Use of a Prognostic Treadmill Score in Identifying Diagnostic Coronary Disease Subgroups

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INTRODUCTION

Exercise Treadmill: used in the evaluation of symptomatic patients to predict the presence and extent of coronary artery disease and the short- and long-term prognosis.

Exercise ECG: used as a standard for comparison with other clinical and testing risk markers. It is also the **least costly** of all provocative noninvasive tests.

INTRODUCTION

- The **limited sensitivity** and **specificity** of standard exercise ECG testing for detection of coronary artery disease have stimulated increased use and development of **noninvasive stress imaging technologies**.
- The added diagnostic accuracy of stress imaging tests is associated with substantially **higher cost**.

INTRODUCTION

- Diagnostic and prognostic predictive accuracy increase when multiple pieces of information from the **patient's clinical history** and **the Treadmill Test** are integrated.
- **Mark & Colleagues:** A prognostic exercise score based on:

  1) Duration of exercise;

  2) ST-segment deviation (depression or elevation);

  3) Presence and severity of angina during exercise.

INTRODUCTION

- The purpose of this report is to examine the diagnostic accuracy of the **Duke prognostic Treadmill Score** and to examine the incremental value of treadmill test information beyond clinical data.

METHODS: Original & Validation Patients

- **Original Sample:** 2758 symptomatic patients who underwent exercise treadmill testing followed by cardiac catheterization at Duke University Medical Center from 1969 through 1980.
- **Validation Sample:** 467 patients who underwent exercise treadmill testing and cardiac catheterization from 1984 through 1990 were used as the validation.

METHODS: Original & Validation Patients

- Patients included: if their cardiac catheterization was performed < = 90 days from their exercise test;
- Patients Excluded:

1) Asymptomatic,

2) Significant valvular or congenital heart disease, recent myocardial infarction,

3) Prior revascularization procedure,

4) Uninterpretable exercise ECG,

5) Percutaneous or coronary surgery intervention < = 3 months from the exercise test.

METHODS: ***Clinical, Catheterization & Follow up***

- Clinical, Catheterization Data: As Mark DM et al.
- Follow-up information: Obtained by clinic visit, mailed questionnaire, or telephone interview at 6 months, 1 year, and then yearly thereafter.
- The reasons for death: Classified as cardiac versus noncardiac by a review committee unaware of the patient's clinical or exercise test data.

METHODS: ***Exercise Treadmill Testing***

- All patients underwent symptom-limited exercise testing according to the ***standard Bruce protocol***.
- *Resting heart rate*, *blood pressure*, and 12-lead ECGs were recorded in the supine and upright positions before exercise.
- During each minute of exercise, heart rate and blood pressure measurements as well as a 12-lead ECGs were recorded.

METHODS: *Exercise Treadmill Testing*

- Exercise testing was discontinued if /I. *Exertional hypotension*, /II. *Malignant ventricular arrhythmias*, /III. *Marked ST depression (>= 3 mm)*, or /IV. *Limiting chest pain* was reported.
- An abnormal exercise ST response:

  1) >= 1 mm of horizontal or downsloping ST depression (J point+80 ms) or;

  2) >= 1 mm of ST-segment elevation in leads without pathological Q waves (excluding AVR lead).

METHODS: Exercise Treadmill Testing

- Exercise-induced ST-segment deviation was coded to the *nearest 0.25 mm* for horizontal and downsloping ST-segment depression and ST-segment elevation in a non–Q-wave lead.

METHODS: Duke Treadmill Score

- The equation for calculating the Duke treadmill score **(DTS)**:

DTS= Exercise time-(5 × ST deviation)-(4 × exercise angina), with 0 = None, 1 = Non-limiting, and 2 = Exercise-limiting.

METHODS: ***Duke Treadmill Score***

- The score typically ranges from - 25 to +15.
- These values correspond to ***low-risk (with a score of >= +5)***, ***moderate-risk (with scores ranging from -10 to +4)***, and ***high-risk (with a score of <= -11) categories***.

METHODS: Data Analysis

- Descriptive statistics were generated with percentages for discrete variables and means and SDs for continuous variables.
- Discrete variables were compared by x^2 analyses.
- Continuous variables were compared with the DTS risk groups by the Wilcoxon rank-sum test, and continuous variables were compared by an unpaired *t* test.

METHODS: ***Model End Points***

- We assessed the utility of the DTS for risk-stratifying 3 different but related outcomes

  (1)The presence of significant disease (defined as a > = 75% stenosis in at least 1 major epicardial coronary artery),

  (2)The presence of severe coronary disease (defined as a 3-vessel coronary disease or > = 75% left main disease),

  (3)Cardiac survival.

METHODS: Model End Points

- For the first 2 outcomes, we used logistic regression analysis.
- For the survival outcome, we used a Cox proportional hazard regression analysis for assessing individual relations among clinical history and exercise testing variables that assess time to cardiac death.
- Kaplan-Meier curves were used to compare time to cardiac death among the DTS risk groups.

METHODS: *Model Construction Step 1*

- All clinical history and physical examination parameters were entered into the model to reflect the pretest probability or what was known about the patient before testing.
- Separate clinical history and physical examination models for significant and severe coronary disease as well as cardiac mortality have been developed by Pryor et al (Table 5).

TABLE 5. Clinical History and Physical Examination Parameters Considered for the Significant CAD, Severe Coronary Disease, and Cardiac Survival Multivariable Risk-Adjusted Models

Variables	Significant CAD	Severe CAD	Cardiac Survival
Age	x	x	x
Sex	x	x	x
Chest pain			
Type	x	x	x
Frequency	—	—	—
Course	—	x	—
Nocturnal	—	x	—
Length of time present	—	x	x
Diabetes mellitus	x	x	—
Smoking	x	x	—
Hyperlipidemia	x	x	—
Hypertension	—	x	—
Prior MI	x	x	—
Vascular disease	—	x	x
PVD history	—	—	x
CHF	—	—	x

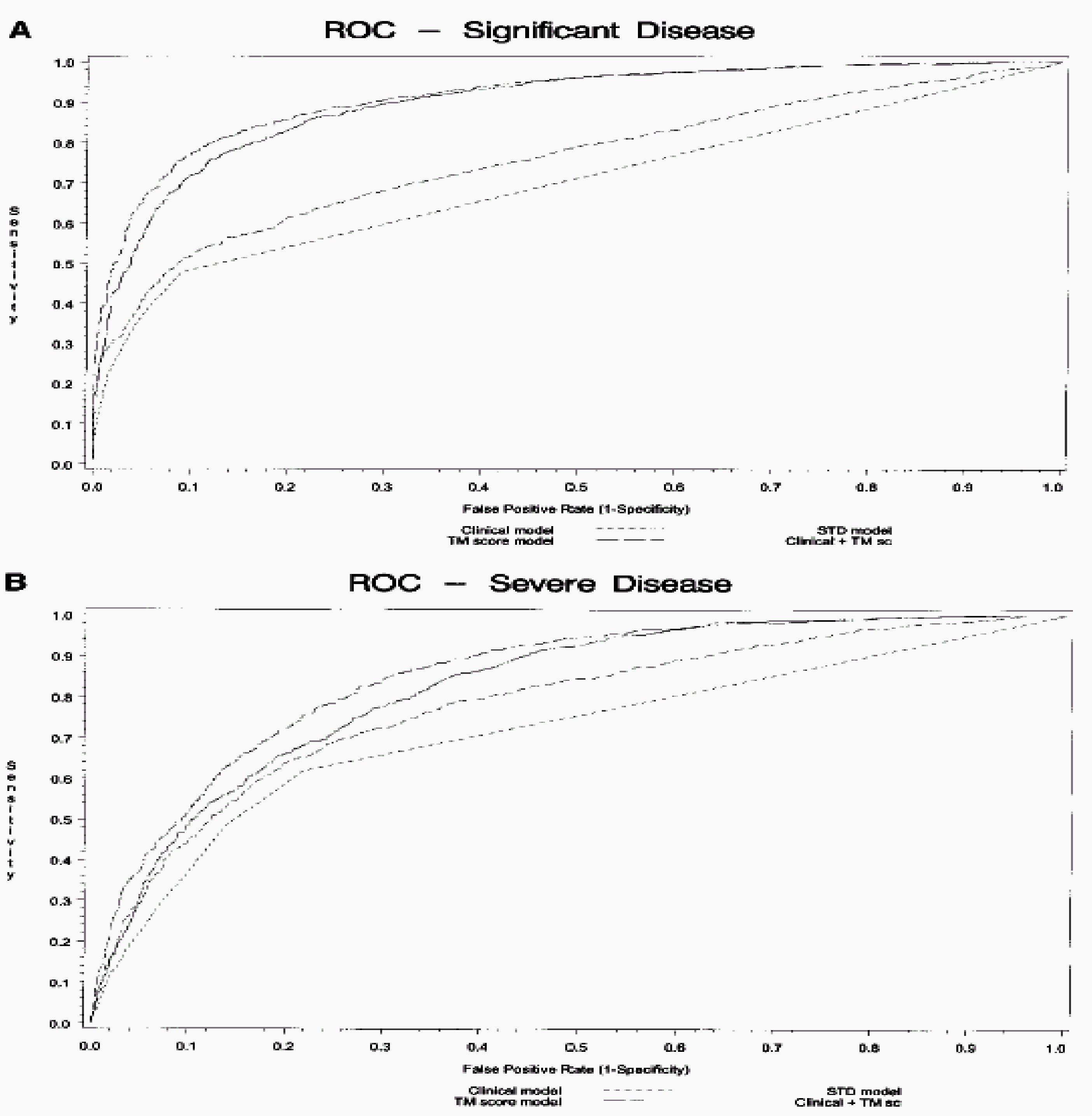
CAD indicates coronery artery disease; MI, myocardial infarction; PVD, peripheral vascular disease; and CHF, congestive heart failure. — indicates variable not included in the final multivariable model.

METHODS: ***Model Construction Step 2***

- Second, the DTS was added to the model.
- Finally, a **combined model** that included the **clinical history**, **physical examination** variables, and the **DTS** were evaluated for each of the above-listed regression models.

METHODS: Model Construction Step 2

- To assess the incremental value of the exercise test data, for survival, we calculated the difference in the log likelihood ratio x^2 statistic from the overall model with and without the DTS.
- The accuracy of the models for predicting significant and severe coronary disease was assessed by calculating the area under the receiver operating characteristics (ROC) curve for the model predictions. (Figure 2)



A
ROC – Significant Disease
Sensitivity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
False Positive Rate (1-Specificity)
Clinical model
TM score model
STD model
Clinical + TM sc
B
ROC – Severe Disease
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False Positive Rate (1-Specificity)
Clinical model
TM score model
STD model
Clinical + TM sc

RESULTS: Study Populations (Table 1)

- The validation sample patients were older, with diabetes, hypertension, and vascular disease occurring more frequently, whereas prior myocardial infarction occurred less often.

TABLE 1. Clinical Characteristics of the 2758 Original and 467 Test Sample Patients

Variable	Original Sample (n=2758)	Test Sample (n=467)	*P*
Male sex, %	70	66	0.054
Age, y	49 (43,55) [49]	58 (50,66) [57]	0.001
Clinical history, %			
Diabetes	9	14	0.001
Hypertension	34	45	0.001
Hyperlipidemia	22	31	0.001
Peripheral vascular disease	4	7	0.001
Prior myocardial infarction	30	16	0.001
Symptoms			
Typical angina, %	47	49	0.439
Atypical angina, %	38	49	0.001
Nonanginal pain, %	15	2	0.001
Episodes per week	5 (2,12) [10]	3.5 (1.5,7) [5.3]	0.001
Months with symptoms	16 (5,52) [38]	13 (2,55) [42]	0.001
Progressive symptoms, %	32	45	0.001
Exercise test			
Peak heart rate, bpm	140 (125,147) [135]	141 (122,156) [140]	
Peak systolic blood pressure, mm Hg	160 (140,180) [164]	180 (160,200) [180]	0.001
ST deviation, mm	0.0 (0,1.25) [0.62]	1.20 (0.0,2.0) [1.30]	0.001
Exercise duration, min	6.5 (4.1,9.0) [6.7]	5.3 (3.6,7.7) [5.8]	0.001
Exercise chest pain, %	50	51	0.86
Treadmill score	2.3 (−4.0,6.8) [0.7]	−3.3 (−8.5,1.8) [−3.3]	0.001
Cardiac catheterization			
Significant coronary disease, %	61	56	0.07
Severe coronary disease, %	27	23	0.088
Ejection fraction, %	60 (50,61) [56]	60 (54,66) [59]	0.001
Outcome status			
5-Year mortality, %	8.2	7.0	0.98

Values are n, median (25th, 75th) [mean].

RESULTS: DTS Risk Groups (Table 2)

- High-risk patients were more often older and male, with a greater frequency of cardiac risk factors, typical anginal symptoms, congestive heart failure, and prior myocardial infarction.
- During the treadmill test, peak heart rate, systolic blood pressure, and exercise time were lower for high-risk than for low- or moderate-risk DTS patients.
- All of the high-risk patients had >= 1 mm of ST-segment deviation, and 94% had exertional chest pain.

TABLE 2. Frequency of Clinical History, Exercise, Cardiac Catheterization Data, and Cardiac Death by DTS Risk Group for 2758 Medically Treated Coronary Artery Disease Patients From the Original Sample

Variables	Low-Risk DTS (n=990)	Moderate-Risk DTS (n=1515)	High-Risk DTS (n=253)	*P*
Clinial history				
Male sex, %	71	67	91	0.001
Age, y	46 (39,51) [45]	51 (45,56) [51]	53 (47,60) [53]	0.001
Risk factors, %				
Diabetes	7	10	11	0.008
Hypertension	28	36	40	0.001
Hyperlipidemia	18	23	31	0.001
Symptoms				
Typical angina, %	25	54	87	0.001
Atypical angina, %	47	36	12	0.001
Nonanginal chest pain, %	28	9	1	0.001
Anginal frequency per week	3 (1,7) [7]	7 (2,4) [14]	10 (4,20) [15]	0.001
Congestive heart failure, %	3	6	9	0.001
Prior myocardial infarction, %	25	32	39	0.001
Exercise test				
Peak heart rate, bpm	147 (140,152) [144]	136 (120,145) [131]	127 (110,135) [124]	0.001
Peak systolic blood pressure, mm Hg	164 (150,190) [169]	160 (140,180) [161]	160 (130,180) [159]	0.005
≥1-mm ST depression, %	2	36	100	0.001
Exercise chest pain, %	15	67	94	0.001
Exercise duration, min	9.3 (7.3,10.5) [9.1]	4.8 (3.4,7) [5.5]	4 (3,5) [4.2]	0.001
Catherization results				
Ejection fraction, %	60 (56,61) [58]	60 (49,61) [55]	52 (46,60) [52]	0.001
Significant coronary disease, %	40	67	100	0.001
Severe coronary disease, %	9	31	74	0.001

Values as in Table 1.

RESULTS: Frequency of Coronary Disease Subsets (Table 3)

- Three-vessel or left main disease was present in 37%, 40%, and 53% of patients with exertional chest pain, exercise duration <= 6 minutes, and >= 1 mm of ST-segment deviation, respectively.
- By comparison, 83% of high-risk DTS patients had 2- (with proximal left anterior descending) or 3-vessel or left main coronary disease. Low-risk patients typically had no coronary lesion, <= 75% (60%) or 1-vessel coronary disease (16%).

RESULTS: ***Frequency of Coronary Disease Subsets (Table 3)***

- Only 0.4% of high-risk DTS patients were without a significant coronary lesion.
- The comparison of significant coronary disease by DTS risk groups was statistically significant for the original and validation samples (P<0.0001 for both).

TABLE 3. Frequency of Coronary Disease Subsets and 5-Year Cardiac Survival for ST-Segment Depression, Chest Pain, and Exercise Duration Compared With the DTS for 2758 Medically Treated Coronary Artery Disease Patients From the Original Sample

	5-Year Mortality	No Stenosis ≥75% (n=1089)	1-VD ≥75% (n=363)	2-VD or Proximal LAD (n=349)	2-VD With LAD (n=214)	3-VD or Left Main (n=743)
ST depression ≥1 mm (29.3%)	18.5	11.5	9.7	15.0	10.5	53.3
Exercise chest pain (50%)	12.2	27.8	11.5	13.6	10.0	37.1
Exercise duration ≤6 min (45.2%)	12.7	28.7	10.2	11.8	9.6	39.7
DTS						
Low risk (35.9%)	3.1	59.9	16.4	10.3	3.9	9.5
Moderate risk (54.9%)	9.5	32.7	12.3	14.5	10.0	30.6
High risk (9.2%)	35.0	0.4	5.9	10.7	9.5	73.5

VD indicates vessel disease; LAD, left anterior descending. Values are percentages.

P<0.001 for mortality and disease subgroups.

RESULTS: Predicting Significant Coronary Disease (Table 4)

- For high-risk DTS patients, the odds of significant coronary disease were 376-fold (risk-adjusted: 97-fold) for high-risk versus low-risk patients.
- In the validation sample, moderate- and high-risk patients were 4.7 (pretest risk adjusted: 2.4) and 18.1 (pretest risk-adjusted: 8.2) times more likely to have significant coronary disease than low-risk DTS patients.

TABLE 4. Unadjusted and Pretest Risk-Adjusted Odds Ratio* for the DTS in Predicting Significant and Severe Coronary Disease

DTS	Unadjusted Odds Ratio (95% CI)	Wald χ^2 (*P*)	Adjusted Odds Ratio (95% CI)	Wald χ^2 (*P*)
Significant CAD				
Original sample		LL† χ^2=439.6		LL χ^2=1640.8
Moderate risk	3.1 (2.6–3.6)	175.4 (0.0001)	2.0 (1.6–2.5)	40.8 (0.0001)
High risk	376.4 (52.6–2693.3)	34.9 (0.0001)	96.9 (13.3–707.1)	20.4 (0.0001)
Test sample		LL χ^2=53.3		LL χ^2=189.1
Moderate risk	4.7 (2.6–8.5)	26.2 (0.0001)	5.1 (2.2–11.8)	14.7 (0.0001)
High risk	18.1 (7.2–45.3)	38.1 (0.0001)	10.2 (3.2–32.2)	15.5 (0.0001)
Severe CAD				
Original sample		LL χ^2=435.0		LL χ^2=864.2
Moderate risk	4.2 (3.3–5.3)	138.3 (0.0001)	2.4 (1.8–3.1)	42.9 (0.0001)
High risk	26.5 (18.6–37.6)	334.7 (0.0001)	8.2 (5.6–12.0)	114.7 (0.0001)
Test sample		LL χ^2=34.5		LL χ^2=90.1
Moderate risk	8.1 (2.5–26.5)	11.8 (0.0006)	10.2 (2.3–45.1)	9.5 (0.0023)
High risk	19.2 (5.4–68.0)	20.9 (0.0001)	17.3 (3.6–83.8)	12.5 (0.0004)

*Risk-adjusted by the clinical history models listed in Appendix 1.

†LL indicates model log likelihood ratio statistic; CAD, coronary artery disease.

RESULTS: Predicting Significant Coronary Disease

- In predicting significant coronary disease, the treadmill score also added independent predictive information while contributing 8% to 9.6% of the total model information for the original and validation samples (Figure 1, *P*= 0.0001 for both groups).

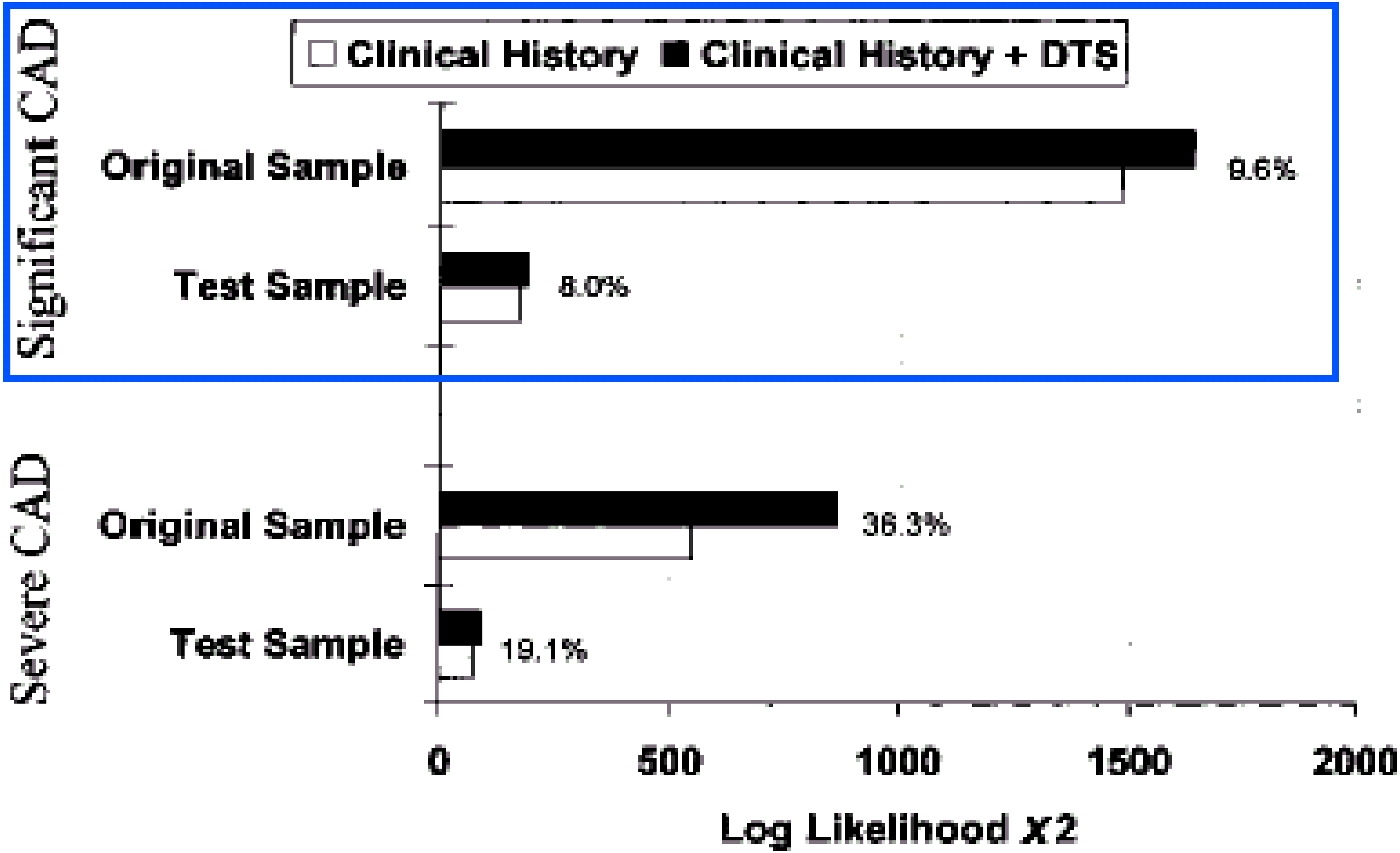
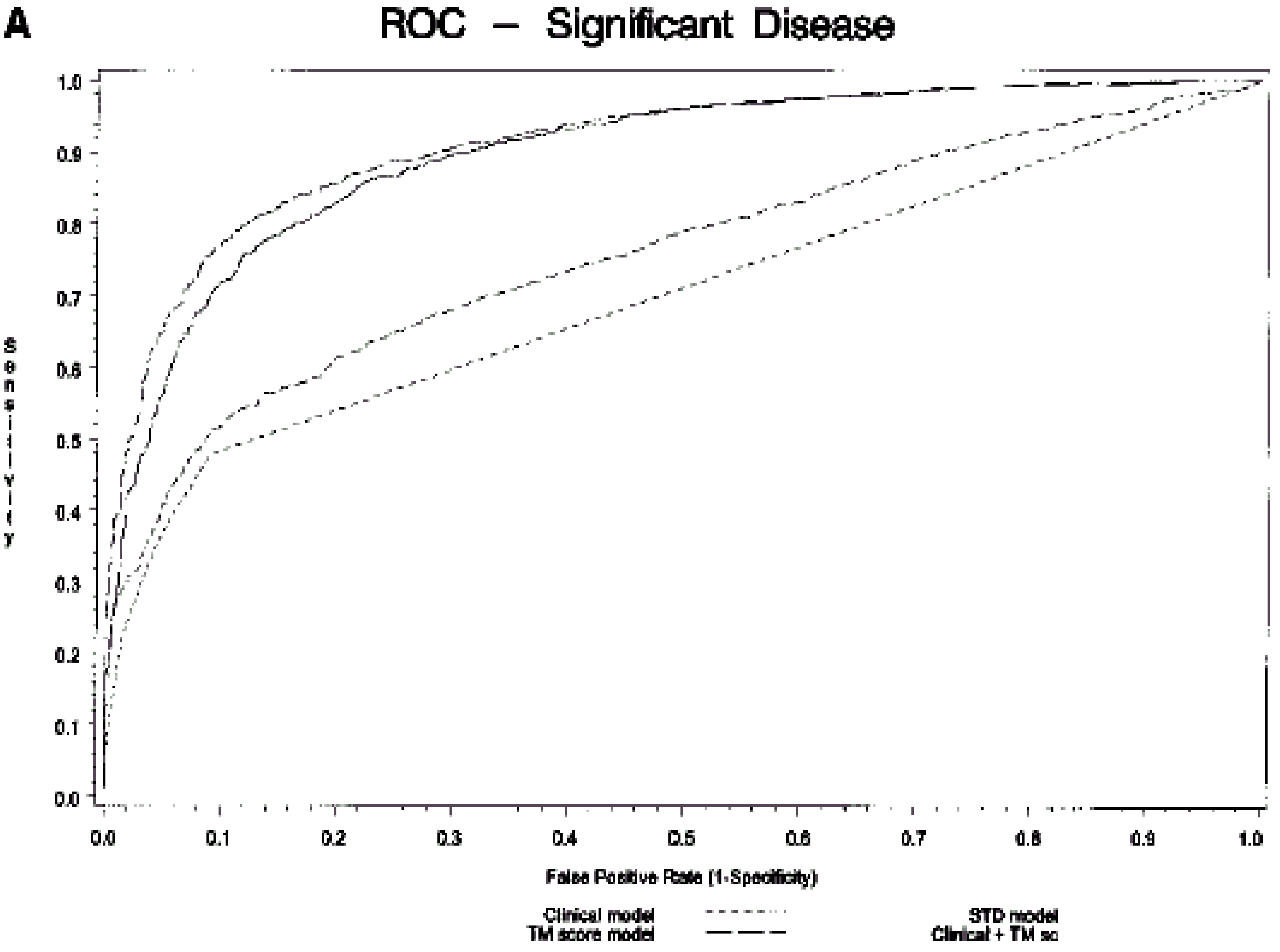


Figure 1. Incremental value of DTS in predicting significant coronary disease (CAD) (8% to 9.6% new information) and severe coronary disease (CAD) (19.1% to 36.3% new information).

RESULTS: Predicting Significant Coronary Disease

- The area under the ROC curves for predicting significant coronary disease was 0.70 for ST deviation alone, 0.76 for the DTS alone, and 0.91 for posttest DTS + clinical history results (Figure 2A).

A



ROC – Significant Disease
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Sensitivity
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
False Positive Rate (1-Specificity)
Clinical model
TM score model
STD model
Clinical + TM sc

RESULTS: Predicting Severe Coronary Disease (Table 4)

- For high-risk DTS patients, the odds of extensive disease were 26.5-fold (pretest risk-adjusted: 8.2-fold) for high-risk versus low-risk patients.
- In the validation sample, the odds of severe disease were 8.1-fold (pretest risk-adjusted: 10.2-fold) and 19.2-fold (pretest risk-adjusted: 17.3-fold) for moderate- and high-risk compared with low-risk DTS patients.

TABLE 4. Unadjusted and Pretest Risk-Adjusted Odds Ratio* for the DTS in Predicting Significant and Severe Coronary Disease

DTS	Unadjusted Odds Ratio (95% CI)	Wald χ^2 (*P*)	Adjusted Odds Ratio (95% CI)	Wald χ^2 (*P*)
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†LL indicates model log likelihood ratio statistic; CAD, coronary artery disease.

RESULTS: Predicting Severe Coronary Disease

- When predicting severe coronary disease, the treadmill score also added independent predictive information, contributing 19.1% to 36.3% of the total model information (*P*=0.0001, Figure 1).

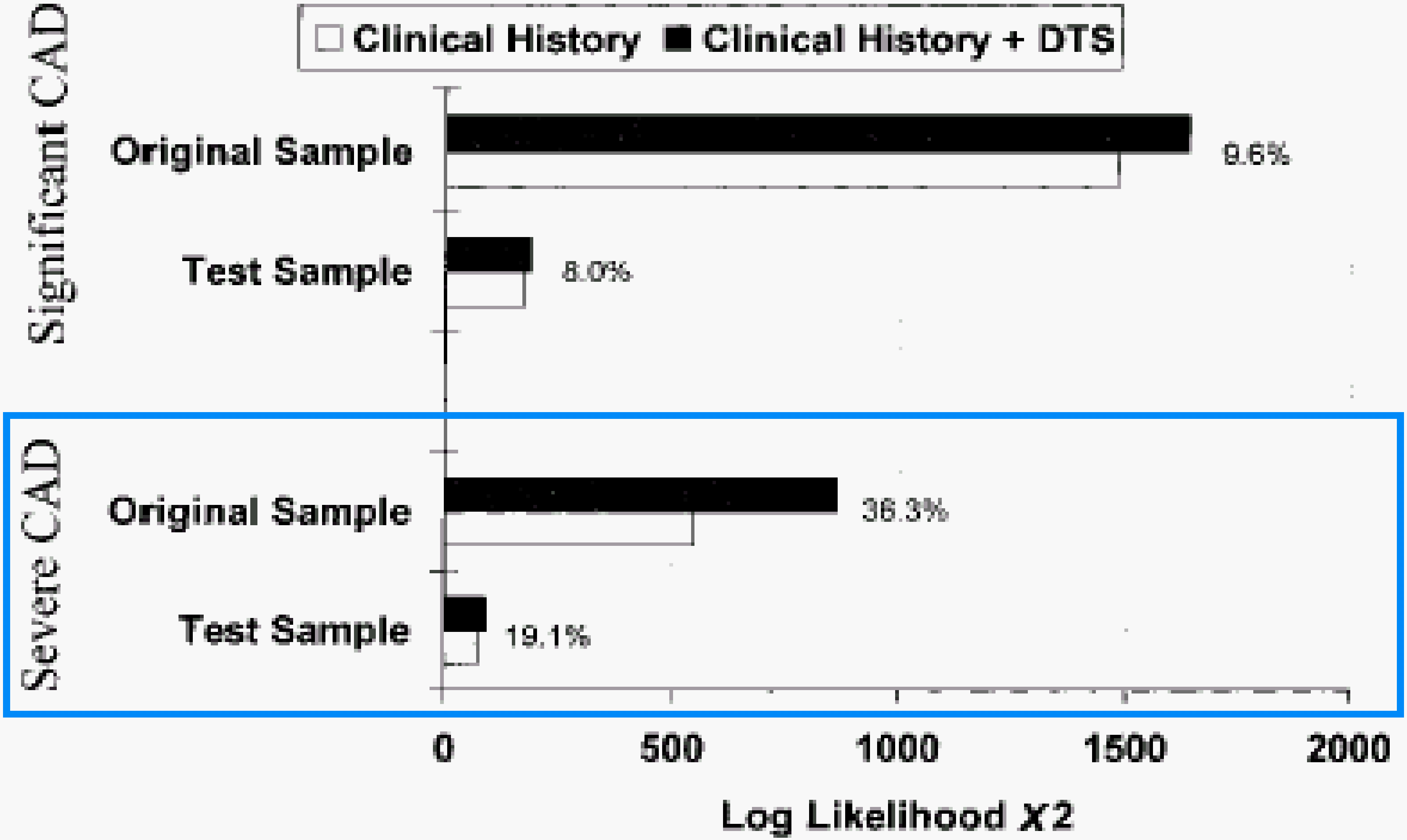

Figure 1. Incremental value of DTS in predicting significant coronary disease (CAD) (8% to 9.6% new information) and severe coronary disease (CAD) (19.1% to 36.3% new information).

RESULTS: ***Predicting Severe Coronary Disease***

- When predicting severe coronary disease, the area under the ROC curve was highest for posttest DTS results at 0.85 (compared with 0.72 for ST-segment depression alone, *P*=0.0001).

RESULTS: Predicting Survival

- Five-year cardiac death rates in the original sample were high for patients with ST-segment depression >= 1 mm (19%), exertional chest pain (12%), and exercise duration <= 6 minutes (13%) (Table 3, Figure 3).
- A Kaplan-Meier survival curve of the original sample is plotted in Figure 3 for low-, moderate-, and high-risk DTS patients.

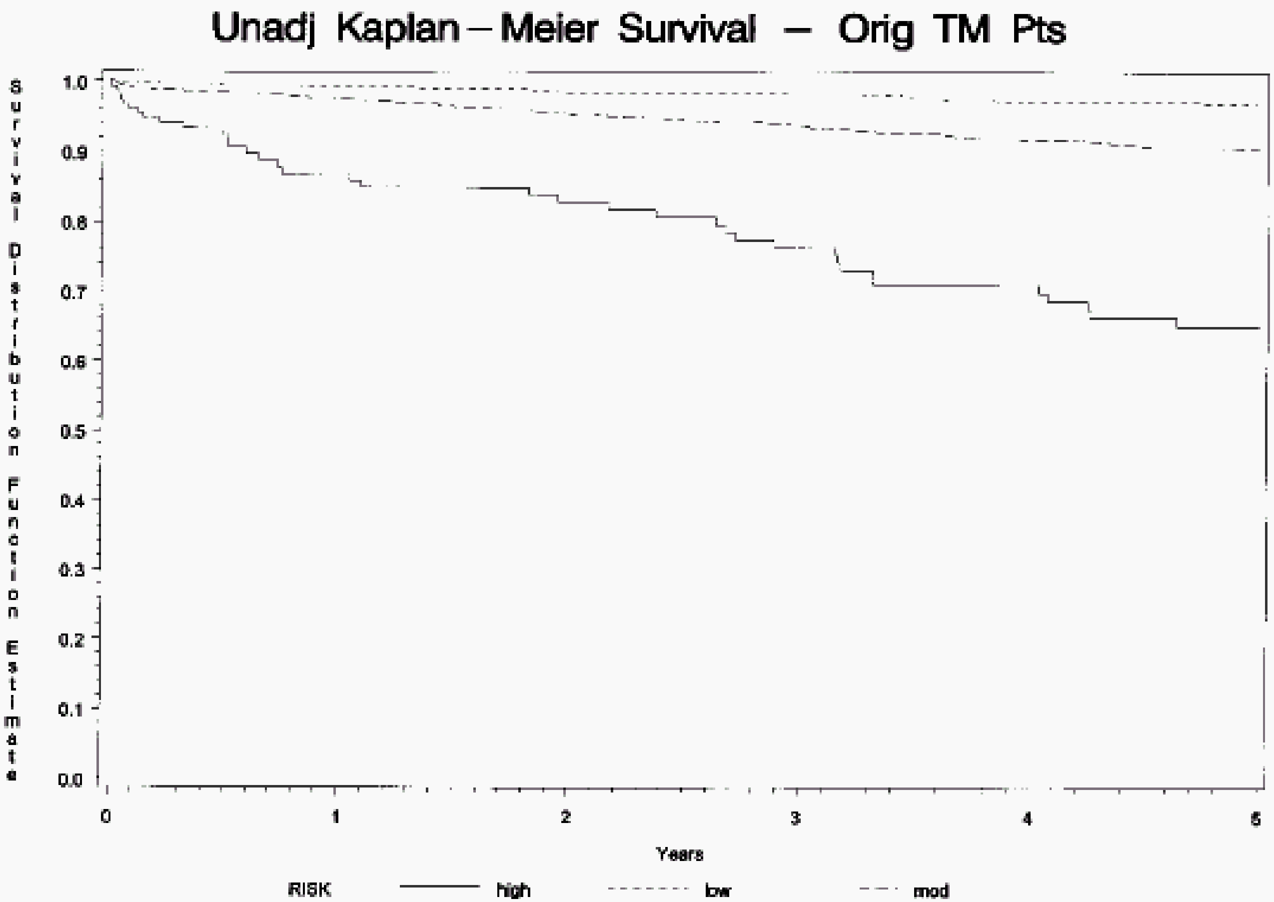

Figure 3. Overall 5-year survival was 97%, 90%, and 65% for low-, moderate- (mod), and high-risk patients ($P<0.00001$). Unadj indicates unadjusted; Orig, original; TM, treadmill; and Pts, patients.

RESULTS: Predicting Survival

- The treadmill score provided 15.4% of independent, prognostic information beyond a patient's clinical history data for predicting survival ($P < 0.0001$).

DISCUSSION

- The results of the current report reveal that, in addition to providing accurate prognostic estimates, the DTS also provides valuable information about *the presence and severity of coronary disease*.
- The DTS adds *independent predictive information* about these end points to the standard clinical (pretest) assessment.

***DISCUSSION**-Using the Treadmill Score to Improve Risk Estimates*

Bobbio M et al: (J Am Coll Cardiol. 1992;19:11-18)

- *When exercise test* information is used, the sensitivities of ST-segment depression and ST/heart rate index in detecting severe 3-vessel or left main disease were 75% and 78% in a 2270-patient multicenter registry

DISCUSSION-Using the Treadmill Score to Improve Risk Estimates

Ribisl PM et al: (Arch Intern Med. 1992;152:1618-1624)

- In a population of 607 male veterans, maximum ST depression during exercise or recovery was the single greatest discriminator among groups with differing disease severities.

DISCUSSION-*Using the Treadmill Score to Improve Risk Estimates*

- Furthermore, for patients with >= 2 mm of ST-segment depression, the sensitivity was 55% and the specificity was 80% for predicting 3-vessel or left main disease.

***DISCUSSION**-Using the Treadmill Score to Improve Risk Estimates*

- Exercise test indices have been developed by use of multiple pieces of information from the stress evaluation:

  ST depression,

  Chest pain,

  Exercise time,

  Peak systolic blood pressure,

  Heart rate.

DISCUSSION-Using the Treadmill Score to Improve Risk Estimates

Morrow et al: (Ann Intern Med. 1993;118:689-695)

VA score: (within a population of older, male veterans)

- This index includes:

  Change in systolic blood pressure,

  Peak metabolic equivalents,

  A history of congestive heart failure,

  Digoxin use,

  Exercise-induced ST depression.

DISCUSSION-Using the Treadmill Score to Improve Risk Estimates

Morrow et al: (Ann Intern Med. 1993;118:689-695)

VA score: (within a population of older, male veterans)

- Annual mortality was ,2%, 7%, and 15% for low-risk (77% of population), moderate-risk (18% of cohort), and high-risk (6% of patients) VA patients.

DISCUSSION-Using the Treadmill Score to Improve Risk Estimates

Morrow et al: (Ann Intern Med. 1993;118:689-695)

VA score: (within a population of older, male veterans)

Our experience with the VA score is that:

It does not risk-stratify lower-risk populations,

As well as higher-risk patients.

- This is probably a function of the components of the score, including digoxin use, impaired systolic function, and poor exercise tolerance.

DISCUSSION-Using the Treadmill Score to Improve Risk Estimates

DTS Score

- Prognostic and diagnostic subsets may also be discerned on the basis of information presented in the present and previous series.
- The DTS contributed from 8% to 36% of the predictive information when predicting significant or severe coronary disease and cardiac mortality.
- Of the current series, >80% of high-risk patients had 2-vessel coronary disease with left anterior descending involvement or 3-vessel disease.

DISCUSSION-*Using the Treadmill Score to Improve Risk Estimates*

- Of those classified as low risk in our 3225-patient series, most had either no significant (>= 75% stenosis) lesions or single-vessel coronary disease.

DISCUSSION-*Using Pretest Risk Estimates to Maximize Posttest Predictions*

The True Benefit of DST in Clinical Practice

- Although the treadmill test should not be considered to replace any imaging modality, if the efficient use of low-cost clinical data and risk stratification with a low-cost stress test are emphasized, evaluation costs may be reduced for many patients.

DISCUSSION-Using Pretest Risk Estimates to Maximize Posttest Predictions

- Noninvasive testing has the potential to improve the efficiency of resource use by:

Excluding patients at low risk from further intervention who have minimal disease and few cardiac events.

DISCUSSION-Using Pretest Risk Estimates to Maximize Posttest Predictions

- ***Suggested Protocol***

Low Risk Patient (36% of the population)

They may be risk-stratified by the treadmill test

This patient cohort may be managed safely with watchful waiting as well as symptomatic medical therapy without further testing.

DISCUSSION-Using Pretest Risk Estimates to Maximize Posttest Predictions

- ***Suggested Protocol***

High Risk Patient

*They may be considered candidates for **more aggressive management** that may include **cardiac catheterization**.*

DISCUSSION-Using Pretest Risk Estimates to Maximize Posttest Predictions

- ***Suggested Protocol***

Moderate Risk Patient

*Use of an **imaging modality** has been proposed to further risk-stratify these patients.*

DISCUSSION-Using Pretest Risk Estimates to Maximize Posttest Predictions

- Benefit Result Observed

Only ≈ 50% of our study population would require a stress imaging study before patient management is decided on.

This provides a method for selective use of more expensive imaging or invasive testing.

DISCUSSION-Study Limitations

- Catheterization VS Non-catheterization?
- Early and later referral to revascularization among members of the study population.

DISCUSSION-Conclusions

- The DTS is useful for risk-stratifying important diagnostic and prognostic patient subsets.
- The majority of low-risk patients had no coronary disease or single-vessel coronary disease, whereas high-risk treadmill score patients had more extensive or multi-vessel coronary disease.
- Although constructed to predict prognosis, the DTS is also able to differentiate relevant coronary artery subsets, both alone and in conjunction with clinical data.