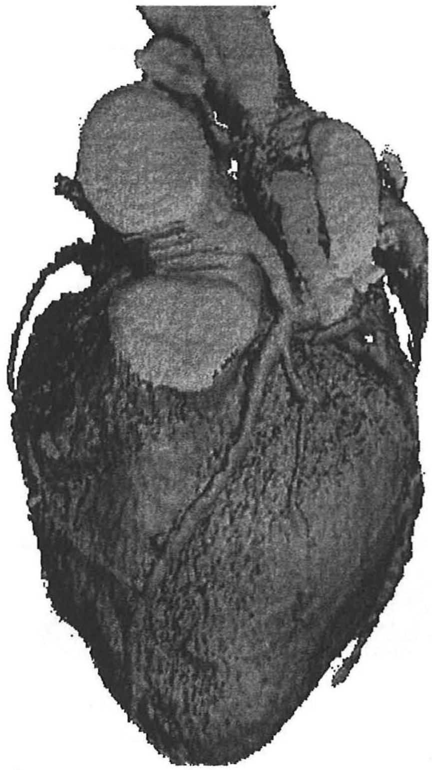
SCREENING FOR CORONARY ARTERY DISEASE

University of Texas Southwestern Medical Center at Dallas
Internal Medicine Grand Rounds
Thomas C. Andrews, MD
July 29, 1999



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This is to acknowledge that Thomas C. Andrews, MD serves as a consultant for Merck.

Thomas C. Andrews, MD
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I am a clinical cardiologist with an active role in Cardiology services at Parkland Memorial Hospital. My research has focused on understanding the determinants of abnormalities of vascular function in patients with preclinical atherosclerosis. A secondary interest is exploring the interplay between ethnicity, socioeconomic status and cardiovascular outcomes. In the coming years, I will combine these two areas of investigation through close collaboration with the Human Biology Laboratory of the newly-established UT Southwestern Medical Center Reynolds Cardiovascular Clinical Research Program.

Special thanks to my daughters Healy and Jia
for their understanding and patience.

Introduction: why screen for coronary artery disease?

Despite advances in both prevention and treatment, coronary artery disease remains the top cause of mortality in men and women in the United States. In addition, this disease accounts for an estimated annual economic loss of $90 billion. Once clinically apparent, coronary artery disease is usually quite advanced, as over 50% of patients initially present with acute myocardial infarction or sudden cardiac death. Hence, prevention of coronary disease is an important goal for both cardiologists and primary care physicians. Some have taken advantage of patient's concern about potential coronary disease for economic gain. For example, some advocate therapies of questionable or unproven benefit, while others have advertised diagnostic tests directly to consumers. The growth of the internet has increased the availability of medical information to consumers, and serves as a method to advertise some more questionable "medical products." Electron-Beam Computed Tomography (EBCT) of the heart is aggressively promoted to the lay public as an appropriate screening tool for coronary artery disease. These grand rounds will explore whether available data support such a role for this new technology.

- ACUPUNCTURE
- HERBS
- NUTRITION
- HORMONE THERAPY
- PSYCHIATRIC CONSULTATION
- HYPNOSIS
- CHELATION THERAPY - INTRAVENOUS EDTA
- INTRAVENOUS DIMETHYL SULFOXIDE
- INTRAVENOUS HYDROGEN PEROXIDE
- INTRAVENOUS VITAMINS AND MINERALS

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www.mediausa.com/chelation/index.htm

Figure 1: Alternative medicine on the world wide web

The public's growing concern about possible coronary artery disease has led to widespread acceptance of legitimate primary prevention programs with drugs such as the HMGCoA reductase inhibitors. Early randomized trials of the primary prevention of coronary disease with "statins" concentrated on patients at the highest risk. For example, the West of Scotland study enrolled subjects with mean baseline total cholesterol of 272 mg/dl and a relatively high incidence of other coronary risk factors. More recent studies, such as the AFCAPS/TexCAPS study, enrolled patients with cholesterol values near that of the "average" patient in the United States. Although the results of these trials all indicate that lowering cholesterol is effective in the prevention of coronary disease mortality and morbidity, the widespread application of these results to the US population would be at a great economic cost. Currently the annual cost of statin therapy approaches $1000 per patient. Extending the current guidelines to include the low risk population studied in AFCAPS/TexCAPS would lead to treatment of over half the US adult population at an estimated cost of over $50 billion. Pitts and Rubenfire estimate that treating 1000 patients with lovastatin for 5 years would prevent 12 myocardial infarctions, 7 episodes of unstable angina and 17 revascularization procedures. By inference, 964 patients of the 1000 treated would gain no apparent benefit from treatment. In addition to the initial cost of therapy, there is worry that coronary events will not be completely prevented by statin therapy, rather simply delayed—leading to an overall increase in costs to society. (1) Thus, efforts have been undertaken to identify patients who are more likely to benefit from preventative therapy.

	West of Scotland (pravastatin)	**AFCAPs/TexCAPs** (lovastatin)
Baseline total cholesterol	272 mg/dl	218 mg/dl
Diabetes mellitus	1%	6%
Cigarette use (at entry)	44%	12%
Hypertension	16%	22%
Annual total mortality (placebo)	0.82%	0.45%
Annual CHD mortality (placebo)	0.46%	0.14%
Risk reduction with statin Total mortality	22%	(+)4%
CHD mortality	32%	34%
Fatal/non-fatal MI	33%	40%

Table 1: Comparison of two primary prevention studies with statins.

In order to achieve more cost effective targeting of prevention, panels of experts have suggested that intensity of risk factor management should be matched with the overall hazard for a coronary event. (2) The guidelines established by the National Cholesterol Education Program Adult Treatment Panel II are based on risk modeling.

Using age, sex, LDL-cholesterol levels and the presence of other cardiac risk factors, 15% of the adult population is identified which are likely to represent approximately 45% of the US coronary deaths. Although there is controversy among experts, high-risk primary prevention patients may be considered those with annual rates of fatal or non-fatal myocardial infarction of 1-2%. (3, 4) Combining the categories of risk based on cholesterol (from the NCEP guidelines) and blood pressure (from JNC-V guidelines) the Framingham investigators have refined their coronary disease prediction algorithm. The

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-1	[-1]
35-39	0	[0]
40-44	1	[1]
45-49	2	[2]
50-54	3	[3]
55-59	4	[4]
60-64	5	[5]
65-69	6	[6]
70-74	7	[7]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-3
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	1
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-3]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[2]
≥280	≥7.25	[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	2	[2]
35-44	0.91-1.16	1	[1]
45-49	1.17-1.29	0	[0]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-1	[-2]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) <80	80-84	85-89	90-99	≥100
<120	0 [0] pts				
120-129		0 [0] pts			
130-139			1 [1] pts		
140-159				2 [2] pts	
≥160					3 [3] pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

(sum from steps 1-6)

Step 7

Adding up the points	
Age	______
LDL-C or Chol	______
HDL - C	______
Blood Pressure	______
Diabetes	______
Smoker	______
Point total	______

(determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
<-3	1%		
-2	2%		
-1	2%	[<-1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥14	≥56%	[≥14]	[≥53%]

(compare to average person your age)

Step 9

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	3%	1%	2%
35-39	5%	4%	3%
40-44	7%	4%	4%
45-49	11%	8%	4%
50-54	14%	10%	6%
55-59	16%	13%	7%
60-64	21%	20%	9%
65-69	25%	22%	11%
70-74	30%	25%	14%

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dl, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Figure 2: Framingham coronary risk prediction algorithm in men (5)

area under the receiver operating characteristic curve ("c" statistic) for CHD prediction with this algorithm is approximately 0.74, with 1 representing a test with perfect predictive discrimination, and 0.5 representing random discrimination. (5) Hence, any new test attempting to stratify patients based on coronary risk--or to identify patients with preclinical coronary disease--should provide information beyond that of the Framingham risk model.

Screening for coronary artery disease with exercise tolerance testing

In a landmark paper published in 1979, Diamond and Forrester described the pretest likelihood of significant coronary disease in subgroups of patients based on symptomatic status, age, and gender. (6) From these data, it is clear that relying on the presence of typical symptoms will misclassify a large proportion of patients with chest pain. For example, in the lowest risk group (women aged 30-39) only 26% of patients with typical angina have obstructive coronary disease on angiography or autopsy. Similarly, in the highest risk group (men aged 60-69), chest pain categorized as "non-anginal" is associated with a 28% chance of significant coronary disease. Thus, the presence of typical symptoms alone is not adequate to exclude coronary disease in low risk patients, and the absence of typical symptoms is not adequate to exclude coronary disease in a high risk patient.(table 2)

	Non-anginal chest pain		**Atypical angina**		**Typical angina**	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30-39	5.2	0.8	21.8	4.2	69.7	25.8
40-49	14.1	2.8	46.1	13.3	87.3	55.2
50-59	21.5	8.4	58.9	32.4	92	79.4
60-69	28.1	18.6	67.1	54.4	94.3	90.6

Table 2: Pretest likelihood of CAD in symptomatic patients according to age and sex (6)

Exercise testing has long been the "gold standard" noninvasive test for the evaluation of patients with possible coronary artery disease. Gianrossi and colleagues preformed meta-analysis of 147 consecutively published reports comparing ST segment depression on exercise testing to coronary disease by angiography. Over 20,000 patients underwent both tests. Wide variability was noted in test sensitivity and specificity. Sensitivity ranged from 23 to 100% (mean 68%) and specificity from 17 to 100% (mean 77%). (7)

Note: The sensitivity of a test is the probability that the result is positive given that the person has disease. The specificity of a test is the probability that the result is negative given that the person does not have disease. (8)

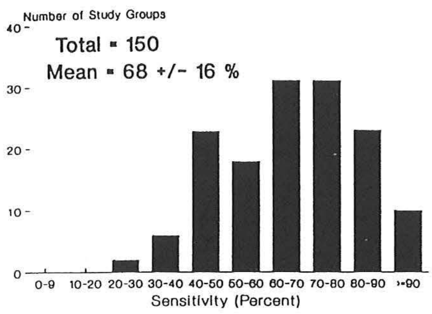


FIGURE 2. *Distribution of sensitivities for the 150 study groups for which this was reported. Values are mean±SD.*

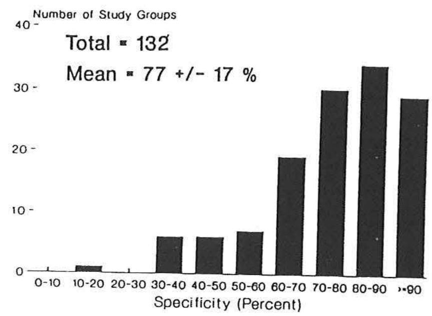


FIGURE 3. *Distribution of specificities for the 132 study groups for which this was reported. Values are mean±SD.*

Figure 3: Sensitivity and specificity of ST segment depression in the prediction of coronary artery disease (7)

Exercise stress testing has been coupled with risk factors and symptoms to develop likelihood ratios for prediction of coronary disease from ST segment response to exercise. (figure 3) For example, a 55 year old man with typical angina has a pretest probability of coronary disease of 92%. After stress testing, a "negative" result (i.e. absence of ischemic ST segment depression) reduces the post-test probability to approximately 65%, while a "positive" test increases the probability to nearly 100%. In patients with atypical symptoms and risk factors for coronary disease (pretest probability of 50%), stress testing can greatly aid in the diagnosis of coronary disease. However, when used to screen asymptomatic populations, conventional stress testing is less useful. For example, the 45 year old male with hypertension, diabetes mellitus and dyslipidemia has an 18% pretest likelihood of coronary disease. A "negative" test reduces the likelihood to 3%, whereas a "positive" test increases the likelihood to only 28%. Screening low risk, asymptomatic patients results in even less discrimination. In an asymptomatic 45 year old male with no risk factors, the pretest probability of coronary disease is approximately 2-3%, and a positive test increase the likelihood only to 7%. Hence, by Bayes' rule, the predictive value of a test can be expressed as a function of sensitivity, specificity, and probability of disease in the general population. By applying stress testing to an asymptomatic population with low probability of disease, the predictive value is greatly diminished. Since the sensitivity and specificity of exercise testing are less than optimal, use of this test to screen low risk population for silent coronary disease is of questionable benefit. (9)

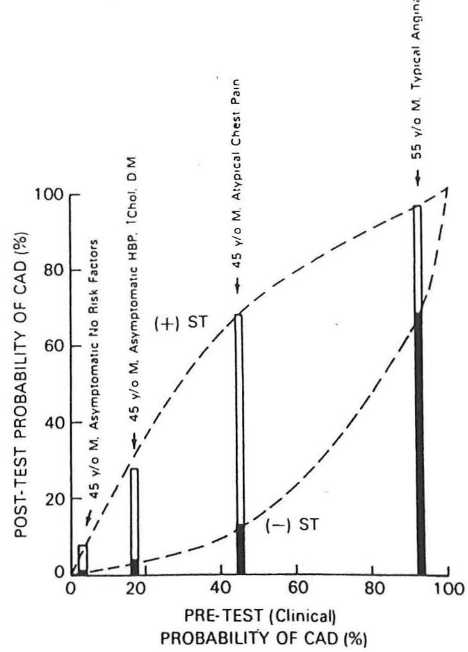


Figure 4: Use of Bayes' theorem to calculate the probability of coronary disease from results of exercise testing. (9)

Although exercise tolerance testing is of questionable benefit in the diagnosis of coronary disease in asymptomatic populations, a "positive" test result does increase the likelihood of suffering from a cardiac event. When angina is included as an endpoint along with death, myocardial infarction and coronary revascularization, the positive predictive value of ischemia on exercise testing is 26% and the pooled risk ratio of a positive test is approximately 9 fold over a subject without ischemia on testing. However, when angina is excluded as an endpoint, the positive predictive value drops to 6% for predicting a coronary event, and the risk ratio drops to only 4 fold. (10)

	Number	Years followed	Incidence of CHD (%)	Sens. (%)	Spec. (%)	Predictive value + (%)	Risk ratio
Bruce	221	5	2.3	60	91	14	14×
Aronow	100	5	9.0	67	92	46	14×
Cumming	510	3	4.7	58	90	25	10×
Froelicher	1390	6	3.3	61	92	20	14×
Allen	356	5	9.6	41	79	17	2.4×
Manca	947	5	5.0	67	84	18	10×
	508(w)	5	1.6	88	73	5	15×
MacIntyre	578	8	6.9	16	97	26	4×
McHenry	916	13	7.1	14	98	39	6×
			AVERAGES*	48	90	26	9×

CHD, Coronary heart disease; *Sens.*, sensitivity; *Spec.*, specificity; *w*, women.
*Averages do not include women.

Table 3: ETT in the prediction of cardiovascular events (angina included) (10)

	Number	Years followed	Incidence of CHD (%)	Sens. (%)	Spec. (%)	Predictive value + (%)	Risk ratio
Seattle Heart Watch	2365	6	2.0	30	91	5	3.5×
MRFIT (SI)	6217	6-8	1.7	17	88	2.2	1.4×
(UC)	6205		1.9	34	88	5.2	3.7×
LRC (Gordon)	3630	8	2.2	28	96	12	6×
(Ekelund)	3806	7	1.8	29	95	7	5×
			AVERAGES	27	91	6	4×

LRC, Lipid Research Clinics Coronary Primary Prevention Trial; *MRFIT*, Multiple Risk Factor Intervention Trial; *SI*, special intervention group; *UC*, usual care group.

Table 4: ETT in the prediction of cardiovascular events (angina excluded) (10)

Pilote and colleagues at the Cleveland Clinic reported the clinical yield and cost of exercise testing used to screen for coronary disease as part of preventative medicine or executive physical programs. 4,334 adults underwent exercise testing, and 15% demonstrated an abnormal test. Additional testing was performed in 215 patients, including coronary angiography in 110 and thallium scintigraphy in 105. An additional 16 patients underwent coronary angiography after a positive thallium scan. Of the entire cohort, severe coronary artery disease as identified in 19 (0.44%). They estimated the cost of this approach to identify one case of coronary disease for which surgery would provide survival benefit as $39,623. The estimated cost per year of life saved was $55,274. In this population, there was no difference is survival between those with and without ST segment depression on stress testing. The authors concluded that in actual practice, screening exercise testing has a low yield and is costly. (11) Some experts have argued that exercise testing is no longer an appropriate part of the "executive physical." (1) The most recent guidelines for exercise testing from the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures lists routine screening of asymptomatic men or women as a Class III indication (a condition for which there is general agreement that exercise testing is of little or no value, inappropriate or contraindicated by risk).

TABLE I Demographic and Cardiac Risk Factor Profiles of 4,334 Asymptomatic Adults Undergoing Exercise Treadmill Testing

Characteristic	Men (n = 3,593)	Women (n = 741)
Age (yrs)	52 ± 11	53 ± 11
Current smoking	446 (12%)	81 (11%)
Diabetes mellitus	168 (5%)	29 (4%)
Hypertension	734 (20%)	150 (20%)
β-blocker use	175 (5%)	42 (6%)
Calcium blocker use	209 (6%)	65 (9%)
Hypercholesterolemia	149 (4%)	28 (4%)
Pretest risk of CAD	8.4 ± 3.1	3.7 ± 2.7
1 risk factor*	1003 (28%)	197 (27%)
≥2 other risk factors*	232 (6%)	41 (6%)

Values given are means ± SDs or numbers (percentages).
*Including smoking, diabetes mellitus, hypertension, or hypercholesterolemia aside from sex.

TABLE II Test Results of 4,334 Asymptomatic Adults Undergoing Exercise Treadmill Testing

Characteristic	Men	Women
Protocol		
Bruce	2991 (83%)	308 (42%)
Modified Bruce	499 (14%)	359 (48%)
Other	104 (3%)	74 (10%)
Peak METs	10.9 ± 2.2	8.7 ± 2.2
Failure to reach 85% MPHR	130 (4%)	47 (6%)
Hypotensive SBP response	38 (1%)	9 (1%)
Ischemic ST segments	363 (10%)	57 (8%)
Anginal chest pain	35 (<1%)	23 (3%)
Ventricular tachycardia	19 (<1%)	1 (<1%)

Values given are means ± SDs or numbers (percentages).
MPHR = maximum age-predicted heart rate; SBP = systolic blood pressure.

Table 5: Demographic characteristics and test results in 4,334 asymptomatic adults undergoing ETT (11)

Electron Beam Computed Tomography (EBCT) in screening for coronary artery disease

Recently, electron beam computed tomography (EBCT) or "ultrafast CT" has been promoted as an alternative screening test to exercise testing for the identification of preclinical coronary artery disease. This technique utilizes an electron beam directed at stationary tungsten targets which enables rapid scanning times. Transaxial images are obtained in 100 msec with a thickness of 3 mm during breath holding. In comparison, conventional mechanical scanners require 300 to 600 msec exposure times which results in more motion and blurring of coronary calcium. Thirty to 40 scans are obtained in a single breath hold, and the data is retrospectively gated to the EKG near end-diastole. When used along with intravenous iodinated contrast material, EBCT yields detailed three-dimensional reconstruction of the heart and coronary arteries and is useful for the detection of coronary stenoses. (12) Without contrast enhancement, this technique relies upon the detection of calcium deposits in the coronary arteries as a marker for coronary atherosclerosis.

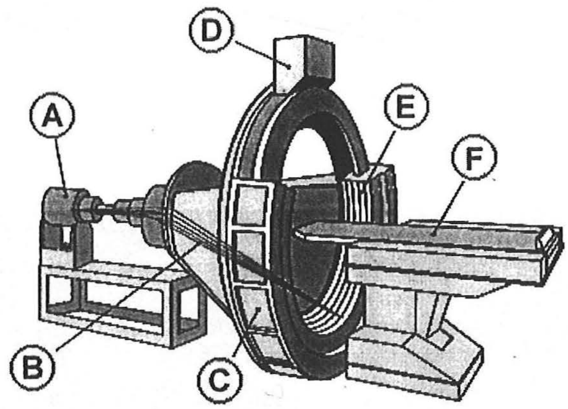


Figure 5: Electron Beam CT. A=electron gun; B=electron beam; C=self-contained cooling system; D=data acquisition system; E=tungsten target ring; F=Precise, high-speed couch motion

Images are analyzed off-line using software to quantify calcium area and density. Through a number of histological studies, tissue densities greater or equal to 130 Hounsfield units have been shown to represent calcium. A calcium score is determined by the method of Agaston by multiplying the lesion area by a density factor derived from the maximal Hounsfield unit within this area. (13) The calcium score is directly related to the likelihood of angiographic coronary artery disease, and as the log of the calcium score increases, so does the probability of multivessel disease. (14) One group has suggested that EBCT scanning offers improved discrimination over conventional risk factors in the identification of patients with coronary disease. (15, 16)

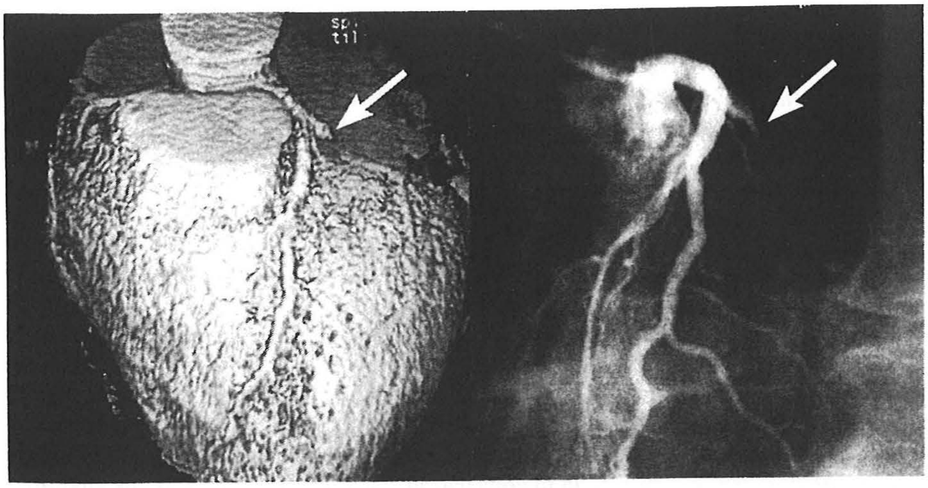


Figure 6: 3-dimensional reconstruction using EBCT with iodinated contrast compared with coronary angiography (12)

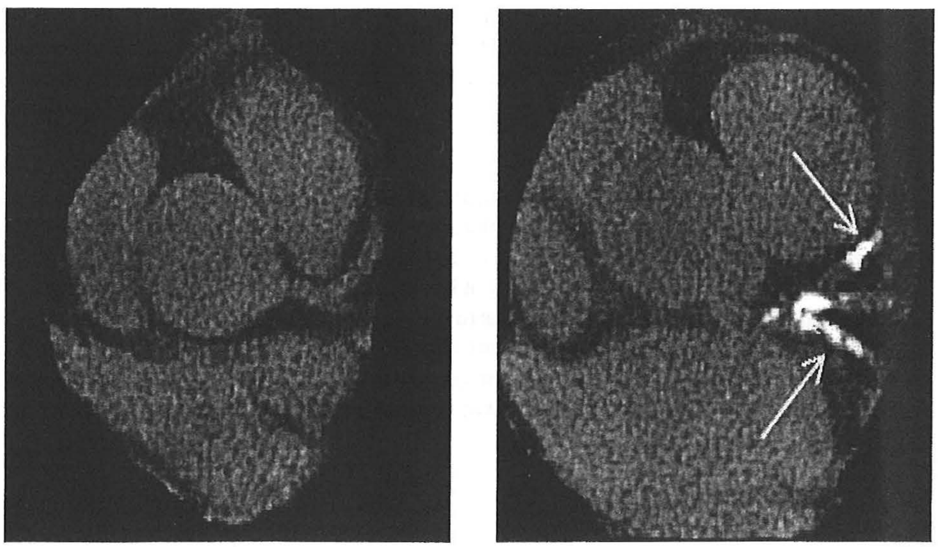


Figure 7: EBCT in patients with and without coronary calcium. Arrows point to coronary calcium (www.imitron-web.com)

Calcium, in the form of hydroxyapatite, is an important component of the atherosclerotic plaque. (17) Early studies utilizing cardiac fluoroscopy demonstrated that the presence of calcium is predictive of the presence of obstructive coronary artery disease, (18, 19) although less predictive in African-American patients compared with Caucasian or Asian patients. (20) In addition, calcium detected by fluoroscopy is associated with adverse coronary events such as myocardial infarction or cardiac death in symptomatic and asymptomatic patients. (19, 21, 22) Electron-beam computed tomography (EBCT) offers considerable advantages over fluoroscopy in the detection of coronary calcium. Autopsy studies show strong correlation between calcium detection by EBCT, histologic calcium quantification and direct measurement of plaque size. (23-26) Numerous studies of *symptomatic* patients have compared EBCT to coronary angiography in the detection of coronary artery disease. The sensitivity and specificity of EBCT ranges from 66 to 100% and specificity from 21 to 100% depending upon the definition of coronary disease (e.g. "any disease" versus "significant disease") and threshold value for coronary artery calcium score. (17) Intravenous contrast improves the sensitivity and specificity of EBCT for the detection of high-grade coronary stenoses to as high as 92 and 94% respectively. (12) In symptomatic patients, an elevated calcium score is associated with increased risk of subsequent cardiac events. (27) In *asymptomatic* patients, coronary calcium score does predict the severity of coronary obstruction. (15) although there is conflicting data regarding an association between calcium detected by EBCT and the occurrence of future cardiac events in this population (19, 28, 29) In general, EBCT is most sensitive for the detection of stenoses greater than 50% in severity and cannot detect lesions that are not calcified. Nevertheless, EBCT remains the most promising widely available tool for rapid, non-invasive detection of early coronary artery disease. (17)

Much of the controversy currently surrounding EBCT arises from widespread self-referral of patients to for-profit imaging centers promoting EBCT as a means for risk stratification for occult coronary artery disease. Currently, about 50 scanners are in use in the United States, and the number is projected to grow quickly in the next years. This test is appealing to patients because it is non-invasive, requires less than 15 minutes to perform, and is simple (for example, patients are scanned in their street clothes). Many centers that perform this test advertise directly to consumers, and the World Wide Web has become a favorite place for patient testimonials. (see figure 8)

Former US Senator Paul Simon on HeartScan
Democrat (Illinois)

USA Today June 23, 1999

"I went to Rush-Presbyterian Hospital in Chicago *(for EBCT testing)* and the result was not good. They told me in clear terms that I had a problem that needed to be dealt with. The angiogram confirmed the HeartScan report. The physicians at St. John's said I needed a heart bypass and I requested that they do it the next day. I had portions of six arteries replaced, and **for a few weeks after the operation my energy level was not high; any cough or sneeze caused great pain, and even a simple thing like driving on our somewhat rough country road gave me problems**. The operation occurred Jan. 5. I am typing this on May 10 and I feel no pain. **I do run out of breath easily when I walk or play tennis, but they assure this impatient patient that will gradually change."**

www.usatoday.com/life/cyber/bonus/0699/cb012.htm

Figure 8: A self-referred patient, almost back to baseline quality of life 6 months after EBCT led to coronary angiography and bypass surgery.

One center suggests that EBCT is "an appropriate tool for otherwise healthy individuals who may be at risk for heart disease." Specifically, they suggest that all men over the age of 35, and anyone who has risk factors such as high cholesterol, family history of early coronary disease, diabetes, high blood pressure, smoking history, sedentary living, and being overweight. (www.coloradoheart.com). Using these criteria most of the US population would "benefit" from screening. Patients with a negative EBCT scan are reassured that "all is well." Recommendations for patients with a positive scan are less consistent, and these patients often undergo a battery of diagnostic tests, sometimes resulting in coronary angiography and revascularization for asymptomatic coronary stenoses. (30) One group recommends a stepwise approach based on calcium score. (figure 9) The American Heart Association has discouraged the use of this procedure in low-risk asymptomatic populations until more data are available. (31)

- **SCORES: Zero**
  - Healthy Diet (low in saturated fat and cholesterol)
  - Smoking Cessation
  - Weight Loss
- **SCORES: 1-10**
  - All recommendations above ***PLUS:***
  - Tight control of Diabetes and Hypertension
  - Consider use of Statins in cases of High Cholesterol
- **SCORES: 11-100**
  - All Recommendations above ***PLUS:***
  - Estrogen for Post-Menopausal Women
  - Aspirin Use
  - Use of Statins in cases of High Cholesterol
- **SCORES: 101-400**
  - All recommendations of above ***PLUS:***
  - Exercise program
  - Use of Statins in cases of high and borderline cholesterol levels
  - Consider use of Folic Acid, Vitamin E, Fish Oils
- **SCORES: Greater than 400**
  - All recommendations of above ***PLUS:***
  - Exercise Test to rule out obstructive disease
  - Consider angiogram for symptomatic patients or those in high risk occupations

Figure 9: General recommendations for patients based on EBCT calcium scores (www.heartct.humc.edu/noframes_sld007.htm)

Coronary calcification in the pathobiology of coronary atherosclerosis

In a special report form the Committee on Vascular Lesions of the Council on Arteriosclerosis of the American Heart Association, Stary and colleagues defined six types of atherosclerotic lesions. Type 1 lesions consist of adaptive intimal thickening. Type II lesions include macrophage foam cells, and type III lesions (preatheroma) include those with small pools of extracellular lipid. The Type IV lesion (atheroma) include a core of extracellular lipid and is prone to rupture. In type V lesions (fibroatheroma) there is accelerated smooth muscle proliferation and collagen deposition, and calcium is frequently present. Type VI (complicated) lesions represent ruptured plaques with superimposed thrombosis. It is clear from Stary's scheme that uncalcified type IV lesions have the potential for rupture with subsequent thrombosis, myocardial infarction and/or sudden cardiac death. (32)

Doherty and colleagues performed a detailed pathologic study of coronary arteries and compared the location of calcium with the location of coronary stenoses. They found that calcium is more common than stenoses in the proximal coronary arteries, while in the more distal vessels, stenoses are more common than calcium. Hence, although there is a relationship between the location of calcium and stenoses, the link is not consistent. (33) Some have suggested that coronary calcium may even help to stabilize the atherosclerotic plaque, thus making it less vulnerable to rupture. (33) Others believe that plaques may become less likely to rupture after extensive calcification, whereas lesser amounts of calcium may increase the likelihood. (17) It is possible that the hard calcium deposits interspersed amongst other plaque elements weakened by inflammation may be a structure most likely to rupture. (34) Farb and colleagues analyzed a series of complex plaques and found calcium in 69% of ruptured plaques and 25% of eroded plaques. (35) Hence, although calcium is a frequent component of the atherosclerotic plaque, it is not a universal component. Most important, non-calcified plaques may be particularly prone to rupture.

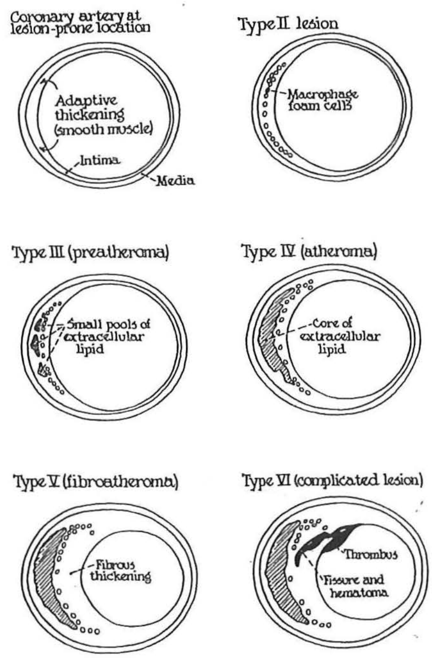
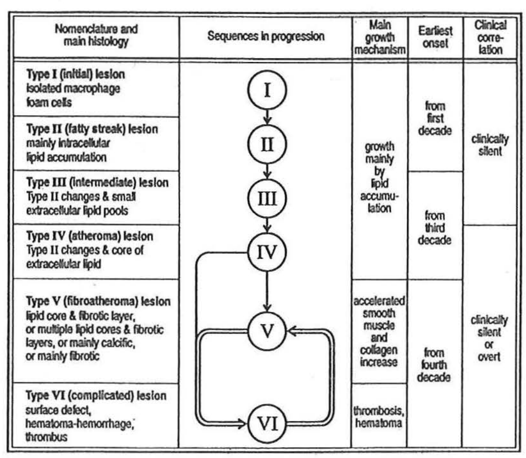


Figure 9: Stary classification of coronary atheroma (32)



Nomenclature and main histology	Sequences in progression	Main growth mechanism	Earliest onset	Clinical corre-lation
Type I (initial) lesion isolated macrophage foam cells	I	growth mainly by lipid accumu-lation	from first decade	clinically silent
Type II (fatty streak) lesion mainly intracellular lipid accumulation	II			
Type III (intermediate) lesion Type II changes & small extracellular lipid pools	III		from third decade	
Type IV (atheroma) lesion Type II changes & core of extracellular lipid	IV			clinically silent or overt
Type V (fibroatheroma) lesion lipid core & fibrotic layer, or multiple lipid cores & fibrotic layers, or mainly calcific, or mainly fibrotic	V	accelerated smooth muscle and collagen increase	from fourth decade	
Type VI (complicated) lesion surface defect, hematoma-hemorrhage, thrombus	VI	thrombosis, hematoma		

Figure 10: Progression of coronary atheroma (32)

Particularly in younger patients, these lipid-rich and rupture-prone plaques may predominate. The PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study examined autopsy material from 2876 subjects between 14 and 34 years old at the time of deaths of external cause. The extent, prevalence, and topography of atherosclerotic lesions were determined in the aorta and right coronary arteries of each subject. Table 6 shows the prevalence of fatty streaks, fibrous plaques, and complicated lesions as determined by pathological examination of gross specimens and evaluation of calcium by soft tissue radiography. Although fibrous plaques were present in 12 to 33% of subject's aged 15 to 24, there were no calcified lesions found. Male subjects between 30 and 34 displayed a 50% incidence of fibrous plaques, but calcium was present in less than 3%. Thus, in male subjects less than 35 years of age, atherosclerosis is common, but calcification is not. (36)

Age (y)	No of cases	Fatty streak (%)	Fibrous plaque (%)	Complicated (%)	Calcified (%)
White men					
15-19	207	45.4	23.7	0	0
20-24	246	57.3	27.6	0	0
25-29	287	70.0	39.4	0.7	2.4
30-34	244	80.3	51.2	1.6	2.9
Black men					
15-19	248	20.8	24.2	0	0
20-24	323	64.1	32.5	0	0
25-29	326	72.4	41.7	0.3	0.3
30-34	222	76.6	49.1	1.8	2.7
White women					
15-19	73	57.5	6.8	0	0
20-24	95	46.3	14.7	0	0
25-29	103	46.6	21.4	1.0	1.0
30-34	90	65.6	32.2	0	5.6
Black women					
15-19	67	47.8	17.9	0	0
20-24	74	59.5	12.2	0	0
25-29	96	64.6	25.0	0	0
30-34	87	74.7	37.9	1.1	1.1

Table 6: From the PDAY group. Prevalence of various different lesions by race, sex and age.(36)

Does the absence of coronary calcification "rule out" significant coronary disease?

Tanenbaum and colleagues from the University of Illinois published one of the first series comparing EBCT with coronary angiography. The study group consisted of 54 subjects, 36 men and 18 women. Coronary calcium was detected in 38 patients and all had angiographic coronary artery disease. Sixteen patients had no coronary calcium, and of those 5 had significant coronary disease. The overall sensitivity for coronary calcium in the prediction of angiographic coronary disease was 88%.(37) Budoff et al performed a multicenter study to determine the relationship between EBCT and coronary angiography in a large group of symptomatic patients. They found that the test characteristics (specificity, sensitivity, positive predictive value, negative predictive value) varied widely for the prediction of single, double, triple vessel disease and triple vessel disease plus left main disease.(Table 7) In addition, the sensitivity increased and specificity decreased with advancing age. (Table 8)

No. of Calcified Vessels	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
1-Vessel calcification	92%	54%	84%	71%
2-Vessel calcification	76%	78%	90%	55%
3-Vessel calcification	56%	88%	93%	43%
4-Vessel calcification	20%	98%	96%	31%

UFCT indicates ultrafast computed tomography. Four-vessel disease represents coronary calcification in the left anterior descending, right coronary, left main, and circumflex arteries.

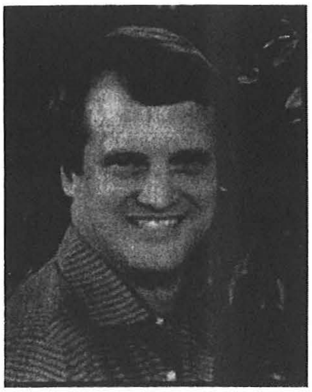
Table 7: Test characteristics of EBCT in predicting 1,2,3 and 4 vessel coronary disease in symptomatic patients (14)

	Age, y		
	<40 (n=53)	40-50 (n=178)	>50 (n=478)
Sensitivity	13/19 (68)	84/100 (84)	305/306 (99)
Specificity	25/34 (74)	41/78 (53)	58/172 (34)
Positive predictive value	13/22 (59)	84/121 (69)	305/419 (73)
Negative predictive value	25/31 (81)	41/57 (72)	58/59 (98)

UFCT indicates ultrafast computed tomography.
Percentages are shown in parentheses. Trends are all highly significant ($P<.0001$).

Table 8: Test characteristics of EBCT vary with age. (14)

Budoff and coworkers suggest that in younger patients, in whom advanced coronary disease is less prevalent, a positive study correlates well with presence of disease (specificity of 74%). Furthermore, in the older population the absence of coronary calcification may be an important predictor of absence of disease. (14) In comparison, the results of Fallavollita et al suggest a lower specificity in younger patients (45%) than the Budoff study. (38) However, given the lack of histological calcium in most plaques from younger patients, and a negative predictive value of only 81% of patients under 40 in the Budoff study, younger patients without calcium on EBCT who are high risk by other criteria should not be falsely reassured that they are "free of disease," with license to ignore general preventative measures. (figure 11)



"I've always been worried about my heart. I've got high cholesterol and a strong history of heart disease in my family. Now that my Coronary Artery Scan was negative, my enjoyment of life has increased 100%. I still try to maintain a healthy diet, but let me tell you, that occasional steak, French fries or ice cream sure taste a whole lot better without the guilt."

www.heartcheckamerica.com

Figure 11: Testimonial of a patient after a negative EBCT. Has he been falsely reassured?

Does the presence of calcium by EBCT indicate increased risk for coronary events?

Certainly, the presence of coronary calcification is strongly correlated with the presence of coronary atherosclerosis. In fact, one investigator has written, "the presence of quantifiable coronary artery calcium is for all practical purposes pathognomonic of the presence of coronary atherosclerotic plaque disease." (39) Moreover, there is a direct relationship between the amount of coronary calcium (the calcium score) and "atherosclerotic burden" (the extent of disease) as measured histologically (40) or in vivo with intracoronary ultrasound. (41) However, this technique cannot distinguish between "vulnerable plaque" (i.e. those prone to rupture and lead to coronary events) and stable plaque (i.e. not prone to rupture). There have been three studies examining the relationship between the presence of calcium on EBCT and subsequent coronary events in asymptomatic subjects.

Agaston and coworkers Mount Sinai Medical Center, Miami Beach, reported follow-up data from 367 asymptomatic subjects undergoing EBCT. Clinical follow-up ranged from 36 to 72 months, and 26 patients sustained coronary events (angina, myocardial infarction, coronary angiography, and revascularization). There were no reported deaths. Mean calcium score for those with and without events was 399+-424 and 76+-207 respectively. They used multivariate analysis do adjust for coronary risk factors and found that calcium score greater than 50 was associated with an adjusted odds ratio of 6.9 (95%CI: 1.7-28.5). The value of this report is diminished since it has been published only in abstract form, there is no demographic information provided, and the small number of "hard" cardiovascular endpoints (no deaths, 10 non-fatal infarctions). (42)

Arad and coworkers at St Francis Hospital in Rosyln, New York followed 1173 asymptomatic subjects who underwent EBCT in 1993 and 1994. In separate reports, they published clinical follow-up data at 19 and 3.6 years. (43, 44) Patients were by physician or self referred in response to advertisement. The test was described as "potentially useful for screening purposes only." Mean age of the subjects was 53+-11 at entry, and the median calcium score was 4. The method of follow-up was not explicitly defined, but was primarily via telephone contact. By 3.6 years, 40 patients had sustained at least one cardiac event, with 2 deaths, 14 non-fatal infarctions, and 24 revascularization procedures. Using a calcium score of >-160 as a cut off point, the odds ratio for cardiac events (including revascularization) was 23. Although there was no clear indications listed for revascularization, the authors state they "do not believe subjects with high calcium scores underwent bypass surgery or angioplasty preferentially, because EBCT has not been accepted by the local medical community, no subjects went directly from EBCT to coronary angiography, all stress tests were done for clinical indications, and all revascularization procedures not preceded by an MI were performed for clinical indications." Considering only the endpoints death or nonfatal myocardial infarction, the odds ratio for an event was 22. Other test characteristics are listed in table 7.

Events	Sensitivity	Specificity	PPV	NPV	Overall accuracy	Odds ratio	P
All	0.80	0.85	0.16	0.992	0.85	23	<0.0001
Death/MI	0.81	0.82	0.07	0.997	0.84	22	<0.0001

Table 9: Test characteristics of EBCT in predicting cardiovascular events (43,44)

The most recent report of the prognostic utility of EBCT comes from Detrano's group at UCLA. (45) They studied 1196 subjects recruited for the South Bay Heart Watch, a government-funded, prospective study to explore the value of risk-factor assessments and coronary calcium in predicting cardiac outcome in initially asymptomatic adults. Thus, this study differs from previous ones, in that subjects were not self-referred--rather they were recruited by mailing 100,000 letters of invitation to households whose heads were at least 45 years old. Subjects with 2 or more risk factors for coronary disease were invited to participate, and 5023 respondents were screened. Using the Framingham risk equation, subjects with less than 10% 8 year risk were excluded. 1461 subjects were enrolled in the cohort and followed yearly with visits or phone calls. Thirty months after initial enrollment, subjects were invited to come for a second evaluation which included EBCT. 1196 were still asymptomatic and agreed to participate. The mean age of the cohort was 66 years with annual cardiac risk of about 1% by Framingham risk equations. More than two-thirds had detectable coronary calcium. The receiver operating characteristic area under the curve for the Framingham risk score and the calcium score were similar (0.69+-0.05 vs. 0.64+-0.05), and the calcium score did not provide additional information when added to conventional risk models.

Although the South Bay Heart Watch study represented an attempt to answer the question regarding EBCT and prognosis in a rigorous fashion, this study was seriously flawed. The original report from this cohort described calcium detected by cinefluoroscopy as a significant predictor of future events. Thus, patients with coronary calcium who had events in the first 30 months of follow-up were excluded from the EBCT substudy. Furthermore, subjects were made aware of their test results, and consequently a treatment bias may have led to fewer events in the group with coronary calcium. Finally, the study group was relatively old, and a very high percentage had calcium on EBCT scanning. Thus, these results may not be generalizable to the younger population, which may be a more appropriate target for primary prevention. (1)

In summary, the available data are insufficient to determine whether EBCT is an appropriate test for risk stratification for coronary events. The Agaston study was small and included an inadequate number of "hard endpoints." Subjects included in the Arad study were primarily self-referred and follow-up methodology was not rigid. The Detrano study suffers from a "fatal flaw" of methodology from the exclusion of a large number of subjects with calcification on fluoroscopy that suffered events prior to EBCT. In response to the lack of convincing data, the NIH has sponsored a large, prospective trial (Subclinical Cardiovascular Disease Study) which will prospectively evaluate EBCT (and other tests) as a marker for future coronary events. Eighteen thousand men and women aged 35 to 84 will be recruited for initial examination, and a subset will undergo EBCT scanning. The results of this 10-year prospective trial should become available in 2008.

Summary and conclusions

Further refinements in risk modeling have resulted in useful methods to estimate intermediate term cardiac risk from readily available clinical data. Exercise testing of asymptomatic low- or intermediate-risk populations is expensive because the incidence of significant coronary disease is low and positive tests frequently results in further testing to "rule out" disease. Furthermore, exercise testing cannot identify patients with less than 70% coronary artery stenoses, and thus many patients with "negative" exercise tests have advanced coronary disease and are falsely reassured.

The routine screening of asymptomatic subjects with EBCT cannot be embraced based on currently available data. Especially in younger patients, atherosclerosis often is present in the absence of radiographic calcification. Therefore, high risk younger patients should not be reassured by a negative test, although a positive test in an intermediate risk patient may indicate a very high risk group suitable for intensive risk factor modification. In older subjects, calcification is common and EBCT may not provide prognostic information above and beyond the Framingham risk model. Until more data is available, coronary risk should be estimated from clinical models such as the Framingham risk score, and risk factor modification adjusted accordingly.

Asymptomatic young patients who seek counsel regarding a positive EBCT for coronary calcium should have an evaluation of traditional coronary risk factors. Weight loss, smoking cessation, and exercise should be encouraged. Aggressive lipid-lowering therapy is probably warranted, although the clinical utility of this approach has not been tested. Prophylactic anti-platelet agents should be considered. Patients should be counseled regarding symptoms of coronary artery disease. Many patients will require exercise testing for reassurance, although results must be interpreted with caution. Restraint must be used regarding further expensive and/or invasive testing.

Asymptomatic older patients with coronary calcification should be counseled regarding general "heart healthy" preventative measures. Based on previous trials, many will benefit from aspirin therapy for primary prevention regardless of calcium score. Lipid lowering therapy should be prescribed based on current guidelines. As with younger patients, many will demand further testing for reassurance.

The future of EBCT as a screening test will be defined by the results of large clinical trials. Until such data are available, EBCT is a useful research tool to non-invasively quantify coronary atherosclerosis.

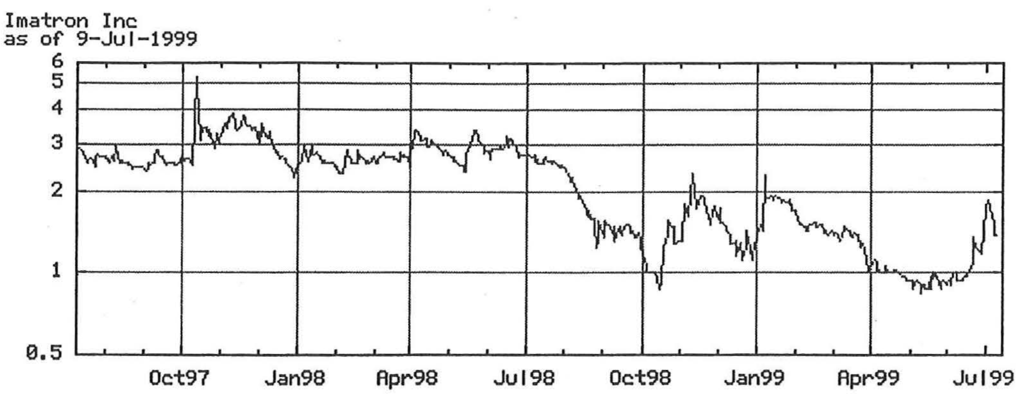


Figure 12: 1997-1999 stock price for Imatron Inc, a manufacturer of a popular EBCT device.

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