

# Predictive Implications of Stress Testing

## Follow-up of 2700 Subjects After Maximum Treadmill Stress Testing

By MYRVIN H. ELLESTAD, M.D., AND MAURICE K. C. WAN, M.D.

### SUMMARY

Follow-up data on 2700 subjects who had had maximum stress tests were assembled in life tables. A positive test, characterized by ST-segment depression of 1.5 mm, 0.08 sec from the J point, predicted an incidence of some new coronary event of 9.5% a year, as compared with 1.7% in those with a negative test.

The incidence of infarction and death was also significantly higher than in the negative responders. Early onset of ischemia occurring at moderate exercise (4 metabolic equivalents-METS) resulted in an incidence of all coronary events of 15% a year, while ischemia first manifested at the seventh minute of exercise (approximately 8 METS) results in an incidence of only 4% per year. The magnitude of ST depression and the age of onset of ischemia failed to influence the incidence of coronary events. A myocardial infarction previous to the test increased the incidence of events in both positive and negative responders. The positives with a previous infarction had more than double the incidence of coronary events than the positive responders with no pre-existing infarction. Those with chronotropic incompetence had a high incidence of coronary events even though the ECG response to exercise was normal.

### Additional Indexing Words:

ST-segment depression  
Chronotropic incompetence

Exercise electrocardiography

Life tables

THERE HAS BEEN considerable criticism of stress testing because of its failure to distinguish with certainty those with coronary heart disease from those without.<sup>1</sup> This study was designed to determine the incidence of coronary events in subjects who had been subjected to a maximum stress test by evaluating follow-up information. Robb and Marks<sup>2</sup> published follow-up data on patients who had been tested with a Master's Test in 1957 and established for the first time the prognostic significance of findings obtained on stress testing. Since then stress testing has evolved into a more strenuous and complex procedure, but adequate follow-up data to correlate this with future events has not been assembled.

### Materials and Methods

Follow-up information on 2700 of 8000 subjects who un-

derwent maximum treadmill stress testing in the laboratory at Memorial Hospital Medical Center was collected from the referring doctors' records. Either the doctors filled out a questionnaire or the doctors' aides and a trained research clerk reviewed the records together to obtain the following data.

1. The incidence and dates of myocardial infarctions.
2. The presence and severity of angina. If angina had progressed in severity or if it had appeared for the first time since the test, it was labeled progression of angina.
3. The date and cause of death.

The information was computerized and filed on disc in a CDC 3300 computer. The output provided the number of patients in each cohort, the number lost to follow-up, standard deviation of the mean, and the accumulative percentage of events at each interval. The vertical lines at each interval on the life tables indicate two standard deviations. When these limits do not overlap, the groups are significantly different ( $P < 0.01$ ) by Chi square analysis.

Stress testing was performed according to a progressive protocol previously reported, with continuous monitoring until a maximum predicted pulse had been reached.<sup>3</sup> Termination of the test prior to this target pulse was often due to anginal pain, evidence of severe ischemia on the electrocardiogram, arrhythmias, progressively decreasing pulse or blood pressure, or overwhelming fatigue.

The patient population consisted of subjects referred for routine screening tests as part of an annual physical, for confirmation of suspected coronary insufficiency, or for quantitation of the degree of known coronary disease. The type of treatment subsequent to the stress test was not taken into

From the Division of Clinical Physiology and Section of Cardiology, Memorial Hospital Medical Center of Long Beach, California.

Supported by grants from the Long Beach Heart Association, Central Valley Heart Association and Memorial and Childrens Medical Center Foundation.

Address for reprints: Memorial Hospital Medical Center, c/o Clinical Physiology Department, 2801 Atlantic Avenue, Long Beach, California 90801.

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consideration in the follow-up study. The follow-up events were analyzed by the life table method of Cutler and Ederer.<sup>4</sup> The time of follow-up was from six months to nine years.

Subjects who had a pulse rate for the achieved workloads outside the 95% confidence limits of the established normal for age and sex were labeled as having chronotropic incompetence. (Data for normal pulse responses to our protocol have been published.<sup>5</sup>) Subjects involved in vigorous exercise programs or on a medication that might reduce their pulse rates were not so designated.

#### Criteria for a Positive Test

The subjects were diagnosed as having a positive response if they had ST-segment depression of 1.5 mm or more, 0.08 sec from the J point. ST-segment slopes characterized as flat, upsloping, or downsloping were included. ST elevation of 1 mm when compared to control was also designated as positive. Those diagnosed as having an equivocal response included ST-segment depression of 0.5 mm to 1.4 mm and those with multifocal or frequent premature contractions initiated by exercise, even if there was no S-segment depression.

Predicted pulse response for our protocol are available on request.

#### Age Distribution

The age and sex distribution of the subjects reported is depicted in table 1. Approximately 80% of the total population was found to be between 31 to 60 years. The majority of the patients were male although a small group of females was included. A breakdown as to the percentage of subjects who were thought to be normal prior to the test as compared to those with known disease was not available.

**Table 1**

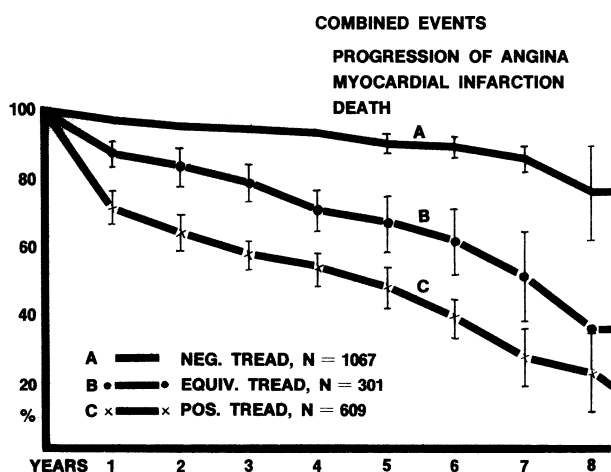
*The Age and Sex Distribution of Subjects in This Study*

Age	Males	Females	Total
0-20	15	7	25
21-30	59	35	84
31-40	343	58	401
41-50	922	158	1080
51-60	681	144	855
61-70	214	92	306
71-99	7	9	16

#### Results

##### Combined Coronary Events: Progression of Angina, Myocardial Infarctions and Death

The incidence of all coronary events (either one, two, or three of the listed events was counted as a single event) in the positive responders is depicted in figure 1. The incidence of coronary events in the positive responders is almost 10% a year. The four-year incidence of events in the positive responders is 46%, as contrasted with 7% for the negative responders (line labeled A), a sevenfold difference. A four-year incidence among equivocal responders (line B) of 25% was found. After eight years 76% of the positive responders had had some coronary event, an eight-year average of 9.5% per year. When the male and female positive responders were analyzed



**Figure 1**

Life table display with two standard deviations of the mean at each year calculated. A) The incidence of all coronary events in the negative responders. B) Incidence of events in equivocal responders (those with ST depression from 0.5 to 1.4 mm). C) Classically positive responders (ST depression of 1.5 or more mm).

The percentages indicate those subjects not having an event. The number of subjects analyzed according to year is as follows:

A.	Sample#	1067	825	714	608	459	368	262	146	19
	Year	0	1	2	3	4	5	6	7	8
B.	Sample#	301	140	110	94	63	43	23	11	1
	Year	0	1	2	3	4	5	6	7	8
C.	Sample#	609	408	283	214	164	116	56	25	8
	Year	0	1	2	3	4	5	6	7	8

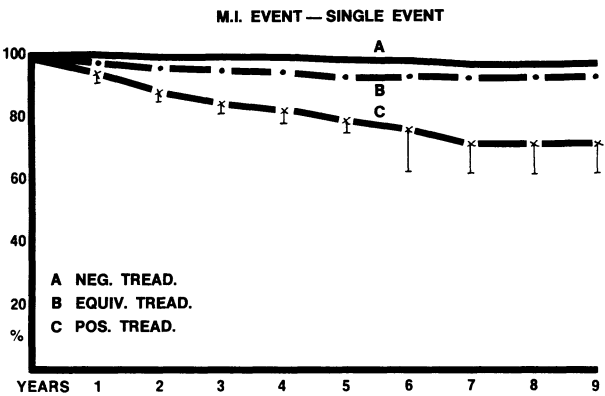


Figure 2

Incidence of myocardial infarction only in negative (A), equivocal (B), and positive responders (C).

A.	Sample#	1013	732	633	533	412	335	241	140	23
	Year	0	1	2	3	4	5	6	7	8
B.	Sample#	269	148	115	96	65	44	24	12	1
	Year	0	1	2	3	4	5	6	7	8
C.	Sample#	578	195	144	106	83	61	34	12	10
	Year	0	1	2	3	4	5	6	7	8

separately, there was no statistical difference between the sexes.

Myocardial Infarction

In figure 2 the incidence of myocardial infarction is shown. The four-year incidence of infarction in the positive responders is 15%, as compared to 1% in the negative responders. Those with equivocal response had a 5% incidence of infarction in four years. The eight-year incidence of myocardial infarction of 27% results in an average infarct incidence of 3.5% per year in positive responders as opposed to less than ½% a year in negative responders.

Death

Figure 3 illustrates the mortality rate of 13.2% over four years, which is more than ten times the 1.1% incidence in negative responders. Again there was no statistical difference in the death rate of males and females at four years.

Time of Onset of Ischemia

When the incidence of all coronary events is analyzed according to the time of onset of ischemia, the incidence of events is as depicted in figure 4. Those with 2 mm ST depression which appeared by 3

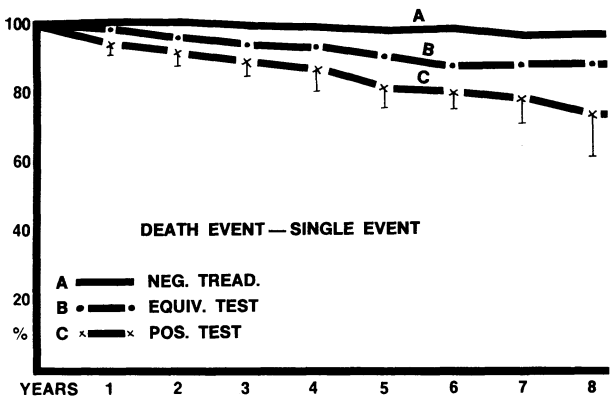


Figure 3

Incidence of death in the negative (A), equivocal (B), and positive responders (C).

A.	Sample#	1219	733	636	537	416	339	243	142	24
	Year	0	1	2	3	4	5	6	7	8
B.	Sample#	397	152	121	100	70	46	25	13	2
	Year	0	1	2	3	4	5	6	7	8
C.	Sample#	658	203	152	111	87	67	40	14	4
	Year	0	1	2	3	4	5	6	7	8

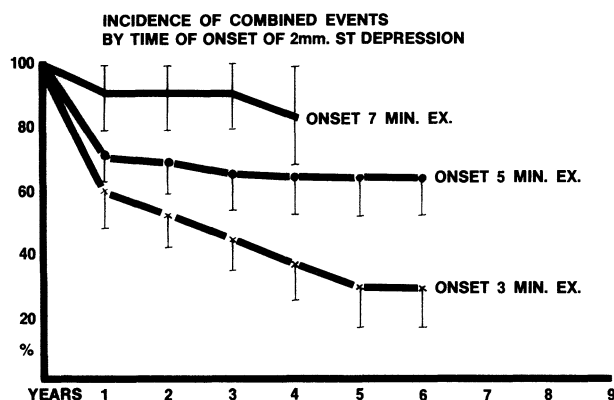


Figure 4

Incidence of combined events. When the onset of 2 mm ST-segment depression is at 3 minutes or before, the prognosis is significantly worse than when it is manifested first at 5 minutes. When ST depression is first manifested at 7 minutes, which is near peak capacity, the incidence of coronary events is only slightly greater than those with a negative test.

Onset 7 min	Sample#	42	26	22	18	13		
	Year	0	1	2	3	4		
Onset 5 min	Sample#	93	61	39	33	25	18	6
	Year	0	1	2	3	4	5	6
Onset 3 min	Sample#	131	75	46	34	28	17	9
	Year	0	1	2	3	4	5	6

min on the treadmill (a workload equivalent to 4 METS) have an incidence of 15% a year. Those whose ischemic ST depression does not appear until 5 min on our protocol (a workload equivalent to the double Master's Test) have an incidence of approximately 8% a year while those whose ischemia does not become evident until 7 min (a workload very near the peak capacity of most subjects) have an incidence of coronary events of only 4% per year. These differences are statistically significant ( $P = 0.01$ ).

The incidence of combined events as related to the time of recovery from ischemic ST change was analyzed. Those whose ST depression returned to normal at one minute following the test and those whose

ST depression returned to normal 3 min following the test had the same incidence of coronary events as when all positives were lumped together.

#### Magnitude of ST-Segment Depression

In order to study the magnitude of ST-segment depression, the incidence of all coronary events of those subjects manifesting 4 mm or more ST-segment depression at any time during the test was compared with the incidence in those with 2 mm ST-segment depression. Figure 5 reveals that their prognosis for future problems appears to be almost the same as those positive responders with a lesser degree of depression. The assumption that people with extreme

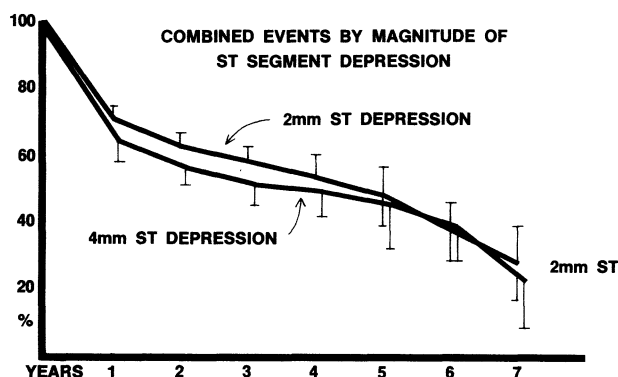


Figure 5

When the incidence of coronary events in those with 4 mm or more ST depression are compared with those with 2 mm depression, the incidence of events is not significantly different.

4mm ST Dep	Sample#	432	279	187	145	109	70	31	16
	Year	0	1	2	3	4	5	6	7
2mm Pos Tread	Sample#	609	408	283	214	164	116	56	25
	Year	0	1	2	3	4	5	6	7

degrees of ischemic ST-segment depression are in more danger than those with 1½ to 2 mm depression was not substantiated by this data.

#### Effects of Age

The patients were divided into three age groups, zero to 40, 41 to 50, and 51 to 99, and the positive responders were analyzed. The incidence of all coronary events was the same. The group under 40 years of age was too small to be tested for statistical significance, but there appears to be no long-term difference in the outlook of those who have an early onset of ST-segment depression as compared to those who develop it later. When the negative responders are separated into age groups and analyzed for occurrence of myocardial infarction alone, there is a slight tendency for the older subjects to have an increased incidence of myocardial infarction.

#### Effect of a Previous Myocardial Infarction

Figure 6 demonstrates that a negative stress test in a subject with previous infarction does not insure that a coronary event may not occur later. These subjects had a four-year incidence of coronary events of 40% as compared to the positive responders with a previous infarction who had a four-year incidence of 70%. Subjects who had never had a myocardial infarction but have a positive stress test have a 30% incidence of

coronary events in four years, which is 16% less than all positives in our total study. Therefore the likelihood of having a new coronary event is more than twice as great in positive responders who have had a previous infarction as in those with no infarction.

#### Chronotropic Incompetence

Subjects with normal ST segments but with a reduced heart rate response to the stress test protocol when compared to normals of the same age and sex were found to have the same incidence of all coronary events as patients with ischemic ST segments classified as positive. Those who had reason to be well conditioned by their exercise history were excluded.

Figure 7 illustrates that the incidence of all coronary events in those with a slow pulse and with a normal ECG pattern was similar to those classified as positive responders. Approximately 20% of the subjects died and the remaining events were infarction and the onset of angina.

#### Discussion

The high incidence of coronary events in the equivocal responders in our study indicate to us that the lower limit for a positive stress test should be modified to at least 1.0 mm rather than the 1.5 mm

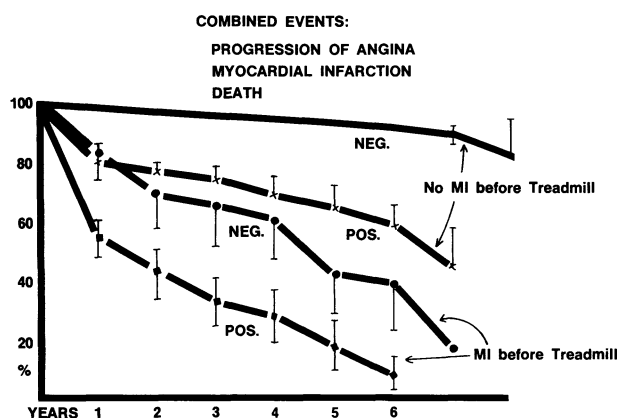


Figure 6

The incidence of all coronary events in the negative and positive responders who had not had a previous infarction is compared with the negative and positive responders who had a previous myocardial infarction.

NEG-No MI  
Before Tread

Sample#	1127	836	718	611	461	369	265	153	23
Year	0	1	2	3	4	5	6	7	8

POS-No MI  
Before Tread

Sample#	427	303	214	168	133	97	49	20	2
Year	0	1	2	3	4	5	6	7	8

NEG TREAD  
MI Before  
Tread

Sample#	92	70	56	43	33	24	13	4
Year	0	1	2	3	4	5	6	7

POS TREAD  
MI Before  
Tread

Sample#	231	139	88	62	38	24	9	5
Year	0	1	2	3	4	5	6	7

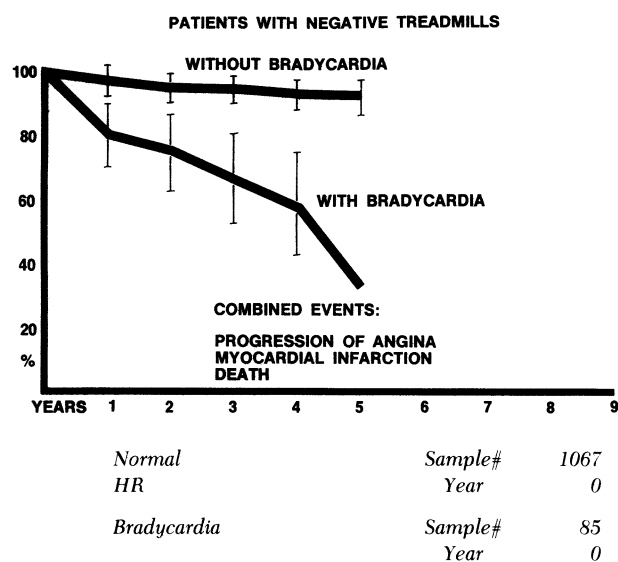


Figure 7

*Chronotropic incompetence. Those with bradycardia (pulse fell below the 95% confidence limits for age and sex) and normal ST segments have a high incidence of combined events (similar to those with ST depression).*

level now used. Bruce<sup>6</sup> and others<sup>7</sup> have recommended 1.0 mm ST depression be required for positivity, and if the ST segment is horizontal or downsloping, we would concur in this conclusion. The high incidence of coronary events in the positive responders has established the importance of this data in patient management. By using 1.5 mm instead of 1.0 mm as the criteria for positivity, the specificity was probably improved but the sensitivity decreased.

The recognition that the positive test is more serious in patients who have had a previous myocardial infarction as compared to those who have not had an infarct is of special importance. The use of this information in evaluating the response to certain therapeutic interventions such as vein graft surgery should be especially interesting.

It was surprising to us to find that those subjects having 4 mm or more ST-segment depression did not show a higher incidence of coronary events than those with 2 mm. It is well known that previous myocardial infarction decreases the incidence of positive stress tests<sup>8</sup> and it would be our opinion that it also decreases the incidence of deep ST-segment depression. Thus subjects with myocardial scars would actually fall into the group with less ST-segment depression than for example those with left ventricular hypertrophy and ischemia, who are inclined to have greater ST depression.

The high proportion of those with an inadequate chronotropic response to exercise developing some new coronary event, even when they did not develop ischemic ST-segment changes, confirms our suspicions about this still poorly understood process. Hinkle, Carver, and Plakum<sup>9</sup> have described an increased incidence of sudden death in subjects with a reduced heart rate response to exercise. They did not present a

satisfactory mechanism for this finding, however. Studies now underway in our laboratory suggest that a high proportion of these patients have poor left ventricular function and most have severe three vessel coronary disease. Thirty percent have had previous myocardial infarction. Improvement after successful vein graft surgery may occur, a fact which establishes that the process may be reversible, but this response is by no means the rule. The mechanisms responsible for this phenomenon are now under study and will be the subject of another report.

It must be emphasized that this study includes many subjects known to have advanced coronary disease as well as many who were believed to be perfectly normal. The incidence of events would be different if we had restricted our data to a group of people believed to be normal. No selection was made in sampling subjects except that follow-up information be available.

The types of treatment subjects may have been under was also not taken into consideration. Many were on no treatment, some on so-called coronary dilators, anticoagulants, and some even in exercise programs. One hundred and forty-six had undergone coronary bypass surgery. No separation of these will be presented in this report, but it was determined that they had no significant statistical impact on the outcome.

The heterogeneous nature of the subjects in the cohort studied should be re-emphasized. The fact that follow-up data was the sole criteria for inclusion may introduce a bias due to the failure to include either those who were unknown deaths and possibly those who did well may not have reported back to their family physicians.

It seems that information obtained from stress tests,

when combined with associated risk factors and eventually effects of various treatment protocols, should contribute to more reliable predictions of future coronary events and mortality in subjects with coronary heart disease.

### Acknowledgments

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### References

1. EPSTEIN SE: Exercise stress testing held overused in coronary artery disease diagnosis, lack of sensitivity cited. *Clin Trends in Cardiol* **2**: 4, 1973
2. ROBB GP, MARKS HH: Post exercise electrocardiogram in arteriosclerotic heart disease. *JAMA* **200**: 110, 1967
3. ELLESTAD MH, ALLEN W, WAN MCK, KEMP GL: Maximal treadmill stress testing for cardiovascular evaluation. *Circulation* **39**: 517, 1969
4. CUTLER SJ, EDERER F: Maximum utilization of the life table method in analyzing survival. *Biostatistics* **8**: 699, 1958
5. ELLESTAD MH: Stress testing: Principals and practice. Philadelphia, FA Davis, 1975
6. BRUCE RA, ALEXANDER R, LI YB, CHIAGG BN, TING N, HORNSTEIN TR: Measurements in exercise electrocardiography. Springfield, Illinois, Charles C Thomas and Co, 1969, ch 17
7. MARTIN CM, MCCONAHAY DR: Maximum treadmill exercise electrocardiography: Correlations with coronary arteriography and cardiac hemodynamics. *Circulation* **46**: 956, 1972
8. KASSER IS, BRUCE RA: Comparative effects of aging and coronary heart disease on submaximal and maximal exercise. *Circulation* **29**: 759, 1969
9. HINKLE LE, CARVER ST, PLAKUM A: Slow heart rates and increased risk of cardiac death in middle aged men. *Arch Intern Med* **129**: 5, 1972