Editor's key points

- Despite the prevalence of chest pain among patients seeking care from their family physicians, the investigation of stable chest pain in patients at low or intermediate risk is a complicated and changing landscape owing to evolving technologies. This might be particularly true for female patients, for whom conventional functional testing might have lower accuracy.
- This article summarizes 6 available investigations for the workup of stable chest pain and highlights some of the strengths and limitations of each. A comparative analysis of these options supports coronary computed tomography angiography (CCTA) as a first-line test.
- Coronary computed tomography angiography has the highest negative predictive value for ruling out coronary artery disease in patients at low or intermediate risk and should be considered as the first-line investigation strategy on account of its potential to reduce overinvestigation and time to diagnosis. The widespread use of CCTA supports preventive medicine, as its usefulness in detecting nonobstructive cardiovascular disease is important for prognostication and early initiation of optimal medical therapy. However, access to timely CCTA might be limited depending on the location of practice.

Chest pain investigation in patients at low or intermediate risk

What is the best first-line test to rule out coronary artery disease?

Connor T.A. Brenna Fahmeen J. Afgani MB BS Kate Hanneman MD MPH FRCPC Deborah Levitan MD CCFP Jacob A. Udell MD MPH FRCPC R. Sacha Bhatia MD MBA FRCPC Paula J. Harvey BM BS PhD FRACP Elsie T. Nguyen MD FRCPC

Abstract

Objective To compare different methods for investigation of stable, low-risk chest pain and identify the best first-line test for patients at low or intermediate risk of coronary artery disease (CAD).

Sources of information The MEDLINE database was searched for articles on chest pain investigation from 1978 to 2019 using the following key terms: *chest pain, exercise electrocardiography, nuclear perfusion imaging, stress echocardiography, cardiovascular magnetic resonance imaging, coronary computed tomography angiography,* and *catheter angiography.* Results were limited to English-language, peer-reviewed journal publications.

Main message Chest pain is a common chief concern among patients presenting to primary care physicians. Several investigative options exist, and each method has inherent strengths and limitations resulting in variable performance depending on the pretest likelihood of CAD. Controversy exists regarding which is the best first-line test among low- or intermediate-risk patients. Coronary computed tomography angiography is emerging as the best first-line test for chest pain investigation in patients who are at low or intermediate risk of CAD. Invasive catheter angiography remains the reference standard, although it is usually reserved for high-risk patients or for confirmation of positive noninvasive test results.

Conclusion Several investigative options exist for the evaluation of stable, low-risk chest pain. A review of the literature reveals an emerging role for CCTA as a first-line test, particularly in low- or intermediate-risk populations without known CAD.

Lack of clear guidelines on the best first-line test for coronary artery disease (CAD) leads to overinvestigation, particularly in patients at low or intermediate risk. Is coronary computed tomography angiography (CCTA), with its high negative predictive value, the best option to rule out CAD, thereby reducing overinvestigation, time to diagnosis, health care costs, and overall radiation exposure? The objective of this article is to review the literature on chest pain investigation methods and to provide a summary of current evidence-based approaches and recommendations in patients at low or intermediate risk.

Case

A 65-year-old woman presented to her family physician with chest pain that had been present for months. The pain was intermittent and retrosternal,

but did not occur on physical exertion and was not relieved by rest. She had a history of prediabetes and chronic hypertension controlled with a β-blocker, but had no other cardiovascular risk factors and no known history of CAD. She was referred for stress echocardiography (SE), but when this failed to offer a definitive diagnosis because she was unable to exercise enough to reach the target heart rate, she was referred for a nuclear perfusion scan. Nuclear perfusion scan findings revealed a possible anterior ischemia but reported that breast attenuation might have caused a false-positive result. She subsequently underwent catheter angiography that showed normal coronary arteries.

Sources of information

The MEDLINE database was searched for articles from 1978 to 2019 relating to the various methods of investigating chest pain using combinations of the key terms *chest pain, exercise electrocardiography, nuclear perfusion imaging, stress echocardiography, cardiovascular magnetic resonance imaging, coronary computed tomography angiography,* and *catheter angiography*. Results were limited to English-language and peer-reviewed journal publications. The search identified 589 articles, which were reviewed to yield the 69 articles included in this clinical review. The quality of evidence cited in this paper ranges from level I to level II (**Box 1**).

Main message

Chest pain is a common chief concern among patients presenting to primary care physicians in the ambulatory setting, but no standardized approach exists to guide investigation and diagnosis in patients who are at low or intermediate risk of CAD.[1] Typical chest pain associated with CAD is also known as *angina* and is often described as retrosternal chest pain that might radiate to the jaw or arm, is triggered by physical exertion or emotional stress, and is relieved by rest or nitroglycerin.[2] Stable chest pain is pain that does not meet criteria for acute coronary syndromes, which includes ST-segment elevation and non–ST-segment elevation myocardial infarction as well as unstable angina. All 3 of these entities result in varying degrees of coronary artery obstruction secondary to rupture of an atherosclerotic plaque in 1 or more coronary arteries leading to ischemia and, in the case of myocardial infarction, a range of myocardial injury and tissue death.

Box 1. Levels of evidence

Level I: Multiple large randomized controlled trials and systematic reviews

Level II: 1 or 2 small randomized controlled trials

Level III: Cohort and case-control studies

Level IV: Consensus

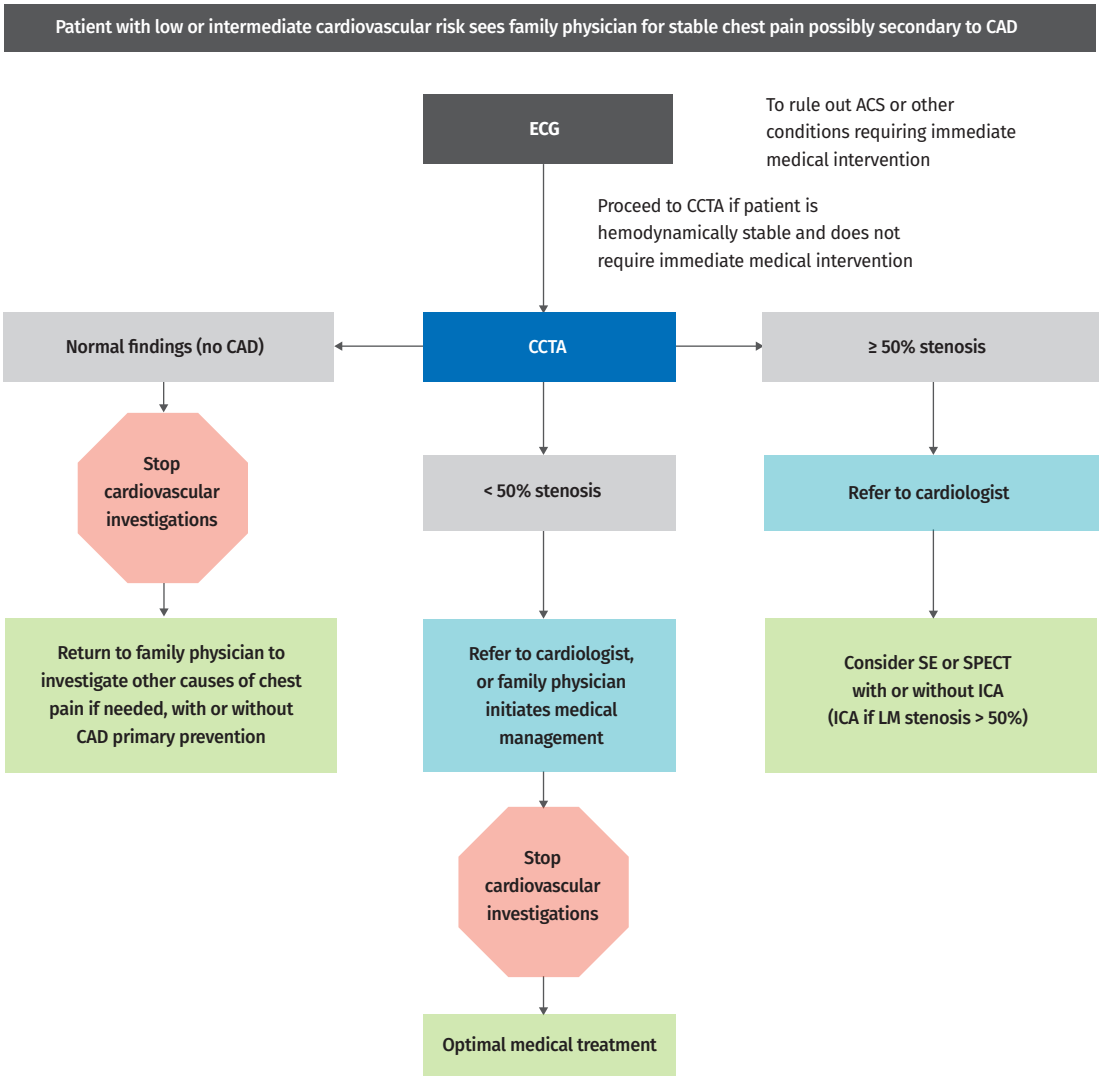
Stable chest pain referred to in this review is low-risk, often atypical chest pain that does not meet the criteria for typical angina or acute coronary syndromes. It does not increase in severity or frequency, and is not felt at rest when previously it was felt on exertion (unlike unstable angina, which tends not to respond to rest). Stable chest pain presents without concerning electrocardiography (ECG) features or hemodynamic instability. A variety of noninvasive testing methods are used in the investigation of stable chest pain, including exercise electrocardiography (GXT), nuclear perfusion single-photon emission computed tomography, SE, cardiovascular magnetic resonance imaging (CMR), and CCTA. The results from these noninvasive testing methods are often compared with invasive catheter angiography, which is the reference standard for assessment of CAD.

Without evidence-based guidelines to direct the investigation of stable chest pain, particularly in patients at low or intermediate risk, primary care providers are often left responsible for understanding the strengths and limitations of each of these tests and might inadvertently overinvestigate patients who are unlikely to have important CAD. Primary care physicians might also choose to refer all of their patients presenting with stable chest pain to a cardiologist to rule out important CAD as an underlying cause. However, this approach might not result in the best patient care, as it not only increases the time to diagnosis but also increases health care costs related to referral. The decision to proceed with any investigation in a patient with stable, low-risk chest pain is at the discretion of the primary care physician using risk stratification systems and clinical judgment, but is often influenced by patient factors such as a strong family history of CAD. A suggested diagnostic pathway in the primary care outpatient setting for patients presenting with chest pain who are at low or intermediate risk of CAD is shown in **Figure 1**.

Noninvasive functional diagnostic methods. Noninvasive testing methods can be divided into *functional testing* and *anatomic testing*. Functional testing involves a stress component (where exercise is preferable to pharmacologic stress owing to its greater sensitivity in the detection of ischemia) and an imaging component. The purpose of functional testing is to determine how the heart works under exercise or pharmacologic stress conditions to evaluate ischemia as a potential cause of chest pain and to provide prognostic information regarding cardiovascular fitness level.

Exercise electrocardiography: Exercise electrocardiography involves the measurement of cardiac rate, rhythm, and blood pressure while the heart is subjected to physiologic stress by means of a treadmill. This test is readily available in most communities, is inexpensive, and does not involve radiation.[3] Exercise electrocardiography is limited by variance in exercise capacity, especially

Figure 1. Suggested diagnostic pathway for patients with chest pain at low or intermediate risk of CAD



ACS—acute coronary syndromes, CAD—coronary artery disease, CCTA—coronary computed tomography angiography, ECG—electrocardiography, ICA—invasive catheter angiography, LM—left main coronary artery, SE—stress echocardiography, SPECT—single-photon emission computed tomography.

in old or sick patients, as well as by lower sensitivity and specificity compared with other functional imaging methods.[4-8] The lower sensitivity of GXT might be explained by the fact that regional wall motion abnormalities often precede chest pain or electrical changes.[9] While many factors in a patient's clinical history, disease severity, and treadmill performance will affect the sensitivity and specificity of GXT, a meta-analysis performed by the American Heart Association (level I evidence) declared the sensitivity and specificity to fall within the ranges of 45% to 50% and 85% to 90%, respectively, for obstructive CAD.[6] Abnormalities in the baseline ECG, such as left bundle branch block, frequently render the results of GXT uninterpretable, requiring further investigations.[10] Additionally, the diagnostic sensitivity and accuracy of GXT might be lower in women, who are often unable to achieve target heart rates, and who often experience less predictive symptoms or nonspecific ECG changes.[11-13]

Stress echocardiography: Similar to GXT, SE relies on cardiac stress to reveal functional status through ultrasound imaging. This stress can be induced either through exercise (preferable if the patient is able to exercise) or through pharmacologic agents such as dobutamine (increases heart rate and myocardial contractility) or vasodilators such as dipyridamole that act to increase concentrations of endogenous and exogenous adenosine.[14] Stress echocardiography has been reported as a

superior test to GXT for discriminating between patients with low and intermediate risk of CAD.[15,16] Advances in technologies surrounding image application, digital display, use of contrast agents, and tissue Doppler have enabled accurate measurements of wall motion through SE.[17] Studies comparing dobutamine and dipyridamole SE have reported similar sensitivities and specificities, while other reports suggest greater sensitivity and lower specificity in exercise SE than in pharmacologic SE.[17,18] The European Society of Cardiology guidelines on stable CAD (level I evidence) suggest that the sensitivity and specificity of SE fall in the ranges of 79% to 85% and 80% to 88%, respectively.[8] Frailty or low exercise capacity limit SE similarly to GXT, and stress-inducing pharmacologic agents are not always readily available to primary care physicians. Furthermore, SE has reduced sensitivity for the detection of single-vessel disease owing to compensatory segments or poor visualization of the lateral wall (eg, owing to shadowing from the adjacent lung).[19,20]

Nuclear perfusion scans: Nuclear perfusion scans use radioactive isotopes to provide a window into the physiologic function of internal organs. Single-photon emission computed tomography is a type of nuclear perfusion scan that relies on radionucleotide imaging to describe myocardial perfusion abnormalities and allows cross-sectional imaging that improves localization of abnormalities. Similar to SE, exercise is the preferred stress but when the patient is unable to exercise, pharmacologic stress agents such as dobutamine or vasodilator stress agents such as dipyridamole or adenosine are used. Currently, the most common radionucleotide agent for this test is sestamibi labeled with technetium 99m and injected 45 to 60 minutes before imaging.[21] An alternative tracer agent is tetrofosmin labeled with technetium 99m, which has been demonstrated to provide higher patient throughput and reduce the need for repeated scans despite variability in image quality depending on the route of injection.[22,23] The results of several meta-analyses indicated that the sensitivity and specificity of single-photon emission computed tomography for detecting CAD are in the ranges of 76% to 91% and 70% to 90%, respectively (level I evidence).[8,24-26] The diagnostic accuracy of nuclear perfusion scanning might be reduced in women owing to false-positive results from breast attenuation artifacts.[12,27]

Cardiovascular magnetic resonance imaging: Cardiovascular magnetic resonance imaging is a radiation-free but relatively expensive option for the investigation of chest pain. Much like pharmacologic SE, stress perfusion CMR leverages the vasodilating properties of administered adenosine or dipyridamole to demonstrate myocardial ischemia, areas of infarct, and microvascular obstruction that results from infarcted myocardium.[28] Cardiovascular magnetic resonance imaging has the advantage of imaging multiple components of the ischemic cascade including areas of reduced myocardial perfusion, regional wall motion abnormalities, and global systolic function. It distinguishes areas of subendocardial versus transmural infarct to help guide decision making regarding revascularization with percutaneous coronary intervention or coronary artery bypass grafting. Technological advances since the inception of CMR have drastically improved image quality and decreased imaging time, making it a feasible diagnostic investigation for chest pain.[29] Meta-analyses have reported CMR to have sensitivities in the range of 79% to 91% and specificities in the range of 80% to 92% (level I evidence), with the introduction of late gadolinium enhancement resulting in sensitivities and specificities in the upper end of each of these ranges.[30,31] However, access to CMR by family physicians might be limited outside of hospital-affiliated centres.

Noninvasive anatomic diagnostic methods

Coronary computed tomography angiography: Unlike the previous noninvasive imaging modalities, CCTA is an investigative technique that uses computed tomography imaging and injected iodine containing contrast agents to produce high-resolution, 3-dimensional anatomic evaluation of the coronary arteries. Many institutions also perform a noncontrast computed tomography scan to assess the coronary artery calcium (Agatston) score that has validated prognostic usefulness independent of the information on coronary artery plaque burden and estimated percent of stenosis provided by the angiogram. The optimization of computed tomography imaging techniques and technology within the past 20 years has improved its efficiency and diagnostic accuracy, shaping CCTA into a strong contender for the first-line test in the investigation of stable chest pain.[32-35] For example, with faster gantry rotation times and a larger number of detector rows, multidetector computed tomography technology can now image the beating heart with exquisite detail. To achieve consistent, high-quality images at a low radiation dose, intravenous or oral β-blockers are often administered before CCTA to lower the heart rate (ideally to less than 60 beats/min).[36] Both the SCOT-HEART (Scottish Computed Tomography of the Heart) and PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trials have indicated that CCTA is underused in the investigation of stable chest pain (level I evidence).[37,38] The application of CCTA for emergency department patients with symptoms suggestive of acute coronary syndromes has improved the efficiency of clinical decision making, as well as reducing overall downstream testing, radiation exposure, hospital length of stay, and health care costs.[39,40]

Computed tomography–derived fractional flow reserve (FFRCT): Recent application of FFRCT, a novel technique to estimate the flow-limiting effect of individual coronary artery stenoses, has been shown in some studies to improve the specificity and positive predictive value of CCTA and has added the "functional" element

missing from traditional CCTA.[41-43] In FFRCT used to examine flow dynamics on either side of a plaque, a cut-off value of 0.8 or less identifies a flow-limiting coronary stenosis with very high precision compared with invasive catheter angiography–derived fractional flow reserve.[44] Computed tomography–derived fractional flow reserve can be performed on standard CCTA images using dedicated software to complete sophisticated analysis of the hemodynamic importance of coronary artery stenosis due to atherosclerotic plaque. Meta-analyses have demonstrated sensitivity and specificity values for FFRCT in the ranges of 84% to 93% and 65% to 83%, respectively (level I evidence).[45-48] However, FFRCT is not currently widely available in Canada for clinical use but has become part of routine clinical practice at many centres in the United States. Even without the addition of FFRCT, CCTA has the highest negative predictive value of all of the conventional noninvasive investigations for stable chest pain, reported to be between 95% and 100% (level II evidence).[45,46] Coronary computed tomography angiography also has the advantage of being the best test to identify patients with nonobstructive CAD, facilitating an opportunity to start optimal medical therapy (eg, lipid-lowering agents) to reduce the risk of future cardiovascular events. Disadvantages of CCTA include the requirement for intravenous injection of iodinated contrast agents that might be problematic for patients with substantial renal dysfunction, and exposure to ionizing radiation. Coronary computed tomography angiography radiation doses have high variability between and within centres and depend on scan parameters and patient body habitus.[49] However, with recent imaging protocols, radiation doses as low as 1.34 to 2.7 mSv can be achieved for CCTA compared with 10 to 15 mSv for a nuclear perfusion scan.[49-51]

Invasive diagnostic methods. Invasive catheter angiography is the current reference standard for the investigation of suspected CAD, but requires the insertion of a catheter and the injection of contrast material and ionizing radiation—typically at least twice the amount of radiation associated with CCTA.[52] As with CCTA, the functional information provided by fractional flow reserve to catheter angiography has improved outcomes by decreasing the average number of stents required and the amount of contrast agent used.[44] The usefulness of invasive catheter angiography is limited by its availability and its invasive nature, which bears risks of stroke, aortic and coronary artery dissection, allergic reaction, infection, nephropathy, cholesterol embolism, hematoma, arteriovenous fistula, and myocardial infarction.[53]

Applications. The approach to patients with stable chest pain has not been widely agreed upon, in part owing to changing technologies with limited randomized controlled trial data.[54] Currently, a variety of systems exist to stratify patients based on cardiovascular risk. These include systems such as the Framingham Risk Score, American Heart Association scoring, and the Reynolds Risk Score that calculate an individual's risk of experiencing a cardiovascular event during the next 10 years based on the presence of cardiac risk factors.[55] Other systems, such as the Diamond-Forrester risk model, evaluate an individual's current pretest probability of having substantial CAD based on age, sex, and type of chest pain.[55,56]

For those patients identified as low or intermediate risk, there are several diagnostic options with varying sensitivities and specificities reported in patient populations with stable chest pain and either known or suspected CAD (**Table 1**).[8,24-26,30,31,35,45,46,57-64] Several large clinical trials, including the PROMISE trial,[38] have demonstrated clinical equipoise between CCTA and other noninvasive methods, with no difference in outcomes at 2 years.[54] More recently, the United Kingdom's National Institute for Health and Care Excellence guidelines suggest CCTA be used as a first-line test in their public health care system for all patients with typical or atypical stable chest pain (level I evidence), including high-risk populations.[65,66] Coronary computed tomography angiography has the highest negative predictive value for ruling out disease in patients at low or intermediate risk and should be considered as the first-line investigation strategy owing to its potential to reduce overinvestigation and time to diagnosis.[40,67,68] The widespread use of CCTA supports preventive medicine, as its usefulness in detecting nonobstructive cardiovascular disease is important for prognostication and early initiation of optimal medical therapy. However, similar to CMR, access to timely CCTA might be limited depending on the location of practice.

Table 1. Performance of various imaging methods for patients with stable chest pain and either known or suspected CAD compared with invasive catheter angiography as the reference standard

METHOD	SENSITIVITY, %	SPECIFICITY, %	PPV, %	NPV, %
GXT[8,57,58]	45-50	85-90	75	91
SE[8,57-59]	79-85	80-88	40	90
SPECT[8,24-26,60]	76-91	70-90	67	68
CMR[30,31,61]	79-91	80-92	77	91
CCTA[8,35,45,46]	78-91	31-68	44-64	95-100
FFRCT[45,46,60,62-64]	84-93	65-83	52-82	84-100

CAD—coronary artery disease, CCTA—coronary computed tomography angiography, CMR—cardiovascular magnetic resonance imaging, FFRCT—computed tomography–derived fractional flow reserve, GXT—exercise electrocardiography, NPV—negative predictive value, PPV—positive predictive value, SE—stress echocardiography, SPECT—single-photon emission computed tomography.

Conclusion

Approximately 30% of the general population will, in their lifetime, present to a primary care physician with a chief concern of chest pain.[69] Despite the prevalence of chest pain among patients seeking care from their family physicians, the investigation of stable chest pain in patients at low or intermediate risk is a complicated and changing landscape owing to evolving technologies. This might be particularly true for female patients, for whom conventional functional testing might have lower accuracy. In this article, we summarized 6 available investigations for the workup of stable chest pain and highlighted some of the strengths and limitations of each. A comparative analysis of these options supports CCTA as a first-line test to rule out important CAD in low- or intermediate-risk patients to reduce overinvestigation and minimize delays in diagnosis, health care costs, and patient radiation exposure.

Mr Brenna is a medical student at the University of Toronto in Ontario. **Dr Afgani** is Research Coordinator in the Women's College Research Institute at Women's College Hospital in Toronto. **Dr Hanneman** is Assistant Professor in the Joint Department of Medical Imaging at Toronto General Hospital. **Dr Levitan** is a family physician in the Department of Family Medicine at Women's College Hospital. **Dr Udell** is Associate Professor in the Division of Cardiology at Women's College Hospital. **Dr Bhatia** is a cardiologist and Director of the Institute for Health System Solutions and Virtual Care in the Division of Cardiology at Women's College Hospital. **Dr Harvey** is Director of the Cardiovascular Research Program in the Division of Cardiology at Women's College Hospital. **Dr Nguyen** is Associate Professor in the Joint Department of Medical Imaging at Toronto General Hospital.

Contributors

Mr Brenna, Dr Afgani, and **Dr Nguyen** contributed to the literature review and interpretation, and all authors contributed to preparing the manuscript for submission.

Competing interests

None declared

Correspondence

Dr Elsie T. Nguyen; e-mail **elsie.nguyen@uhn.ca**

References

1. Christenson J, Innes G, McKnight D, Boychuk B, Grafstein E, Thompson CR, et al. Safety and efficiency of emergency department assessment of chest discomfort. *CMAJ* 2004;170(12):1803-7.
2. Davies SW. Clinical presentation and diagnosis of coronary artery disease: stable angina. *Br Med Bull* 2001;59(1):17-27.
3. Vaidya GN. Application of exercise ECG stress test in the current high cost modern-era healthcare system. *Indian Heart J* 2017;69(4):551-5. Epub 2017 Jun 17.
4. Acampa W, Assante R, Zampella E. The role of treadmill exercise testing in women. *J Nucl Cardiol* 2016;23(5):991-6. Epub 2016 Jul 25.
5. Miller TD. Stress testing: the case for the standard treadmill test. *Curr Opin Cardiol* 2011;26(5):363-9.
6. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, et al. ACC/AHA guidelines for exercise testing: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *Circulation* 1997;96(1):345-54.
7. Hlatky MA, Pryor DB, Harrell FE Jr, Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. *Am J Med* 1984;77(1):64-71.
8. Task Force Members; Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the Management of Stable Coronary Artery Disease of the European Society of Cardiology. *Eur Heart J* 2013;34(38):2949-3003. Epub 2013 Aug 30. Erratum in: *Eur Heart J* 2014;35(33):2260-1.
9. Wohlgelernter D, Cleman M, Highman HA, Fetterman RC, Duncan JS, Zaret BL, et al. Regional myocardial dysfunction during coronary angioplasty: evaluation by two-dimensional echocardiography and 12-lead electrocardiography. *J Am Coll Cardiol* 1986;7(6):1245-54.
10. Orzan F, Garcia E, Mathur VS, Hall RJ. Is the treadmill exercise test useful for evaluating coronary artery disease in patients with complete left bundle branch block? *Am J Cardiol* 1978;42(1):36-40.
11. Shaw LJ, Mieres JH, Hendel RH, Boden WE, Gulati M, Veledar E, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation* 2011;124(11):1239-49. Epub 2011 Aug 15.
12. Stangl V, Witzel V, Baumann G, Stangl K. Current diagnostic concepts to detect coronary artery disease in women. *Eur Heart J* 2008;29(6):707-17. Epub 2008 Feb 12.
13. Shaw LJ, Olson MB, Kip K, Kelsey SF, Johnson BD, Mark DB, et al. The value of estimated functional capacity in estimating outcome: results from the NHBLI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol* 2006;47(3 Suppl):S36-43.
14. Pellikka PA. Stress echocardiography in the evaluation of chest pain and accuracy in the diagnosis of coronary artery disease. *Prog Cardiovasc Dis* 1997;39(6):523-32.
15. Jeetley P, Burden L, Senior R. Stress echocardiography is superior to exercise ECG in the risk stratification of patients presenting with acute chest pain with negative troponin. *Eur J Echocardiogr* 2006;7(2):155-64. Epub 2005 Jun 20.
16. Hoffmann R, Lethen H, Kleinhans E, Weiss M, Flachskampf FA, Hanrath P. Comparative evaluation of bicycle and dobutamine stress echocardiography with perfusion scintigraphy and bicycle electrocardiogram for identification of coronary artery disease. *Am J Cardiol* 1993;72(7):555-9.
17. Senior R, Monaghan M, Becher H, Mayet J, Nihoyannopoulos P; British Society of Echocardiography. Stress echocardiography for the diagnosis and risk stratification of patients with suspected or known coronary artery disease: a critical appraisal. Supported by the British Society of Echocardiography. *Heart* 2005;91(4):427-36.
18. Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. *Cardiovasc Ultrasound* 2008;6:30.
19. Marwick TH. Stress echocardiography. *Heart* 2003;89(1):113-8.
20. Takagi T, Yoshikawa J, Yoshida K, Akasaka T, Honda Y, Maenishi A. Usefulness and limitations of dobutamine stress echocardiography for detection of coronary artery disease [article in Japanese]. *J Cardiol* 1994;24(5):347-55.
21. Jeudy J, White CS. Evaluation of acute chest pain in the emergency department: utility of multidetector computed tomography. *Semin Ultrasound CT MR* 2007;28(2):109-14.
22. Ravizzini GC, Hanson MW, Shaw LK, Wong TZ, Hagge RJ, Pagnanelli RA, et al. Efficiency comparison between 99m Tc-tetrofosmin and 99m Tc-sestamibi myocardial perfusion studies. *Nucl Med Commun* 2002;23(3):203-8. Erratum in: *Nucl Med Commun* 2006;27(4):411.
23. Vrachimis A, Hermann S, Máthé D, Schober O, Schäfers M. Systematic evaluation of 99m Tc-tetrofosmin versus 99m Tc-sestamibi to study murine myocardial perfusion in small animal SPECT/CT. *EJNMMI Res* 2012;2(1):21.
24. Al Moudi M, Sun Z, Lenzo N. Diagnostic value of SPECT, PET and PET/CT in the diagnosis of coronary artery disease: a systematic review. *Biomed Imaging Interv J* 2011;7(2):e9. Epub 2011 Apr 1.
25. Loong CY, Anagnostopoulos C. Diagnosis of coronary artery disease by radionuclide myocardial perfusion imaging. *Heart* 2004;90(Suppl 5):v2-9.
26. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2012;126:e354-471. Epub 2012 Nov 19. Erratum in: *Circulation* 2014;129(16):e463.
27. Mieres JH, Shaw LJ, Hendel RC, Heller GV. The WOMEN study: what is the optimal method for ischemia evaluation in women? A multi-center, prospective, randomized study to establish the optimal method for detection of coronary artery disease (CAD) risk in women at an intermediate-high pretest likelihood of CAD: study design. *J Nucl Cardiol* 2009;16(1):105-12. Epub 2009 Jan 20.
28. Hamirani YS, Kramer CM. Cardiac MRI assessment of myocardial perfusion. *Future Cardiol* 2014;10(3):349-58.
29. Van der Geest RJ, Reiber JHC. Quantification in cardiac MRI. *J Magn Reson Imaging* 1999;10(5):602-8.
30. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. *J Am Coll Cardiol* 2007;50(14):1343-53. Epub 2007 Sep 17.
31. Desai RR, Jha S. Diagnostic performance of cardiac stress perfusion MRI in the detection of coronary artery disease using fractional flow reserve as the reference standard: a meta-analysis. *AJR Am J Roentgenol* 2013;201(2):W245-52.
32. Torres FS, Crean AM, Nguyen ET, Paul N. Strategies for radiation-dose reduction and image-quality optimization in multidetector computed tomographic coronary angiography. *Can Assoc Radiol J* 2010;61(5):271-9. Epub 2010 Jun 4.
33. Shariat M, Thavendiranathan P, Nguyen E, Wintersperger B, Paul N, Rakowski H, et al. Utility of coronary CT angiography in outpatients with hypertrophic cardiomyopathy presenting with angina symptoms. *J Cardiovasc Comput Tomogr* 2014;8(6):429-37. Epub 2014 Sep 19.
34. Gorenoi V, Schönermark MP, Hagen A. CT coronary angiography vs. invasive coronary angiography in CHD. *GMS Health Technol Assess* 2012;8:Doc02. Epub 2012 Apr 16.
35. Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. *Heart* 2008;94(11):1386-93. Epub 2008 Jul 31.
36. Sabarudin A, Sun Z. Beta-blocker administration protocol for prospectively ECG-triggered coronary CT angiography. *World J Cardiol* 2013;5(12):453-8.
37. Newby DE, Williams MC, Flapan AD, Forbes JF, Hargreaves AD, Leslie SJ, et al. Role of multidetector computed tomography in the diagnosis and management of patients attending the rapid access chest pain clinic, the Scottish computed tomography of the heart (SCOT-HEART) trial: study protocol for randomized controlled trial. *Trials* 2012;13:184.
38. Mark DB, Anstrom KJ, Sheng S, Baloch KN, Daniels MR, Hoffmann U, et al. Quality-of-life outcomes with anatomic versus functional diagnostic testing strategies in symptomatic patients with suspected coronary artery disease: results from the PROMISE randomized trial. *Circulation* 2016;133(21):1995-2007. Epub 2016 Apr 27.

39. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med* 2012;367(4):299-308.
40. Grunau B, Leipsic J, Purssell E, Kasteel N, Nguyen K, Kazem M, et al. Comparison of rates of coronary angiography and combined testing procedures in patients seen in the emergency room with chest pain (but no objective acute coronary syndrome findings) having coronary computed tomography versus exercise stress testing. *Am J Cardiol* 2016;118(2):155-61. Epub 2016 May 4.
41. Hecht HS, Narula J, Fearon WF. Fractional flow reserve and coronary computed tomographic angiography: a review and critical analysis. *Circ Res* 2016;119(2):300-16.
42. Zarins CK, Taylor CA, Min JK. Computed fractional flow reserve (FFTCT) derived from coronary CT angiography. *J Cardiovasc Transl Res* 2013;6(5):708-14. Epub 2013 Aug 10.
43. Peña E, Rubens F, Stiell I, Peterson R, Inacio J, Dennie C. Efficiency and safety of coronary CT angiography compared to standard care in the evaluation of patients with acute chest pain: a Canadian study. *Emerg Radiol* 2016;23(4):345-52. Epub 2016 May 24.
44. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van 't Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360(3):213-24.
45. Gonzalez JA, Lipinski MJ, Flors L, Shaw PW, Kramer CM, Salerno M. Meta-analysis of diagnostic performance of coronary computed tomography angiography, computed tomography perfusion, and computed tomography-fractional flow reserve in functional myocardial ischemia assessment versus invasive fractional flow reserve. *Am J Cardiol* 2015;116(9):1469-78. Epub 2015 Aug 14.
46. Baumann S, Renker M, Hetjens S, Fuller SR, Becher T, Loßnitzer D, et al. Comparison of coronary computed tomography angiography-derived vs invasive fractional flow reserve assessment. Meta-analysis with subgroup evaluation of intermediate stenosis. *Acad Radiol* 2016;23(11):1402-11. Epub 2016 Sep 14.
47. Green R, Cantoni V, Petretta M, Acampa W, Panico M, Buongiorno P, et al. Negative predictive value of stress myocardial perfusion imaging and coronary computed tomography angiography: a meta-analysis. *J Nucl Cardiol* 2018;25(5):1588-97. Epub 2017 Feb 15.
48. Lee D, Li D, Jug B, Papazian J, Budoff M. Diagnostic accuracy of 64 slice multidetector coronary computed tomographic angiography in left ventricular systolic dysfunction. *Int J Cardiol Heart Vasc* 2015;8:42-6.
49. Carpeggiani C, Picano E, Brambilla M, Michelassi C, Knuuti J, Kauffman P, et al. Variability of radiation doses of cardiac diagnostic imaging tests: the RADIO-EVINCI study (RADIationdOse subproject of the EVINCI study). *BMC Cardiovasc Disord* 2017;17(1):63.
50. Al-Mallah MH, Aljizeeri A, Alharthi M, Alsaileek A. Routine low-radiation-dose coronary computed tomography angiography. *Eur Heart J Suppl* 2014;16(Suppl B):B12-6.
51. Tan SK, Yeong CH, Ng KH, Abdul Aziz YF, Sun Z. Recent update on radiation dose assessment for the state-of-the-art coronary computed tomography angiography protocols. *PLoS One* 2016;11(8):e0161543.
52. Crowhurst JA, Whitby M, Thiele D, Halligan T, Westerink A, Crown S, et al. Radiation dose in coronary angiography and intervention: initial results from the establishment of a multi-centre diagnostic reference level in Queensland public hospitals. *J Med Radiat Sci* 2014;61(3):135-41. Epub 2014 Aug 4.
53. Tavakol M, Ashraf S, Brener SJ. Risks and complications of coronary angiography: a comprehensive review. *Glob J Health Sci* 2012;4(1):65-93.
54. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;372(14):1291-300. Epub 2015 Mar 14.
55. Versteylen MO, Joosen IA, Shaw LJ, Narula J, Hofstra L. Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events. *J Nucl Cardiol* 2011;18(5):904-11. Epub 2011 Jul 19.
56. Masson W, Epstein T, Huerín M, Lobo LM, Molinero G, Angel A, et al. Cardiovascular risk stratification in patients with metabolic syndrome without diabetes or cardiovascular disease: usefulness of Metabolic Syndrome Severity Score. *High Blood Press Cardiovasc Prev* 2017;24(3):297-303. Epub 2017 May 13.
57. Gershlick AH, de Belder M, Chambers J, Hackett D, Keal R, Kelion A, et al. Role of non-invasive imaging in the management of coronary artery disease: an assessment of likely change over the next 10 years. A report from the British Cardiovascular Society Working Group. *Heart* 2007;93(4):423-31.
58. Bigi R, Galati A, Curti G, Coletta C, Barlera S, Partesana N, et al. Prognostic value of residual ischaemia assessed by exercise electrocardiography and dobutamine stress echocardiography in low-risk patients following acute myocardial infarction. *Eur Heart J* 1997;18(12):1873-81.
59. Afridi I, Quiñones MA, Zoghbi WA, Cheirif J. Dobutamine stress echocardiography: sensitivity, specificity, and predictive value for future cardiac events. *Am Heart J* 1994;127(6):1510-5.
60. Sand NPR, Veien KT, Nielsen SS, Nørgaard BL, Larsen P, Johansen A, et al. Prospective comparison of FFR derived from coronary CT angiography with SPECT perfusion imaging in stable coronary artery disease: the ReASSESS study. *JACC Cardiovasc Imaging* 2018;11(11):1640-50. Epub 2018 Jun 13.
61. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012;379(9814):453-60. Epub 2011 Dec 22.
62. Celeng C, Leiner T, Maurovich-Horvat P, Merkely B, de Jong P, Dankbaar JW, et al. Anatomical and functional computed tomography for diagnosing hemodynamically significant coronary artery disease: a meta-analysis. *JACC Cardiovasc Imaging* 2019;12(7 Pt 2):1316-25. Epub 2018 Sep 6.
63. Driessen RS, Danad I, Stuijfzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol* 2019;73(2):161-73.
64. Danad I, Szymonifka J, Twisk JWR, Norgaard BL, Zarins CK, Knaapen P, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J* 2017;38(13):991-8.
65. Timmis A, Roobottom CA. National Institute for Health and Care Excellence updates the stable chest pain guideline with radical changes to the diagnostic paradigm. *Heart* 2017;103(13):982-6. Epub 2017 Apr 26.
66. Villines TC, Shaw LJ. Coronary computed tomographic angiography—the first test for evaluating patients with chest pain? *JAMA Intern Med* 2017;177(11):1631-2. Erratum in: *JAMA Intern Med* 2018;178(1):157.
67. Nguyen E, Lemieux V, Udell J, Hanneman K, Bhatia S, Ivers N, et al. Reducing over investigation of women with stable chest pain at low/intermediate risk for coronary artery disease: the rationale for the RESOLVE trial [abstract]. *Can J Cardiol* 2018;34(4):e5.
68. Meinel FG, Schoepf UJ, Townsend JC, Flowers BA, Geyer LL, Ebersberger U, et al. Diagnostic yield and accuracy of coronary CT angiography after abnormal nuclear myocardial perfusion imaging. *Sci Rep* 2018;8(1):9228.
69. Bösner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sönnichsen AC, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract* 2009;15(3):141-6.

This article is eligible for Mainpro+ certified Self-Learning credits. To earn credits, go to **www.cfp.ca** and click on the Mainpro+ link.

This article has been peer reviewed. *Can Fam Physician* 2020;66:24-30

La traduction en français de cet article se trouve à **www.cfp.ca** dans la table des matières du numéro **de janvier 2020** à la **page e1**.