Herz 2016 · 41:384–390
DOI 10.1007/s00059-016-4451-3
Published online: 22 June 2016

R. Shah · B. Foldyna · U. Hoffmann
Cardiac MR PET CT Program, Department of Radiology, Massachusetts General Hospital, Boston, USA

Outcomes of anatomical vs. functional testing for coronary artery disease

Lessons from the PROMISE trial

Introduction

The need for PROMISE

The development of coronary artery disease (CAD) is a major, final common pathway in heart disease worldwide [1]. In the US, 50 million stress tests are performed each year and management of patients with suspected CAD approaches $ 14 billion per year, making it one of the most common and costly clinical scenarios. Functional testing including exercise and pharmacological testing with or without imaging has been the diagnostic cornerstone in the management of these patients for 40 years. The detection of myocardial ischemia in the appropriate clinical context typically triggers a referral to invasive coronary angiography and – if a significant stenosis is detected – to coronary revascularization. Several studies, among them the COURAGE trial [2], suggest that the success of an up-front revascularization strategy is rivaled by optimal medical therapy, with provisional revascularization for severe symptoms, heart failure, or electrical instability.

In this context, coronary computed tomography angiography (CCTA) has emerged as a noninvasive alternative to functional testing as a first-line test for CAD detection but is complimentary in its nature. The benefits of CCTA include the unique ability to visualize the presence and extent of CAD as well as morphology and composition similar to intravascular ultrasound (IVUS), noninvasively in a quick, robust, well-tolerated examination. A wealth of single and multicenter studies have demonstrated the impressive diagnostic performance of CCTA for the detection of significant luminal stenosis in selected patient populations ranging from low to high clinical risk [3–5]. A consistent hallmark of these studies has been the high negative predictive value (nearly 100 %) and more modest positive predictive value (closer to 80 %) compared with invasive coronary angiography. In addition, the presence and extent of CAD by CCTA are strongly related to prognosis, with normal CCTA associated with near-zero event rates over short-term follow-up [6]. Finally, observational data suggest that over 30–40 % of patients undergoing CCTA demonstrate nonobstructive CAD, with an accompanying increased risk for cardiovascular events [7].

Differences in clinical opinion favoring functional imaging of myocardial ischemia versus CCTA testing have culminated in divergent professional society guideline recommendations: While the American Heart Association guidelines on stable chest pain largely recommend functional evaluation of myocardial ischemia (Class IA recommendation) with provisional CCTA only for inconclusive stress tests or those unable to exercise [1], the National Institute for Health and Care Excellence (NICE) guidelines recommend a coronary calcium score for risk stratification in symptomatic patients with a pretest probability between 10–29 % [8]. Moreover, European Society of Cardiology guidelines recommend CCTA as an alternative to stress testing in patients with intermediate pretest risk, those with inconclusive tests, or patients with contraindications to stress testing [9].

Of note, while randomized studies in the acute coronary syndrome setting have demonstrated a potential role for CCTA to identify low-to-intermediate risk patients safe for discharge, they report increased rates of invasive coronary angiography that may be secondary to limited positive predictive value and potential increased prevalence of obstructive CAD (as compared with positive functional studies) [10]. The divergent professional society recommendations suggest equipoise in functional and anatomic cardiac risk assessment. Does the use of CCTA earlier in the evaluation of patients with CAD improve outcomes over functional testing? Is the potential for increased downstream angiography and/or revascularization a cost-effective and safe approach for initial risk stratification? How does radiation and contrast exposure figure into the risk calculation? The PROMISE trial was designed to address these specific questions in a practical clinical study.

The PROMISE trial

Design and methods

PROMISE was a randomized comparative effectiveness study of 10,003 patients across 193 sites in the United States and

R. Shah and B. Foldyna contributed equally to this study.

Table 1 Radiation exposure in CCTA and SPECT in PROMISE

	CCTA	SPECT	*p*
Median (quartile borders 25 %, 75 %)	8.8 (5.3, 14.6)	12.6 (11.3, 14.6)	< 0.0001
Mean ± SD	10.5 ± 6.6	14.1 ± 5.6	< 0.0001
Number of cases over 10 mSv	43 %	86 %	< 0.0001

CCTA coronary computed tomography angiography, *SPECT* single-photon emission computed tomography, *SD* standard deviation

Canada (both academic and private practice) targeted at patients with symptoms suggestive of CAD referred for further noninvasive clinical evaluation [11]. The *primary hypothesis* of PROMISE was that individuals with suspected CAD undergoing CCTA as a primary mode of risk stratification would have superior health outcomes relative to those undergoing functional testing (including stress electrocardiography, echocardiography or nuclear testing). Inclusion criteria (aimed at enriching the study population for CAD) comprised men over 45 and women over 50 years of age with symptoms potentially related to CAD, without prior CAD. Individuals with symptoms or signs of unstable acute coronary syndromes, a history of (or recent evaluation for) CAD, or contraindications to CCTA or functional testing were excluded. In addition, PROMISE was funded by the National Institutes of Health, without any contributions from vendors involved in CCTA. Enrolled participants were randomized to CCTA or functional testing (with type of functional testing prescribed by the attending physician). In keeping with the aim of the study to test "strategies" of care, CCTA and functional testing was reviewed on site, with subsequent management at the behest of the attending physician (not the study investigators). Protocol-driven follow-up at 6-month intervals after randomization for a period of at least 1 year was performed. The primary endpoint of PROMISE was a composite of major adverse cardiovascular events, including all-cause mortality, myocardial infarction, unstable angina hospitalization, and complications of diagnostic testing within 72 h of testing (e. g., stroke, bleeding, renal failure, anaphylaxis; all events adjudicated independent of study investigators). The investigators examined a variety of secondary endpoints as well, focused on safety (radiation) and effectiveness (downstream healthcare expenditure and nonobstructive CAD patterns by angiography). The trial defined a "positive" (abnormal) CCTA if there was at least ≥ 70 % stenosis in any of three epicardial arteries or ≥ 50 % stenosis in the left main coronary artery. A functional (stress) test was defined as "positive" (abnormal) if there was a reversible perfusion defect with or without accompanying infarction in at least one myocardial region.

Study population

Of the initial 10,003 patients entered into randomization, all but 404 patients underwent specified initial testing, with 1-year follow-up available in nearly 94 % of patients. Study characteristics were balanced across functional versus CCTA groups, and had significant CAD risk factors (2–3 CAD risk factors on average). Over half of the enrolled individuals had hypertension, dyslipidemia, or prior or current smoking, and nearly half were receiving aspirin, statin therapy, or antihypertensive medication. The primary presenting symptom was chest pain (in over 70 %), primarily of an atypical nature (78 %). As an aggregate measure of risk, the average pretest probability of obstructive CAD by the combined Diamond–Forrester and Coronary Artery Surgery Study model was over 50 %. Individuals randomized to functional testing most commonly underwent stress testing with some form of cardiac imaging (nuclear in 67.5 % vs. echocardiography in 22 %), and 29.4 % tests required pharmacologic stress agents. Collectively, these characteristics were overall in keeping with a low-to-moderate-risk population, an ideal clinical circumstance for evaluation of comparative effectiveness of functional versus anatomic strategies.

Primary outcome

Over a median 25-month follow-up, the trial did not meet the primary endpoint with 164 (3.3 %) participants in the CCTA arm and 151 (3.0 %) in the functional test arm experiencing an adverse clinical event (HR = 1.04 %, 95 % CI = 0.93–1.29, p = 0.75). This result was similar when follow-up was truncated at 12 months, or for any combination of CAD-related endpoints examined. There was no specific subgroup in which CCTA or functional testing was associated with improved hazard of any outcome.

Safety, test results, downstream testing, and coronary revascularization

PROMISE demonstrated that both CCTA and functional testing are clinically safe: No severe adverse event related to testing occurred, and the rate of mild adverse events was very low (n = 58; 0.6 %). Overall radiation exposure was higher in the CCTA group, probably because one third of patients in the functional arm did not undergo any test associated with radiation exposure. Nevertheless, a direct comparison between nuclear perfusion imaging and CCTA demonstrated significantly lower radiation exposures by CCTA (median exposure in the functional testing group, 12.6 mSv; CCTA, 10.1 mSv; p < 0.001; **Table 1**).

Overall, a relatively small number of patients had either obstructive CAD (CCTA arm; n = 517, 10.7 %) or myocardial ischemia (functional arm; n = 556, 11.7 %). While patients randomized to CCTA underwent downstream angiography at 90 days after randomization more frequently as compared with those randomized to functional testing (609 in CCTA, 12.2 % vs. 406 in functional group, 8.1 %), the diagnostic yield was higher for CCTA as obstructive CAD was observed in a greater frequency in patients randomized to CCTA (72.1 %) compared with those randomized to functional testing (48.5 %). Not surprisingly, this resulted in a greater frequency of coronary revascularization (6.2 % in CCTA vs. 3.2 % in functional testing). The corresponding results are shown in

Fig. 1. Finally, approximate total costs (including downstream testing) were similar between CCTA and functional testing.

Lessons from PROMISE

The strengths of the PROMISE study included: a large sample size (n > 10,000) over a geographically diverse area and involving both academic and private centers; the inclusion of women and minorities; recruitment of patients with a 50 % probability of obstructive CAD (by Diamond and Forrester criteria), most of whom had atypical chest pain and two to three major cardiovascular risk factors, which represents a guideline-conforming clinical referral population of patients with suspected CAD for advanced diagnostic testing. In addition, the PROMISE trial provided a snapshot of real-world clinical care across North America and its effect on clinical and economic outcomes. While the results of the trial did not support the investigators' prespecified hypothesis (specifically did not demonstrate the superiority of CCTA), the trial provides significant insights and lessons.

Lesson 1

Patients with stable chest pain have much lower rates of positive test findings and cardiovascular events as compared with 25 years ago – emphasizing the critical need for improved selection instruments for noninvasive diagnostic testing.

First, the overall event rates in PROMISE were lower than expected for the level of clinical risk anticipated. Indeed, only 11 % of the CCTA arm of the study population had obstructive CAD, far lower than would have been expected from pretest clinical risk estimates (given Diamond–Forrester risk at 53 %). Moreover, the event rates were low at 3.1 %, relative to the projected 8 % based on United Health Care data. Some of these results are not surprising: In a registry study of 14,048 individuals with clinically indicated CCTA tests, typical angina was associated with the highest prevalence of any epicardial vessel stenosis over 70 % (27 % in men and 11 % in women).

Abstract · Zusammenfassung

Herz 2016 · 41:384–390 DOI 10.1007/s00059-016-4451-3

R. Shah · B. Foldyna · U. Hoffmann

Outcomes of anatomical vs. functional testing for coronary artery disease. Lessons from the PROMISE trial

Abstract

The development of coronary artery disease (CAD) is a major, final common pathway in heart disease worldwide. With a rise in stress testing and increased scrutiny on cost-effectiveness and radiation exposure in medical imaging, a focus on the relative merits of anatomic versus functional characterization of CAD has emerged. In this context, coronary computed tomography angiography (CCTA) is a noninvasive alternative to functional testing as a first-line test for CAD detection but is complimentary in its nature. Here, we discuss the design, results, and implications of the PROMISE trial, a randomized comparative effectiveness study of 10,003 patients across 193 sites in the United States and Canada comparing the prognostic and diagnostic power of CCTA and standard stress testing. Specifically, we discuss the safety (e. g., contrast, radiation exposure) of CCTA versus functional testing in CAD, the need for improved selection for noninvasive testing, the frequency of downstream testing after anatomic or functional imaging, the use of imaging results in clinical management, and novel modalities of CAD risk determination using CCTA. PROMISE demonstrated that in a real-world, low-to-intermediate risk patient population referred to noninvasive testing for CAD, both CCTA and functional testing approaches have similar clinical, economic, and safety-based outcomes. We conclude with open questions in CAD imaging, specifically as they pertain to the utilization of CCTA.

Keywords

Coronary artery disease · Coronary angiography · Computed tomography · Treatment outcome · Functional testing

Ergebnisse der anatomischen vs. funktionellen Untersuchung bei koronarer Herzkrankheit. Erkenntnisse aus der PROMISE-Studie

Zusammenfassung

Die koronare Herzkrankheit (KHK) ist weltweit die häufigste Ursache für kardiale Erkrankungen. Mit der Etablierung funktioneller Tests und gleichzeitigen Weiterentwicklungen der kardialen Bildgebung mit Abnahme von Strahlenbelastung und Untersuchungskosten entstand eine Diskussion über die relativen Vorteile der anatomischen gegenüber der funktionellen Charakterisierung und Detektion der KHK. Unterdessen entwickelte sich die koronare Computertomographie-Angiographie (CCTA) zu einer nichtinvasiven ergänzenden Modalität derzeitiger diagnostischer Methoden zur Erkennung der KHK. In dieser Arbeit werden das Design, die Ergebnisse und die Auswirkungen der PROMISE-Studie erörtert, einer randomisierten, vergleichenden Wirksamkeitsstudie mit 10.003 Patienten aus insgesamt 193 Standorten in den Vereinigten Staaten und Kanada. Die PROMISE-Studie verglich die prognostische und diagnostische Stärke der CCTA gegenüber den funktionellen Standardtests. Insbesondere wird die Sicherheit (Kontrastmittel-, Strahlenbelastung) der CCTA im Vergleich zu den Funktionstests, die Notwendigkeit einer verbesserten Patientenselektion für nichtinvasive Tests und die Häufigkeit der nachgeschalteten Untersuchungen in der anatomisch und funktionell getesteten Gruppe beschrieben. Des Weiteren werden die Verwendung der bildgebenden Ergebnisse der CCTA für die klinische Versorgung und neuartige Wege zur KHK-Risiko-Bestimmung mittels CCTA dargestellt. Die PROMISE-Studie zeigte, dass im klinischen Alltag bei Patienten mit niedriger bis intermediärer Vortestwahrscheinlichkeit für eine KHK in der CCTA und den Funktionstests ähnliche klinische, wirtschaftliche und sicherheitsspezifische Ergebnisse erzielt werden.

Schlüsselwörter

Koronare Herzkrankheit · Koronare Computertomographie-Angiographie · Klinisches Ergebnis · Anatomische Prüfung · Funktionelle Prüfung

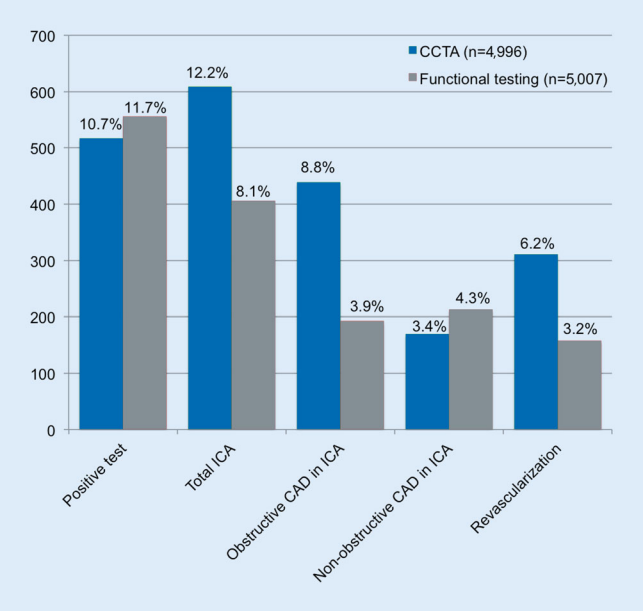

Fig. 1 ◀ Results of testing and downstream invasive coronary angiography (*ICA*), as well as results at ICA, stratified by CCTA and functional testing. *CAD* coronary artery disease, *CCTA* coronary computed tomography angiography

In this study, the pretest risk (based on a composite of Diamond and Forrester angina classification and ACC/AHA prescribed pretest probabilities) overestimated the observed prevalence of CAD significantly, regardless of age or sex, which appeared driven primarily by atypical angina (the primary form of chest pain symptom in PROMISE) [12]. Aside from poor calibration of clinical risk estimators, the overall prevalence of myocardial ischemia in the past 20 years has declined from 40.9 % in 1991 to 8.7 % in 2009 [13].

Because pretest clinical risk estimators for CAD prevalence are not well calibrated to contemporary practice, more efficient utilization of *either* CCTA or functional imaging demands improvement in patient selection to optimize cost and benefit [14, 15]. Several studies have suggested a systematic overestimation of significant anatomic CAD by traditional Diamond–Forrester classification of chest pain [16] or Duke treadmill score [15], with lack of discrimination especially in women. In addition, clinical risk estimates for asymptomatic individuals do not necessarily apply to symptomatic individuals referred for evaluation of suspected CAD [17]. Nevertheless, recent additions, and details from ancillary investigations (e. g., left ventricular function or coronary artery calcification [18]), may help clinicians direct noninvasive tests to the most appropriate cadre of patients. In recent work, Genders and colleagues extended the traditional Diamond–Forrester classification to include more comprehensive lipid-based and historical risk factors (e. g., diabetes) as well as coronary calcification in prediction models for CAD, based on invasive angiography and CCTA [15]. These investigators noted improvement in risk discrimination and 35 % risk reclassification based on extended models, suggesting that a comprehensive approach based on clinical, historical, and extended (e. g., calcium score) risk factors for CAD improves risk prediction in symptomatic individuals. These results require confirmation in large, transnational populations, and PROMISE affords a unique opportunity to validate composite risk scores (inclusive of coronary plaque morphology and calcification).

Moreover, some advocates of limiting diagnostic imaging may support a "no testing" approach, wherein symptomatic individuals with multiple risk factors (as in PROMISE, with 2–3 CAD risk factors) automatically receive CAD prevention. Given the low event rate and the low test positivity rate in PROMISE [12], this approach may appear attractive. Moreover, there is a complete paucity of data as far as the feasibility of such a strategy is concerned. Furthermore, patients and caregivers would face uncertainties around needs for revisits and follow-up, legal and cost considerations, and a general strategy. While it appears on the surface as an attractive approach, data are needed to warrant further consideration.

Ultimately, the development of more efficient approaches to identify candidates for imaging are warranted, including risk stratification algorithms that are based on contemporary populations and perhaps novel biomarkers that have discriminatory value. This would enable more efficient diagnostic imaging (whether it be nuclear perfusion or CCTA) and will avoid unnecessary exposure to radiation, need for follow-up of incidental findings, and normal results on diagnostic angiography for suspected CAD.

Lesson 2

Combining anatomic with functional information is the key to improve patient selection for invasive angiography and coronary revascularization.

Similar to randomized trials in the acute chest pain setting, PROMISE observed increased downstream utilization of invasive coronary angiography and revascularization with CCTA. Within 90 days of initial diagnostic test, 609 patients (12.2 %) in the CCTA group underwent invasive angiography, compared with 406 (8.1 %) in the functional group. However, while 28 % of the individuals undergoing angiography after CCTA had normal coronary arteries at catheterization (3.4 % of the overall CCTA group), nearly 58 % of individuals in the functional group demonstrated normal coronary arteries (4.3 % of the overall functional group, $p = 0.02$ vs. CCTA). Further interpretation of these comparisons is limited by the PROMISE study design, which left the decisions for downstream angiography and revascularization to the treating physicians. In effect, rates of revascularization were higher in individuals who had previously undergone CCTA versus those who had functional tests (6.2 vs. 3.2 %, $p < 0.001$).

While thorough site certification and quality control were performed in

Table 2 Selected large studies in CCTA evaluating performance of FFR-CT

Study	Year	Reference standard	Study design	Number of patients	FFR-CT Sensitivity/ Specificity (%)	FFR-CT Accuracy (%)
Budoff et al. [27]	2016	ICA	Prospective, multicenter	252	79/63	69
Coenen et al. [28]	2015	ICA	Retrospective	106	88/65	75
Min et al. [24]	2012	ICA	Prospective, multicenter	252	90/54[a]	73
Koo et al. [25]	2011	ICA	Prospective	103	88/82	84
Gonzalez et al. [29]	2015	CCTA/ICA	Meta-analysis	1535	92/72	–

CCTA computed tomography angiography, *ICA* invasive coronary angiography
[a]Operating characteristics of CCTA (vs. gold standard ICA) in this study included CCTA lesions > 50 % stenosis in addition to FFR-CT data

PROMISE, image interpretation and downstream clinical management were left to the discretion of each local site, which in their entirety of 193 sites represented a large amount of heterogeneity in experience, equipment, and clinical management style, which is desirable given that that the results should be broadly generalizable. It is quite easy to imagine that the quality of the test is associated with its interpretation and suggested further management. The quality of CCTA depends on the equipment (e. g., 64- vs. 128-slice or higher-slice CT scanners), appropriate use of medication to dilate the coronary arteries and reduce cardiac motion (e. g., nitroglycerin and beta-blockade therapy), and composition of atherosclerosis (e. g., blooming artifacts with greater coronary calcification). It is further clear that the expertise of readers has a substantial influence on further management, and studies have shown that the diagnostic yield of CCTA imaging improves with reader expertise [19, 20]. Not directly test-related factors are differences in a cardiologist's interpretation of the test results and the subsequent actions such a medical treatment or referral for intervention. The interpretation of test results, medical guidelines, and personal management styles (e. g., "confirmatory" diagnostic angiography for any lesion > 50 % vs. functional testing after CCTA) certainly affect downstream testing and safety of diagnostic imaging [21]. Overall, the results support the notion that real-world clinical management of angiographic findings after CCTA is largely based on anatomic but not functional information, despite a wealth of randomized evidence supporting a combined approach of anatomy and physiology. Tonino and colleagues reported the results of 1005 patients with multivessel CAD who underwent anatomic and functional assessment during angiography using fractional flow reserve (FFR) assessments. Individuals who underwent FFR-guided therapy had a lower rate of cardiovascular events at 1 year (13.2 %) relative to the anatomic-guided only approach (18.3 %; $p = 0.02$) [22]. The merits of a composite anatomic and functional approach to invasive CAD risk stratification have since been extended to longer follow-up [23].

In light of these results, CCTA has adopted this approach: Recent data involving CT-based assessments of fractional flow reserve (FFR-CT) have been put forth to address this important aspect of CAD risk stratification [24]. In an early study of 103 individuals with CCTA, FFR-CT methods were validated against FFR by diagnostic angiography, with sensitivity 84 % and specificity 82 % for per-vessel ischemia [25]. In this study, invasive FFR and FFR-CT were highly correlated ($r = 0.72$, $p < 0.001$). In a study by the same group, Min and coworkers demonstrated that FFR-CT methods improved discrimination for significant ischemic territories over obstructive CAD by CCTA (with catheterization as the gold standard) [24]. These observations have been replicated by other groups [26–28], including a recent large meta-analysis reaffirming the utility of CT-FFR [29]. The summary of most recent FFR-CT studies is shown in **Table 2**. While the FFR-CT calculations depend on several key assumptions about coronary flow (including a simulation of hyperemic flow), the assessment of FFR and anatomic lesion severity appears to improve discrimination of risk. Additional evaluation in the PROMISE study to assess whether FFR-CT assessments impact prognosis are underway, and should provide an added dimension to the data offered by CCTA.

Lesson 3

Testing choice was not associated with better clinical outcomes, but it may not be the fault of the test.

A central result of PROMISE was that choice of the initial diagnostic modality (functional vs. anatomic) did not affect clinical outcomes. While at first blush this suggests equipoise between the different modalities, one has to consider that many things happen between the test and a future event, which may or may not be related to the test itself. We discussed test-related and nonrelated factors affecting management in the prior paragraph.

More importantly, a recent meta-analysis of the PROMISE, SCOT HEART Trial, and COMPASS trials by Bittencourt and colleagues reported a 31 % reduction in the odds of having a downstream myocardial infarction with the use of CCTA (vs. functional approaches) [30], suggesting that the direct visualization of CAD may indeed enable improved outcomes. These data are corroborated by several observational studies demonstrating that a normal CCTA was associated with a very low 0.15 % annualized risk of death, similar to general population risk [21]. Another factor that may favorably affect outcomes after CTA is the ability to visualize the presence and extent of nonobstructive CAD. Several studies have shown that this finding, while not resulting in immediate events, is associated with a threefold increase in cardiovascular events.

Another discussion has evolved around the appropriateness and benefits of how to proceed with diagnostic angiography in CCTA lesions with > 50 % obstruction and myocardial ischemia

[31]. There is no definite proof and consensus on which patients (except those with left main or triple vessel disease) may benefit from coronary revascularization. This question is being investigated in the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) study – a large, contemporary investigation of medical versus interventional approaches in patients with moderate-to-severe ischemia. Appropriately, the design includes CCTA prerandomization to exclude left main disease [32]. We await the results of studies assessing the relative merits of ischemic and anatomic testing versus medical therapy alone (a "no testing" strategy).

Lesson 4

Diagnostic testing is very safe.

An important question within PROMISE was assessment of the relative safety profile of a functional strategy versus CCTA. An ongoing concern in contemporary literature on advanced cardiovascular imaging is safety with respect to contrast and radiation exposure. In PROMISE, the number of patients with any safety event was similar between CCTA and stress testing arms. While contrast reactions (mild and extravasation) were by definition more common with CCTA, renal failure and anaphylaxis were nonexistent. Although PROMISE did not show any differences in procedure-based risks between CCTA and functional testing, it is worth noting that angiography was used more frequently in individuals randomized to CCTA and is associated with further use of contrast agents.

Given increasing concerns over long-term malignancy risk, radiation exposure has become a major issue in modern imaging applications. While mean cumulative radiation exposure on average was higher in the CCTA arm versus the functional testing arm (12.0 vs. 10.1 mSv), this was largely due to confined radiation exposure in the nuclear stress testing arm. Indeed, when compared with individuals in the nuclear perfusion imaging arm, CCTA had a lower overall radiation exposure (12.0 vs. 14.1 mSv; $p < 0.001$). These results are consistent with prior results from other studies: In the Rule Out Myocardial Infarction Using Computer-Assisted Tomography (ROMICAT) study, CCTA radiation dose was 11.3 ± 5.3 vs. 14.1 ± 4.8 mSv for SPECT, with lower doses in those individuals who had a 128-slice dual-source scan [33]. Differences were smaller but still in favor of CCTA in the Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) study (11.5 vs. 12.8 mSv SPECT) [34]. In a large observational registry of nearly 2000 patients with CCTA over 50 sites, the median dose was 12 mSv with variability by scanner platform and location [35]. While these studies suggest stability in CCTA radiation dose, over the past several years, innovations in CCTA technology and improved recognition of methods to reduce radiation exposure have progressively cut radiation exposure by over 50 % (in some cases, nearly to 1–2 mSv with prospectively ECG-triggered modalities). However, it should be noted that while in PROMISE (and in the US) nuclear perfusion stress testing is the most frequently performed functional test (67 % of patients), in other countries, such as Germany, other functional tests such as exercise treadmill or stress echocardiography are more frequently performed, which would have resulted in a significant lower radiation dose in the functional testing treatment arm. On the other hand, such practice patterns often result in a more frequent referral of patients to invasive coronary angiography.

Conclusion

Despite the limitations of PROMISE, it is clear that in a real-world, low-to-intermediate-risk patient population referred to noninvasive testing for delineation of CAD, both anatomic (CCTA) and functional (stress testing) approaches are associated with similar clinical, economic, and safety-based outcomes. However, several key questions remain as potential foci of future investigation: Does discovery of nonobstructive CAD by CCTA lead to increased utilization of preventative therapies and by extension to improved outcomes? Do assessments of coronary physiology by FFR-CT improve selection of candidates for invasive coronary angiography minimizing costs but perhaps also improving outcomes? Do novel clinical biomarkers of myocardial injury (e. g., high-sensitivity troponin [36]) add to (or obviate the need for) assessments of coronary anatomy or physiology? It is clear that tools enabling a more nuanced diagnosis and management of these patients are necessary to manage this large population appropriately and efficiently.

Corresponding address

U. Hoffmann, MD
Cardiac MR PET CT Program, Department of Radiology, Massachusetts General Hospital
165 Cambridge Street, Suite 400, 02114 Boston, MA, USA
uhoffmann@partners.org

Compliance with ethical guidelines

Conflict of interest. R. Shah, B. Foldyna, and U. Hoffmann declare that they have no competing interests.

The accompanying manuscript does not include any studies on humans or animals performed by any of the authors.

References

1. Fihn SD, Blankenship JC, Alexander KP, Bittl JA et al (2015) 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Thorac Cardiovasc Surg 149(3):e5–e23
2. Boden WE, O'Rourke RA, Teo KK, Hartigan PM et al (2007) Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 356(15):1503–1516
3. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A et al (2008) Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 359(22):2324–2336
4. Budoff MJ, Dowe D, Jollis JG, Gitter M et al (2008) Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY

(assessment by coronary computed tomographic Angiography of individuals undergoing invasive coronary Angiography) trial. J Am Coll Cardiol 52(21):1724–1732
5. Habib PJ, Green J, Butterfield RC, Kuntz GM et al (2013) Association of cardiac events with coronary artery disease detected by 64-slice or greater coronary CT angiography: a systematic review and meta-analysis. Int J Cardiol 169(2):112–120
6. Min JK, Shaw LJ, Devereux RB, Okin PM et al (2007) Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol 50(12):1161–1170
7. Patel MR, Peterson ED, Dai D, Brennan JM et al (2010) Low diagnostic yield of elective coronary angiography. N Engl J Med 362(10):886–895
8. NICE guidelines (2010) Chest pain of recent onset: assessment and diagnosis. https://www.nice.org.uk/guidance/cg95/chapter/1-guidance. Accessed 30 April 2016
9. Task Force M, Montalescot G, Sechtem U, Achenbach S et al (2013) 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 34(38):2949–3003
10. Litt HI, Gatsonis C, Snyder B, Singh H et al (2012) CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med 366(15):1393–1403
11. Douglas PS, Hoffmann U, Patel MR, Mark DB et al (2015) Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 372(14):1291–1300
12. Cheng VY, Berman DS, Rozanski A, Dunning AM et al (2011) Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation 124(22):2423–2432 (2421–2428)
13. Rozanski A, Gransar H, Hayes SW, Min J et al (2013) Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. J Am Coll Cardiol 61(10):1054–1065
14. Diamond GA, Forrester JS (1979) Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 300(24):1350–1358
15. Genders TS, Steyerberg EW, Hunink MG, Nieman K et al (2012) Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 344:e3485
16. Genders TS, Steyerberg EW, Alkadhi H, Leschka S et al (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 32(11):1316–1330
17. Goff DC Jr., Lloyd-Jones DM, Bennett G, Coady S et al (2014) 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the american college of cardiology/american heart association task force on practice guidelines. J Am Coll Cardiol 63(25 Pt B):2935–2959
18. Yeboah J, McClelland RL, Polonsky TS, Burke GL et al (2012) Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 308(8):788–795
19. Malago R, Pezzato A, Barbiani C, Tezza M et al (2013) Learning curve in multidetector CT coronary angiography (MDCT-CA). Radiol Med 118(8):1281–1293
20. Pugliese F, Hunink MG, Gruszczynska K, Alberghina F et al (2009) Learning curve for coronary CT angiography: what constitutes sufficient training? Radiology 251(2):359–368
21. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD et al (2011) Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. J Am Coll Cardiol 57(10):1237–1247
22. Tonino PA, De Bruyne B, Pijls NH, Siebert U et al (2009) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 360(3):213–224
23. Pijls NH, Fearon WF, Tonino PA, Siebert U et al (2010) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (fractional flow reserve versus Angiography for Multivessel evaluation) study. J Am Coll Cardiol 56(3):177–184
24. Min JK, Leipsic J, Pencina MJ, Berman DS et al (2012) Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 308(12):1237–1245
25. Koo BK, Erglis A, Doh JH, Daniels DV et al (2011) Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 58(19):1989–1997
26. Norgaard BL, Gaur S, Leipsic J, Ito H et al (2015) Influence of coronary calcification on the diagnostic performance of CT angiography derived FFR in coronary artery disease: a substudy of the NXT trial. JACC Cardiovasc Imaging 8(9):1045–1055
27. Budoff MJ, Nakazato R, Mancini GB, Gransar H et al (2016) CT angiography for the prediction of hemodynamic significance in intermediate and severe lesions: Head-to-head comparison with quantitative coronary angiography using fractional flow reserve as the reference standard. JACC Cardiovasc Imaging 9(5):559–564
28. Coenen A, Lubbers MM, Kurata A, Kono A et al (2015) Fractional flow reserve computed from noninvasive CT angiography data: diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. Radiology 274(3):674–683
29. Gonzalez JA, Lipinski MJ, Flors L, Shaw PW et al (2015) 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 116(9):1469–1478
30. Bittencourt MS, Hulten EA, Murthy VL, Cheezum M et al (2016) Clinical outcomes after evaluation of stable chest pain by coronary computed tomographic angiography versus usual care: a meta-analysis. Circ Cardiovasc Imaging 9(4):e004419
31. Patel MR, Bailey SR, Bonow RO, Chambers CE et al (2012) ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol 59(22):1995–2027
32. Stone GW, Hochman JS, Williams DO, Boden WE et al (2016) Medical therapy with versus without revascularization in stable patients with moderate and severe ischemia: the case for community equipoise. J Am Coll Cardiol 67(1):81–99
33. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET et al (2012) Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med 367(4):299–308
34. Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S et al (2011) The CT-STAT (coronary computed tomographic angiography for systematic triage of acute chest pain patients to treatment) trial. J Am Coll Cardiol 58(14):1414–1422
35. Hausleiter J, Meyer T, Hermann F, Hadamitzky M et al (2009) Estimated radiation dose associated with cardiac CT angiography. JAMA 301(5):500–507
36. Everett BM, Brooks MM, Vlachos HE, Chaitman BR et al (2015) Troponin and Cardiac Events in Stable Ischemic Heart Disease and Diabetes. New Engl J Med 373(7):610–620