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Combining Coronary Angiography and Myocardial Perfusion by Computed Tomography in the Identification of Flow-Limiting Stenosis – The CORE320 study:

A Coronary CTA/Myocardial CTP Integrated Analysis

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Abstract

Background—The combination of coronary computed tomography angiography (CTA) and myocardial CT perfusion (CTP) is gaining increasing acceptance, but a standardized approach to be implemented in the clinical setting is necessary.

Objectives—To investigate the accuracy of a combined coronary CTA and myocardial CTP comprehensive protocol compared to coronary CTA alone, using a combination of invasive coronary angiography (ICA) and Single-Photon Emission Computed Tomography (SPECT) as reference.

Methods—Three-hundred eighty-one patients included in CORE320 trial were analyzed in this study. Flow-limiting stenosis was defined as the presence of ≥ 50% stenosis by ICA with a related perfusion deficit by SPECT. The combined CTA+CTP definition of disease was the presence of a ≥ 50% stenosis with a related perfusion deficit. All data sets were analyzed by two experienced readers, aligning anatomical findings by CTA with perfusion deficits by CTP.

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Results—Mean patient age was 62±6 years (66% male), 27% with prior history of myocardial infarction. In a per-patient analysis, sensitivity for CTA alone was 93% specificity was 54%, positive predictive value (PPV) was 55%; negative predictive value (NPV) 93% and overall accuracy was 69%. After combining CTA and CTP, sensitivity was 78%, specificity 73%, NPV 64%; PPV 0.85% and overall accuracy was 75%. In a per-vessel analysis, overall accuracy of CTA alone was 73% as compared to 79% for the combination of CTA and CTP ($p<0.0001$ for difference).

Conclusions—Combining coronary CTA and myocardial CTP findings through a comprehensive protocol is feasible. While sensitivity is lower, specificity and overall accuracy are higher than assessment by coronary CTA when compared against a reference standard of stenosis with an associated perfusion deficit.

Keywords

Coronary Computed Tomography Angiography; Myocardial Computed Tomography Perfusion; Myocardial Perfusion Imaging; Multislice Computed Tomography; Hybrid Imaging

Introduction

The diagnosis and management of obstructive coronary artery disease (CAD) has changed in recent years. While previous practice was supported by the results of invasive coronary angiography (ICA) alone to guide revascularization therapy, new guidelines recommend the assessment of related myocardial ischemia to proceed with percutaneous coronary intervention¹.

Coronary computed tomography angiography (CTA) is a well-established tool for the diagnosis of obstructive CAD, showing good accuracy to detect stenosis when compared to anatomical standards²⁻⁴. However, identification of epicardial obstructions related to flow limitations (and thus myocardial ischemia) is not an achievable goal using purely anatomical models^{5,6}, and further tests are necessary to have this complementary information.

Recently, evaluation of myocardial computed tomography perfusion (myocardial CTP) has become feasible⁷. Prior studies have reported that CT perfusion imaging can help accurately diagnose CAD compared with various reference standards including single photon emission computed tomography (SPECT), invasive coronary angiography, magnetic resonance (MR) imaging, and fractional flow reserve⁸⁻¹³. These encouraging results stimulated the development of a multicenter, multinational trial to test the diagnostic performance of an integrated protocol of coronary angiography and myocardial perfusion by CT in a single exam, to detect stenoses related to perfusion deficits using SPECT-MPI and ICA as the reference¹⁴.

Combining anatomical and functional information provided by the same exam is a tremendous advance for the detection of stenosis related to abnormal myocardial perfusion. The ability to align coronary anatomy and myocardial territories by the same observer is an important goal to accomplish if we intent to make this promising technique available in the clinical setting.

The aim of this study was to test the diagnostic performance of a combined/comprehensive protocol to align the results of coronary CTA to myocardial CTP by the same reader, using the results of combined SPECT-MPI and ICA as the reference standard.

Material and Methods

Patient population

The CORE320 study (www.clinicaltrials.gov, NCT00934037) is a multicenter prospective multinational study (16 centers, 8 countries) designed to evaluate the performance of coronary CTA and myocardial CTP in the diagnosis of obstructive CAD (>50% stenosis with a matching perfusion deficit), using the combination of ICA plus SPECT-MPI as the reference standard¹⁴⁻¹⁶. All 381 patients with complete imaging dataset reported in the main analysis were included in this secondary analysis.

Patients between 45 and 85 years of age clinically referred for ICA were included in the study. Exclusion criteria included: known allergy to iodinated contrast media, elevated serum creatinine (> 1.5mg/dl) or calculated creatinine clearance of <60ml/min, atrial fibrillation, second or third degree atrio-ventricular block, previous cardiac surgery, coronary intervention within the past 6 months, evidence of acute coronary syndrome with thrombolysis in myocardial infarction risk score ≥ 5 or elevated cardiac enzymes in the past 72 hours, high radiation exposure (≥ 5.0 rems) in the 18 months before consent and body mass index ≥ 40 m/kg² among others¹⁶. The study design included coronary CTA, adenosine stress CTP, SPECT-MPI (in a validated CORE320 laboratory, within 60 days before invasive coronary angiography), and ICA.

CTA Image acquisition

CTA methods for CORE320 have been detailed elsewhere¹⁶. Briefly, rest imaging, including both coronary calcium scoring and coronary CTA, was performed before the stress CTP acquisition, all using a 320×0.5 mm row detector CT (Aquilion One, Toshiba Medical Systems, Otawara, Japan). Prospectively ECG-triggered rest coronary angiography images were performed using iodinated contrast (Iopamidol 370 mg iodine/mL [50–70 mL] injected intravenously at 4.0-5.0 mL/sec) using bolus tracking in the descending aorta.

Myocardial CTP Image acquisition

The myocardial CTP acquisition protocol has also been described elsewhere¹⁶. After rest images were obtained, adenosine (140µg/kg/min) was infused continuously for 6 minutes, and a second bolus of iodinated contrast (Iopamidol 370 mg iodine/mL [50–70 mL] was injected intravenously at 4.0-5.0 mL/sec) using bolus tracking in the descending aorta, with a prospective ECG-triggered acquisition.

Coronary CTA and Myocardial CTP data analysis

The raw data from calcium scoring, rest and stress scans were independently reconstructed and processed in a central laboratory. Two experienced readers analyzed both coronary CTA and myocardial CTP images using a Vitrea™ fX version 3.0 workstation (Vital Images, Minnetonka, MN, USA), through a stepwise approach (figure 1). The first step of the

algorithm was coronary CTA interpretation, grading stenosis in main epicardial vessels and branches >1.5mm in diameter by visual assessment. When lumen analysis was compromised by artifacts, excessive calcification and/or stent with poor luminal assessment, the vessel was recorded as uninterpretable. Myocardial CTP assessment was performed using qualitative metrics, defined by presence of any perfusion deficit as well as its reversibility. Finally, the readers combined anatomical and perfusion information on a visual basis, according to individual anatomical variations, in order to match 50% stenosis with related fixed or reversible perfusion deficits (providing the definition of positivity for the combined analysis). Uninterpretable segments in coronary CTA that could be associated to reversible perfusion deficits were classified as “positive” for stenosis (50% stenosis). Additionally, readers were able to “reclassify” borderline or equivocal stenosis by CTA, upgrading or downgrading lesions according to the findings of the myocardial CTP analysis. Representative cases of combining CTA and CTP findings are displayed in figure 2.

Reference Standard Imaging

The results of the combined assessment of ICA and SPECT-MPI (CORE320 reference standard) were independently evaluated in specific core laboratories, and have been previously described¹⁶. For ICA, coronary segmentation and quantitative coronary angiography (QCA) were performed using standard software (CAAS II QCA Research version 2.0.1 software, Pie Medical Imaging) for all lesions above 30% by visual assessment. Rest/stress 99mTc SPECT myocardial perfusion imaging was performed either using a treadmill exercise test or a pharmacological stress test (adenosine or dipyridamole) and the images were analyzed by two experienced readers. Flow limiting disease was defined on a per vessel-territory basis as 50% stenosis from ICA/QCA plus an associated myocardial perfusion deficit in SPECT-MPI (summed stress score [SSS]>0). Stenosis related to ischemia was defined as 50% stenosis by ICA/QCA with a related reversible perfusion deficit by SPECT-MPI (summed difference score [SDS]>0). A blinded adjudication was performed to align ICA and SPECT findings, using a dedicated algorithm¹⁷.

Statistical Analysis

Clinical and imaging databases were integrated and analyzed in the statistical core laboratory at the Bloomberg School of Public Health. The primary analysis compared the diagnostic accuracy of coronary CTA combined with myocardial CTP versus coronary CTA alone, using ICA/SPECT-MPI as the reference standard. The comparison was based on the parameters of sensitivity, specificity, predicted values and overall accuracy, using a cut-off of 50% stenosis for CTA alone, and 50% stenosis related to a perfusion deficit by myocardial CTP. All data are reported with 95% confidence intervals. For patient-level and individual vessel analyses, confidence intervals were calculated exactly by the binomial method. For simultaneous analysis of all vessels, GEE was used to account for repeated measurements within patients. Statistical analysis was performed using SAS 9.2, Stata 11, and SPlus 8.0.

Results

Patient Population

All patients included in CORE320 study who had interpretable CTA and CTP scans were included in this analysis. Clinical and demographic characteristics of the 381 patients included in the analysis are displayed in Table 1. Additional data including patient flow, adverse events, radiation exposure and use of medications have been described in detail elsewhere¹⁴. The majority of the subjects was male (66%), with a previous history of coronary artery disease (confirmed by either history of documented myocardial infarction [27%] or percutaneous coronary intervention [30%]). Most of the patients were referred to ICA after presenting with anginal symptoms (83%).

Diagnostic performance of combined Coronary CTA and Myocardial CTP and Coronary CTA alone in the identification of flow-limiting stenosis

Diagnostic performance of coronary CTA alone to predict stenosis (QCA $\geq 50\%$), and myocardial CTP alone to predict perfusion deficits by SPECT (SSS ≤ 1) are displayed in table 2. At the patient level, diagnostic performance (overall accuracy) of combined CTA and CTP to detect flow-limiting stenosis was 0.75 (95%CI: 0.70–0.79), compared to 0.69 for CTA alone (95%CI: 0.64–0.75; $p = 0.004$ for difference) (table 3). In the group of patients with no prior history of CAD, combined CTA + CTP accuracy was 0.81 (95%CI: 0.76–0.86) while CTA alone was 0.72 (95%CI: 0.66–0.78; $p < 0.0001$ for difference). These results were achieved mainly by a decrease in sensitivity (0.93 [95%CI: 0.88–0.97] vs. 0.78 [95%CI: 0.70–0.84]) and an increase in specificity (0.54 [95%CI: 0.47–0.60]) vs. 0.73 ([95%CI: 0.67–.79] comparing CTA alone to combined CTA and CTP, respectively for all patients) (table 3). Parameters of sensitivity, specificity, positive and negative predictive values at the patient level are also displayed in table 3.

In a vessel-based analysis, the addition of CTP led to an improvement in the diagnostic accuracy of the combined analysis when compared to coronary CTA alone (0.79 [95%CI: 0.77–0.82] vs. 0.73 [95%CI: 0.70–0.76] respectively; $p < 0.0001$ for difference) (table 4). The analysis of diagnostic performance of CTA and CTA + CTP in a specific vessel-territory approach showed non-significant increments in accuracies. Left anterior descending artery (LAD) was associated with higher sensitivity, but lower specificity values when evaluated with CTA + CTP. Combined CTA and CTP analysis in LCx and RCA territories showed low sensitivity, but high specificity for detection of flow-limiting stenosis (table 4).

Discussion

The CORE320 study was designed to compare the performance of combined coronary CTA and myocardial CTP using as reference standard hemodynamically significant lesions defined as $\geq 50\%$ stenosis by QCA related to perfusional deficits by SPECT-MPI. To minimize bias and consider CT under the most rigorous conditions, each of the four imaging modalities underwent blinded interpretation from independent core laboratories. This approach mandated a comprehensive mathematical strategy to correlate lesions between angiography and perfusion. However, for CT to be implemented in practice, CTP images

will be used in conjunction with the CTA images by a single cardiovascular imager to improve management decisions. Thus, this study relaxes the methodology of the main paper to test a clinically realistic comprehensive protocol to integrate the anatomical and perfusion findings by the same reader.

The current methodology was design to validate a clinical workflow implementation, by integrating the CTA and CTP findings by the same reader (figure 1). On the other hand, the main CORE320 study performed independent coronary CTA and myocardial CTP analysis, and CTA and CTP readers independently recorded their findings in a database. In a second step, adjudication sessions were required to align coronary obstructions and perfusion deficits. This approach was imperative to avoid bias in both anatomy and perfusion interpretations, but it does not offer a straightforward algorithm to be implemented in the routine workflow.

In practice, we hypothesize that myocardial CTP can provide “tiebreaker” data when the CTA images reveal borderline lesions or when coronary segments are difficult to interpret because of dense calcium, stents, or other artifact. On the converse, CTA images can be useful to determine false-positive perfusion deficits related to artifacts (in those cases with no obstructions in the coronary CTA) or to help identify perfusion deficits related to microvascular disease. The rationale for integrating coronary CTA and myocardial CTP into a single read is based on the fact that the presence of coronary lumen obstruction identified by CT alone are not strongly related to ischemia^{18,19}.

Smaller studies report combined coronary CTA and myocardial CTP interpretation. Rocha-Filho et al²⁰ analyzed thirty-five high-risk patients referred to ICA with a stress-rest coronary CTA / myocardial CTP protocol. The high plaque burden likely limited the diagnostic accuracy for the coronary CTA alone; the positive predictive value increased substantially after inclusion of the myocardial CTP readings. Combined coronary CTA / myocardial CTP protocols were also applied in evaluation of patients with stents, using the same rationale – to overcome the limitation of luminal assessment by coronary CTA, with encouraging results^{21,22}. Additionally, previous data highlighted the importance of myocardial perfusion deficits in prognosis, showing independent value to predict events in follow-up^{23,24}.

Pilot data combining 320-detector-row coronary CTA plus myocardial CTP²⁵, used the same reference standard and rest-stress CT protocol as CORE320 with an improved accuracy when CTP was added to CTA data. Overall, the accuracy assessed by the area under receiver-operator characteristics curve (AUC ROC) was better with the addition of myocardial perfusion assessed by CT (AUC ROC = 0.92 for coronary CTA alone vs 0.96 for coronary CTA + myocardial CTP, in both per patient and per-vessel analysis).

Using the CORE320 data myocardial CTP analysis when interpreted with coronary CTA substantially increased the specificity (with a drop in the sensitivity) to identify stenosis related to myocardial perfusion deficits. These findings were consistent among patients with and without previous CAD, both in per-patient and in per-vessel analyses. Unlike the original CORE 320 study, the same reader performed both coronary CTA and myocardial

CTP reports in this analysis. The advantage of this approach is the simultaneous alignment between anatomy and perfusion. Notably, besides the increment in specificity in both per-patient and per-vessel levels, addition of CTP to standard CTA did not offer a substantial increase in positive predictive values.

The ability to detect rest and stress CT perfusion deficits with matched coronary stenosis using the same modality is promising. The ischemic burden related to coronary obstruction defines the best approach (either optimal medical treatment alone or combined with revascularization)²⁶. This analysis showed that combined CTA+CTP is superior to CTA alone to detect stenoses matched to both rest and stress perfusion deficits (including non-viable infarcted areas) (table 4).

The results provided by this analysis support the implementation of a rest-stress coronary CT protocol in the clinical setting. After performing coronary CTA, if no evidence of obstructive lesion ($\geq 50\%$ stenosis) is found, the myocardial CTP could be aborted. Given the high negative predictive value of coronary CTA alone to identify stenosis related to myocardial perfusion deficits, the addition of myocardial CTP analysis in this scenario would not provide much useful information. However, if lesions above 50% (or uninterpretable segments) were identified, then myocardial CTP scan could be considered if clinical data (i.e., characteristics of symptoms, risk factors, etc.) and results of other tests (i.e, ECG, prior SPECT when available) were not enough to clarify the diagnosis of obstructive CAD.

We recognize some limitations in this study. The CORE 320 study protocol selected patients referred for invasive angiography (including patients with positive SPECT-MPI studies), which represent a selected population. Additionally, rest-stress CT protocols require intravenous administration of β -blockers before the perfusion images, which theoretically could interfere in the identification of ischemia²⁷. However, given that CTA and CTP identified more false positives than false negatives, this effect was minimal¹⁴. Technical limitations related to the nature of the CTP exams, including artifacts related to motion and beam-hardening, were present in some scans, which contributed to false-positive results. The selection of SPECT-MPI as the perfusion reference standard was based on clinical availability and widespread acceptance. However, other modalities including MR perfusion or fractional flow reserve could offer better sensitivity. Finally, the addition of a stress phase for myocardial perfusion evaluation increases the exam duration.

Conclusions

Combined coronary CTA and myocardial CTP analysis is superior compared to coronary CTA alone in the identification of $\geq 50\%$ stenosis by ICA related to myocardial perfusion deficits identified by SPECT-MPI. We also showed the feasibility of a comprehensive protocol to integrate the findings of both modalities by the same reader, in order to translate this novel approach to the clinical practice.

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Abbreviations list

AUC ROC	Area Under Receiver Operating Characteristics Curve
BMI	Body Mass Index (Kg/m ²)
CAD	Coronary Artery Disease
CT	Computed Tomography
CTA	Computed Tomography Angiography

CTP	Computed Tomography Perfusion
ECG	Eletrocardiogram
GEE	Generalized Estimated Equations
ICA	Invasive Coronary Angiography
IQR	Inter-Quartile Range
LAD	Left Anterior Descending Artery
LCx	Left Circumflex Artery
NPV	Negative Predictive Value
PCI	Percutaneous Coronary Intervention
PPV	Positive Predictive Value
QCA	Quantitative Coronary Angiography
RCA	Right Coronary Artery
SDS	Summed Difference Score
SPECT-MPI	Single-Photon Emission Computed Tomography – Myocardial Perfusion Imaging
SSS	Summed Stress Score

Highlights

- Combined coronary CT angiography and Myocardial CT perfusion is gaining acceptance.
- Analysis of both methods by the same reader is feasible and superior to CTA alone.
- A natural workflow is presented aiming the implementation in the clinical setting.

Figure 1.

Workflow for interpretation of coronary CTA and myocardial CTP findings. CTA – Computed tomography angiography; CTP – Computed tomography perfusion

Figure 2.

Combining CTA and CTP data in diagnostic of flow-limiting stenosis. **Patient 1** - (A) Left Anterior Descending (LAD) artery with a mixed plaque leading to an intermediate (50-69%) stenosis (CTA **positive** for 50% stenosis - arrow). (B, C) Stress/Rest images showing no evidence of perfusional deficits in anterior wall, with correspondent findings in SPECT-MPI (combined CTA + CTP **negative** for 50% stenosis with related perfusion deficit) (D, E). (F) Invasive angiography showing borderline stenosis in LAD (arrow), but with no relation to myocardial ischemia according to SPECT results (reference standard **negative** for 50% stenosis with related perfusion deficit). **Patient 2** - (G) Significant stenosis in distal Right Coronary Artery (RCA) (CTA **positive** for 50% stenosis - arrow), with a corresponding perfusional deficit (most reversible) in left ventricle inferior wall ((H, I). Combined CTA and CTP was **positive** for 50% stenosis with related perfusion deficit. Reference standard images show similar reversible perfusion deficit in inferior wall by SPECT-MPI (J, K), and the related stenosis by ICA (L). CTA - Computed Tomography Angiography; CTP - Computed Tomography Perfusion; ICA - Invasive Coronary Angiography; SPECT -MPI - Single-Photon Emission Computed Tomography - Myocardial Perfusion Imaging.

Table 1**Baseline characteristics**

Characteristic	Median [IQR] or N (%)
Age, years	62 (56 – 68)
Male	252 (66)
Body mass index (BMI), kg/m ²	27 (24 – 30)
Race	
-White	213 (56)
-Black	40 (10)
-Asian	123 (32)
-Other	5 (1)
Diabetes	131 (34)
Smoking	
-Current	64 (18)
-Past	133 (37)
-Never	167 (46)
Dyslipidemia	254 (68)
Hypertension	297 (78)
Family history of CAD	162 (45)
Prior history of myocardial infarction	103 (27)
Prior history of revascularization (PCI)	113 (30)
Asymptomatic	26 (7)
Anginal Symptoms (typical or atypical)	315 (83)
Non-Cardiac Chest Pain	5 (2)

BMI – Body Mass Index; CAD – Coronary Artery Disease; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention.

Table 2

Per-patient diagnostic performance of coronary CTA and myocardial CTP alone according to the respective gold-standard (n = 381).

Group/Test	Gold Standard	Sensitivity	Specificity	PPV	NPV
CTA 50% or uninterpretable	QCA 50%	93 (88-96)	79 (72-85)	87 (82-91)	88 (81-93)
Any CTP perfusion deficit positive	Global SPECT	75 (68-81)	54 (47-62)	63 (56-69)	68 (60-75)

CTA – Computed Tomography Angiography; CTP – Computed Tomography Perfusion; PPV – Positive Predictive Value; NPV – Negative Predictive Value.

Table 3
Per-patient diagnostic performance of Combined Coronary CTA + myocardial CTP and coronary CTA alone for detection of flow-limiting stenosis*

	Overall		Previous CAD		No previous CAD	
	CTA	CTA+CTP	CTA	CTA+CTP	CTA	CTA+CTP
Sensitivity, %	93 (88-97)	78 [†] (70-84)	89 (80-95)	71 [†] (60-80)	98 (91-100)	87 [†] (76-94)
Specificity, %	54 (47-60)	73 [†] (67-79)	27 (17-40)	57 [†] (44-70)	63 (56-70)	79 [†] (73-85)
PPV, %	55 (48-61)	64 (56-71)	61 (52-70)	68 (57-78)	49 (40-58)	60 (49-70)
NPV, %	93 (87-96)	85 (79-89)	65 (44-83)	60 (47-72)	99 (95-100)	95 (90-98)
Accuracy %	69 (64-73)	75 [†] (70-79)	62 (54-70)	65 (56-73)	72 (66-78)	81 [†] (76-86)

* Gold-standard definition for disease is a 50% stenosis by QCA with related SPECT SSS (Summed Stress Score) 1 in one of the three vessels: LAD, LCX, or RCA.

[†] p<0.05 for difference from CTA alone by McNemar's test. Statistical comparisons of PPV and NPV were not performed.

CAD – Coronary Artery Disease; CTA – Computed Tomography Angiography; CTP – Computed Tomography Perfusion; PPV – Positive Predictive Value; NPV – Negative Predictive Value.

Table 4
Per-vessel-territory diagnostic performance of Combined Coronary CTA + myocardial CTP and coronary CTA alone for detection of flow-limiting stenosis*

	Overall			LAD			LCX			RCA		
	CTA	CTA + CTP	CTA	CTA	CTA+CTP	CTA	CTA	CTA+CTP	CTA	CTA	CTA+CTP	CTA
Sensitivity, %	83 (77-88)	58 ^{††} (51-64)	86 (77-92)	86 (77-92)	72 [†] (62-81)	81 (72-89)	81 (71-88)	59 [†] (48-70)	81 (71-88)	41 [†] (31-52)		
Specificity, %	70 (66-74)	86 ^{††} (83-88)	60 (54-66)	60 (54-66)	77 [†] (72-82)	78 (73-83)	72 (66-77)	90 [†] (85-93)	72 (66-77)	91 [†] (87-94)		
PPV, %	45 (40-50)	55 (48-61)	40 (33-47)	40 (33-47)	49 (40-58)	52 (43-61)	46 (38-54)	62 (51-73)	46 (38-54)	56 (43-69)		
NPV, %	93 (91-95)	87 (84-90)	93 (88-96)	93 (88-96)	90 (86-93)	94 (90-96)	93 (88-96)	88 (84-92)	93 (88-96)	84 (79-88)		
Accuracy %	73 (70-76)	79 [†] (77-82)	66 (61-71)	66 (61-71)	76 [†] (71-80)	79 (74-83)	74 (69-78)	83 (78-86)	74 (69-78)	79 [†] (75-83)		

* Gold-standard definition for disease is a 50% stenosis by QCA with related SPECT SSS (Summed Stress Score) 1.

[†] p<0.05 for difference from CTA alone by Wald test (Overall) or McNemar's test (vessel-specific). Statistical comparisons of PPV and NPV were not performed.

^{††} indicates that statistical difference was also dependent on vessel.

CAD – Coronary Artery Disease; CTA – Computed Tomography Angiography; CTP – Computed Tomography Perfusion; PPV – Positive Predictive Value; NPV – Negative Predictive Value.