Best Practice

STRAIGHT TO THE POINT

Coronary artery disease: Part 1. Epidemiology and diagnosis

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EPIDEMIOLOGY

Incidence and prevalence

- Coronary artery disease (CAD) is the leading cause of death in Americans, accounting for about 500,000 deaths each year. The annual incidence of myocardial infarction (MI) is about 1.5 million.
- As many as 2 million middle-aged men may have silent myocardial ischemia.[1]

[1] *Cohn PF. Silent myocardial ischemia. Ann Intern Med 1988;109:312-317.*

Risk factors

- Lipid levels: Low high-density-lipoprotein (HDL) levels (<0.91 mmol/L [<35 mg/dL]) and high low-density-lipoprotein (LDL) levels are independently associated with CAD (HDL especially in women).
- Diabetes mellitus: Increased risk is related to hyperglycemia and hyperinsulinemia, both of which are atherogenic.
- Hypertension: Systolic and diastolic blood pressures are independent risk factors, but the systolic is the preferred marker.
- Smoking: Promotes atherogenesis, ischemia, and thrombogenesis. Risk mostly disappears within 3 years after cessation.
- Family history: Especially premature disease (parent with MI before age 60), but the independent effect is difficult to quantify.
- Left ventricular hypertrophy: A powerful independent risk factor for CAD (more so than diabetes mellitus or smoking).
- Homocysteine: Observational studies demonstrate that higher levels are associated with a 20% to 40% increased risk of cardiovascular events.[2] Nine randomized trials are currently evaluating the effect of treating high homocysteine levels.
- C-reactive protein: Observational studies demonstrate that the prevalence of CAD is increased by 50% for each doubling of the C-reactive protein level.[3] The pathophysiologic significance of this relationship remains unclear, although aspirin and statin drugs could possibly exert their benefit by decreasing coronary artery inflammation.

Multivariate risk: A 50-year-old healthy man has a 10-year risk of CAD of 6%. His risk would increase incrementally to the following levels by adding risk factors in sequence: smoking, 9%; diabetes, 13%; hypertension (165/90 mm Hg), 21%; and hypercholesterolemia, 27%. Calculated using the excellent risk factor formula presented in *Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. Circulation 1991;83:356-362.*

[2] *Eikelboom JW, Lonn E, Genest J Jr, Hankey G, Yusuf S. Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. Ann Intern Med 1999;131:363-375.*

[3] *Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ 1996;312:1061-1065.*

- Other risk factors: These include obesity,[4] high levels of uric acid, triglycerides,[5] lipoprotein Lp(a), tissue plasminogen activator antigen, fibrinogen, and leukocytes.
- Protective factors: These include exercise (?causal), moderate alcohol use (1-2 drinks per day), and high HDL levels (>1.55 mmol/L [>60 mg/dL]).

DIAGNOSIS

Overview of strategy

- Assess pretest probability of CAD by history, physical examination, and laboratory test results.
- Perform noninvasive testing if indicated.
- Perform cardiac catheterization if indicated.
- Initiate treatment accordingly.

The decision to catheterize should be based on post-test probability, prognostic factors, and severity and stability of symptoms (see below)

History

- Demographics: Age and sex (table 1). Note the decreasing importance of gender with advancing age.
- Description of symptoms (table 1): Classic angina is substernal chest pressure occurring predictably with exertion and relieved within a few minutes by rest.
- Associated risk factors: Diabetes, hypertension, family history, hyperlipidemia, lipids, smoking, and menopausal status all modify the probability of disease.

Physical examination and laboratory tests

- Physical assessment for risk factors should include blood pressure (for hypertension), funduscopic examination (for diabetes and hypertension), and cardiac examination (for left ventricular hypertrophy and heart failure).
- Physical assessment for associated conditions should include peripheral vascular examination (for peripheral vascular disease) and neurologic examination (for cerebrovascular disease).
- Fasting lipid profile and glucose or glycosylated hemoglobin level.
- Electrocardiogram (ECG) for left ventricular hypertrophy, ST-T segment changes, abnormal conduction, or old MI.

A normal ECG does not exclude the possibility of CAD.

Table 1 *Prevalence of CAD by age, sex, and symptoms*†*

Age, yr	Nonanginal chest pain (1)		Atypical angina (2)		Typical anginia (3)	
	Men	Women	Men	Women	Men	Women
30-39	0.05	0.01	0.22	0.04	0.70	0.26
40-49	0.14	0.03	0.46	0.13	0.87	0.55
50-59	0.22	0.08	0.59	0.32	0.92	0.79
60-69	0.28	0.19	0.67	0.54	0.94	0.91

*The 3 features of angina are (1) substernal location, (2) precipitation by exertion, and (3) relief by rest or nitroglycerin. The presence of of all 3 features indicates typical angina; of 2 features, atypical angina; and of 1 feature, nonanginal chest pain.
†Adapted from Diamond and Forrester.[6]

Operating characteristics of exercise stress tests

- A positive result on exercise stress testing (EST) is usually defined as nonupsloping ST-segment depressions of 1 mm or greater. Sensitivity is about 65%

[4] *Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983;67:968-978.* The effect of obesity is diminished but still present after adjusting for lipids, hypertension, and glucose tolerance.

[5] *Wilson PW. Established risk factors and coronary artery disease: the Framingham Study. Am J Hypertens 1994;7(pt 2):7S-12S.* A good brief overview of risk factors, it states that triglyceride levels add little after adjusting for HDL levels. Other studies, however, show that triglyceride levels are independent risk factors for MI (but not for angina).

[6] *Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350-1358.* An excellent discussion of pretest and post-test probabilities of CAD replete with tables and diagrams. Note that the gap between men and women narrows after age 50. Caution: the symptoms and labels used in this table are somewhat different from those used in standard clinical practice.

to 70%, and specificity is about 80% to 85% (likelihood ratio, 4.3). In general, the more severe the disease, the higher the sensitivity. For left main artery disease, the sensitivity probably exceeds 90%.

- The probability of disease is further influenced by the exact amount of ST depression (table 2).

Table 2 *Probability that patients with CAD and healthy patients will achieve given levels of ST depression on exercise stress testing**

ST depression, mm	Diseased patients	Healthy patients	Likelihood ratio
0.0-0.5	0.14	0.63	0.2
0.5-1.0	0.21	0.23	0.9
1.0-1.5	0.23	0.11	2.1
1.5-2.0	0.09	0.02	4.5
2.0-2.5	0.13	0.01	13.0
>2.5	0.20	<0.01	39.0

*Adapted from Diamond and Forrester.[6]

The likelihood ratio may be interpreted as the probability that a diseased patient will have a result in the indicated range, divided by the probability that a healthy patient will have a result in that range. Thus, patients with CAD are about a fifth (0.2) as likely as healthy patients to have ST depressions in the range of 0 to 0.5 mm but 39 times as likely as healthy patients to have ST depressions greater than 2.5 mm.

Rules of thumb in EST interpretation

- EST is a useful but imperfect diagnostic test for CAD. The high number of false-positive and false-negative results can be misleading.
- EST is least useful as a diagnostic tool when the physician is fairly certain of the presence or absence of disease. It is most helpful when the pretest probability approaches 50% (table 3).
- Interpretation of the EST result should take into account the degree of ST-segment depression. Greater degrees of ST depression make a diagnosis of CAD more likely.
- For diagnostic purposes, sensitivity is increased by discontinuing antianginal medications for 24 to 48 hours before the test (aspirin should be continued). For prognostic purposes, it may be preferable to perform EST while the patient is taking all medications.

Achieving a high rate-pressure product increases the sensitivity of the EST and, therefore, improves the predictive value of a negative result because high workloads help prevent false-negatives. Conversely, achieving a lower workload increases the specificity of the test and improves the predictive value of a positive result (fewer false-positives). A reasonable goal is to aim for 85% of the target heart rate.

A negative stress test is associated with a good prognosis, even if it is a false-negative result. An improvement in EST by the use of medications may also have positive prognostic value.

Table 3 *Examples of probabilities before and after EST**

Patient	Probability before EST	Result (ST↓), mm	Probability after EST
38-year-old woman	0.04	0.0	0.01
with atypical angina	0.04	1.5	0.16
48-year-old man with	0.52	0.0	0.17
atypical angina	0.52	1.5	0.82
58-year-old man with	0.92	0.0	0.70
typical angina	0.92	1.5	0.98
68-year-old woman	0.94	0.0	0.76
with typical angina	0.94	1.5	0.99

*Combining tables 1 and 2.

For diagnosis: A result of 1.5-mm ST depression in the 38-year-old woman still leaves her with a diagnostic probability of only 16%, and a fully negative result in the 58-year-old man still leaves him with a post-test probability of 70%. In neither case would the EST produce a change in the preclinical assessment, although some physicians would perform an EST in the second patient for prognostic purposes. Note that the 68-year-old woman has about the same pretest probability as the 58-year-old man.

Thallium imaging

- Increases accuracy (table 4) and cost of EST.
- Assesses patients with left bundle branch block or otherwise uninterpretable ECGs.
- Increases sensitivity in patients unable to maximally exert.
- Provides additional prognostic markers (see below).
- Cannot accurately predict the presence of surgically treatable disease.

Table 4 *Diagnostic accuracy of ECG, thallium imaging, and echocardiographic (echo) EST**

Definition of positive test	Sensitivity	Specificity
Positive with EST-ECG alone	0.65	0.85
Positive with thallium imaging alone	0.84	0.87
Positive with EST-ECG or with thallium test	0.94	0.74
Positive with EST-ECG and with thallium test	0.55	0.98
Positive with EST-echo alone†	0.85	0.77

*From Kotler and Diamond.[7]
†From Fleischmann et al.[8]

Additional notes on thallium-EST

- A common criterion for positivity is *either* an abnormal ECG response *or* an abnormal image. Thus, the addition of thallium imaging results in an increase in sensitivity at the expense of specificity (fewer false-negatives but more false-positives).
- Using specific patterns of uptake as predictors of left main or triple-vessel disease, thallium-EST has a sensitivity of 46% and specificity of 73% for detecting surgically treatable disease (likelihood ratio <2.0).
- A completely normal thallium-EST is an excellent predictor of a good prognosis (mortality rate <1% per year); however, imaging appears to add little information to other markers.
- The best use of thallium imaging is in patients with uninterpretable ECGs and in those with submaximal ESTs after an MI. Thallium imaging is also used to identify the functional effect of lesions before catheterization or angioplasty.
- ESTs of all types appear to be less specific—that is, more false-positives—in women.[9]
- The use of right-sided chest leads may increase sensitivity of the EST.[10]

Factors associated with a worse prognosis

- Demographics: Older age, male sex.
- Clinical: Left ventricular (LV) dysfunction, especially an ejection fraction of less than 35%, a history of MI, or peripheral vascular disease.
- EST: Shorter duration of exercise, higher magnitude of ST-segment depression, exertion-limiting angina, or drop in blood pressure.
- Thallium-EST: More ischemic segments, increased lung uptake.

For prognosis: The average man older than 55 years with stable angina has a 4-year survival rate of 94%. If he does poorly on his EST, his survival rate becomes 81%. If he does well, it increases to 98%.

In left bundle branch block, persantine-thallium imaging is the test of choice.

[7] *Kotler TS, Diamond GA. Exercise thallium-201 scintigraphy in the diagnosis and prognosis of coronary artery disease. Clinical Practice Guidelines Approved by the American College of Physicians, 1995 ed. II-43-63.* The best evidence-based review available on this subject.
[8] *Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? a meta-analysis of diagnostic test performance. JAMA 1998;280:913-920.*

Note: An adequately sensitive noninvasive assessment for left main artery disease has not yet been developed. The probability of left main artery disease is increased by the presence of the bad prognostic markers, but the absence of those markers does not rule it out.

[9] *Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999;83:660-666.* EST-ECG had sensitivity of 61% and specificity of 70%; EST-thallium had sensitivity of 78% and specificity of 64%.

[10] *Michaelides AP, Psomadaki ZD, Dilaveris PE, et al. Improved detection of coronary artery disease by exercise electrocardiography with the use of right precordial leads. N Engl J Med 1999;340:340-345.*

Of all the prognostic factors in CAD, LV dysfunction may be clinically the most important. A clinical assessment of LV function is essential to the proper management of CAD.

Alternative stress tests

- Persantine-thallium imaging: Useful in patients unable to exercise; accuracy similar to thallium-EST; contraindicated in patients with bronchospasm and unstable angina; the ECG portion is not useful because true ischemia is not induced (only the thallium image should be assessed).
- Dobutamine-echocardiography: Cheaper than persantine-thallium imaging and about as accurate; able to measure LV function as a prognostic marker; contraindicated in patients with atrial fibrillation and unstable angina.
- Dobutamine-thallium imaging: Useful in patients with bronchospasm or asthma who are unable to exercise.

By generally vasodilating the coronary vasculature, the use of persantine highlights stenotic segments as relatively underperfused areas.

Electron-beam computed tomography (EBCT)

- Detects coronary calcification.
- Coronary calcification is associated with coronary artery obstructive disease by angiography.
- Studies assessing coronary artery calcification as a predictor of future coronary events have produced conflicting results.[11,12]
- The American Heart Association concluded that the evidence is insufficient to support the clinical application of EBCT.[13]

Reasons to perform a catheterization

- Attain a diagnosis in a patient who may have CAD.
- Assess the extent of disease in a patient known to have CAD.
- Prepare for surgery or angioplasty when indicated.

Possible indications for cardiac catheterization

- Increased severity of symptoms (eg, with minimal exertion).
- Instability of symptoms (eg, new onset or rest angina).
- Presence of bad prognostic markers (eg, LV dysfunction).
- Surgically treatable disease (ie, left main or 3 vessel) may be present.
- Age of the patient (younger patients have lower risk of catheterization).
- Medications failing to control symptoms.
- Patient desires to undergo the procedure.

[11] *Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries: 19-month follow-up of 1173 asymptomatic subjects. Circulation 1996;93:1951-1953.* Subjects with a calcium score (coronary artery calcification) greater than 100 had an odds ratio of 20 for coronary events.

[12] *Detrano RC, Wong ND, Doherty TM, et al. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. Circulation 1999;99:2633-2638 [errata published in Circulation 2000;101:697; 1355].* The calcium score (ROC curve, 0.64) did not improve on the Framingham risk profile (ROC curve, 0.69).

[13] *Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications: a statement for health professionals from the American Heart Association. Circulation 1996;94:1175-1192.*

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