Matters of the Heart

Coronary Artery Disease in Women

By Steven K. Wong, MD, FRCPC

In this article:

1. Review of recent data on the presentation and diagnosis of CAD.
2. Discussion of emerging data on alcohol consumption and cardiac risk.
3. What are the controversies surrounding hormone replacement therapy?

Case

Mrs. C.S. is 68 years old, of Fijian descent with no prior coronary artery disease. She wants to discuss her health with you, as a close friend of hers has just had a myocardial infarction (MI). Reviewing her history, you see she has no history of chest pain, diabetes, or smoking. She is hypertensive and has been on hydrochlorothiazide, 12.5 mg daily, for the last eight years, and her blood pressure (BP) is typically 145/85 mmHg. Her total cholesterol last year was high at 6.8 mmol/L. Her family history is positive since her father suffered an MI at age 58, and her brother developed angina in his early '50s. Her current medications include hydrochlorothiazide, 12.5 mg daily, conjugated estrogen, 0.625 mg daily, and progesterone, 2.5 mg daily. She has been on hormone replacement therapy (HRT) for the last 15 years, initially started for flushing symptoms and "to prevent a heart attack." On exam, she is obese, with a body mass index of 31. Her BP with a large cuff is 142/88 mmHg, and heart rate is 84. Her lungs are clear, there are normal heart sounds, and she has mild dependent edema. She is worried about recent news reports about HRT and wonders if she should have a stress test done as well.

What measures would you take? What tests, if any, would you order at this time? Would you do a stress test? How would you advise her about HRT?

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CAD in Women

We are still learning about the presentation, management and outcomes of coronary artery disease (CAD) in women, although it is extremely common. Most cardiovascular trials, until recently, enrolled mostly men, limiting our knowledge of this disease process in women.

What are the misperceptions?

Most of us have heard numerous times that physicians underdiagnose, underinvestigate, and undertreat women with CAD. Some recent data suggest that despite ongoing CME in this area, this status remains true.

In the U.S., the age-adjusted rate of myocardial infarction (MI) is going up in women, but decreasing in men. From 1979 to 1994, the overall age-adjusted MI rate in men decreased by 8% (including a reduction of 31% in men under age 40), compared to a 36% increase in women over the same period.[1] Most worrisome is the striking 50% increase in MI rates in women over 80.

From 1979 to 1994, the overall age-adjusted MI rate in men decreased by 8%, compared to a 36% increase in women over the same period.

Women also appear to receive differential treatment strategies (typically less invasive) than their male counterparts. At the 2002 American College of Cardiology Conference, Dr. Heidenreich reported the relative angiography rate for women at 0.83 (compared to men). At the time of referral for coronary artery bypass grafting, 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. Rathore et al recently reviewed the practice patterns of male and female physicians and their referral rates for angiography.[2] Adjusting for cardiac risk, female patients had an absolute difference in catheterisation rates of 3% to 3.5% compared to men, regardless of the physician's gender.

How much do women know?

In a survey of 1,004 women, only one third thought heart disease was the number 1 killer of women.[3] Three quarters of women aged 25 to 34 felt cancer was their main health concern. When asked where women were getting their heart health information in the last year, 43% reported magazines and 21% listed television as their main sources, compared with 20% who cited their doctors.[3]

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 cardiovascular (CV) health. This may be even more important in young and middle-aged women who still have the chance to address their risk factors for heart disease but may be currently more concerned about cancer (despite a higher lifelong risk of CAD).

How do you assess cardiac risk?

Diagnosis of CAD in women can be particularly difficult: presentations of angina can be silent or often

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Table 1
Stress Testing Characteristics

	Sensitivity	Specificity
Standard ETT	70%	75%
Standard ETT in women	45% - 75%	50% - 75%
MIBI	85%	90%
Dobutamine or stress echo	89%	85%

ETT = Exercise Treadmill Test

atypical, and electrocardiograms (ECGs) and standard stress testing have poorer sensitivity and specificity in women (Table 1). These drawbacks lead to higher numbers of false positives and negatives in this population.[4]

Risk stratification should be used to determine the pre-test likelihood of CAD (Table 2). As our knowledge grows, watch for emerging risk factors. Currently, most authorities do not recommend checking all of these as a general screen, but they may be helpful in patients who either have a striking family history, are from certain ethnic groups (*e.g.,* patients of Fijian or South Asian descent), or who have had a cardiac event despite no other overt "traditional" risk factors.

In my practice, I routinely use a Palm-based clinical prediction tool for my own calculations and as a tool to counsel patients. A free Framingham risk calculator for Palm PDAs (STATCholesterol) can be downloaded at *www.statcoder.com.* Another can be found in MedCalc (*http://medcalc.media.net*), another free clinical calculator that includes over 30 other useful calculations. Patients often respond quite positively to actually seeing how each risk factor adds to their calculated event rate. I feel this can carry more weight than the tired messages of "stop smoking and lose weight" since they can actually see an objective risk assessment.

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" (Table 3).[4]

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

Table 2
Risk Factors for CAD

"Traditional"	Emerging
DM	Ethnicity *i.e.,* South Asian, Fijian
Elevated LDL and/or TG/low HDL	Homocysteine
Smoking	Bone mineral density
Male sex/ post menopausal female	Lipoprotein(a)
LVH	C-reactive protein
Family history (male < 55, female < 65)	Quantitative abdominal Obesity
Stress, personality type	Sedentary lifestyle
Hypertension	Carotid intimal-medial thickness U/S

LDL = Low-density lipoprotein, TG = Triglycerides,
HDL = High-density lipoprotein, U/S = Ultrasound
LVH = Left ventricular hypertrophy

On the other hand, if the pre-test likelihood is quite high, tests cannot rule out the diagnosis (even if negative). Instead, consider using non-invasive testing for risk stratification. Some cases will need to go to angiography for a "gold standard" definitive diagnosis.

Given these considerations, non-invasive testing should be reserved for patients with intermediate pre-test probabilities, usually including patients with atypical chest pains, probable angina or patients with other risk factors.

How to Choose a Testing Modality

In general, standard exercise stress testing (EST) has only intermediate sensitivity and specificity. The performance characteristics of EST are even worse in women, with reported sensitivities and specificities ranging from 45% to 75% (at worst, a shot in the dark).[4] Adding an imaging modality (*i.e.,* MIBI scanning or stress echo) typically improves the sensitivity and specificity by 10%, significantly improving the utility of these non-invasive tests (Table 1). Many advocate 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 testing does have its merits—it can objectively determine exercise capacity/fitness, as

Table 3
Determining Pre-Test Probability

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

High > 90%, Intermediate 10%-90%, Low < 10%, Very low < 5%

Adapted from Gibbons et al: Exercise Testing Guidelines. JACC 1997; 30(1):260-315.

well as exercise-inducibility of arrhythmias and blood pressure responses. In terms of a risk stratifying procedure, EST can predict low-risk patients (1% to 2% two-year mortality, if patient has a negative post-MI EST).

EST requires careful screening of a patient. Be sure they can actually exercise (*i.e.,* walk briskly for more than five minutes). Since the standard EST relies on ST shifts, the baseline ECG cannot have ST-segment depression > 1 mm, repolarisation 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. Severe, uncontrolled hypertension (*i.e.,* > 200/100), uncontrolled angina, recent MI (< 2 days), and aortic stenosis are relative contraindications to EST.

Imaging modalities can circumvent many of the technical limitations of EST. MIBI scanning is the most common imaging modality and has sensitivities and specificities approaching 90%.[4,5] It can be paired with standard exercise testing, but pharmacologic stress testing (using persantine or dobutamine) is available for those patients who cannot exercise or get to target heart rate. In general, baseline ECG abnormalities do not adversely affect MIBI's ability to look for reversible ischemia.

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.

If using a pharmacologic stress test, recall that persantine 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.

Any patient with typical symptoms of angina or other worrisome features (*e.g.,* nausea and diaphoresis with exertion, resolving at rest) should be referred to angiography even with a negative non-invasive test.

HOW ALCOHOL AFFECTS THE FEMALE HEART

Although recommendations of moderate alcohol intake (two to three drinks/day) are commonly quoted, are they applicable to women? The recently published Health Professionals Follow-up Study[6] was widely picked up by the media, reporting that drinking at least three to four days per week, regardless of

Table 4
Hypertension Risk and Alcohol Intake in Women

Drinks/day	Risk of hypertension versus nondrinker
≤ 1/4	- 4%
1/4 - 1/2	- 14%
1/2 - 1	- 8%
1 - 1 1/2	equivalent
1 1/2 - 2	+ 20%
> 2	+ 31%

Adapted from: Nicolas JM, Fernandez-Sola J, Estruch, et al: The effect of controlled drinking in alcoholic cardiomyopathy. Arch Intern Med 2002; 162(5):569-74.

the type of alcohol, reduces the risk of developing CAD. What most media reports failed to point out is that this study was only done in men.

The Framingham Study looked at the development of congestive heart failure and alcohol intake.[7,8] An interesting finding from this study was that men who consumed any amount of alcohol (light, moderate, or heavy) had a lower risk of developing congestive heart failure. This benefit was not apparent in women.

The Nurses' Health Study followed 70,891 women, aged 25 to 42 for eight years for the development of hypertension, and subsequently correlated this data with the amount of alcohol intake.[9] This demonstrated a "J-shaped" curve. Compared to nondrinkers, women who drank an average of 1/4 to 1/2 of an alcoholic drink per day had a 14% reduced risk of developing hypertension. Increasing intake to more than two drinks per day led to a 31% increase in hypertension (Table 4).

Until more data become available, it may be prudent to make more gender-specific alcohol consumption recommendations, with slightly lower levels suggested for women compared to men.

IS HRT PREVENTIVE?

This is very controversial. I will briefly review recent literature and offer my (current) opinion.

The story of HRT and CV disease spans many decades: up until recently, it was believed HRT was a very effective intervention for preventing CV events. This would seem to make sense: long-term observational data like the Nurses' Health Study indicated women who took HRT had fewer heart attacks. The randomised, controlled PEPI (Postmenopausal Estrogen/Progestin Intervention) Trial demonstrated that HRT reduced low-density lipoprotein (LDL), increased high-density lipoprotein (HDL) and increased triglycerides.[10]

Unfortunately, it is difficult to account for confounders in observational trials like the Nurses' Health Study—women who took estrogens may have been generally more health conscious, which resulted in fewer CV events. Also, while supportive, surrogate markers, such as cholesterol levels, are not the same as actual clinical events, making the PEPI results somewhat less rigorous in that regard.

In the ERA trial, after 3.2 years, there was a reduction in LDL by 9% to 16% and an increase in HDL by 12% to 14%, but no effect on progression of CAD.

The controversial HERS (Heart and Estrogen/Progestin Replacement Study) was the largest randomised, controlled secondary prevention trial in HRT.[11] In this trial, 2,763 women with documented CAD were randomised to HRT or placebo, and after five years there was no significant difference in CV events. Interestingly, there was an initial increase in CV events in the first year among women given HRT, with a subsequent lower rate in the next four to five years. The increased rate of deep venous thrombosis (DVT) and pulmonary embolism

in the treatment group (relative hazard 2.89) was also worrisome.

Another smaller study, the ERA (Estrogen Replacement and Atherosclerosis), trial looked at 309 women with documented CAD and performed baseline and followup angiograms on each patient.[12] Women were randomised to receive conjugated estrogen, conjugated estrogen and progesterone or placebo. After 3.2 years, although there was a reduction in LDL by 9% to 16% and an increase in HDL by 12% to 14%, there were no effects on the progression of CAD. There was a non-significant trend towards more DVTs in the treatment arms.

The WEST (Women's Estrogen for Stroke Trial) followed 654 women for 2.8 years who had a prior stroke or transient ischemic attack (TIA).[13] Subjects were randomised to estrogen or placebo and followed for end points of death, recurrent stroke, and neurologic outcomes after recurrent strokes. In the first six months, there was a surprising relative risk of 2.3 for a stroke in the treatment arm, although overall, there was no significant difference between the study groups after three years. In addition, patients receiving estrogen who had a recurrent stroke were more likely to have persistent and significant neurologic deficits and were less likely to return to functional independence.

Based on these studies, it would appear that HRT is ineffective for secondary prevention of CV events. The remaining question of primary prevention was unanswered until very recently.

The Women's Health Initiative (WHI) is the largest-ever randomised, controlled trial of HRT in the primary prevention setting. This massive trial is looking at 161,809 women aged 50 to 79 in an attempt to answer questions in three key areas in women's health, including the effect of HRT versus placebo in preventing CAD. The HRT arm of the WHI was just recently published, creating another upheaval of controversy.[14]

The size of the WHI allows for widespread applicability. It included women ranging across ethnicities and age groups (50 to 79). It should be noted that these women had an intact uterus and were mostly healthy at baseline. The analyses for heart disease were consistent across demographic characteristics. The HRT arm of WHI included 16,608 women, randomised to conjugated estrogen 0.625 mg/day and medroxyprogesterone 2.5 mg/day versus placebo.

This arm of the WHI was stopped early due to concerns about a 26% increase in invasive breast cancer [hazard ratio (HR)=1.26] seen as part of the safety monitoring. In the final analysis, cumulative hazards for various outcomes included a trend towards increased CAD [HR 1.29, 95% adjusted confidence interval (aCI) 0.85-1.97], stroke (HR

1.41, aCI 0.86-2.31), and pulmonary embolism (HR 2.13, aCI 0.99-4.56).

Increases in CAD consisted mostly of excess non-fatal MI, with no differences in CV deaths or revascularisation (coronary artery bypass surgery or angioplasty). The 41% increase in stroke was due to an increase in non-fatal events. There was a statistically significant twofold increase in venous thromboembolic events.[14] Each of the adverse outcomes was seen early after randomisation, with the event rates continuing to be worse in the HRT arms over the course of the study.

With the growing mass of randomised, controlled trial data, it would appear that the question of HRT and CV disease has been answered. Certainly, estrogen plus progesterone does not show a benefit in either secondary or primary prevention of CV events.

THE WORD ON HRT

Despite the results of these trials, all the questions in this area have not been answered. For example, the unopposed estrogen arm of the WHI is still underway (this arm involves 10,739 women who do not have a uterus). The risk/benefit ratio of transdermal formulations is unknown. Some experts are investigating whether it may be a patient selection issue and perhaps more data looking at genetic susceptibility and other factors will emerge. Given the massive size of the WHI and HERS, it would be surprising to see other megatrials re-addressing this area. CME

Take-home message

The diagnosis and management of CAD in women remains a challenging area of practice. As more data emerge from contemporary trials, we should be able to refine recommendations in this critical area of medicine.

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Check out the new Frequently Asked Questions on page 20 for a quick review of this article!

FAQs

Mending a broken heart: CAD

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1. What about HRT?

I tell patients if they are taking hormone replacement therapy (HRT) for cardiovascular reasons alone, then they should stop. Other indications, like osteoporosis (for which bisphonates have better efficacy) and vasomotor symptoms (for which HRT is very effective), may be reasons to continue, but I ask any patient on HRT for more than 4 or 5 years to discuss its risks and benefits, according to the Canadian guidelines for HRT.

Web sites for patients and physicians:
www.sogc.org/hrt/index_e.shtml
www.sogc.org/SOGCnet/sogc_docs/common/guide/pdfs/rev_recommend.pdf

2. How much should I tell a woman to drink?

While women probably benefit from alcohol consumption in terms of cardiovascular risk, they probably should take somewhat less than men do, perhaps an average of 1 drink/day at most. Recent data supporting at least 3 to 4 drinking days/week was based on a study involving men only (a fact not reported in most news sources).

3. How should I test for CAD?

Given the high false-positive and false-negative rates of exercise stress testing in women, I generally do not test women with a very low pre-test likelihood of coronary artery disease (CAD), *i.e.,* under age 40, atypical symptoms, with no risk factors. The "muddier" cases are probably best tested with an imaging modality like MIBI or stress echo, which improves the sensitivity and specificity of these tests significantly. Some have argued that the high frequency of re-testing with standard stress testing makes this a cost-effective strategy.

4. When should I check homocysteine and C-reactive protein levels?

The role of these emerging risk factors is not yet clear, although these appear to be strong predictors of future events. Currently, it is not recommended to do these tests as routine screens, but if you have a patient with a striking family history, an early presentation of CAD (especially without "traditional" risk factors) or a higher risk ethnic background (*i.e.,* Fijian, South Asian descent), it may be useful to test.

While homocysteine can be treated with folate and B-vitamins, C-reactive protein levels can respond to statin therapy. Other agents, such as ace-inhibitors and glitazones, are currently being researched. There are no hard end point data to suggest treating any of these factors at this time.

For an in-depth article on CAD in women, please go to page 71.