

Final Key Questions and Background

Cardiac Nuclear Imaging

Background

Coronary artery disease (CAD) is among the most common chronic conditions in the U.S., affecting over 16 million adults. CAD is estimated to cause over 1 million acute coronary events and over 400,000 deaths in this country each year.

Due to its prevalence, and because several options (e.g., surgery, medication) exist to reduce CAD-related morbidity and mortality, accurate diagnosis of CAD is critical. Currently the definitive standard for diagnosis is invasive coronary angiography (ICA). There are risks associated with ICA, however, such as infection, artery trauma, and heart arrhythmias. For this reason non-invasive methods have been explored to document the presence and severity of CAD; a growing number of such tests have been developed to identify CAD lesions significant enough to affect the flow of blood to the heart (i.e., myocardial perfusion). These functional tests are typically performed under exercise- or pharmacologically-induced stress to determine whether blood flow deteriorates when the stressor is introduced.

The most common tests of cardiac function include the stress-electrocardiogram (EKG or ECG), or treadmill test, which measures cardiac activity via electrical signals, and the stress-echocardiogram (ECHO), which uses ultrasound to measure abnormalities in heart wall motion as an indicator of myocardial ischemia using 2-dimensional imagery. Stress-EKG has fallen out of favor for use in patients at higher risk of CAD, however, as it has relatively low sensitivity and specificity for CAD, while stress-ECHO has been found to be less sensitive for detecting single-vessel vs. multi-vessel disease and may produce suboptimal imagery in obese patients, those with chronic respiratory conditions, and patients with chest deformities or pre-existing myocardial damage.

To address such concerns, nuclear imaging tests been developed to provide direct measurement of myocardial perfusion in a broad spectrum of patients. The most longstanding of these is single photon emission computed tomography (SPECT), which uses a radioactive tracer and gamma camera to obtain 3-dimensional images. Positron emission tomography (PET) scanners are also used with a radiotracer, and are felt by some to provide better image resolution in heavier patients and those with dense breast tissue. Complicating the picture further, “hybrid” modalities, originally

developed for oncology, have also been applied to cardiac imaging to provide joint perfusion/anatomic data (i.e., PET/CT, SPECT/CT) and/or to compare perfusion measurement methods (i.e., PET/MRI).

Policy Context

The above tests differ in terms of their diagnostic and prognostic capabilities, cost, availability, impact on downstream testing, potential to harm, and other relative advantages and disadvantages. There is therefore significant benefit in conducting a comprehensive evaluation of the evidence on the comparative clinical effectiveness and comparative value of cardiac nuclear imaging tests. In addition, the Washington State Health Care Authority (HCA) has noted an increase in the use and costs of these tests for cardiac indications, and has therefore commissioned a health technology assessment to compare the performance of nuclear imaging tests for a variety of cardiac uses.

Project Scope

This project scope is described in more detail below, focusing on the most relevant populations, interventions, comparators, and outcomes for evaluation of cardiac nuclear imaging tests.

Population: Populations of interest for this evaluation will include (1) patients with symptoms suggestive of myocardial ischemia who are at low, intermediate, or high risk of obstructive CAD; (2) those without symptoms but who are considered at higher risk of CAD due to one or more risk factors (e.g., diabetes); and (3) patients with known CAD who are candidates for prognostic testing to guide treatment selection and/or conduct post-procedure or post-event monitoring. All relevant settings for testing will be considered (e.g., emergency department vs. outpatient, ordered by primary care physicians vs. specialists).

Other potential uses of nuclear imaging, such as pre-operative assessment of cardiovascular risk in patients undergoing noncardiac surgery and assessment of congenital defects or valvular disorders will not be considered, as these uses represent a small percentage of nuclear imaging test volume at HCA agencies and/or are not considered to be major areas of controversy regarding appropriate use. In addition, while studies exist of the prognostic capabilities of nuclear imaging tests in apparently healthy individuals, such studies will be used for background purposes only, as major clinical societies do not recommend the use of nuclear imaging tests for general population screening.

Intervention: The imaging tests of primary interest for this evaluation will be those that involve visualization of myocardial perfusion: single photon emission computed tomography (SPECT) and

positron emission tomography (PET). Hybrid tests also will be considered that have at least one component focused on myocardial perfusion, including PET/MRI, PET/CT, and SPECT/CT. All of these tests may be performed in conjunction with exercise- or pharmacologically-induced stress. Attention will be focused on tests and imaging protocols that represent the current “state of the art”; for example, use of attenuation correction and EKG gating for reduction of image or motion artifacts.

Comparators: The comparator tests of interest will include stress-EKG and stress-ECHO as the other non-invasive tests commonly employed to provide information on inducible myocardial ischemia. Non-invasive tests that visualize coronary anatomy *only* (e.g., electron beam computed tomography, coronary computed tomography angiography) will not be considered in this evaluation.

Outcomes: Outcomes of interest for each type of test will include the impact of test use on subsequent testing and clinical management, the correlation of test results with future major cardiovascular events as well as cardiovascular-related and all-cause mortality, the incidence of indeterminate or equivocal test findings, the frequency of incidental findings (i.e., outside the heart), and test as well as total diagnostic strategy utilization and costs. Note that the studies of interest in this evaluation will focus on the diagnostic and/or prognostic ability of nuclear imaging tests in comparison to an alternative method (e.g., test A vs. test B, testing pathways with vs. without test A). Studies that provide only data correlating results of a single testing strategy with downstream outcomes will not be considered, as such studies provide no information on the incremental predictive capabilities of the test of interest.

Information on test accuracy (e.g., sensitivity/specificity, positive/negative predictive values) will not be a primary focus of this evaluation. This is because the reference standard for CAD diagnosis has historically been *anatomic* evidence of significant artery stenosis on invasive coronary angiography (ICA). The use of ICA as the gold standard for functional testing has been called into question, as the presence of stenosis has been found to correlate poorly with that of “functionally significant” lesions, especially at moderate levels of stenosis (e.g., 50-70%).¹ In a recent randomized controlled trial, treatment guided by ICA that included measurement of the “fractional flow reserve” (FFR), a measure of myocardial ischemia, resulted in significantly fewer major

¹ Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *Am J Coll Cardiol* 2010;55:2816-21.

cardiovascular events at one year than treatment guided by ICA alone (i.e., without FFR measurement).²

Where available, however, any diagnostic accuracy data involving the use of an independent functional reference standard (e.g., cardiac MRI, FFR) will be summarized. Historical accuracy data using anatomic reference standards will also be summarized for background purposes and used as a means to estimate progression through testing pathways in the decision-analytic model.

Key Questions

- 1) How do SPECT, PET, and relevant hybrid imaging modalities compare to other non-invasive functional tests (e.g., stress-ECHO, stress-EKG) in their ability to guide the management and improve the outcomes of:
 - A. Patients at low-to-intermediate risk of CAD who have symptoms suggestive of myocardial ischemia? (diagnosis)
 - B. Patients at high risk of CAD who have symptoms suggestive of myocardial ischemia? (diagnosis)
 - C. Asymptomatic patients at high risk of CAD due to existing comorbidities? (diagnosis)
 - D. Patients with known CAD who have changes in symptoms? (diagnosis)
 - E. Patients with known CAD who have no changes in symptoms? (prognosis)
- 2) What are the risks associated with these tests, including contrast and radiotracer reactions, patient anxiety, and radiation exposure?
- 3) What is the impact on the comparative benefits and risks of these tests of differences in:
 - A. Patient age, sex, race or ethnicity, and comorbidities (e.g., obesity)
 - B. Clinical setting (e.g., emergency department vs. outpatient)
 - C. Selection of test by primary care vs. specialty physician
 - D. Scan vendor, type of assessment (i.e., quantitative vs. qualitative), type of radioisotope, and type of stressor (e.g., adenosine, exercise)

² Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.

- 4) What are the costs and the incremental cost-effectiveness of these testing options when used within patient populations that vary by underlying prevalence of CAD and other patient characteristics?

Public Comment & Response

See *Key Question Public Comment and Response* document published separately.

[For additional information on key questions and public comments](#)