Title
A randomized, multicenter, multivendor study of myocardial perfusion imaging with regadenoson CT perfusion vs single photon emission CT

Permalink
https://escholarship.org/uc/item/66s9c4rk

Journal
Journal of Cardiovascular Computed Tomography, 9(2)

ISSN
1934-5925

Authors
Cury, RC
Kitt, TM
Feaheny, K
et al.

Publication Date
2015

DOI
10.1016/j.jcct.2015.01.002

Peer reviewed
A randomized, multicenter, multivendor study of myocardial perfusion imaging with regadenoson CT perfusion vs single photon emission CT

Ricardo C. Cury MDa,b,*, Therese M. Kitt MDc, Kathleen Feaheny MSD, Ron Blankstein MDsf, Brian B. Ghoshhajra MDf,g, Matthew J. Budoff MDh, Jonathon Leipsic MDi, James K. Min MDj,k, Jamie Akin BS, MSHSd, Richard T. George MDl

aDepartment of Radiology, Baptist Hospital of Miami, 8900 North Kendall Drive, Miami, FL 33176, USA
bMiami Cardiac and Vascular Institute, Miami, FL, USA
cAstellas Scientific and Medical Affairs, Inc., Northbrook, IL, USA
dAstellas Pharma Global Development, Inc., Northbrook, IL, USA
eCardiovascular Division, Department of Radiology, Brigham and Women’s Hospital, Boston, MA, USA
fHarvard Medical School, Boston, MA, USA
gDepartment of Radiology, Massachusetts General Hospital, Boston, MA, USA
hDepartment of Medicine, Harbor UCLA Medical Center, Los Angeles, CA, USA
iDivision of Cardiology, Department of Medical Imaging, St Paul’s Hospital, Vancouver, British Columbia, Canada
jDepartment of Radiology, Weill Cornell Medical College and The New York-Presbyterian Hospital, New York, NY, USA
kDepartment of Medicine, Weill Cornell Medical College and The New York-Presbyterian Hospital, New York, NY, USA
lDivision of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA

Abstract

Background: Myocardial CT perfusion (CTP) is a promising tool for the detection of myocardial ischemia. We hypothesize that regadenoson CTP is noninferior to regadenoson single photon emission CT (SPECT) for detecting or excluding myocardial ischemia.

Conflict of interest: Ricardo C. Cury has received grants and research support from Astellas. Therese M. Kitt, Kathleen Feaheny, and Jamie Akin are employees of Astellas. Ron Blankstein has received grants and research support from Astellas. Matthew J. Budoff has received grants and research support from Astellas and GE Healthcare. Jonathon Leipsic has received consulting fees and honoraria from GE Healthcare and Heartflow and fees for image reading from ICON and Astellas for this study. James K. Min has research agreements with Philips Healthcare and Vital Images, has received consulting fees and honoraria from Abbott Vascular, GE Healthcare, and Heartflow, has served on medical advisory boards for Arineta, and holds equity interest in Autoplaq, MDDX, and TC3. Richard T. George has received consulting fees and honoraria from ICON Medical Imaging, has served on advisory boards for Astellas, has received grants and research support from Toshiba and GE Healthcare, educational grants from Toshiba, holds a patent for an x-ray CT apparatus and myocardial perfusion image generating system (US 7,853,309, issued December 2010), and has a pending patent for “combined multi-detector CT angiography and CT myocardial perfusion imaging for the diagnosis of coronary artery disease” (US 2011/0110,488, filed September 2008). Brian B. Ghoshhajra has no potential conflicts of interest to declare. The study was supported by Astellas Pharma Global Development. Medical writing support was provided by Emily Howard and Tara N Miller, PhD, and by medical writers at Envision Scientific Solutions, and was funded by Astellas Scientific and Medical Affairs, Inc.

* Corresponding author.

E-mail address: rcury@baptisthealth.net (R.C. Cury).
Myocardial perfusion imaging (MPI) is an integral component for the diagnosis and management of patients with coronary artery disease (CAD). Single photon emission CT (SPECT) is the most frequently requested and widely available noninvasive MPI modality. Importantly, it provides an accurate assessment of the presence or absence of myocardial ischemia and infarction, yields incremental prognostic information, and contributes to therapeutic decision making.¹⁻⁶

Coronary CT angiography (CTA) is a noninvasive procedure with high diagnostic performance for the detection and exclusion of obstructive coronary stenosis.⁷⁻¹⁰ Although CTA offers high sensitivity and negative predictive value, its specificity and positive predictive value are less robust and indicate a systematic overestimation of stenosis severity.¹¹⁻¹³ Furthermore, even for high-grade stenoses correctly identified by CTA, comparison with a fractional flow reserve or SPECT reference standard indicates that more than half do not cause ischemia.¹³,¹⁴ These findings have evoked concerns that CTA without adjunctive physiologic data may promote excess referral to invasive angiography and/or revascularization.

Stress myocardial CT perfusion (CTP) provides a combined assessment of both cardiac anatomy and physiology. Multiple single-center studies have established its feasibility using stress agents such as adenosine and dipyridamole, with similar diagnostic accuracy compared with other techniques, including SPECT, fractional flow reserve, cardiac magnetic resonance imaging, and invasive coronary angiography.¹⁵⁻²²

To date, however, the diagnostic performance of regadenoson CTP has not been tested in a prospective, multicenter study. Moreover, all prior investigations have been confined to single CT scanner vendors. Thus, the hypothesis of this multicenter, multivendor phase 2 trial is to evaluate whether regadenoson CTP is noninferior to regadenoson SPECT for the detection or exclusion of myocardial ischemia.

### Methods

Patients (men ≥45 years; women ≥50 years) with known or suspected coronary artery disease (n = 124) were randomized to 1 of 2 diagnostic sequences: rest and regadenoson SPECT on day 1, then regadenoson CTP and rest CTP (and coronary CT angiography [CTA]) (CTA; same acquisition) on day 2 or regadenoson CTP and rest CTP (and CTA) on Day 1, then rest and regadenoson SPECT on day 2. Scanning platforms included 64-, 128-, 256-, and 320-slice systems. The primary analysis examined the agreement rate between CTP and SPECT for detecting or excluding reversible ischemia in ≥2 myocardial segments as assessed by independent, blinded readers.

#### Results

Complete and interpretable CTP and SPECT scans were obtained for 110 patients. Regadenoson CTP was noninferior to SPECT for detecting or excluding reversible ischemia with an agreement rate of 0.87 (95% confidence interval [CI], 0.77–0.97) and sensitivity and specificity of 0.90 (95% CI, 0.71–1.00) and 0.84 (95% CI, 0.77–0.91), respectively. The agreement rate for detecting or excluding ≥1 fixed defects by regadenoson CTP and SPECT was 0.86 (95% CI, 0.74–0.98). With SPECT as the reference standard, the diagnostic accuracies for detecting or excluding ischemia by regadenoson CTP and CTA alone were 0.85 (95% CI, 0.78–0.91) and 0.69 (95% CI, 0.60–0.77), respectively.

#### Conclusions

This study establishes the noninferiority of regadenoson CTP to SPECT for detecting or excluding myocardial ischemia.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0).
regadenoson-stress CTP scan and a rest CTP (and CTA) scan on day 1, then a rest SPECT scan and a regadenoson-stress SPECT scan on day 2.

The efficacy analysis set included all randomized subjects with interpretable SPECT and CTP scans as determined by at least 2 of the 3 blinded readers. The safety analysis set included all randomized subjects who received at least 1 dose of regadenoson.

2.2. Myocardial perfusion imaging

Regadenoson was used as the stress agent for both the SPECT and CTP imaging procedures. At least 24 hours were required between each dose of regadenoson. Subjects’ symptoms, heart rates, blood pressures, and electrocardiograms (ECGs) were closely monitored throughout the imaging procedures.

2.2.1. SPECT imaging

All SPECT MPI procedures were performed as previously described and according to the American Society of Nuclear Cardiology guidelines. For the stress scan, regadenoson was administered as a single bolus injection delivered over 10 seconds via an intravenous (IV) catheter, followed immediately by a 5-mL saline flush. The radiotracer (dose according to investigator discretion or site standard of care) was administered 10 to 20 seconds after the saline flush, and stress SPECT scans were performed 60 (±10) minutes after radiotracer administration.

2.2.2. CTP imaging

For CTP procedures, the stress scan was performed before the rest scan to avoid potential contamination of delayed contrast from the rest scan into the stress scan. The CTP imaging protocol, including scanner-specific information, has been previously described in detail. In summary, the following principles were maintained across scanner platforms: (1) real-time bolus tracking was implemented to trigger the onset of imaging; (2) prospective ECG triggering was used when adequate heart rate control was maintained; (3) when retrospective ECG gating was required (because of higher heart rates), tube current modulation was used, with peak current from 40% to 80% of the R-R interval for stress CTP and 10% of mid-diastole for rest CTP; and (4) tube voltage and current were adjusted according to body mass index with 100 kV used for smaller subjects.

Just before the stress scan, subjects with a heart rate of >65 beats/min and blood pressure >100/60 mm Hg were given oral metoprolol 50 to 100 mg. Regadenoson was administered as a single bolus injection delivered over 10 seconds via an IV catheter, followed immediately by a 5-mL saline flush. Approximately 1 minute after regadenoson administration, the subject’s heart rate was obtained to update the scanner parameters (for retrospective ECG gating in general when heart rate >65 beats/min, or prospective ECG triggering if heart rate was ≤65 beats/min). Provided that the subject was deemed stable, 50 to 75 mL (depending on scanner platform and subject size) of iodinated contrast was administered into the same catheter no later than 1.5 minutes after regadenoson administration, with images acquired no later than 2 minutes after regadenoson administration while the subject performed a breathhold.

The rest CTP and CTA scans (same acquisition) were performed at least 30 minutes after the stress CTP scan, allowing for any regadenoson-related symptoms to resolve and the subject’s heart rate to return to within 10 beats/min of baseline. Just before the rest scan, if the subject’s heart rate remained elevated, IV metoprolol 5 mg was administered every 3 to 5 minutes (up to 20 mg). Sublingual nitroglycerin 0.4 mg was administered 3 minutes before image acquisition to achieve coronary vasodilation. A second 50- to 75-mL (depending on scanner platform and subject size) bolus of iodinated contrast was then administered (with the total dose for the stress and rest procedures not to exceed 150 mL) and images acquired while the subject performed a breathhold.

2.2.3. Imaging data interpretation

Reconstructed image data were transferred from all sites to a core laboratory for processing and analysis. Images were evaluated by 3 independent blinded expert readers for each modality.

Using parallel methods in the SPECT and CTP core laboratories and the American College of Cardiology/American Heart Association 17-segment model for standardized myocardial segmentation with exclusion of the apex, each segment was scored for perfusion defect severity using a semiquantitative scoring system (0 = normal perfusion; 1 = mild reduction in counts or mild reduction in attenuation <1/3 transmurality, not definitively abnormal; 2 = moderate reduction in counts or moderate reduction in attenuation >1/3 to <50% transmurality, definitely abnormal; 3 = severe reduction in counts or severe reduction in attenuation >50% transmurality; 4 = absent uptake or absent perfusion with myocardial thinning). For each of the 17 segments, both fixed and reversible defects were identified, and the total number of each calculated for each subject. The number of reversible defects was calculated as the number of segments with positive differences (stress score – rest score) for segments with a stress score >1. A subject was determined to be ischemic if ≥2 segments had reversible defects according to the median count across the 3 readers. If the segment was scored ≥1 and was equal at both rest and stress, the segment was counted as having a fixed defect. A subject was determined to have the presence of fixed defects if ≥1 segment had a fixed defect according to the median count across the 3 readers.

Coronary CTA analysis was performed at least 30 days after the CTP review by 2 of the CTP readers. Readers were blinded to the SPECT and stress CTP images and results. All coronary segments with a diameter >1.5 mm were analyzed for percent stenosis using an 18-segment model, following the Society of Cardiovascular Computed Tomography guidelines, and a categorical scale (0%, 1%–24%, 25%–49%, 50%–69%, 70%–99%, 100%). Differences in assessments between the readers were resolved by consensus.
2.3. Safety assessments

Adverse events were collected immediately after the first dose of regadenoson through the day 3 follow-up, and serious adverse events were collected through the day 30 follow-up. The incidence of adverse events observed from the time of regadenoson administration to 24 hours after regadenoson administration within each modality was summarized by modality.

Radiation exposure was examined in all subjects who completed rest and stress scans for each modality. For CT, radiation dose was estimated from the dose-length product reported by each scanner and converted to whole body effective dose using the factor $k = 0.014 \, \text{mSv/mGy-cm}$. For SPECT, whole body effective dose was estimated using the administered radiopharmaceutical dose and the methodology of International Commission on Radiological Protection (ICRP-80). Specifically, the administered activity millicuries was converted to an estimated whole body effective dose (in mSv) using a factor of $0.285 \, \text{mSv/mCi of Tc99-sestamibi}$ and a factor of $0.23 \, \text{mSv/mCi of Tc99-tetrofosmin}$.

2.4. Variables

The primary variable was the median count (across the 3 independent blinded expert readers) of the number of segments with reversible defects detected by SPECT and CTP, categorized as absence ($0–1$ segments) or presence ($\geq 2$ segments) of ischemia. Secondary variables include the absence ($0$) or presence ($\geq 1$) of fixed defects as detected by SPECT and CTP. The absence ($0–1$) or presence ($\geq 2$) of reversible defects detected by SPECT was also compared with CTA ($<50\%$ or $\geq 50\%$ stenosis).

2.5. Statistical methodology

As previously described, the sample size calculation determined that 88 subjects imaged with CTP and SPECT would provide $80\%$ power to demonstrate noninferiority of CTP compared with SPECT in terms of detecting the presence ($0–1$ reversible defect) or absence ($\geq 2$ reversible defects) of ischemia using a 1-sided $z$ level of $0.025$.

Continuous variables were summarized with descriptive statistics. Discrete variables were summarized by number and/or percentage of subjects in each category. With SPECT as the reference standard, agreement rates were calculated as the average of true-positive results divided by the total number of true-positive and false-negative results plus true-negative results divided by the total number of true-negative results and false-positive results. On the basis of the pivotal regadenoson studies, the agreement rate between the 2 modalities was estimated to be $0.78$, on the basis of the dichotomous classification of presence or absence of ischemia. A $0.15$ margin corresponded to noninferiority boundaries of $0.63$ and $0.93$. As such, if the lower boundary of the $95\%$ confidence interval (CI) for the primary variable was $>0.63$, regadenoson-stress CTP would be determined to be noninferior to SPECT.

Negative predictive values were calculated as the number of true-negative results divided by the total number of true-negative and false-negative results, whereas positive predictive values were calculated as the number of true-positive results divided by the total number of true-positive and false-positive results. Prevalence was calculated as the number of true-positive results plus false-negative results divided by the total number of subjects. Analysis of negative predictive values, positive predictive values, and prevalence were all conducted post hoc.

Sensitivity was calculated as the number of true-positive results divided by the total number of true-positive and false-negative results, and specificity as the number of true-negative results divided by the total number of true-negative and false-positive results using SPECT as the reference standard.

A receiver operating characteristic plot (post hoc analysis) was constructed with summed difference score by CTP and presence or absence of ischemia ($\geq 2$ or $0–1$ reversible defects) by SPECT. The area under the curve and associated $95\%$ CIs were calculated, and the optimal cutoff point determined according to the maximum sum of sensitivity and specificity.

A post hoc analysis of the diagnostic accuracy of regadenoson CTP vs CTA alone ($<50\%$ or $\geq 50\%$ and $70\%$ or $>70\%$ stenosis) with SPECT as the reference standard was conducted, the statistical significance of which was tested using an extended McNemar test. Diagnostic accuracy was calculated as the number of true-positive results plus true-negative results divided by the total number of subjects. A post hoc summary of diagnostic performance and effective radiation dose by site experience and CT scanner was also done.

A post hoc analysis of the inter-rater agreement including $95\%$ CIs between each reader pair for each modality was performed. Inter-rater agreement was calculated as the number of subjects who were classified exactly the same for each category of number of defects divided by the total number of subjects.

3. Results

3.1. Subjects

Of 124 subjects randomized, 110 comprised the efficacy analysis set (Fig. 1). Most subjects were white males (Table 1), and the mean age was $61.6 \pm 9.3$ years. A total of $39\%$ of subjects had a history of CAD, and other comorbid conditions were commonplace, with the most frequently observed being hypertension and hyperlipidemia (Table 1). The number of subjects at each site is available in Supplementary Table 1.

3.2. Efficacy

Example images are presented in Figure 2.

The primary analysis demonstrated that regadenoson CTP was noninferior to SPECT for detecting or excluding ischemia ($\geq 2$ or $0–1$ reversible defects, respectively), with an agreement rate of $0.87$ (95\% CI, 0.77–0.97; Table 2). The sensitivity and specificity of regadenoson CTP to detect or exclude ischemia were $0.90$ (95\% CI, 0.71–1.00) and $0.84$ (95\% CI, 0.77–0.91), respectively (Table 2). Sixteen false-positive results by CTP were compared with SPECT for the detection of reversible
defects. Of these subjects, 5 had total occlusion, 3 had severe stenosis (>70%), 5 had moderate stenosis (50%–69%), and 1 had nonobstructive disease (<50%) by CTA; 2 more subjects had nonevaluable CTAs. When the summed stress score was categorized as normal or equivocal (0–3), mildly abnormal (4–7), moderately abnormal (8–11), and severely abnormal (≥12), the overall agreement rate comparing CTP to SPECT for these categories was 0.63 ± 0.046.

The agreement rate for the detection of ≥1 fixed defects by regadenoson CTP and SPECT was 0.86 (95% CI, 0.74–0.98), and the sensitivity and specificity were 0.77 (95% CI, 0.54–1.00) and 0.95 (95% CI, 0.90–0.99), respectively (Table 3). When the summed rest score was categorized as normal or equivocal (0–3), mildly abnormal (4–7), moderately abnormal (8–11), and severely abnormal (≥12), the overall agreement rate comparing CTP to SPECT for these categories was 0.76 ± 0.041.

Supplementary Table 2 describes the combined analysis of fixed and reversible defects detected by regadenoson CTP and SPECT.

Receiver operating characteristic analysis demonstrated high diagnostic accuracy of CTP summed difference score to detect or exclude ischemia (≥2 or 0–1 reversible defects, respectively), with an area under the curve (± confidence interval) of 0.93 (95% CI, 0.87–0.99; Fig. 3). The optimal summed difference score cutoff of ≥2 reversible defects yielded a sensitivity of 0.90 and a specificity of 0.93.

When the absence (0–1) or presence (≥2) of reversible defects detected by SPECT was compared with CTA (<50% or ≥50% stenosis), the agreement rate was 0.83 (95% CI, 0.78–0.87) and was similar to the agreement rate when compared with CTP (Table 4). Post hoc analysis demonstrated that the diagnostic accuracies for detecting or excluding ischemia by regadenoson CTP alone and CTA alone (≥50% or <50% stenosis) with SPECT as the reference standard were 0.85 (95% CI, 0.78–0.92) and 0.69 (95% CI, 0.60–0.78), respectively; the overall P value (P < .001) indicated CTP significantly improved diagnostic accuracy vs CTA and was driven primarily by specificity (P < .001). Results for comparisons with CTA (<70% or ≥70% stenosis) and SPECT are summarized in Table 5. The diagnostic accuracy was 0.81 (95% CI, 0.73–0.89) and the agreement rate was 0.81 (95% CI, 0.68–0.94).

The inter-rater agreement for CTP between readers 1 and 2, 1 and 3, and 2 and 3 for reversible perfusion defects was 0.77 (0.69–0.85), 0.84 (0.77–0.91), and 0.80 (0.72–0.88), respectively, and for fixed perfusion defects was 0.72 (0.63–0.81), 0.86 (0.79–0.92), and 0.74 (0.66–0.83), respectively. The inter-rater agreement for SPECT between readers 1 and 2, 1 and 3, and 2 and 3 for reversible perfusion defects was 0.92 (0.86–0.97), 0.91 (0.85–0.96), and 0.95 (0.91–0.99), respectively, and for fixed perfusion defects was 0.96 (0.93–1.00), 0.95 (0.91–0.99), and 0.97 (0.94–1.00), respectively.

Diagnostic performance and effective radiation dose by site experience and CT scanner platform are summarized in Supplementary Table 3.

### 3.3. Safety

A total of 69% (81 of 118) subjects experienced an adverse event, most of which were considered mild [43.2% [51 of 118]]. The incidence of adverse events within 24 hours of the last dose of regadenoson was similar between the treatment modalities (45.3% for SPECT and 50.9% for CTP; Table 6). Four subjects experienced severe adverse events that were considered probably or possibly related to regadenoson (angina pectoris, dyspnea, jaw pain, and vomiting). Two
Fig. 2 — Example images. Example images from a 69-year-old male patient presenting with chest pain. Coronary CTA demonstrates stenoses of > 50% severity in all 3 vessels (A). CTP shows a large-sized, severe, partially reversible defect in the mid-to-apical anterior wall, apical wall, apical septal wall, and apical lateral wall (B). SPECT shows a moderate sized, mild to moderate severity, partially reversible defect in the mid-to-apical anterior wall, apical wall, and apical lateral wall (C). CTA, CT angiography; CTP, CT perfusion; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; SPECT, single photon emission CT. Arrows demonstrate an area of inducible ischemia in the anterior wall (LAD distribution).
subjects experienced serious adverse events that led to discontinuation from the study (gastritis [within 24 hours of regadenoson administration] and uncontrolled hyperglycemia [>24 hours after regadenoson administration]); neither event was considered to be regadenoson-related. Other than the subject with gastritis, no other serious adverse events were reported within 24 hours after regadenoson administration. No deaths were reported.

Four subjects had a systolic blood pressure <90 mm Hg, 1 of whom was successfully treated with aminophylline. One subject had a diastolic blood pressure >200 mm Hg; the subject did not receive treatment and the blood pressure returned to normal by 60 minutes after regadenoson administration. One subject experienced ventricular tachycardia 2 minutes after regadenoson administration that lasted 1 minute and did not require intervention.

The total mean (± standard deviation) radiation dose was significantly higher for regadenoson CTP (17.7 ± 6.8 mSv) compared with regadenoson SPECT (11.2 ± 1.8 mSv; P = .001).

4. Discussion

This is the first study demonstrating the diagnostic accuracy of regadenoson CTP compared with regadenoson SPECT in a multicenter, multivendor trial. Consistent with the findings of previous studies,15–22 this study demonstrates that both anatomic and perfusion information can be gleaned from a single examination, with comparable diagnostic accuracy to regadenoson SPECT.

The primary analysis of this study confirmed that regadenoson-stress CTP was noninferior to regadenoson-stress SPECT in detecting the presence or absence of ischemia (>2 or 0–1 reversible defects, respectively) with high agreement rate (0.87 [95% CI, 0.77–0.97]). Moreover, the agreement rate for the detection of ≥1 fixed defects by
Regadenoson CTP and SPECT was also high (0.86; 95% CI, 0.74–0.98). As such, these results demonstrate that regadenoson CTP can detect or exclude myocardial ischemia (reversible defects) and myocardial infarct (fixed defects) with similar diagnostic performance to SPECT.

Further analyses demonstrated that regadenoson CTP had a significantly higher diagnostic accuracy to detect myocardial ischemia compared with CTA alone (with SPECT as the reference standard). This finding confirms prior results that stress CTP can provide incremental value to CTA alone in improving the diagnostic accuracy to detect hemodynamically significant stenosis.15–22 The combined evaluation of stress CTP (physiology) and CTA (anatomy) in a single setting is attractive for certain patient populations, particularly in patients where guidance to define the best therapeutic options are needed, or in patients presenting with intermediate or borderline coronary stenoses by coronary CTA where, historically, further downstream functional testing may have been required.

The CORE 320 study recently assessed the diagnostic accuracy of adenosine-stress CTP and adenosine- or exercise-stress SPECT for the diagnosis of obstructive CAD (>50% stenosis).33 The study demonstrated that CTP had greater diagnostic accuracy compared with SPECT for diagnosing obstructive CAD. Furthermore, the results of the CORE 320 study demonstrated incremental improvement in diagnostic accuracy when adding CTP to CTA for diagnosing vessels with hemodynamically significant stenosis.33 As such, these 2 large multicenter trials are complementary, and the present study further expands the use of stress CTP to multiple CT vendors and to sites with limited experience in stress CTP.33

Administration of regadenoson was well tolerated in this study. Adverse events were consistent with the known safety and tolerability profile of regadenoson, and safety profiles were similar for the 2 imaging modality sequences. The increased radiation exposure of the regadenoson CTP protocol in this trial compared with the SPECT protocol may be attributed primarily to 3 reasons: (1) many different CT vendors were used with predominant 64-slice CT technology; (2) the stress CTP protocol required a retrospective gating acquisition that was a conservative approach to ensure good image quality at the expense of increased radiation dose; and (3) this relatively obese population directly influenced radiation exposure and tube settings such as kVp and mAs. It is highly likely that regadenoson CTP radiation doses will drop as increased use of new detectors, iterative reconstruction, and software updates will continue to allow for radiation dose reduction, as discussed previously.23,34

This study has some limitations. First, invasive coronary angiography with fractional flow reserve, which currently is considered the gold standard to detect hemodynamic significance of a specific lesion, was not used as the reference standard. Second, because of the relatively low number of subjects with significant ischemia, definitive conclusions cannot be drawn in an analysis by extent or severity of ischemia, and limits conclusions that can be drawn from subset analyses. Third, this study assessed myocardial perfusion using visual and semiquantitative methods. There

### Table 4 — Numbers of coronary stenoses detected by CTA (<50% or ≥50% stenosis) as compared with reversible defects detected by regadenoson SPECT.

<table>
<thead>
<tr>
<th>Number of perfusion defects</th>
<th>Regadenoson SPECT (reference standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Condition positive (≥2)</td>
</tr>
<tr>
<td>CTA test outcome</td>
<td></td>
</tr>
<tr>
<td>Test outcome positive (≥50%)</td>
<td>10 (true positive)</td>
</tr>
<tr>
<td>Test outcome negative (&lt;50%)</td>
<td>0 (false negative)</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Agreement rate ± SE (95% CI)</td>
<td>0.83 ± 0.024 (0.78–0.87)</td>
</tr>
<tr>
<td>Specificity ± SE (95% CI)</td>
<td>0.65 ± 0.049 (0.56–0.75)</td>
</tr>
<tr>
<td>Sensitivity ± SE (95% CI)</td>
<td>1.00 ± 0.000 (1.00–1.00)</td>
</tr>
<tr>
<td>Negative predictive value (95% CI)</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Positive predictive value (95% CI)</td>
<td>0.23 (0.10–0.36)</td>
</tr>
<tr>
<td>Prevalence (95% CI)</td>
<td>0.10 (0.04–0.16)</td>
</tr>
<tr>
<td>Diagnostic accuracy (95% CI)</td>
<td>0.69 (0.60–0.78)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CTA, coronary CT angiography; SE, standard error; SPECT, single photon emission CT.

### Table 5 — Numbers of coronary stenoses detected by CTA (<70% or ≥70% stenosis) as compared with reversible defects detected by regadenoson SPECT.

<table>
<thead>
<tr>
<th>Number of perfusion defects</th>
<th>Regadenoson SPECT (reference standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Condition positive (≥2)</td>
</tr>
<tr>
<td>CTA test outcome</td>
<td></td>
</tr>
<tr>
<td>Test outcome positive (≥70%)</td>
<td>8 (true positive)</td>
</tr>
<tr>
<td>Test outcome negative (&lt;70%)</td>
<td>2 (false negative)</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Agreement rate ± SE (95% CI)</td>
<td>0.81 ± 0.066 (0.68–0.94)</td>
</tr>
<tr>
<td>Specificity ± SE (95% CI)</td>
<td>0.81 ± 0.040 (0.73–0.89)</td>
</tr>
<tr>
<td>Sensitivity ± SE (95% CI)</td>
<td>0.80 ± 0.126 (0.55–1.00)</td>
</tr>
<tr>
<td>Negative predictive value (95% CI)</td>
<td>0.97 (0.93–1.00)</td>
</tr>
<tr>
<td>Positive predictive value (95% CI)</td>
<td>0.31 (0.13–0.49)</td>
</tr>
<tr>
<td>Prevalence (95% CI)</td>
<td>0.10 (0.04–0.16)</td>
</tr>
<tr>
<td>Diagnostic accuracy (95% CI)</td>
<td>0.81 (0.73–0.89)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CTA, coronary CT angiography; SE, standard error; SPECT, single photon emission CT.
Table 6 – Adverse events within 24 hours of the last dose of regadenoson.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Regadenoson SPECT (n = 117)</th>
<th>Regadenoson CTP (n = 116)</th>
<th>Total (n = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>53 (45.3)</td>
<td>59 (50.9)</td>
<td>81 (68.6)</td>
</tr>
<tr>
<td>Any severe event</td>
<td>2 (1.7)</td>
<td>4 (3.4)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Any serious event</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Any event resulting in discontinuation</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)*</td>
</tr>
<tr>
<td>Most common events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>18 (15.4)</td>
<td>26 (22.4)</td>
<td>40 (33.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (12.8)</td>
<td>23 (19.8)</td>
<td>38 (32.4)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>11 (9.4)</td>
<td>9 (7.8)</td>
<td>20 (17.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (9.4)</td>
<td>6 (5.2)</td>
<td>17 (14.4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13 (11.1)</td>
<td>10 (8.6)</td>
<td>23 (19.8)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>4 (3.4)</td>
<td>9 (7.8)</td>
<td>13 (11.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (7.7)</td>
<td>6 (5.2)</td>
<td>15 (12.8)</td>
</tr>
</tbody>
</table>

CTP, myocardial CT perfusion; SPECT, single photon emission CT.
* A second subject discontinued the study after a serious adverse event of uncontrolled hyperglycemia >24 hours after regadenoson administration on the day he was to undergo the CTP procedure. The event was not considered to be regadenoson related.

are ongoing efforts to quantify myocardial perfusion in absolute terms.\textsuperscript{35} Fourth, the high prevalence of subjects with known CAD (39%) likely resulted in a high number of falsely positive CTA findings. At the same time, the prevalence of myocardial ischemia was low providing an advantage for CTP. This limits the generalizability of the study findings to other populations. Finally, almost half of the participant sites had limited experience with stress CTP before, and thus, accuracy would be expected to be even higher and radiation dose lower in sites that have more experience in acquisition of CTP. However, the results support the fact that this technique can be generalized and used across a wide range of sites, not just in “expert” centers.

Future research studies should address how this combined evaluation of stress CTP and CTA in a single setting can be cost-effective and improve patient outcomes for specific patient populations by guiding better therapeutic options.

5. Conclusion

This multicenter, multivendor study demonstrates good diagnostic accuracy of CTP for the detection of ischemia compared to SPECT as the reference standard. The results met the predefined noninferiority of regadenoson CTP to SPECT for detecting or excluding myocardial ischemia; regadenoson CTP provides improved diagnostic accuracy over CTA alone for detection of myocardial ischemia.

Acknowledgments

The authors thank the study investigators, of whom the following have given permission to be acknowledged: Karthikeyan Ananthasubramaniam, MD, FACC (Henry Ford Hospital, Detroit, MI); Juan Batlle, MD (Baptist Hospital of Miami and Baptist Cardiac and Vascular Institute, Miami, FL); Marcio Bittencourt, MD (Brigham and Women’s Hospital, Boston, MA); Stephen Bloom, MD (Midwest Cardiology Associates, Overland Park, AL); Alvaro Gomez, MD (Cardiovascular Research Center of South Florida, Miami, FL); Eddie Hulten, MD, MPH, FACC, FSCCT (Brigham and Women’s Hospital, Boston, MA); John J. Mahmarian, MD, FACC (Houston Methodist DeBakey Heart & Vascular Center, Houston, TX); Michael Shapiro, DO (Oregon Health & Science University, Portland, OR); Mark Zhuk (Elite Imaging LLC, Aventura, FL).

All authors critically reviewed and revised the article drafts and approved the final version for submission.

REFERENCES


**Supplementary Table 1 – Number of subjects at each site.**

<table>
<thead>
<tr>
<th>Site</th>
<th>CT machine</th>
<th>Regadenoson SPECT-MDCT (N = 55), n (%)</th>
<th>Regadenoson MDCT-SPECT (N = 55), n (%)</th>
<th>Total (N = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Siemens Definition Flash; 128 × 0.6</td>
<td>2 (3.6)</td>
<td>4 (7.3)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>B</td>
<td>Toshiba Aquilion ONE 320; 320 × 0.6</td>
<td>7 (12.7)</td>
<td>5 (9.1)</td>
<td>12 (10.9)</td>
</tr>
<tr>
<td>C</td>
<td>Phillips 256 ITC; 128 × 0.625</td>
<td>7 (12.7)</td>
<td>4 (7.3)</td>
<td>11 (10.0)</td>
</tr>
<tr>
<td>D</td>
<td>GE Lightspeed VCT 64 × 0.625</td>
<td>5 (9.1)</td>
<td>1 (1.8)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>E</td>
<td>GE VCT 64; 64 × 0.625</td>
<td>4 (7.3)</td>
<td>4 (7.3)</td>
<td>8 (7.3)</td>
</tr>
<tr>
<td>F</td>
<td>GE Lightspeed VCT; 64 × 0.625</td>
<td>3 (5.5)</td>
<td>2 (3.6)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>G</td>
<td>Phillips Brilliance 64; 64 × 0.625</td>
<td>11 (20.0)</td>
<td>9 (16.4)</td>
<td>20 (18.2)</td>
</tr>
<tr>
<td>H</td>
<td>Phillips Brilliance 64; 64 × 0.625</td>
<td>0</td>
<td>1 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>I</td>
<td>GE VCT 64; 64 × 0.625</td>
<td>6 (10.9)</td>
<td>14 (25.5)</td>
<td>20 (18.2)</td>
</tr>
<tr>
<td>J</td>
<td>Siemens Definition 64; 64 × 0.6</td>
<td>0</td>
<td>1 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>K</td>
<td>Siemens Sensation 64; 64 × 0.6</td>
<td>10 (18.2)</td>
<td>10 (18.2)</td>
<td>20 (18.2)</td>
</tr>
</tbody>
</table>

MDCT, multidetector computed tomography; SPECT, single photon emission CT.

**Supplementary Table 2 – Number of fixed and reversible perfusion defects detected by regadenoson CTP and SPECT.**

<table>
<thead>
<tr>
<th>Number of fixed defects or reversible defects (*)</th>
<th>Regadenoson SPECT (reference standard)</th>
<th>Condition positive</th>
<th>Condition negative</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test outcome positive</td>
<td></td>
<td>18 (true positive)</td>
<td>16 (false positive)</td>
<td>34</td>
</tr>
<tr>
<td>Test outcome negative</td>
<td></td>
<td>2 (false negative)</td>
<td>74 (true negative)</td>
<td>76</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>20</td>
<td>90</td>
<td>110</td>
</tr>
</tbody>
</table>

Agreement rate ± SE (95% CI) 0.86 ± 0.039 (0.78–0.94)
Specificity ± SE (95% CI) 0.82 ± 0.040 (0.74–0.90)
Sensitivity ± SE (95% CI) 0.90 ± 0.067 (0.77–1.00)
Negative predictive value (95% CI) 0.97 (0.93–1.00)
Positive predictive value (95% CI) 0.53 (0.36–0.70)
Prevalence (95% CI) 0.18 (0.11–0.25)
Diagnostic accuracy (95% CI) 0.84 (0.77–0.91)

CI, confidence interval; CTP, CT perfusion; SE, standard error; SPECT, single photon emission CT.
* Positive: ≥1 fixed or ≥2 reversible; negative: 0 fixed and 0 to 1 reversible.
### Supplementary Table 3 – Diagnostic performance and effective radiation dose by site experience and CT scanner platform.

<table>
<thead>
<tr>
<th>Experience</th>
<th>Number of subjects</th>
<th>Agreement ± SE (95% CI)</th>
<th>Specificity ± SE (95% CI)</th>
<th>Sensitivity ± SE (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
<th>Prevalence (95% CI)</th>
<th>Diagnostic accuracy (95% CI)</th>
<th>Effective dose (mSv), mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior experience with CTP</td>
<td>70</td>
<td>0.91 ± 0.024 (0.86–0.96)</td>
<td>0.82 ± 0.049 (0.73–0.92)</td>
<td>1.00 ± 0.000 (1.00–1.00)</td>
<td>1.00 (1.00–1.00)</td>
<td>0.42 (0.20–0.64)</td>
<td>0.11 (0.04–0.18)</td>
<td>0.84 (0.75–0.93)</td>
<td>17.34 (6.71)</td>
</tr>
<tr>
<td>Limited prior experience with CTP</td>
<td>40</td>
<td>0.68 ± 0.179 (0.33–1.00)</td>
<td>0.87 ± 0.055 (0.76–0.98)</td>
<td>0.50 ± 0.354 (0.00–1.00)</td>
<td>0.97 (0.91–1.00)</td>
<td>0.17 (0.00–0.47)</td>
<td>0.05 (0.00–0.12)</td>
<td>0.85 (0.74–0.96)</td>
<td>18.17 (7.25)</td>
</tr>
<tr>
<td>CT model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GE Lightspeed VCT</td>
<td>39</td>
<td>0.78 ± 0.139 (0.51–1.00)</td>
<td>0.89 ± 0.052 (0.79–0.99)</td>
<td>0.67 ± 0.272 (0.13–1.00)</td>
<td>0.97 (0.91–1.00)</td>
<td>0.33 (0.00–0.71)</td>
<td>0.08 (0.00–0.17)</td>
<td>0.87 (0.76–0.98)</td>
<td>18.41 (8.23)</td>
</tr>
<tr>
<td>Siemens Definition</td>
<td>7</td>
<td>N/A</td>
<td>0.86 ± 0.132 (0.60–1.00)</td>
<td>N/A</td>
<td>1.00 (1.00–1.00)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.86 (0.60–1.00)</td>
<td>16.12 (10.58)</td>
</tr>
<tr>
<td>Toshiba Aquilion ONE</td>
<td>12</td>
<td>0.94 ± 0.058 (0.82–1.00)</td>
<td>0.88 ± 0.117 (0.65–1.00)</td>
<td>1.00 ± 0.000 (1.00–1.00)</td>
<td>1.00 (1.00–1.00)</td>
<td>0.80 (0.45–1.00)</td>
<td>0.33 (0.06–0.60)</td>
<td>0.92 (0.77–1.00)</td>
<td>15.80 (5.59)</td>
</tr>
<tr>
<td>Phillips iCT</td>
<td>11</td>
<td>0.95 ± 0.047 (0.86–1.00)</td>
<td>0.90 ± 0.095 (0.71–1.00)</td>
<td>1.00 ± 0.000 (1.00–1.00)</td>
<td>1.00 (1.00–1.00)</td>
<td>0.50 (1.00–1.00)</td>
<td>0.09 (0.00–0.26)</td>
<td>0.91 (0.74–1.00)</td>
<td>14.30 (5.01)</td>
</tr>
<tr>
<td>Siemens Somatom Sensation 64</td>
<td>20</td>
<td>N/A</td>
<td>0.90 ± 0.067 (0.77–1.00)</td>
<td>N/A</td>
<td>1.00 (1.00–1.00)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.90 (0.77–1.00)</td>
<td>18.63 (4.97)</td>
</tr>
<tr>
<td>Phillips Brilliance</td>
<td>21</td>
<td>0.82 ± 0.055 (0.71–0.92)</td>
<td>0.63 ± 0.111 (0.41–0.85)</td>
<td>1.00 ± 0.000 (1.00–1.00)</td>
<td>1.00 (1.00–1.00)</td>
<td>0.22 (0.00–0.49)</td>
<td>0.10 (0.00–0.23)</td>
<td>0.67 (0.47–0.87)</td>
<td>18.60 (5.56)</td>
</tr>
</tbody>
</table>

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SE, standard error.