“Diagnosing Coronary Artery Disease in Women: An Update on Cardiac Imaging Modalities”

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1. Is there a role for using extended lipid panels to estimate pretest probability of coronary heart disease in women? Would the presence of abnormalities of lipid particle size or elevated lipoprotein (a) 1 levels affect the choice of diagnostic tests as described by the algorithm presented in the paper?

Response from Drs. Sheldon E. Litwin and Tiffany C. Priester:

The usefulness of extended lipid panels, including measurement of Lp(a), in guiding diagnostic testing or therapy for coronary disease remains uncertain. This is true for both women and men. It is our opinion that the direct assessment of atherosclerosis will ultimately prove to be a superior diagnostic strategy when compared to the measurement of any surrogate markers or risk factors for atherosclerosis. In multiple independent studies, coronary calcium scores have been shown to be almost tenfold better at predicting cardiac risk than Framingham risk scores. It seems likely that the same will hold true when other aspects of lipid metabolism are assessed. This conclusion follows from the indisputable fact that lipid abnormalities explain
only a fraction of all cases of myocardial infarction or acute coronary syndrome. In contrast, the presence of coronary atherosclerosis accounts for a much larger proportion of acute coronary events. Thus direct observation of atherosclerosis focuses our attention on the final common pathway leading to the majority of coronary events. In women compared to men, ischemic symptoms are more common in the absence of obstructive atherosclerosis. However, it is uncertain what importance lipid abnormalities have in the generation of the endothelial dysfunction that is thought to be the underlying abnormality in women with cardiac ischemia in the absence of “significant” coronary atherosclerosis. Hence, the findings on extended lipid testing will not give clear guidance on how we should treat patients. At this point in time, conclusive demonstration of coronary atherosclerosis should be a key piece of evidence that directs our subsequent therapeutic endeavors.

2. In developed countries with centralized state-funded healthcare systems, how have the newer testing modalities been utilized?

Response from Drs. Sheldon E. Litwin and Tiffany C. Priester:

Data regarding the current clinical use of cardiac computed tomography (CT) and magnetic resonance imaging (MRI) in both Europe and the United States are sparse. The Society of Cardiovascular Magnetic Resonance and the Society of Cardiovascular Computed Tomography were both contacted prior to writing this manuscript, and neither of these societies had information regarding volume of current clinical use for these modalities. It is clear that there has been early adoption of both CT and MRI in many European centers based on the wealth of publications coming from European countries. Asian countries also have contributed substantially to the growing literature in this field. It seems probable that Europe’s use of CT and MRI may exceed that in the United States where limited insurance coverage continues to be a major barrier. Many of the studies showing cost effectiveness were performed in countries with centralized health care. If research productivity can be used to estimate increasing clinical use,
then Spain, the Netherlands, and Germany are leading the way in incorporation of newer imaging techniques into clinical practice.

There is one recent publication from the European Cardiovascular Magnetic Resonance Registry by Dr. Buder and colleagues that begins to address this issue (J Am Coll Cardiol, 2009; 54:1457-1466). In this pilot phase study from 20 centers in Germany, information was collected on what type of cardiac MRI (CMR) were ordered, the clinical indications, the results, and whether the results changed diagnosis or management for the patient. During less than 2 years of enrollment (April 2007 to January 2009) there were more than 11,000 CMR scans included in the registry. They conclude “CMR is frequently performed in clinical routine, is a safe procedure, has diagnostic image quality in more than 98% of cases, and its results have strong impact on patient management” and “that CMR stress testing is not a research application anymore, but is widely used in clinical routine.” Similar information is not available regarding the clinical volume of cardiac CT. However, some centers in England and Europe report they perform more than 600 cardiac CT studies per year. Thus, while specific numbers are not currently available, it would appear that many European countries with centralized healthcare systems are routinely using cardiac CT and MRI, perhaps more so than in the United States.

3. Because of the frequency of gastrointestinal (GI) components of cardiac symptomatology in women, what specific symptoms would you recommend that obstetrician–gynecologists (ob-gyns) utilize to determine when a cardiology consultation is warranted?

Response from Drs. Sheldon E. Litwin and Tiffany C. Priester:

Gastrointestinal symptoms are very common in both men and women and these symptoms may be the presenting complaints associated with acute coronary syndromes. However, chest discomfort and dyspnea are still the most common symptoms in women with acute coronary syndromes. Historical features such as relationship to eating, relief with antacids, duration of pain and activities causing pain are helpful, but imperfect in distinguishing GI from cardiac
etologies. In general, premenopausal women are at very low risk of obstructive coronary artery disease (CAD) (except in those with significant risk factors such as Type I diabetes).

Young pregnant women are at higher risk for pulmonary embolism, coronary dissection and peripartum cardiomyopathy than coronary artery disease with atherosclerosis. Arrhythmias are also seen with increased frequency in pregnancy and these may cause chest symptoms. Thus, symptoms that warrant additional work up include persistent or exertional chest discomfort, sudden onset or persistent dyspnea or respiratory distress, peripheral edema, orthopnea, and paroxysmal nocturnal dyspnea. Gastrointestinal symptoms that are relieved with treatment for GERD or occur in isolation without any other symptoms do not warrant further cardiovascular work up in young healthy women with no cardiovascular risk factors. However, any worrisome symptoms in women at high risk for cardiovascular disease (such as childhood onset Type I diabetes or smokers who use oral contraceptives), should prompt further work up. In general, history and physical exam, electrocardiogram (ECG), and resting echocardiogram would be the preferred initial testing for pregnant symptomatic women.

4. Does a family history of early coronary artery disease warrant testing of asymptomatic women? Are there genetic markers that may influence the use of cardiac imaging modalities? If so, at what age should imaging be done, and which modality should be utilized?

Response from Drs. Sheldon E. Litwin and Tiffany C. Priester:

The screening of asymptomatic individuals is currently controversial. There are physician groups like the SHAPE Task Force (Am J Cardiol 2006;98[suppl]:2H–15H) that advocate screening the entire middle aged population for early coronary atherosclerosis, much like screening for cervical, breast, and colon cancer. In general, we concur with this approach given the speed, low cost, and predictive power of coronary calcium scoring. However, given that this view is not universally held, our algorithm emphasizes making a clinical assessment of risk to assist in determining what, if any, testing should be done. This includes an option to do coronary
calcium scanning on asymptomatic, middle aged women (55-75) without any significant risk factors. Our rationale is that detecting and aggressively treating early atherosclerosis that would not be detected otherwise should slow or reverse progression of atherosclerosis and result in fewer cardiovascular events. The majority of current guidelines recommend against screening low risk asymptomatic individuals, but state it is appropriate to consider screening asymptomatic individuals that have intermediate to high risk for coronary disease. Standardized risk prediction models, such as Framingham Risk Score, are known to have limited predictive value in healthy young women. Therefore clinicians should also use other markers of risk, such as the presence of family history of premature coronary atherosclerosis, familial hypercholesterolemia, autoimmune disorders known to cause accelerated atherosclerosis, peripheral arterial vascular disease, and elevated hsCRP when estimating any given individual’s risk for cardiovascular events. We believe that a clear family history of premature atherosclerosis warrants an aggressive screening approach.

In those with genetic disorders that put them at higher risk of developing cancer after radiation exposure, it would be prudent to avoid tests that use radiation (ie, coronary CT or calcium scoring). This includes individuals with BRCA 1 and 2 and those at high risk for leukemia. For testing symptomatic individuals with elevated cancer risk, we would recommend stress echocardiography or cardiac MRI, neither of which have any radiation exposure. For asymptomatic individuals, there are no good screening tests without radiation exposure. However, it is our belief that the cancer risk associated with a single coronary calcium scan is quite small and that this risk is markedly outweighed by the benefit of early detection of coronary atherosclerosis.
5. In the absence of cardiac symptoms, how does the presence of other medical conditions such as hypertension, renal disease, or diabetes affect the decision of when to perform testing and which methods to choose?

Response from Drs. Sheldon E. Litwin and Tiffany C. Priester:

Our proposed algorithm includes a decision node based on a clinical assessment of risk. Clearly women with the medical conditions listed in this question are at increased risk for coronary atherosclerosis. Exercise treadmill testing (ETT) has been used for asymptomatic individuals that lead a sedentary lifestyle prior to starting a physical exercise program. Our algorithm and the SHAPE Task Force (Am J Cardiol 2006;98[suppl]:2H–15H) would suggest that asymptomatic women with intermediate clinical risk would likely benefit from screening for subclinical coronary atherosclerosis. ETT is the cheapest form of provocative testing, but unfortunately offers both low sensitivity (particularly for early or single vessel coronary disease) and a relatively high false positive rate in women. Coronary artery calcium (CAC) scoring is extremely specific for coronary atherosclerosis and has a sensitivity above 90% for detecting coronary disease in patients with chest pain or subsequent cardiac events. We offer that ETT and CAC in combination may be a cost effective, low radiation approach that combines physiological stress and limited anatomic assessment, but this combination of tests has not yet been studied prospectively.

Those with diabetes are a very high risk group. In general, diabetes is considered a cardiovascular disease equivalent. Recently the DIAD Study, a large randomized controlled study of asymptomatic diabetics, reported that there was not a significant reduction in cardiovascular events in those who underwent screening with myocardial perfusion imaging (JAMA 2009;301(15):1547-55). In contrast, CAC scoring in a large group of asymptomatic subjects with type II diabetes effectively risk stratified subjects into high and low risk groups (European Heart J 2008;29:2244-2251). Perhaps with cardiac CT and MRI we will more thoroughly understand the complex interaction of diabetes and coronary atherosclerosis.

Patients with renal dysfunction represent a unique challenge. In general, perfusion MRI
cannot be performed in subjects with a GFR less than 30 cc/min because of concerns about nephrogenic systemic fibrosis caused by gadolinium accumulation in tissues. Iodinated contrast administration may be associated with deterioration of kidney function, and this risk goes up as GFR goes down. However, in patients who are dialysis-dependent, use of iodinated contrast is felt to be safe. End stage renal disease (ESRD) is frequently associated with widespread ectopic calcification, including the heart valves and annuli and the coronary arteries. Coronary calcification in renal failure patients may be different than that in other patients with more intimal calcium deposition, rather than medial calcification. The fact that statins are ineffective in reducing the high rate of cardiac events in ESRD patients supports the notion that they have a different form of atherosclerosis. Provocative testing by stress echo or nuclear imaging may be the optimal noninvasive strategy in these patients.

6. Given that epigastric pain and shortness of breath are common in pregnancy, how does the algorithm change for the evaluation of pregnant women with symptoms suggestive of coronary artery disease?

Response from Drs. Sheldon E. Litwin and Tiffany C. Priester:

Pregnancy is a unique and challenging condition. It is rare for women of child bearing age to have significant coronary atherosclerosis. Patients with type I diabetes or strong genetic predispositions (such as familial hypercholesterolemia) may be exceptions to this rule. Pregnancy is associated with structural changes in collagen throughout the body and this predisposes to arterial dissections, including the coronary arteries and aorta. Thus, it would be optimal for any imaging test in a pregnant patient to be capable of detecting these conditions. Pregnancy is also associated with a variety of hemodynamic changes that could lead to chest pain. In particular, patients with undiagnosed congenital heart disease or valve disease (congenital, rheumatic, other) may first come to medical attention during the hemodynamic stress of pregnancy. Preeclampsia, particularly when associated with severe hypertension may
be a cause of chest pain in pregnant patients. Peripartum cardiomyopathy is another consideration for a cause of chest symptoms in the pregnant patient. The majority of these disorders, perhaps with the exception of coronary dissection, can be diagnosed through routine testing with ECG, chest x ray and echocardiography. Because of the ionizing radiation, CT should be avoided in pregnant patients if possible. MRI is feasible and probably safe in pregnant patients, but the effects of the magnetic field on the developing fetus are incompletely known.