AHC Media LLC

Primary Care Reports™

The Practical, Peer-Reviewed Journal for Primary Care and Family Physicians

Volume 14, Number 1 **January 2008**

Primary care physicians (PCPs) are often at the forefront of diagnosing coronary artery disease. Occasionally, it's the legendary patient comment as the doctor has his hand on the door about to leave the office visit, "Doc, what about this chest pain?" Whether it's new onset or established disease, the PCP has an arsenal of diagnostic tests available. The array of tests, however, can be quite daunting in identifying the right test to order, especially in light of sensitivity and specificity, not to mention cost. This issue provides the PCP with a comprehensive survey of the diagnostic tests available, a guide to selection, an estimate of cost, and limitations of each test. Because of the complexity and expense of some of these tests, it is always helpful to coordinate with the patient's cardiologist when appropriate to avoid duplication, unnecessary testing, and to determine when to proceed directly to coronary angiography.

—The Editor

Modalities for Non-Invasive Assessment of Coronary Artery Disease

Authors: **S. Benjamin Bartsch, MD,** Kettering Medical Center, Clinical Instructor, Wright State University, Dayton, OH; **Ryan F. Biegler, MD,** Kettering Medical Center, Clinical Instructor, Wright State University, Dayton, OH; **Lyndetta Schwartz, MD, FACP,** Senior Associate Program Director, Internal Medicine, Kettering Medical Center, Assistant Clinical Professor, Wright State University, Dayton, OH; and **Brian P. Schwartz, MD, FACP, FACC, FSCAI,** Assistant Clinical Professor of Medicine, Wright State University, President Southwest Cardiology, Dayton, OH; Director of Cardiovascular Teaching Service, Kettering Medical Center, Kettering, OH.

Peer Reviewer: **Brian Olshansky, MD**, Professor of Medicine, University of Iowa Hospitals, Iowa City, IA.

Introduction

Atherosclerosis, including coronary artery disease (CAD), remains the major cause of death and premature disability in the United States. Although mortality from CAD has fallen substantially over the past three decades, it remains the leading cause of death in adults. In a study of 7733 participants in the Framingham Heart Study who were initially free of CAD, the lifetime risk of CAD for individuals at age 40 was 49% in men and 32% in women. The lifetime risk was also appreciable in those free of CAD at age 70: 35% in men and 24% in women.[1] The Framingham data further showed that beyond age 65, CAD still predominates, with coronary events comprising 33-65% of atherosclerosis cardiovas-

Statement of Financial Disclosure

To reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief), Dr. Bartsch (author), Dr. Biegler (author), Dr. Lyndetta Schwartz (author), Dr. Brian Schwartz (author), and Dr. Olshansky (peer reviewer) report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

cular events in men and 28-58% in women. The Framingham Heart Study also provided rigorous support for the concept of specific identifiable risk factors correlated with cardiovascular risk. Similar observational studies performed in the United States and abroad provided independent support for the concept of "risk factors" for cardiovascular disease. Based on the National Cholesterol Education Project Adult Treatment Panel III (ATP III) and Framingham data, assessment tools have been established to stratify individuals based on these risk factors.[2] (*See Table 1.*) Patients can be classified as low, intermediate, and high risk with a 10-year event rate of less than 10%, 10-20%, and greater than 20%, respectively. Intermediate and high risk groups need aggressive lifestyle intervention and risk factor modification. Further evaluation is necessary if individuals develop symptoms of CAD in order to determine outcomes and need for additional therapies. However there is also considerable interest in the diagnosis of CAD when patients are still asymptomatic. An increasing number of physicians are screening for asymptomatic CAD, and many participants in wellness programs also are requesting screening for themselves, believing that there are legitimate screening methods for early detection of CAD that are necessary prior to beginning an exercise program. Critical questions remain, however, regarding the appropriateness of screening and the optimal screening test.[3] Until recently, angiography has been the major approach to assess patients for the presence of CAD; however, cardiac catheterization is a less than ideal screening tool since it is expensive, invasive, and it exposes patients to risk of complications such as reactions to contrast media, nephrotoxicity, access site bleeding, and vascular injury.[4,5] For these reasons, approximately 40 million noninvasive tests are performed annually to assess CAD, incurring an annual Medicare reimbursement of $372-749 million.[6]

In determining the best modality for screening or evaluating CAD, the evidence supporting the role of assessment of ischemia versus coronary anatomy must be considered. Data from the Coronary Artery Surgery Study (CASS) registry have shown that even in the setting of anatomic multivessel CAD, a survival benefit from revascularization compared with medical therapy only occurred in the setting of ECG evidence of ischemia, poor exercise tolerance, or both.[7] Catheterization evidence, however, suggests that survival is a function of the anatomic extent of CAD such as multivessel disease, severity of stenosis, and location of stenosis, particularly if involving the left anterior descending artery (LAD). Therefore, the presence of severe CAD is a surrogate of the extent of jeopardized myocardium.[8,9] In selecting an ideal diagnostic approach, anatomy remains an important determinant regarding the suitability of revascularization and may help with determining the role of medical therapy, but a pathophysiological approach continues to play an important role in decisions about medical therapy versus revascularization.

This review discusses currently available modalities used to assess and risk stratify patients with known or suspected coronary artery disease and provides a rationale for proper selection of non-invasive testing. Noninvasive imaging augments ECG evaluation by providing additional information about myocardial perfusion, left ventricular function, and coronary anatomy. This review will discuss various well established techniques including exercise stress testing, stress echocardiography, myocardial perfusion imaging (MPI), multi-slice CT (MSCT), positron emission tomography (PET), cardiac MRI (CMR), and combination MSCT/PET scanners.

Exercise Electrocardiography

Exercise electrocardiography (ETT), one of the least costly tests, has evolved into a modality of considerable importance in the evaluation of patients with known or suspected CAD, and is one of the most commonly used forms of noninvasive cardiac testing. The ETT study is designed to increase myocardial oxygen demand to assess the presence of inducible ischemia based on changes on the 12 lead ECG. An adequate test requires patients to reach 85% of their maximum predicted heart rate (220 - age). Inability to reach this threshold provides sub-optimal or equivocal results.

This test is best suited for patients who are able to exercise without limitations, have no prior evidence of coronary artery disease, and no underlying ECG abnormalities. Ideally, the individual has intermediate risk factors and needs further evaluation and risk stratification.

Exercise stress testing produces ST segment changes in patients with hemodynamically significant CAD and thus suggests the presence of ischemia. Test results can be reported in multiple fashions, but the most common and simplest report would be: normal (no inducible ischemia) or abnormal (ischemic changes). When used alone there is a high false-positive rate. The

Primary Care Reports , ISSN 1040-2497, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
SPECIALTY EDITOR: Shelly Morrow Mark.
MARKETING PRODUCT MANAGER: Shawn DeMario.
GST Registration Number: R128870672.
POSTMASTER: Send address changes to ***Primary Care Reports*** , P.O. Box 740059, Atlanta, GA 30374.

Periodicals postage paid at Atlanta, GA.
Back issues: $26. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.

E-Mail Address: customerservice@ahcmedia.com
Editorial E-Mail Address: shelly.mark@ahcmedia.com
World-Wide Web: http://www.ahcmedia.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $349
Add $17.95 for shipping & handling
(Student/Resident rate: $170).

Multiple Copies
Discounts are available for group subscriptions.
For pricing information, call Tria Kreutzer at (404) 262-5482.
1-9 additional copies: $314 each; 10 or more copies: $279 each.

Canada
Add GST and $30 shipping

Elsewhere
Add $30 shipping

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of 36 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Primary Care Reports has been reviewed and is acceptable for up to 27 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 01/01/08. Term of approval is for one year from this date. Each issue is approved for 2.25 Prescribed credits. Credit may be claimed for 1 year from the date of each issue. The AAFP invites comments on any activity that has been approved for AAFP CME credit. Please forward your comments on the quality of this activity to cmecomment@aafp.org.

This program is intended for primary care and family practice physicians. It is in effect for 24 months from the date of publication.

Questions & Comments

Please call **Shelly Morrow Mark,** Specialty Editor, at (352) 351-2587 or e-mail: shelly.mark@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Table 1. NCEP ATP3/Framingham Assessment Tool for 10-Year Risk of Cardiac Events

CORONARY ARTERY DISEASE (CAD) RISK FACTORS

Major Risk Factors

- -2 Cigarette smoking
- -3 Hypertension (BP ≥ 140/90 mmHg or already on anti-hypertensive medications
- -4 Low HDL-C (< 40 mg/dL) a high level > 60 mg/dL confers negative risk and may remove one risk factor
- -5 Family history of premature CAD male ≤ 55 yr and female ≤ 65 yr
- -6 Age ≥ 45 yr for male and ≥ 55 yr for female

CAD Equivalent Risk Factors

- -7 Prior CAD
- -8 Peripheral vascular disease
- -9 Diabetes mellitus

≤ 1 Risk factor: 0-10% risk of cardiac event in next 10 years
≥ 2 Risk factors: 10-20% risk of cardiac event in next 10 years
CAD equivalent > 20% risk of cardiac event in next 10 years
Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III. *JAMA* 2001;285:2486-2497.

Table 2. Yearly Mortality Rate as Determined for Low-, Moderate-, and High-Risk Patients Based on Duke Criteria for Each Subgroup of Normal, Single, or Multi-Vessel Disease

	NO EVIDENCE FOR DISEASE	SINGLE-VESSEL DISEASE	MULTI-VESSEL DISEASE
Low risk	0.7%	1.8%	3.0%
Moderate risk	2.4%	3.7%	7.0%
High risk	4.7%	5.0%	12.0%

predictive value of an abnormal screening exercise test is determined by the presence or absence of risk factors for CAD. In addition, treadmill scores have been devised to estimate patient prognosis according to test results. The most popular validated treadmill score comes from Duke University based on data from 2758 consecutive patients with chest pain. This score, known as the Duke Treadmill Score (DTS), is based on three clinical variables: the exercise duration, maximal ST segment deviation, and presence of symptoms. The DTS has been shown to stratify prognosis accurately for both inpatient and outpatient symptomatic ischemic heart disease populations. Shaw and colleagues further demonstrated that this non-invasive risk index provided both diagnostic accuracy and prognostic risk estimates. The equation for calculating the DTS is DTS = exercise time-(5 x ST deviation)-(4 x exercise angina), with 0 = none,1 = nonlimiting, and 2 = exercise-limiting. The score typically ranges from –25 to +15. Low risk is a score greater than or equal to +5, moderate risk –10 to +4 and high risk less than or equal to –11.[10,11] This allows individuals to be placed into low, intermediate, or high-risk groups. Those with a low Duke treadmill score had a less than 3% chance of multi-vessel disease or cardiac event in the next 5 years. On the other hand, those in the high-risk group had a 75% chance of multi-vessel disease and a 35% chance of cardiac event in the next 5 years.[10,11]

Other significant prognostic information can be obtained based on how much exercise capacity or workload a patient can perform, as expressed in Metabolic Equivalents (METs). Individuals who can achieve a higher exercise capacity perform better than their counterparts who do not exercise as long.[12,13] Other prognostic information suggesting a higher risk is seen in patients with hypotensive or hypertensive response to exercise.[10,11]

Limitations to ETT occur most notably in women, where there is up to a 50% false-positive rate when used alone. The addition of a myocardial perfusion imaging or wall motion study improves the sensitivity and specificity of this test (discussed later).[14] Other conditions including left ventricular hypertrophy, prior MI, bundle branch block, and other baseline ST-T wave abnormalities may also make the test nondiagnostic. Beta blockers can affect heart rate and may interfere with the ability to reach 85% of maximum predicted heart rate and should be avoided for 24 hours prior to the test unless contraindicated.[15]

Contraindications to exercise testing are active unstable angina, recent myocardial infarction, severe arrhythmias, hypertensive crisis, severe aortic stenosis, and other outflow tract obstruction such as hypertrophic obstructive cardiomyopathy.

Stress Echocardiography

Stress echocardiography provides visualization of the myocardium under physiologic or pharmacologic stress to assess for ischemia demonstrated by regional wall motion abnormalities. As in the case of ETT, a maximum predicted heart rate of 85% must be achieved requiring that the images be obtained during or immediately following exercise. Even a small delay as short as 90 seconds can alter test results. Either method is acceptable since the sensitivity and specificity of each of these methods are similar.[16]

The best candidates for this form of testing have no prior known CAD, are at moderate risk, and must be able to exercise to 85% of his/her maximum predicted heart rate. They should also be non-obese and have a small chest diameter since the distance from the chest wall to the heart can affect image quality. The true utility of this test is to observe for stress-induced ischemic changes in patients who are unable to exercise in a conventional fashion or who have other contraindications to standard ETT, such as left ventricular hypertrophy or other ST-T wave abnormalities that might produce equivocal results of an ETT.

Nishioka and colleagues found a 95% sensitivity for detection of stress-induced regional wall motion abnormalities in patients with or without prior MI, and the specificity for true ischemia was 84%, although in patients with prior MI this was cut in half to 42%.[17]

Another benefit can be noted in patients who are able to use the treadmill for their stress echocardiogram. By using the echo report of normal, single vessel, or multi-vessel disease based on regional wall motion abnormalities and linked with their treadmill score, important mortality predictions can be achieved. Those with low-risk Duke scores and no regional wall motion abnormalities had the best long-term mortality compared to all other groups.[18] (*See Table 2.*)

Image quality is paramount and factors that affect this such as obesity, COPD, or delayed image acquisition can produce equivocal results or uninterpretable images. Since patients with left bundle branch block or severe dysynchrony of the ventricles have abnormal wall motion, the test can be falsely interpreted as ischemic regional wall motion abnormalities. The same contraindications to other forms of stress testing apply here, such as active angina, MI, hypertensive crisis, or syncope, to name a few.[19]

Myocardial Perfusion Imaging (MPI)

Myocardial perfusion imaging (MPI) uses a radionucleotide such as thallium-201 or technetium 99 injected at the time of maximal exercise or after pharmacologically induced coronary vasodilatation with dipyridamole or adenosine. Exercise images are compared to rest images. Coronary artery disease is detected by reversible defects that represent inducible ischemia under myocardial stress. Perfusion defects imply the presence of significant CAD but do not demonstrate the degree or extent of coronary plaque. Perfusion defects yield information regarding the physiology of the CAD and not the anatomy. Technetium 99 has a sensitivity and specificity of 84% for detection of inducible ischemia; thallium has similar sensitivity but a 20% lower specificity.[20] Technetium 99 also delivers lower levels of radiation and hence is widely accepted as the radioisotope of choice.

Patients who need risk stratification as well as identification of flow limiting lesions are ideal candidates for MPI. Virtually any patient is a candidate for this test since either physiologic stress or vasodilatation is used for assessment of inducible ischemic changes. Since exercise yields more information including interpretable ECG changes and is less expensive than pharmacologic agents, it should be used whenever possible. The physiologic stress of exercise or a pharmacologic agent can be used to induce work on the heart, and there does not appear to be any appreciable difference in sensitivity, specificity, or accuracy between the two.[21,22] Dipyridamole, adenosine, and dobutamine have all been used effectively as alternatives to exercise. Dobutamine may have the advantage of achieving target heart rate and thus may have the added benefit of producing ST segment ECG changes in patients with ischemia.[21,23]

When exercise stress testing and nuclear perfusion imaging are combined, it is important to make sure the patient reaches at least 85% of his maximum predicted heart rate. A study by Iskandrian et al showed that patients who did not reach 85% of their maximum predicted heart rate had a much lower rate of detection of flow limiting lesions in patients with proven coronary artery disease.[24] This effect was also shown in a small study of patients who underwent exercise MPI until they had symptom limiting exercise, and all reached 85% of their maximum heart rate. Two days later, the same patients underwent the same testing but stopped at 70% of their maximum heart rate. When the two studies were compared, the area of inducible ischemia was much smaller or even absent when patients stopped at 70% of their maximum predicted heart rate.[25] These two studies demonstrate clearly the need for reaching 85% of maximum predicted heart rate.

Myocardial perfusion studies help with the diagnosis of coronary artery disease; aid in identifying those who are at low, moderate, and high risk for coronary events; and yield information about the degree of myocardium at risk. In a study of 4649 patients followed for 7 years who were at intermediate risk based on the Duke treadmill score and had normal or near-normal MPI studies, there was a 1% risk for cardiac mortality and a 3% risk for myocardial infarction.[26] In patients with any perfusion defect, however, there is a significantly higher rate of cardiac events in the following year at a rate of 8.6% compared to 1.4% of patients with a normal study.[25,27,28]

It has also been shown that post-stress left ventricular dysfunction can have a prognostic value. In patients with an inducible perfusion defect, a left ventricular ejection fraction of > 45% was associated with a yearly mortality of < 1%. Those patients with left ventricular ejection fraction of < 45%, however, had a yearly mortality rate of 6.6%.[13]

A disadvantage of MPI is the exposure to ionizing radiation where doses range from 6-18 millisievert (mSv) depending on the agents used. This can be even higher with Thallium 201. Some women and obese individuals have a large amount of attenuation artifact that can be misinterpreted as false positives leading to additional invasive testing.[29-34] Patients should avoid caffeine and theophylline for 24 hours before the use of adenosine or dipyridamole, although one cup of coffee before the test will not affect the results and should not delay testing.[35] If a patient cannot stop theophylline, the preferred agent is dobutamine.

The major contraindications to adenosine and dipyridamole testing agents include sick sinus syndrome, high degree atria-ventricular block, hypotension, concurrent use of dipyridamole agents, and reactive airway disease.[19]

Multi-Slice Computer Axial Tomography (MSCT)

Imaging of the coronary anatomy by multi-slice computed tomography demonstrates the presence and extent of plaque in the coronary arteries, thus giving an anatomical picture similar to angiography. The entire study takes about 10 minutes from the time the patient is placed on the MSCT scanner table until the imaging is complete.[36] To obtain good quality images, the patient should be in normal sinus rhythm with a heart rate under 70 beats per minute. Most patients are given a beta-blocker to ensure that their heart rate is at a desirable level. Images are obtained as an iodinated contrast bolus passes through the coronary arteries.

Table 3. MSCT Scan to Identify at Least One Stenotic Lesion in Coronary Artery

	NO. OF PATIENTS	SLICES	SENSITIVITY	SPECIFICITY	NEGATIVE PREDICTIVE VALUE	POSITIVE PREDICTIVE VALUE
Mollet	51	16	100	100	100	100
Hoffman	103	16	95	97	94	98
Achenbach	50	16	100	83	100	86
Lescka	53	64	100	100	100	100
Raff	70	64	95	90	93	93
Mollet	52	64	100	92	100	97
Ropers	82	64	96	91	98	83

Adapted from: Ropers D. Multi-slice computed tomography for detection of coronary artery disease. *J Interv Cardiol* 2006;19: 574-582.

Table 4. Detection of Coronary Artery Stenosis on Per Artery or Segment

	NUMBER OF PATIENTS	NUMBER OF SLICES	SENSITIVITY	SPECIFICITY	NEGATIVE PREDICTIVE VALUE	POSITIVE PREDICTIVE VALUE
Kuettner	124	16	85	98	96	87
Mollet	51	16	95	98	99	79
Morgan-Hughes	58	16	83	97	97	80
Hoffmann	103	16	95	98	99	87
Achenbach	50	16	94	96	99	69
Leschka	53	64	94	97	99	87
Raff	70	64	86	95	98	66
Mollet	52	64	99	95	99	76
Ropers	82	64	95	93	99	56
Fine	66	64	95	96	95	97

Adapted from: Ropers D. Multi-slice computed tomography for detection of coronary artery disease. *J Interv Cardiol* 2006;19: 574-582.

Patients most suited for this procedure are those with intermediate risk based on a Duke treadmill score, non-diagnostic test results, contraindication to other modalities, and those who prefer a noninvasive test. This test is best used to rule out coronary artery disease since there is a very high negative predictive value when using MSCT. It can also be used to further evaluate patients who have suspected false-positive stress tests, or those with a low or intermediate pretest probability for coronary artery disease.[37,38] Patients with known disease who will need intervention or those with an existing stent are likely to need additional testing or intervention despite results of the MSCT and therefore are not the best candidates for this procedure.

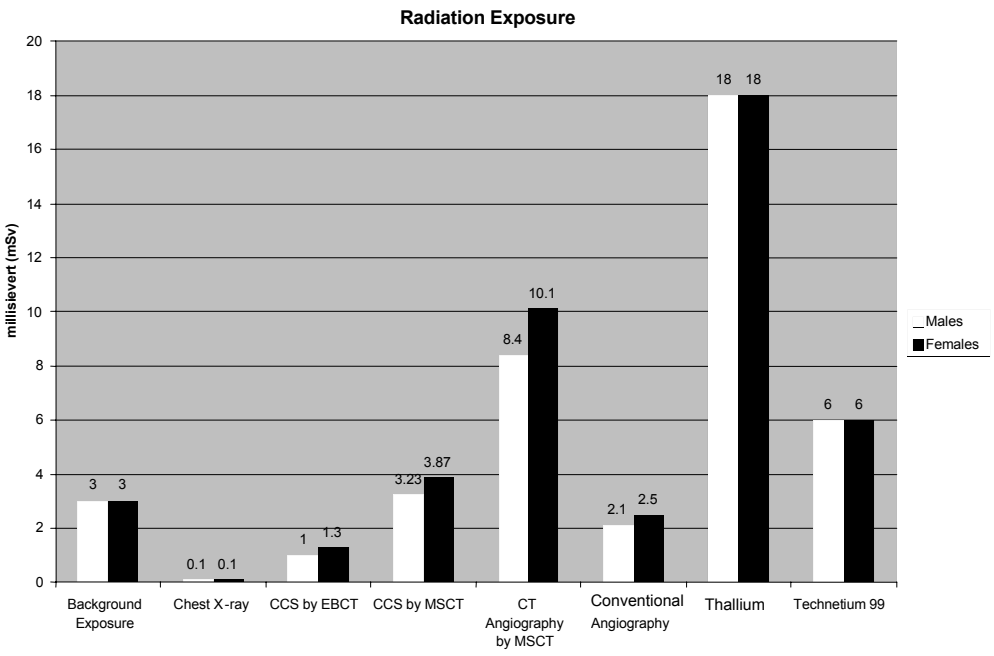
Additional information available using CT includes the Agatston calcium score, which, while controversial, is used for prediction of coronary events and further evaluation of CAD.[39] Patients with a score of 100 or less did not correlate with significant disease and are low risk. Scores over 400 are highly correlated with extensive plaque and would warrant further testing or aggressive risk modification. Scores between 100-400 are not useful to predict disease and are considered equivocal. However there is a 9.6% increase in relative risk for coronary events in patients with a score greater than 100.[40]

Some have argued that the Framingham risk tool provides similar information at a fraction of the cost and without exposure to ionizing radiation and thus do not recommend routine screening or assessment of CAD by coronary calcium score. It has been used effectively, however, in patients with multiple risk factors to predict benefit from the most aggressive medical therapies.

The best use of MSCT is to rule out the presence of disease. Patients who are at risk for multivessel disease or large areas of myocardial ischemia and have anginal symptoms should have their coronary anatomy visualized. This method allows anatomical evaluation without exposure to potential complications of invasive testing. In addition to the presence or absence of significant stenosis, MSCT suggests the extent of the plaque burden that may not be recognized by angiography.

Due to positive remodeling of the artery and compensatory vasodilatation (Glagov phenomenon), significant stenosis of the total diameter of the artery can occur before it becomes flow limiting. This effect allows the lumen to appear relatively unchanged when viewed by conventional angiography despite significant disease. Therefore conventional cardiac angiography is often

Figure 1. Average Exposure to Differing Levels of Radiation Exposure by Modalities[29,31]



referred to as "lumenography."[41,42] The limitation of conventional angiography is eclipsed by MSCT, which allows the reviewing physician to determine the percent of stenosis to the lumen as well as the plaque burden to the entire artery. The plaques are labeled as hard or soft, allowing greater appreciation for unstable plaque burden.[36]

This information can be very important as soft plaque or extensive non-occlusive plaque may lead the clinician to prescribe a more aggressive medical regimen and motivate the patient to make lifestyle changes.

With 16 slice scanners there is a greater then 90% sensitivity and specificity for detection of significant coronary artery disease when segment stenosis is greater than 50%. These results are improved by using a 64-slice MSCT. There are convincing data to support this method of non-invasive evaluation for detection of CAD by arterial segment, and compared to conventional coronary angiography, sensitivity and specificity are very well maintained. There is also a high positive and negative predictive value. However when the artery is assessed as a whole, the sensitivity and specificity decrease, and there is a decrease in positive and negative predictive values.[43] (*See Tables 3 and 4.*)

Radiation exposure is a prime safety concern. Many of these tests result in exposure to ionizing radiation. Diagnostic tests should be chosen that have the highest yield of information while minimizing the exposure. As a reference, the average individual is exposed to approximately 3 millisieverts (mSv) from naturally occurring sources per year. Since different body tissues require different energies to penetrate them, the radiation doses vary according to body size and mass. For example, women on average will receive higher doses of radiation due to breast tissue, and patients who are obese will require larger doses of radiation to penetrate through the fatty tissue.[29] (*See Figure 1.*) The amount of radiation needed to penetrate body tissue should be considered when ordering a test. If the test is not going to change clinical management of the patient, then the risk of exposure to radiation is not justified. The utility of MSCT as a screening tool in asymptomatic patients has not been established and therefore MSCT should not be used routinely for screening of asymptomatic patients who are otherwise low risk for CAD.

Patients likely to have significant stenosis and an interventional procedure should not have MSCT but should receive conventional coronary angiography to avoid excessive ionizing radiation and IV contrast.[38,44]

The contraindications for MSCT relate to the IV contrast. There are limitations to current MSCT, the most important of which is patients with known extensive CAD as heavy calcification may obscure the resolution and lead to artifacts or a non-diagnostic test. Similarly, patients with a prior stent are likely to exhibit artifact in the segment around the stent that may lead to non-diagnostic test results. Currently it is not possible to evaluate for in-stent stenosis. Also those with a very heavy plaque burden have lower specificity for vessel stenosis due to artifact.[36,44]

Cardiac Magnetic Resonance Imaging (CMR)

Cardiac magnetic resonance imaging (CMR) utilizes a standard MRI machine that is equipped with specific additions of hardware and software. Advances in cardiac gating and new software designed to allow free breathing have improved image quality of CMR by minimizing motion artifact, allowing assessment of the entire cardiac arterial tree with minimal motion artifact.[37]

Patients who are the best candidates for this procedure are similar to those who benefit from MSCT where there are equivocal tests or contraindications to other procedures. Obvious advantages of CMR over conventional angiography include no ionizing radiation and no need for radiopaque contrast with the associated side effects of nephrotoxicity and anaphylactoid reaction. Gadolinium has been used as an alternative contrast medium that is superior to iodinated contrast in CMR, however several recent case reports show the potential for skin fibrosis.[45] The major advantage CMR has over MSCT is the ability to detect subendocardial perfusion defects and micro-vessel ischemia.

The strength of this modality is clearly its negative predictive value. When CMR is utilized for the evaluation of 3 vessel disease or strictly left main disease, there is a sensitivity of 100%, specificity of 85%, PPV of 54%, and NPV of 100%. Just as with MSCT, there is decreasing sensitivity and specificity when vessels are viewed as a whole instead of in segments.[46] When CMR

Table 5. Relative Strengths and Weaknesses of Non-invasive Tests for Coronary Artery Disease

	INVASIVE	IONIZING RADIATION	CONTRAST	SENSITIVITY	SPECIFICITY	COST	REMARKS
Cardiac catheterization	YES	2.1-2.5 mSv	YES	100%	100%	$$$$	Currently gold standard for evaluating anatomy but invasive and expensive.
Exercise stress test	NO	NO	NO	64%	85%	$	Widely available and inexpensive but not very sensitive in women.
Adenosine perfusion	NO	6-18 mSv	NO	80-84%	67-84%	$$	Assess myocardial perfusion and flow limiting lesions but high radiation exposure.
Exercise echo	NO	NO	NO	76%	94%	$$	Technically difficult study
Dobutamine echo	NO	NO	NO	72%	95%	$$	Technically easier than exercise echo.
EBCT	NO	1-1.3 mSv	NO	83-100%	83-100%	$	Controversial role for CCS
MSCT	NO	3.2-3.8 mSv	YES	88-100%	90-100%	$$$	Anatomic structure and very fast, also evaluate other structures in the chest.
CMR	NO	NO	Gadolinium	87-100%	82-90%	$$$$	Anatomy as well as prior subendocardial infarcts. Contraindicated in patients with metal implants and pacemakers.
PET	NO	YES	NO	90%	89%	$$$$	Anatomy as well as viability of myocardium but very expensive and not widely available at present.

was used for detection of CAD, Plein et al showed that myocardial perfusion reserve index (the change in signal intensity-time profiles of stress and rest myocardial perfusion by MRI) showed a sensitivity of 88% and a specificity 82%.[47] Other studies have shown similar results with sensitivity 87-90% and specificity of 88-90% for detection of CAD.[48,49]

The technique of late enhancement has been used to determine myocardial viability and micro-vessel ischemia, which is a distinct advantage over MSCT or any other modality discussed so far. After injection of gadolinium-based contrast agent normal myocardium will enhance and then be washed out, leaving areas of ischemia appearing darker. As the contrast is washed out and achieves steady state, the areas of under-perfused tissues or damaged tissue with edema will retain contrast longer allowing these areas to appear "brighter" than the normal areas. This phenomenon is called late enhancement.[50] The late enhancement technique yields results comparable to PET scan techniques, which are considered the gold standard for functional myocardial studies.

This technique is very sensitive to show subendocardial damage and can differentiate between hibernating versus scarred myocardium. A recent study by Holstrum et al.[43] showed that despite normal left ventricular function, some patients with late enhancements were seen to have small subendocardial infarctions. Techniques utilizing parallel acquisition methods, such as sensitivity encoding, have decreased data collection times for cardiac imaging which enables non-uniform signal intensity correction by receiver coils thus allowing for a semi-quantitative and quantitative analysis of perfusion defects in the subendocardium.[51]

As with other studies, CMR also is imperfect. Patients with implanted metallic devices or pacemakers and those who are claustrophobic are not candidates for this procedure. This study is significantly longer than MSCT (30-60 minutes), and many

patients find being in the supine position for this amount of time uncomfortable. The most important drawback is that there are not enough data at present in the form of large multi-center clinical outcomes. This lack of data leads to less standardized protocol and interpretation.[52]

Comparison of MSCT and CMR

When comparing MSCT and CMR it can be difficult to differentiate between the utility of the two modalities. The true power of these tests is their ability to rule out coronary artery disease. CMR, however, has the added benefit of being able to assess for subendocardial infarctions and areas of perfusion defects.

A recent meta-analysis by Schuijf and colleagues has shown a higher sensitivity and specificity for MSCT than for CMR for noninvasive coronary angiography. This may be partially due to the larger body of evidence that is already done for MSCT compared to CMR.[45,53] Since both CMR and MSCT utilize cardiac gating methods, a patient who is not in sinus rhythm will likely have a non-diagnostic result.

Patient safety is also a concern that is paramount. Since there is no ionizing radiation with MRI, it has an advantage over both MSCT and conventional angiography. There are other factors that will influence the use of these tests such as patient preference, cost, and reimbursement. One study comparing MSCT, MRI, and conventional angiography by Dewey et al. showed that patients preferred the shorter time and less invasive nature of MSCT.[38] With the rapid advances in hardware, software, and other technology in all areas of cardiac imaging, it will be very exciting and interesting to see what new developments are over the horizon.

Positron Emission Tomography (PET)

Patients with known CAD or with exercise limiting angina are may benefit from PET testing as it has the distinct advantage of assessing perfusion defects and viability of myocardium. This test is useful when equivocal results are reported with other modalities. There are few contraindications to PET scanning. Virtually all patients are candidates for this test, and it is being used as an alternative to standard perfusion testing as it gives better resolution and fewer problems with artifact. However PET does not give direct visualization of arteries but shows perfusion defects similar to MPI. PET does not have the limitation of soft-tissue attenuation and can be used to measure fractional flow reserve.

Recent work shows that PET has 90% sensitivity for detection of lesions greater than 50% with a specificity of 89%.[8] The distinct advantage of PET is the ability to measure perfusion and viability of myocardium.[54] Therefore, in one test the physician could determine what vessels are diseased with flow limiting lesions and whether the myocardium below the lesion is viable. This differentiates hibernating versus scarred myocardium when perfusion defects are compared at rest and at stress, and then appropriate revascularization therapy can be offered to patients who will truly benefit from it.

Combination PET/CT scanners are becoming more readily available and have the distinct advantage of offering the best of MSCT and PET scan in one. This allows high quality images of the coronary tree by MSCT and the perfusion and viability data of PET. This is essentially a "one stop shop" for assessing coronary artery disease.

Unfortunately this technology is very expensive and only available at limited facilities. As with all newer technologies, over time it will become more widely available for use and will likely replace the use of adenosine perfusion testing where available.

Conclusion

The most appropriate test for a patient is one that yields high quality information, has low risk, and will add further diagnostic or prognostic data. All patients should initially be risk stratified using a Noninvasive Prognostic Index such as Framingham or other risk assessment tool.[55,56]

Initial evaluation of symptomatic patients should be done by an exercise treadmill test as this is easy to perform, inexpensive, easily assesses for CAD, and can be used to predict mortality. If additional information is needed or for patients with high likelihood of false-positive results (women), a myocardial perfusion study (SPECT or PET) can be added to increase sensitivity and specificity or in the event of equivocal test results. The option of stress echocardiogram is a viable alternative and can be a substitute for perfusion imaging.[57]

In patients with high risk, equivocal stress test results or when anatomy of the coronaries is necessary, MSCT is an ideal test. This can definitively rule out coronary disease or make the presence and size of lesions known.

In patients with known disease, or with symptoms that need evaluation for subendocardial perfusion defects or the viability of myocardium, CMR or PET is an excellent choice. Currently these modalities are not recommended for routine screening of low risk patients.[19,35] Combination scanners using PET/CT will likely become the diagnostic test of choice as newer protocols limit the radiation exposure and this combination provides both physiologic and anatomic results.

Regardless of what testing modalities are chosen. All patients need aggressive risk reduction and optimization of medical therapies.

References

1. Lloyd-Jones DM, Larson MG, Beiser A. Lifetime risk of developing coronary heart disease. *Lancet* 1999;353:89.
2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III. *JAMA* 2001;285: 2486-2497.
3. West RR, Ellis GR, Brooks N. Complications of diagnostic cardiac catheterization: Results from a confidential enquiry into cardiac catheter complications. *Heart* 2005 Nov 24.
4. Duffin DC, Muhlestein JB, Allisson SB, et al. Femoral arterial puncture management after percutaneous coronary proce-

dures: A comparison of clinical outcomes and patient satisfaction between manual compression and two different vascular closure devices. *J Invasive Cardiol* 2001;13:354-362.
5. Meyerson SL, Feldman T, Desai TR, et al. Angiographic access site complications in the era of arterial closure devices. *Vasc Endovascular Surg* 2002;36:137-144.
6. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus panel report. *J Cardiovasc Magn Reson* 2004;6:727-765.
7. Weiner DA, Ryan TJ, McCabe CH, et al. The role of exercise testing in identifying patients with improved survival after coronary artery bypass surgery. *J Am Coll Cardiol* 1986;8: 741-748.
8. Di Carli, Hachamovitch R. New technology for noninvasive evaluation of coronary artery disease. *Circulation* 2007;115: 1464-1480.
9. Califf RM, Phillips HR, Hindman MC, et al. Prognostic value of a coronary artery jeopardy score. *J Am Coll Cardiol* 1985;5:1055-1063.
10. Mark DB, Hlatky MA, Harrell FE Jr, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med* 1987;106:793-800.
11. Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation* 1998;98:1622-1630.
12. Roger VL, Jacobson SJ, Pellikka PA, et al. Prognostic value of treadmill exercise testing. *Circulation* 1998;98:2836-2841.
13. Sharir T, Germano G, Kavanagh PB, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. *Circulation* 1999;100:1035.
14. Henneman MM, Schuijf JD, van der Wall EE, et al. Noninvasive anatomical and functional imaging for the detection of coronary artery disease. *Br Med Bull* 2006;79-80:187-202.
15. Shehata AR, Gillam LD, Mascitelli VA, et al. Impact of acute propranolol administration on dobutamine induced myocardial ischemia as evaluated by myocardial perfusion imaging and echocardiography. *Am J Cardiol* 1997;80:268.
16. Flachskampf FA, Hoffmann R, vom Dahl J, et al. Functional assessment of PTCA results by stress echocardiography: When and how to test. *Eur Heart J* 1995; Oct 16 Suppl J: 31-34.
17. Nishioka T, Mitani H, Uehata A, et al. Utility and limitation of treadmill exercise echocardiography for detecting significant coronary stenosis in infarct-related arteries in patients with healed myocardial infarction. *Am J Cardiol* 2002; 89:159.
18. Marwick TH, Case C, Vasey C, et al. Prediction of mortality by exercise echocardiography: A strategy for combination with the Duke treadmill score. *Circulation* 2001;103:2566.
19. Ha JW, Juracan EM, Jahoney DW, et al. Hypertensive response to exercise: a potential cause for new wall motion abnormality in the absence of coronary artery disease. *J Am Coll Cardiol* 2002;39:323.
20. Taillefer R, Gordon D, Udelson J, et al. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG gated-SPECT) in detection coronary artery disease in women. *J Am Coll Cardiol* 1997;29:69.
21. Dagianti A, Penco M, Agati L, et al. Stress echocardiography: Comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. *J Am Coll Cardiol* 1995;26:18-25.
22. Mahmarian JJ, Verani MS. Exercise thallium-201 perfusion scintigraphy in the assessment of coronary artery disease. *Am J Cardiol* 1991;67:2D.
23. Kim C, Kwok YS, Heagerty P, et al. Pharmacologic stress testing for coronary disease diagnosis: A meta-analysis. *Am Heart J* 2001;142:934.
24. Iskandrian AS, Heo J, Kong B, et al. Effect of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease. *J Am Coll Cardiol* 1989; 14:1477.
25. Heller GV, Ahmed I, Tilikemeier PL, et al. Influence of exercise intensity on the presence, distribution, size of thallium-201 defects. *Am Heart J* 1992;123:909.
26. Gibbons RJ, Hodge DO, Berman DS, et al. Long-term outcome of patients with intermediate-risk exercise electrocardiograms that do not have myocardial perfusion defects on radionuclide imaging. *Circulation* 1999;100:2140.
27. Heller GV, Herman SD, Travin MI, et al. Independent prognostic value of intravenous dipyridamole with technetium-99m sestamibi tomographic imaging in predicting cardiac events and cardiac related hospital admissions. *J Am Coll Cardiol* 1995;26:1202.
28. Geleijnse ML, Elhendy A, van Domburg RT, et al. Cardiac imaging for risk stratification with dobutamine-atropine stress testing in patients with chest pain. *Circulation* 1997, 96, 137-147.
29. Hunold P, Vogt FM, Schmermund A, et al. Radiation exposure during cardiac CT: Effective doses at multi-detector row CT and electron-beam CT. *Radiology* 2003;226:145-152.
30. Morin RL, Gerber TC, McCollough CH. Radiation dose in computed tomography of the heart. *Circulation* 2003;107: 917-922.
31. Crean A, Dutka D, Coulden R. Cardiac imaging using nuclear medicine and positron emission tomography. *Radiol Clin North Am* 2004;42:619-634.
32. Rao DV, Shepstone BJ, Wilkins HB, et al. Kinetics and dosimetry of thallium-201 in human testes. *J Nucl Med* 1995; 36:607-609.
33. Setting up a myocardial perfusion scintigraphy service: Clinical and business aspects. Prepared jointly by the British Cardiac Society, the British Nuclear Cardiology Society, and the British Nuclear Medicine Society. *Heart* 2005;91(suppl IV):iv6-iv14.
34. Conti CR. One-stop cardiovascular diagnostic imaging (and radiation dose). *Clin Cardiol* 2005;28:450-453.
35. Zoghbi GJ, Htay T, Aqel R, et al. Effect of caffeine on ischemia detection by adenosine single photon emission

computed tomography perfusion imaging. *J Am Coll Cardiol* 2006;47:2296.
36. Ropers D. Multi-slice computed tomography for detection of coronary artery disease. *J Interv Cardiol* 2006;19: 574-582.
37. Escolar E, Weigold G, Fuisz A, et al. New image techniques for diagnosing coronary artery disease. *CMAJ* 2006;174: 487-495.
38. Dewey M, Teige F, Schnapauff D, et al. Noninvasive detection of coronary artery stenosis with multislice computed tomography or magnetic resonance imaging. *Ann Int Med* 2006;145:407-415, and appendix w123-w126.
39. Berman DS, Rory H, Shaw LJ, et al. Roles of nuclear cardiology, cardiac computed tomography, and cardiac magnetic resonance: Assessment of patients with suspected coronary artery disease. *J Nucl Med* 2006;47:74-82.
40. Berman DS, Hachamovitch R, Shaw LJ, et al. Roles of nuclear cardiology, cardiac computed tomography, and cardiac magnetic resonance: Noninvasive risk stratification and a conceptual framework for the selection of noninvasive imaging tests in patients with known or suspected coronary artery disease. *J Nucl Med* 2006;47:1107-1118.
41. Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;316:1371-1375.
42. Topol E, Nissen S. Our preoccupation with coronary luminology: The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1996.
43. Miia H, Paula V, Helena H, et al. Noninvasive analysis of coronary artery disease with combination MDCT and functional MRI. *Acad Radiol* 2006;13:177-185.
44. Musto C, Simon P, Nicol E, et al. 64-multislice computed tomography in consecutive patients with suspected or proven coronary artery disease: Initial single center experience. *Int J Cardiol* 2007;114.
45. Khurana A, Runge VM, Narayanan M, et al. Nephrogenic systemic fibrosis: A review of 6 cases temporally related to gadodiamide injection. *Invest Radiol* 2007;42:139-145.
46. Kim WY, Danias PG, Stuber M, et al. Coronary magnetic resonance angiography for detection of coronary stenosis. *N Engl J Med* 2001;345:1863-1869.
47. Plein S, Radjenovic A, Ridgway JP, et al. Coronary artery disease: Myocardial perfusion MR imaging with sensitivity encoding verses conventional angiography. *Radiology* 2005; 235:423-430.
48. Al-saadi N, Nagel E, Gross M. Non-invasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. *Circulation* 2000;101: 1379-1383.
49. Schwitter J, Nanz D, Kneifel S. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: A comparison with positron emission tomography and coronary angiography. *Circulation* 2001;103:2230-2235.
50. Barkhausen J, Hunold P, Waltering K. MRI in coronary artery disease. *Eur Radiol* 2004;14:2155-2162.
51. Pruessmann KP, Weiger M, Scheidegger MB, et al. SENSE: Sensitivity encoding for fast MRI. *Magn Reson Med* 1999;42:952-962.
52. Cuocolo A, Acampa W, Imbriaco M. The many ways to myocardial perfusion imaging. *QJ Nucl Med Mol Imaging* 2005;49:4-18.
53. Schuijf JD, Bax JJ, Shaw LJ, et al. Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multi-slice computed tomography for non-invasive coronary angiography. *Am Heart Journal* 2006;151:404-411.
54. Yoshinaga K, Katoh C, Noriyasu K, et al. Reduction of coronary flow reserve in areas with and without ischemia on stress perfusion imaging in patients with coronary artery disease: A study using oxygen 15–labeled water PET. *J Nucl Cardiol* ;10:275-283.
55. Califf RM, Armstrong PW, Carver JR, et al. 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol* 1996;27:1007-1019.
56. Mark DB, Shaw L, Harrell FE Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991;325:849-853.
57. Elhendy A, van Dombury RT, Bax JJ, et al. Accuracy of dobutamine technetium 99m sestamibi SPECT imaging for the diagnosis of single-vessel coronary artery disease comparison with echocardiography. *Am Heart J* 2000;139(2 Pt 1):224-230.

Physician CME Questions

1. Which of the following is *not* considered a cardiac risk factor for CAD?
   A. Tobacco dependence
   B. Alcohol consumption
   C. Diabetes and hypertension

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

D. Low HDL C < 40 mg/dL
E. Family history of premature CAD

2. Conventional cardiac catheterization is best used for which of the following?
   A. Determining degree of stenosis in a vessel or segment
   B. Predicting future myocardial infarction
   C. Proving there are no significant stenotic lesions
   D. Assessing amount of myocardial necrosis

3. Cardiac angiography by MSCT is best used to determine which of the following?
   A. Determining degree of stenosis in a vessel or segment
   B. Predicting future myocardial infarction
   C. Proving there are no significant stenotic lesions
   D. Assessing amount of myocardial necrosis

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

CME Answer Key

1. B
2. A
3. C

In Future Issues:

Physician Quality Reporting Initiative

Did you miss AHC Media's, **When the Worst Happens: Techniques for Managing Medical Error Disclosures** live audio conference?

ORDER THE CD NOW TO EDUCATE YOUR ENTIRE STAFF!

Ethically, financially, and morally, there is sound justification for being upfront with patients and their families when medical errors occur.

John Banja, PhD, will discuss methods for disclosing medical errors and strategies to identify the psychological factors that affect error disclosure conversations.

Rebuild trust and diminish the likelihood of large legal claims following a medical error.

Call 800-688-2421
Or order online at www.ahcmediainteractive.com

Faculty: John Banja, PhD, is a medical error ethicist at Emory University. He is nationally regarded in the area of medical errors and disclosure, and has published over 150 articles and given over 700 invited presentations on medical ethics topics.

CD Price: $299 including accompanying presentation slides. When ordering by phone please mention product code 11T07148.

Did you miss AHC Media's live audio conference — Medical Futility Policies: Are They Ethical or Discriminatory?

Order the CD now to educate your entire staff!

When do you withhold or discontinue life-prolonging treatment in cases deemed medically futile?

With this presentation, recommendations are made that might prevent or mitigate psychological and organizational distress that often accompanies decisions about aggressive treatment in difficult cases. The ethical dimensions of futility will be elaborately explored, as will those ideological and cultural factors that ultimately limit the degree to which ethical reflection, especially as it occurs in the United States, can "solve" the problem of futility. Many practical examples of empathic language are presented helping your staff learn what to say and what not to say to patients and family members.

Order today! Call 800-688-2421 Or order online - www.ahcmediainteractive.com

Presenter: John Banja, PhD, a medical ethicist at Emory University, has taught and lectured on topics in medical ethics through out the United States. He has authored or coauthored over 150 publications and has delivered over 700 invited presentations at regional, national and international conferences.

Medical Futility Policies Audio Conference CD Price: $299 including accompanying presentation slides. When ordering by phone please mention priority code 11T07145.

AHC Media LLC

Supplement to *Primary Care Reports*
January 2008

Primary Care Reports™
The Practical, Peer-Reviewed Journal for Primary Care and Family Physicians

2007 Subject Index

Covering Volume 13

A

B

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5413. E-mail: iris.young@ahcmedia.com.

drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■