51) (Figures 4 and 5). There was a clear trend toward the best outcome for completely revascularized patients with normal stress test results, whereas incomplete revascularization and positive stress test results carried the worst prognosis. Moreover, in a multivariate logistic regression analysis, negative stress test results were independently associated with a lower overall risk of death (odds ratio 0.329, 95% confidence interval 0.120 to 0.905, p = 0.031), and a lower ejection fraction increased the risk for death (odds ratio 0.942, 95% CI 0.897 to 0.989, p = 0.017).

Discussion

Early EST in patients after coronary stenting has been shown to be safe with respect to short-term outcomes (14 days).[1] Long-term clinical outcomes as determined in the present study were characterized by the following 2 major findings: (1) early EST after coronary stenting may serve as a risk stratification tool, and (2) incomplete coronary revas-

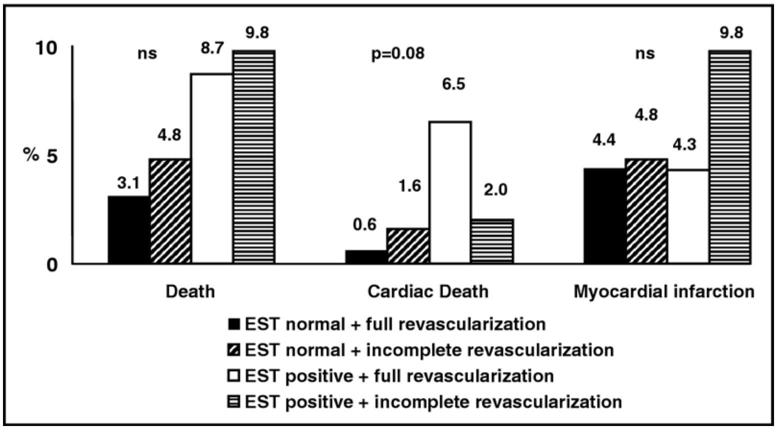

Figure 4. MACEs allocated to revascularization status.

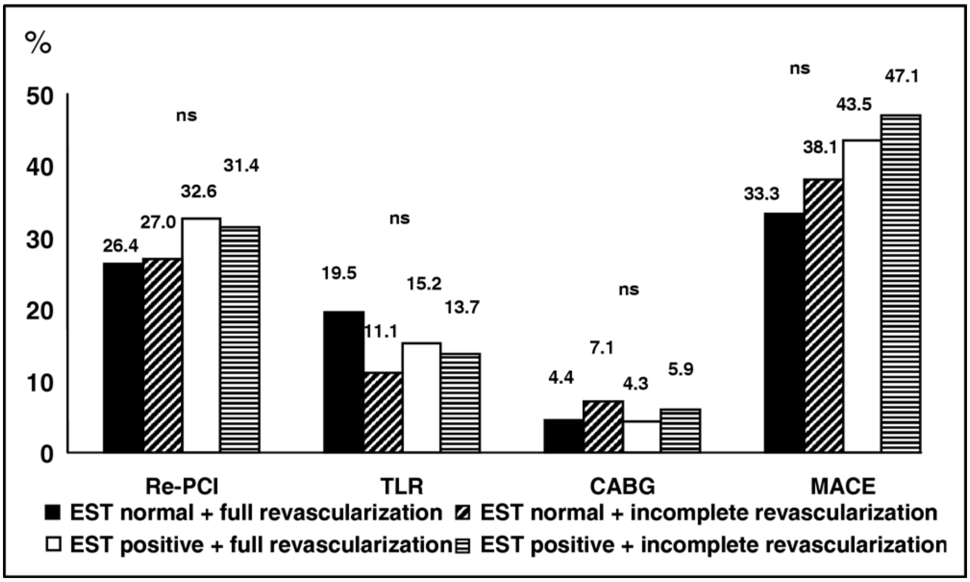

Figure 5. MACEs allocated to revascularization status. CABG = coronary artery bypass grafting; RE-PCI = repeat percutaneous coronary intervention; TLR = target lesion revascularization.

cularization in the context of positive EST results is associated with impaired clinical long-term outcomes.

According to published guidelines,[2] EST after coronary revascularization is useful for the evaluation of restenosis in high-risk or symptomatic patients. EST is usually preformed approximately 6 months after the procedure. Beyond this approach to detect restenosis and predict MACEs,[3,4] the present data suggest that early EST may serve as a risk stratification tool. The observation that even independent of revascularization status, patients with positive EST results showed higher overall mortality and a trend toward higher cardiac mortality supports this hypothesis. This is in line with previous studies reporting increased mortality and morbidity in patients with coronary artery disease in the context of positive EST results.[5–7] Patients with complete revascularization of the large epicardial vessels may still present with positive stress test results, presumably related to microvascular disease. The latter is particularly noted in patients with diabetes and hypertrophic myocardium of hypertensive patients.[8] Positive EST results despite complete revascularization may indicate a particular need for aggressive medical treatment to positively influence clinical outcomes. Rigorous treatment with statins, β blockers, and angiotensin-converting enzyme inhibitors in addition to prolonged dual-antiplatelet therapy might therefore be justified in this patient cohort. Large-scale trials have established that aggressive lipid-lowering therapy is associated with improved long-term outcomes.[9–11] Beta blockers reduce cardiac mortality and MACEs in patients with recent myocardial infarctions or congestive heart failure in the long term.[12–14] Angiotensin-converting enzyme inhibitors were examined in large high-risk patient populations and also significantly reduce MACEs.[15] Last but not least, dual-antiplatelet therapy with acetylsalicylic acid and clopidogrel has been shown to be beneficial in patients with acute coronary syndromes who undergo percutaneous revascularization.[16,17] Dual platelet inhibition may overcome an impaired response to 1 of the antiplatelet drugs[18] in the long run and should therefore be considered in high-risk patients, such as the present patient population, with pathologic stress test results despite coronary revascularization.

Although statistically not significant, the present study showed a strong trend toward impaired clinical outcomes in patients with incomplete revascularization in the context of positive EST results. Previous studies support the concept of obtaining complete revascularization whenever possible, because it is associated with better clinical outcomes.[4,19,20] Early EST might therefore serve as a tool to assess borderline lesions left untreated after the initial revascularization procedure and determine the need for a repeat revascularization procedure. Of note, the combination of incomplete revascularization with positive stress test results portends a particularly poor prognosis requiring medical attention. Our findings may serve as the initiation of a larger trial evaluating differences in mortality according to predefined revascularization and treatment strategies.

The present study has the following limitations. First and most important, the study was not primarily designed to evaluate the long-term prognosis of this patient population. Second, there were no baseline EST data for this patient cohort before the revascularization procedure that might have helped discriminate further between patients with false- and true-positive stress test results. Third, the patient population with positive EST results and the overall event rate were relatively small for reliably assessing predictors of adverse long-term outcomes. Therefore, the results need to be confirmed in a larger trial. Fourth, the applicability of these results for active (drug-eluting) stents requires further study.

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