



Look Out! CAD in Women



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Although extremely common, we are still learning about the presentation, management and outcomes of coronary artery disease (CAD) in women. Until fairly recently, most cardiovascular (CV) trials enrolled mainly men, limiting our knowledge of this disease process in women.

(Mis)perceptions of CAD in women

Most of us have heard numerous times that physicians under-diagnose, under-investigate and under-treat women with CAD. Some recent data suggests that despite ongoing CME in this area, this remains to be the case.

Women also appear to receive differential treatment strategies, typically less invasive, than their male counterparts. At the 2002 American College of Cardiology Conference, Heidenreich reported the relative angiography rate for women as 0.83 (compared to men). At the time of referral for coronary artery bypass graft, women also tended to have more advanced disease than men.

Physician gender differences do not seem to explain the deferential rates of referral for angiography. Rathor, *et al* recently reviewed the practice patterns of male and female physicians and their referral rates to angiography.¹

Mary's case

Mary, 53, was found to have an LDL-cholesterol (LDL-C) level of 4.1 mmol/L, with a ratio of 5.4 on her annual examination.

History

Mary is not diabetic and does not smoke. With hydrochlorothiazide, her BP is 142/84 mmHg. Based on her Framingham risk score (FRS), she falls into the low risk category (6% for the 10-year risk).

However, she tells you that her father had a heart attack at age 52. She is wondering what impact her family history has on her health. She asks if she should be started on cholesterol medications if her cholesterol remains unchanged after lifestyle interventions?

Questions

1. How does family history affect cardiovascular (CV) risk?
2. What are Mary's lipid targets?
3. Is there any way to stratify her further?

For the answers, turn to page 80.

Adjusting for cardiac risk, female patients had an absolute difference in catheterization rates of 3% to 3.5% compared to men, regardless of the gender of the physician.

Consumer heart information

In a survey of 1,004 women, only one-third believed coronary heart disease (CHD) to be the number one killer of women.² The number one health concern of 75% of women aged 25 to 34 years felt it was cancer. When asked about where women were getting their heart health information in the last year, 43% reported magazines and 21% television as their main source, compared with 20% from their doctors.²

These data indicate that a significant challenge remains in educating the general population, but also suggest there is an opportunity for physicians to address issues of CV health. This may be even more important in young and middle-aged women who still have an opportunity to address their risk factors for CHD but may be currently more concerned about cancer (despite a higher lifelong risk of CAD).

Assessing cardiac risk

Diagnosis of CAD in women can be particularly difficult: presentations of angina can be silent, or often atypical. EKGs and standard stress testing have poor sensitivity and specificity in women, leading to higher numbers of false-positives and negatives in this population.³

Risk stratification should be used to determine the pre-test likelihood of CAD. Overall risk is usually determined using the Framingham risk score (FRS) and this remains the basis of current guidelines for treatment,⁴ but emerging markers are gaining recognition.

In my practice, I routinely use a Palm-based clinical prediction tool both for my own calculations, but also as a tool to counsel patients with. A free FRS calculator for Palm personal

digital assistants (PDAs) (e.g., STAT Cholesterol) can be downloaded at www.stat-coder.com, or one can be found included in MedCalc, a collection of online clinical calculators at: <http://www.med-ia.ch/medcalc/>.

Patients often respond quite positively to actually seeing how each risk factor adds to their calculated event rate and I feel this can carry more weight as they can see an objective risk assessment, rather than the tired messages of "stop smoking and lose weight."

Who should I test and how?

Classifying the type of chest pain can be quite useful in determining pre-test likelihoods. Divide the presenting complaints into "typical or definite angina," "atypical or probable angina," "non-cardiac chest pain" and "asymptomatic." Using a table like that presented in Table 1 can help determine the pre-test probability.³

Low pre-test probability

Patients with a very low pre-test likelihood will still have a low post-test likelihood (even with a positive test). Because of a high false-positive rate in this population, consider not testing these patients.

High pre-test probability

If the pre-test likelihood is quite high, tests cannot rule out the diagnosis (even if negative). Instead of this as a means of diagnosis, consider using noninvasive testing for risk stratification. Some cases will need to be sent for angiography to receive a "gold standard" definitive diagnosis.

Table 1

Determining pre-test probability

| Age | Sex | Typical or definite | Atypical or probable | Non-anginal | No symptoms |
|----------|-----|---------------------|----------------------|--------------|-------------|
| 30 to 39 | M | Intermediate | Intermediate | Low | Very low |
| | F | Intermediate | Very low | Very low | Very low |
| 40 to 49 | M | High | Intermediate | Intermediate | Low |
| | F | Intermediate | Low | Very Low | Very low |
| 50 to 59 | M | High | Intermediate | Intermediate | Low |
| | F | Intermediate | Intermediate | Low | Very low |
| 60 to 69 | M | High | Intermediate | Intermediate | Low |
| | F | High | Intermediate | Intermediate | Low |

High: > 90% Intermediate: 10% to 90% Low: < 10% Very low: < 5%

Adapted from Gibbons RJ, Balady GJ, Beasley JW, et al: Exercise testing guidelines. JACC 1997; 30(1):260-315.

Intermediate pre-test probability

Given these considerations, noninvasive testing should be reserved for patients with intermediate pre-test probabilities. This would usually include patients with:

- atypical chest pains,
- probable angina, or
- other risk factors.

Choosing a testing modality

In general, standard exercise stress testing (EST) has only intermediate sensitivity and specificity (approximately 70% to 75%) and the performance characteristics of EST are generally worse in women, with reported sensitivities and specificities ranging from 45% to 75% (at worst, a shot in the dark).³ Adding an imaging modality (e.g., 2-methoxy isobutyl isonitrile [MIBI] scanning or stress echocardiogram) typically improves the sensitivity and specificity to between 85% and 90%.^{3,5} With this in mind, many advocate that we should go straight

to an imaging modality in most women (since re-testing in the end costs more in terms of global costs and patient time).

Exercise stress testing

EST does have its merits: it can objectively determine exercise capacity/fitness, as well as exercise-inducibility of arrhythmias and BP responses. In terms of a risk-stratifying procedure, EST can predict low-risk patients (1% to 2% two-year mortality if a patient has a negative post-MI EST).

Recall that EST requires careful screening of a patient. Be sure they can actually exercise (i.e., walk briskly for more than five minutes).



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Mary's case cont'd...

Questions

1. How does family history affect CV risk?

A FRS does not take into account family history. The current Canadian guidelines suggest doubling the FRS if there is a positive family history (e.g., MI in men < 55 years, women < 65 years). This would move Mary's risk to around 12% (moderate risk category), right at the upper limit of low risk ($\leq 10\%$ for her 10 year cardiac risk)

2. What are Mary's lipid targets?

Assuming low risk, her targets (as of 2006) are LDL-C < 5.0 mmol/L, ratio < 6.0. However, if we take into account her family history, she falls into the moderate risk category (approximately 12% for her 10-year risk), thus the targets would be LDL-C < 3.5 mmol/L, ratio < 5.0.

3. Is there any way to stratify her further?

This is a case where high sensitivity C-reactive protein may offer additional stratification. If it comes back low (e.g., < 1.0 mg/L), then Mary can likely still be classified in the low risk category. Conversely, if it came back moderate or high, you might want to consider stratifying her solidly in the moderate risk (or even high risk) group.

Since the standard EST relies on ST shifts, the baseline EKG cannot have:

- ST segment depression > 1 mm,
- repolarization abnormalities,
- left bundle branch block, or
- predominantly paced rhythm.

Patients should be able to follow instructions (bring a translator) and have good shoes for the test. The following are relative contraindications to EST:

- severe, uncontrolled hypertension (e.g., > 200/100 mmHg),
- uncontrolled angina,
- recent MI (less than two days prior) and
- significant aortic stenosis.

Imaging modalities

Imaging modalities can circumvent many of the technical limitations of EST, such as baseline EKG changes.

MIBI testing

MIBI scanning is the most common imaging modality. It can be paired with standard EST, but pharmacological stress testing (using dipyridamole or dobutamine) is available for those patients who cannot exercise or get to target heart rate. MIBI testing gives other key pieces of information, including:

- the location of old or reversible ischemia,
- the size of defect and
- the ejection fraction.

A normal MIBI scan predicts a < 1% one-year event rate.

Pharmacologic stress test

If using a pharmacologic stress test, recall that dipyridamole is relatively contraindicated in asthmatics (use dobutamine instead). Dobutamine should not be used in patients with severe aortic stenosis. Also, MIBI scanning can miss severe three-vessel CAD (balanced ischemia) since it relies on relative differences in perfusion between rest and stress images. Breast artifact can interfere with interpretation of some segments, but often these can be compensated for with attenuation-correction algorithms.

hs-CRP: promising or confusing?

Recently, the use of high-sensitivity C-reactive protein (hs-CRP), an inflammatory biomarker, in predicting cardiac risk, has gained attention in the lay press and is emerging as a promising marker in cardiac disease stratification. In the Women's Health Study,⁶ hs-CRP provided very strong additional predictive value over and above cholesterol levels. Even at the lowest quartile of cholesterol ratio, elevated hs-CRP levels were associated with as much cardiac risk as the highest ratios.

In the highest risk patients, those who had the highest cholesterol levels had an odds-ratio of three, but if they also had high hs-CRP levels, the odds-ratio jumped to nine.

While this seems very promising, there remain many issues with hs-CRP: the most important being that we do not yet have strong evidence that reducing CRP reduces CV events. Drugs that lower CRP may reduce CV events, such as:

- acetylsalicylic acid,
- angiotensin-converting enzyme inhibitors,
- angiotensin receptors blockers and
- statins.

Conversely, other drugs affecting CRP may also potentially increase CV events (e.g., non-steroidal anti-inflammatory drugs, prednisone), thus making the connection with lowering CRP and event reduction tenuous.


In addition, the very patients at risk of CAD have a high incidence of other problems which raise CRP through inflammation, such as:

- arthritis,
- lung disease,
- infections, etc.

In my practice, I find it difficult to separate the cardiac risk associated with CRP levels > 5 mg/L from other systemic problems.

The Canadian Lipid Guidelines⁴ suggest that hs-CRP may provide additional risk stratification in intermediate-risk patients (by FRS 10% to 19% for the 10-year risk), potentially raising or lowering the patient's risk category. (hs-CRP levels < 1.0 mg/L are considered low risk, 1.0 mg/L to 3.0 mg/L moderate-risk and > 3.0 mg/L high-risk).

Summary

The diagnosis and management of CAD in women remains a challenging area of practice. Judicious screening and appropriate selection of testing improves diagnostic yield. New markers like hs-CRP are promising, but more solid data is needed before wide recommendations for screening or treatment can be based on them. 

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