Noninvasive diagnostic cardiac imaging for CAD with CCTA, stress nuclear imaging and stress echocardiography: final key questions

Background

Clinical

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD) or ischemic heart disease (IHD), is a leading cause of death for both men and women in the United States and is the most common form of cardiovascular disease. The public health and economic burdens of CAD are substantial. Atherosclerosis is the most common underlying cause of CAD and is the result of plaque buildup on artery walls. The buildup of plaque may partially or completely block blood flow (and hence oxygen and nutrient flow) in the coronary arteries via two primary mechanisms: 1) progressive narrowing of the vessel lumen and (2) thrombotic occlusion of the artery wherein the hard surface of the plaque tears away exposing inner fatty prothrombotic and platelet activating components at the site creating enlargement of the obstruction. The resulting decrease in blood flow may be chronic or acute. It may restrict blood supply to the myocardium and impair ability to supply oxygenated blood either at rest or during exertion. Atherosclerotic plaque occurs commonly and is asymptomatic for years and most people with plaque will never develop clinical coronary artery disease. Chest pain (angina) is the most common symptom of obstructive CAD and is the first presenting symptom in most patients. Plaque distribution, presence of collateral circulation and degree of vessel narrowing are factors which may influence symptom development and clinical impact of CAD, however, symptoms do not always correlate with lesion severity.

Diagnosis of CAD

Accurate and early assessment of patients with symptomatic CAD is important for risk stratification and initiation of appropriate treatments to reduce morbidity and mortality. Noninvasive techniques used to diagnose CAD fall into two general categories, those that evaluate the anatomical aspects of vessel occlusion and those that evaluate the functional impact of occlusion on cardiac function. Each has strengths and limitations. Noninvasive anatomic tests provide information on location and extent of blockage and include coronary CT angiography (CCTA) and cardiac magnetic resonance imaging (CMRI). Functional tests allow assessment of whether symptoms are correlated with narrowing leading to ischemic areas and include exercise electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET), pharmacologic stress magnetic resonance imaging (MRI), computed tomography (CT), and Doppler ultrasound–derived flow reserve measurements. The choice of testing is dependent on a variety of patient and other factors, particularly in patients with stable CAD. Clinical decision-making regarding choice of test(s) needs to include consideration of the potential for additional/downstream testing, availability of other tests, cumulative radiation exposure and how results will inform appropriate management strategies and lead to improved outcomes while avoiding additional layers of testing.

Exercise electrocardiogram treadmill testing (ETT) and the imaging tests CTTA, stress nuclear imaging and stress echocardiography have become established as diagnostic tests for CAD. The focus of this HTA will be on the imaging tests and will not include ETT. As established testing modalities, the focus will be on evaluating their impact on clinical decision making for directing management that leads to improved patient outcomes.

Topic background and technologies of interest

Health Technology Assessments (HTAs) on CCTA and stress nuclear imaging were performed in 2008 and 2013 respectively, by the Washington Health Technology Assessment Program (HTAP). The HTAP is interested in re-evaluation of imaging for diagnosis of CAD based on based on newer evidence on the use of CCTA and stress cardiac nuclear imaging as well as evaluation of stress echocardiography (not previously reviewed by HTAP).

Focus for this HTA

The focus of this HTA will be on evaluation of the capabilities of CCTA, stress nuclear imaging and stress echocardiography as *diagnostic tests* for CAD to direct patient management, improve patient outcomes and cost-effectiveness. These are the most common modalities for CAD diagnosis in symptomatic patients, aside from ECG and ECG treadmill testing. Information on diagnostic accuracy (validity) for these modalities will be summarized for context in the background given the clinical maturity of these imaging modalities. Coronary artery calcium scoring (CACS) as a diagnostic test will be excluded as it is not a standalone diagnostic test; further, it was not chosen for re-review by the Health Care Authority. Use of CT (including CACS), CCTA, nuclear imaging and stress echocardiography for *screening* for CAD in *asymptomatic* individuals will be excluded.

Contextual questions, key questions and scope

Three cardiac imaging modalities for diagnosis of CAD in symptomatic patients will be evaluated: CCTA, stress nuclear imaging, and stress echocardiography. For each modality, diagnostic accuracy (validity), impact on clinical outcomes, harms and cost-effectiveness will be evaluated. Diagnostic accuracy will be addressed by a series of **Contextual Questions** (see below) to provide important context on test accuracy/validity consistent with methods used by the US Preventive Services Task Force.[1]   The formal **Research Key Questions** (see below) will address the impact of CCTA, stress nuclear imaging, and stress echocardiography, when used for diagnosis, on clinical outcomes, decision making and harms as well as cost-effectiveness. The Research Questions will be the focus of the systematic review/HTA and will be addressed using accepted methods for systematic review.[2-4]

Contextual questions (diagnostic accuracy/validity)

Prior to addressing research questions related to the impact of cardiac imaging on clinical outcomes *the diagnostic accuracy (validity)* of these modalities compared with invasive coronary angiography (the usual reference standard) will be briefly summarized for context.

In patients with known or suspected CAD who are *symptomatic:*

- What is the diagnostic accuracy of CCTA for anatomical confirmation of obstructive CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
- What is the diagnostic accuracy of CCTA with determination of fractional flow reserve (FFR) for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
- What is the diagnostic accuracy of stress CCTA for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
- What is the diagnostic accuracy of stress nuclear imaging? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
- What is the diagnostic accuracy of stress echocardiography? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

Final

Research key questions

The following Key Questions focus on *the impact on clinical outcomes* for the use of CTTA, stress nuclear imaging, and stress echocardiography to diagnose CAD **in patients with known or suspected CAD who are** *symptomatic.*

1. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) in leading to improved clinical outcomes (e.g., MI, mortality)?

2. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with respect to clinical decision-making including additional testing and treatments?

3. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with regard to harms or adverse events which may result directly from testing or additional, downstream testing?

4. Does effectiveness (in terms of clinical outcomes) or safety differ in special populations (e.g., women, those with comorbidities, the elderly) from noninvasive cardiac anatomic or functional imaging (CCTA, stress nuclear imaging, stress echocardiography)?

5. What is the cost-effectiveness of CCTA, stress nuclear imaging and stress echocardiography for clinical outcomes?

PICOTS/Scope:

Study Component	Inclusion	Exclusion
Patients	Adult patients (≥18 years of age) with symptoms of suspected (previously undiagnosed) CAD who present with: • Stable (nonemergent) typical or atypical symptoms suspicious for CAD (e.g., chest pain, chest tightness, chest burning, shoulder pain, palpitations, jaw pain, or non-chest pain. symptoms, such as dyspnea or worsening effort tolerance) • Suspected acute coronary syndrome (ACS) in emergency departments. • Symptomatic adults with known/established CAD including those who have had prior MI and/or revascularization. For all questions, data on special populations and circumstances including the following will be evaluated: • Women • Patients with atypical symptoms	• Asymptomatic patients • Patients presenting for evaluation of cardiac pathologies other than CAD (e.g., congenital abnormalities, valvular disease, evaluation of cardiomyopathy etiology, CHF) • Patients with STEMI

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Study Component	Inclusion	Exclusion
	• Elderly patients • Patients with comorbidities (including renal insufficiency, DM), LBBB)	
Intervention	• Cardiac CT Angiography (including use of FFR and pharmacologic stress with 64 slice or higher CT) • Stress nuclear imaging (including PET, SPECT) • Stress echocardiography	• CACS • Screening • Novel uses of any of these tests • MRI/MRA • Comparisons of technical performance parameters or variations of a testing modality (e.g., comparison different CT techniques) • Outdated equipment or methods
Comparator(s)	• No testing • Usual care* • Comparison of the above interventions with each other • Invasive coronary angiography	
Outcomes	• Clinical health outcomes (PRIMARY) • MI, cardiac death, all-cause mortality • Clinical decision making • Referral for treatment • Referral for additional testing • Harms, risks and consequences of testing (initial testing and subsequent testing) • Harms of testing (e.g., adverse events related to contrast agents, medication for pharmacologic stress testing), vascular complications (e.g. stroke) • Risks and consequences of testing (radiation exposure, psychological consequences of diagnosis, ramifications of additional testing, other†) • Economic: Incremental cost-effectiveness or similar outcome	• Intermediate outcomes
Timing	• Emergent or non-emergent • Any point in the diagnostic workup	• None
Setting(s)	• Emergency department • Non-emergent settings	• None

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Study Component	Inclusion	Exclusion
Studies	- Focus will be on studies with the least potential for bias. Focus will start with RCT evidence; in the absence of RCTs, high quality comparative observational studies that control for potential confounding will be considered. Observational studies will primarily be considered for test-related harms. - Studies published in English in peer-reviewed journals, technology assessments or publicly available FDA reports. - Full (comparative) economic studies - Studies published after 2000 (except for stress echocardiography)	- Non-comparative studies - Modeling studies for prediction - Prognostic studies - Costing studies - Studies evaluating the incremental benefit of adding a test to another. - Studies published prior to 2000 (except for stress echocardiography)

CACS = coronary artery calcium scoring; CAD = coronary artery disease; CHF = congestive heart failure; CT = computed tomography; DM = diabetes mellitus; FFR = fractional flow reserve; LBBB = left bundle branch block; RCT = randomized controlled trials; MI = myocardial infarction; PET = positron emission tomography; SPECT = single photon emission computed tomography; STEMI = ST-segment elevation myocardial infarction.

*Usual care typically includes no treatment/nothing if low pretest probability, "watchful waiting", or medical treatment if high pretest probability.

†Other may include impact on patients such as days lost from work, procedures cancelled (waiting for tests), vacations cancelled, etc.

References

1. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. 2015; https://www.uspreventiveservicestaskforce.org/uspstf/procedure-manual. Accessed August 25, 2020

2. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.

3. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Vol 4: John Wiley & Sons; 2011

4. Viswanathan M, Patnode CD, Berkman ND, et al. Assessing the risk of bias in systematic reviews of health care interventions. Methods guide for effectiveness and comparative effectiveness reviews [Internet]: Agency for Healthcare Research and Quality (US); 2017

Final