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Incremental diagnostic accuracy of computed tomography myocardial perfusion imaging over coronary angiography stratified by pre-test probability of coronary artery disease and severity of coronary artery calcification: The CORE320 study☆

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ABSTRACT

Background: Myocardial CT perfusion (CTP) has been validated as an incremental diagnostic predictor over coronary computed tomography angiography (CTA) in assessing hemodynamically significant stenosis.
Objectives: To assess the diagnostic performance of CTA and CTP alone versus combined CTA–CTP stratified by Morise's pre-test probability and coronary artery calcium (CAC, Agatston) score.
Methods: 381 individuals (153 low/intermediate-risk for CAD, 83 high-risk, 145 known CAD) were further stratified based on CAC score cut-offs of 1–399 and ≥400. Area under the curve for receiver operating characteristics (AUC) was calculated to assess the diagnostic performance. Reference standards were QCA ≥ 50% stenosis + corresponding SPECT summed stress score ≥1.
Results: In both pre-test risk groups with an Agatston score of 1–399, AUCs of CTA–CTP were not significantly different than that from CTA alone. In the low/intermediate-risk group with CAC score 1–399, AUC for CTA–CTP (89) was higher than that for CTP (76, $p = 0.003$) alone. In the same group with CAC score ≥400, AUCs were higher for CTA–CTP (97) than that for CTA (88, $p = 0.030$) and CTP (83, $p = 0.033$). In high risk/known CAD patients with CAC 1–399, diagnostic performance for CTA–CTP (77) was superior to CTP (71, $p = 0.037$) alone. In the high risk/known CAD group with CAC score ≥400, AUCs for combined imaging were higher (86) than that for CTA (75, $p < 0.001$) as well as CTP (78, $p = 0.020$).
Conclusions: The incremental diagnostic accuracy of CTP over CTA persists in patients across severity spectra of pre-test probability of CAD and coronary artery calcification. In patients with severe coronary calcification (CAC score ≥ 400), combined CTA–CTP has better diagnostic accuracy than CTA and CTP alone.

Abbreviations: CTA, coronary computed tomography angiography; CAD, coronary artery disease; CAC, coronary artery calcium; CTP, myocardial computed tomography perfusion; ICA, invasive coronary angiography; SSS, summed stress score.

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1. Introduction

The predictive value of coronary computed tomography angiography (CTA) is significantly influenced by the prevalence of coronary artery disease (CAD) in a study population [1]. Current guideline statements [2,3] designate the usefulness of CTA in low–intermediate risk population given its excellent negative predictive value (NPV) to rule out obstructive coronary disease. Conversely, the diagnostic accuracy of CTA is reduced in high risk and known CAD patients consistent with the higher prevalence of CAD in this subgroup [1,4,5]. Therefore, it is important to assess the pre-test probability of coronary artery disease prior to testing with any diagnostic modality. Coronary artery calcium (CAC) closely correlates with the prevalence of CAD [6–9] and hence, influences the predictive values of CTA. In addition, the diagnostic performance of CTA is inversely related to the presence and severity of coronary artery calcium [1,10,11]. Realizing the limitation of CTA in patients with severe coronary calcification, many clinicians prefer to obtain a coronary calcium score in order to determine the utility of CTA in the assessment of CAD for an individual patient [12].

Single center [13–15] and multicenter [16] studies have established myocardial CT perfusion (CTP) imaging as an important incremental diagnostic predictor when added to CTA in detecting hemodynamically significant stenosis; the combined information can be obtained using a single imaging platform. Information on the presence of an anatomic stenosis and its hemodynamic relevance is critical for decision making and to determine clinical outcomes in patients with suspected CAD. Similar to other imaging modalities, the diagnostic accuracy of CTP imaging is influenced by the prevalence of CAD in the study population. Since CTP performance is not affected by the presence of coronary calcium, it may be an effective independent imaging modality or adjunct to CTA in the diagnosis of flow-obstructing stenosis, particularly in patients with severe coronary calcification.

Our objective was to assess the diagnostic performance of CTA, CTP and combined CTA–CTP in predicting functionally significant stenosis in the CORE320 study patient population stratified by pre-test probability of CAD and for severity of coronary calcification quantified as the CAC (Agatston) score. Also, we sought to explore the efficacy of CTP as an independent diagnostic test to evaluate flow-obstructive CAD, particularly in patients with severe coronary calcification.

2. Methods

The CORE320 study is a prospective, multicenter, international study (www.clinicaltrials.gov, NCT00934037) that validated the diagnostic accuracy of CT perfusion imaging in predicting functionally significant stenosis. In brief, individuals aged 45–85 years with clinical referral to invasive coronary angiography (ICA) were enrolled in the study. All patients underwent CTA, CTP, and SPECT imaging for non-invasive assessment of coronary anatomy and associated perfusion deficit within 60 days of invasive coronary angiography (ICA). Interpretations of results from individual core laboratories were blinded from each other. The study design, methods [17,18] and main results [16,19] have been published.

Rest CTA and CTP and adenosine stress CTP imaging using a first generation 320 × 0.5 detector-row CT scanner (Aquilion One; Toshiba Medical Systems, Otawara, Japan) were performed as per previously described protocols [17]. CTA and CTP images were reconstructed and independently analyzed at two separate core laboratories.

Exercise or pharmacologic SPECT imaging [20] was performed in site qualified centers as per standardized protocols [17,18] and was analyzed by two independent, experienced observers at the SPECT core laboratory using a 13-segment myocardial model [21]. A 13-segment myocardial model was selected to simplify the registration of coronary anatomy and myocardial segments and to reduce variability among the diagnostic modalities. Differences in reading were resolved using a consensus method similar to the CTP core laboratory. SPECT imaging was performed using 99mTc-labeled imaging agents, with approximately 300 MBq (8 mCi) for rest and 925 MBq (25 mCi) for stress studies. In the analysis, artifacts did not contribute to the summed stress score (SSS) and therefore a SSS ≥1 defined an abnormal SPECT study.

Study participants underwent ICA prior to or within 60 days of CT and SPECT imaging. Images were analyzed at the coronary angiography core laboratory using standard software (PIE medical imaging, Maastricht, the Netherlands). All coronary segments of at least 2 mm were analyzed for percentage diameter stenosis by using quantitative coronary angiography [22].

2.1. Coronary artery calcium (Agatston) score

The calcium score acquisition used the same CT hardware with single heart beat axial prospective ECG gating and the following parameters: tube voltage 120 kV, and tube current of 140 mA [17]. Unenhanced CT images with a 3-mm slice thickness were reconstructed using commercial filtered back projection (FC12 kernel). Mean CAC (Agatston) score was derived using an interactive software platform [22,23]. Calcium scoring was not performed on coronary artery segments with prior stents.

2.2. Statistical analyses

The patients with no known history of CAD were stratified into low, intermediate, and high risk for CAD based on the pre-test probability score described by Morise et al. [24]. Given the very low prevalence of low risk patients (n = 4), low and intermediate risk patients were combined for analysis. Those with known CAD (prior MI, previous CAD documented by invasive angiography or percutaneous coronary intervention) were also analyzed. The study population was stratified by pre-determined CAC score cut-offs of 0, 1–399, and ≥400. Subanalyses were also performed using cut-offs of ≥600 and ≥1000. The reference standard was determined to be QCA ≥ 50% stenosis with a corresponding SPECT deficit of summed stress score (SSS) ≥1. Point characteristic values were calculated with CTA threshold of stenosis ≥50% and pre-specified CTP threshold of SSS ≥2; reference standard being ICA ≥50% stenosis and SPECT threshold of SSS ≥1. Additionally, point characteristics in each group were defined using the optimum CTP threshold derived using ROC curves. The reference standard was used to estimate the prevalence of disease in respective subgroups. All analyses were performed on a per-patient basis.

Receiver operating characteristic (ROC) curves were calculated to summarize the diagnostic accuracy of test imaging predicting the reference standard. ROC curves were constructed with CTP SSS, CTA percent stenosis, and CTA–CTP as the predictor variables; combined CTA–CTP used logistic regression with CTA, CTP and Leaman score as predictors. Areas under the ROC curve (AUCs) were calculated with 95% confidence intervals by the binomial method for CTA and CTP and by bootstrap for CTA–CTP; statistical comparisons of AUCs also utilized bootstrapping. Data analyses were performed in a statistical core laboratory at the Bloomberg School of Public Health. Two-tailed p-value of <0.05 defined statistical significance. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) and Stata 12 (StataCorp, College Station, TX).

3. Results

Out of a total of 436 enrolled participants, 381 individuals (153 low/intermediate-risk, 83 high-risk, 145 known CAD) were analyzed in the study. 55 subjects were excluded because all imaging procedures were not completed (n = 29); technical failure for SPECT (n = 12), CT (n = 3), and ICA imaging (n = 1); and incomplete stress CTP imaging (n = 10). Participant demographics and characteristics are presented in Table 1.

Table 1
Patient demographics and characteristics.

Parameters	All participants (n = 381)	CAC = 0 (n = 64)	CAC 1–399 (n = 196)	CAC ≥400 (n = 120)	Low/intermediate pre-test probability (n = 153)	High pre-test probability (n = 83)	Known CAD (n = 145)
Age, years	62 [56, 68]	58 [52, 62]	63 [56, 68]	64 [58, 72]	60 [54, 66]	65 [60, 71]	63 [55, 68]
Men	252 (66%)	27 (42%)	125 (64%)	99 (83%)	78 (51%)	58 (70%)	116 (80%)
Race							
White	213 (56%)	37 (58%)	107 (55%)	68 (57%)	95 (62%)	43 (52%)	75 (52%)
Black	40 (10%)	12 (19%)	20 (10%)	8 (7%)	19 (12%)	10 (12%)	11 (8%)
Asian	123 (32%)	14 (22%)	66 (34%)	43 (36%)	37 (24%)	29 (35%)	57 (39%)
Other	5 (1%)	1 (2%)	3 (2%)	1 (1%)	2 (1%)	1 (1%)	2 (1%)
BMI, kg/m^2	27 [24, 30]	27 [24, 30]	27 [24, 29]	27 [24, 30]	27 [24, 31]	27 [24, 30]	26 [24, 29]
Hypertension	297 (78%)	34 (55%)	160 (82%)	102 (85%)	96 (63%)	71 (86%)	130 (90%)
Diabetes mellitus	131 (34%)	16 (25%)	68 (35%)	46 (38%)	33 (22%)	55 (66%)	43 (30%)
Dyslipidemia	254 (68%)	32 (50%)	128 (67%)	93 (79%)	73 (49%)	65 (81%)	116 (81%)
Smoking							
Current	64 (18%)	11 (17%)	36 (20%)	17 (15%)	30 (21%)	17 (21%)	17 (12%)
Past	133 (37%)	19 (30%)	67 (36%)	46 (40%)	35 (24%)	37 (46%)	61 (44%)
Never	167 (46%)	34 (53%)	81 (44%)	52 (45%)	80 (55%)	27 (33%)	60 (43%)
FH CAD	162 (45%)	25 (39%)	79 (42%)	57 (53%)	54 (36%)	42 (53%)	66 (52%)
Previous MI	103 (27%)	8 (13%)	58 (30%)	37 (31%)	n/a	n/a	113 (78%)
Prior PCI	113 (30%)	7 (11%)	61 (31%)	45 (38%)	n/a	n/a	103 (71%)
Angina	290 (76%)	55 (86%)	149 (76%)	85 (71%)	109 (71%)	79 (95%)	102 (70%)
CCS class							
0	62 (21%)	19 (35%)	31 (21%)	12 (14%)	38 (35%)	15 (19%)	9 (9%)
1	110 (38%)	23 (42%)	56 (38%)	31 (37%)	43 (39%)	35 (45%)	32 (32%)
2	99 (34%)	13 (24%)	50 (34%)	35 (42%)	25 (23%)	24 (31%)	50 (50%)
3	14 (5%)	0 (0%)	10 (7%)	4 (5%)	4 (4%)	3 (4%)	7 (7%)
4	4 (1%)	0 (0%)	2 (1%)	2 (2%)	0 (0%)	1 (1%)	3 (3%)
CAC score	176 [9, 550]	0 [0, 0]	106 [18, 217]	862 [557, 1396]	24 [0, 272]	340 [110, 850]	265 [74, 640]

BMI — body mass index, FH CAD — family history of premature coronary artery disease, MI — myocardial infarction, PCI — percutaneous coronary intervention, CCS — Canadian Cardiovascular Society, CAC — coronary artery calcium (Agatston) score.

Table 2
AUCs and point characteristics of CTA, CTP and combined CTA–CTP in no known CAD group stratified by pre-test probability of detecting the gold standard of ≥50% stenosis by quantitative invasive angiography with corresponding SPECT summed stress score ≥1.

Group	CTA alone	CTP alone	CTP alone[a]	CTA–CTP
Low–intermediate risk				
Calcium score = 0 (n = 49, 2.0% disease)				
AUC	100 (93–100)	96 (86–100)		100 (93–100)
Sensitivity	100 (3–100)	100 (3–100)		100 (3–100)
Specificity	96 (86–99)	79 (65–90)		98 (89–100)
PPV	33 (1–91)	9 (0–41)		50 (1–99)
NPV	100 (92–100)	100 (91–100)		100 (92–100)
Calcium score = 1–399 (n = 79, 17.7% disease)				
AUC	84 (74–91)	76 (65–85)	76 (65–85)	89 (80–99)
Sensitivity	79 (49–95)	86 (57–98)	64 (35–87)	79 (49–95)
Specificity	58 (46–71)	46 (34–59)	82 (70–90)	68 (55–79)
PPV	29 (15–46)	26 (14–40)	43 (22–66)	34 (19–53)
NPV	93 (80–98)	94 (79–99)	91 (81–97)	94 (82–99)
Calcium score = 400+, (n = 25, 52.0% disease)				
AUC	71 (51–88)	74 (55–91)	74 (55–91)	87 (75–100)
Sensitivity	100 (75–100)	85 (55–98)	77 (46–95)	85 (55–98)
Specificity	8 (0–38)	17 (2–48)	75 (43–95)	25 (5–57)
PPV	54 (33–74)	52 (30–74)	77 (46–95)	55 (32–77)
NPV	100 (3–100)	50 (7–93)	75 (43–95)	60 (15–95)
High risk				
Calcium score = 0 (n = 7, 28.6% disease)				
n/a (numbers too small)				
Calcium score = 1–399 (n = 38, 21.1% disease)				
AUC	83 (66–92)	68 (51–82)	68 (51–82)	86 (74–100)
Sensitivity	88 (47–100)	75 (35–97)	25 (3–65)	63 (24–91)
Specificity	50 (31–69)	50 (31–69)	97 (83–100)	63 (44–80)
PPV	32 (14–55)	29 (11–52)	67 (9–99)	31 (11–59)
NPV	94 (70–100)	88 (64–99)	83 (66–93)	86 (65–97)
Calcium score = 400+ (n = 37, 62.2% disease)				
AUC	88 (75–97)	83 (68–94)	83 (68–94)	97 (92–100)
Sensitivity	100 (85–100)	96 (78–100)	87 (66–97)	96 (78–100)
Specificity	0 (0–23)	14 (2–43)	71 (42–92)	21 (5–51)
PPV	62 (45–78)	65 (46–80)	83 (63–95)	67 (48–82)
NPV	n/a[b]	67 (9–99)	77 (46–95)	75 (19–99)

AUC, area under the curve, PPV, positive predictive value, NPV, negative predictive value.
[a] Point characteristics are defined using the following optimal CTP cut-off, for CAC score = 0, numbers are too small to analyze (n = 1). Low/intermediate risk: SSS ≥ 9 (CAC score 1–399) and SSS ≥ 6 (CAC score ≥ 400). High risk: SSS ≥ 9 (CAC score 1–399) and SSS ≥ 6 (CAC score ≥ 400).
[b] NPV unavailable for CTA alone as all patients were considered positive by CTA.

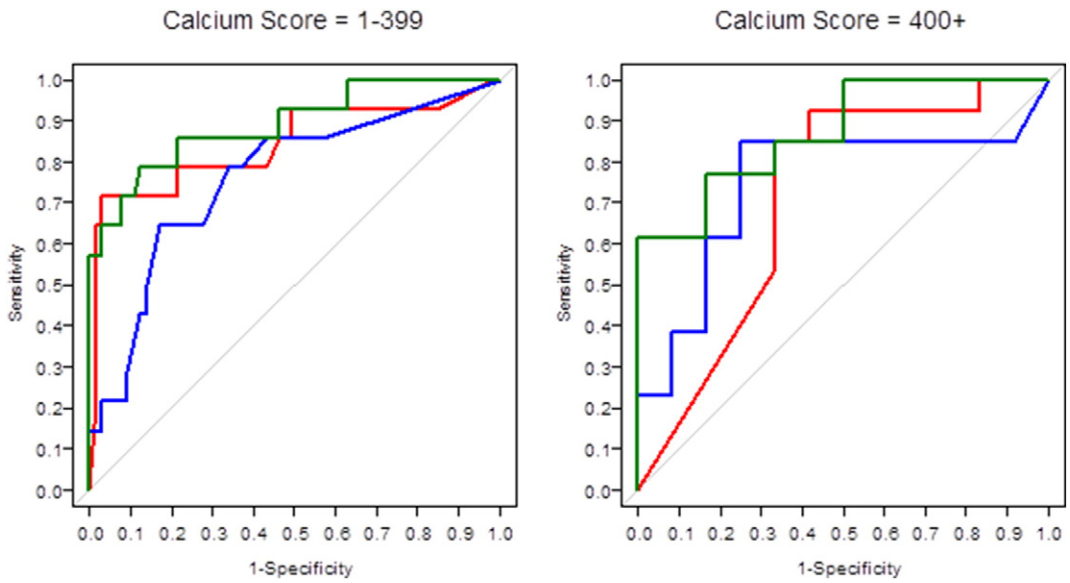

Fig. 1. ROC curves for CTA (red), CTP (blue) and combined CTA–CTP (green) in low/intermediate risk population stratified by coronary calcium score.

3.1. Low/intermediate risk participants

The prevalence of disease by ICA/SPECT in the low/intermediate risk group was 18.3%. Only 1 of the 49 patients (2%) with zero Agatston score had disease.

The AUCs for CTA, CTP and CTA–CTP in individuals categorized into the calcium score 1–399 subgroup were 84 (95% CI 74–91, p = 0.335 for comparison with CTA–CTP), 76 (65–85, p = 0.003 for comparison with CTA–CTP), and 89 (80–99), respectively. AUCs in patients with CAC score ≥400 were higher for CTA–CTP compared to CTA (p = 0.030 vs. CTA–CTP) and CTP (p = 0.033 vs. CTA–CTP) alone. CTA had poor specificity in the group with CAC score ≥400 (Table 2, Fig. 1).

3.2. Patients with high risk for CAD

Disease prevalence was 41.0%. Among the 83/381 patients stratified into the high risk category, only 7 patients had a CAC score of zero. In patients with a CAC score of 1–399, the AUC for CTA–CTP was modestly superior to CTA (p = 0.052 vs. CTA–CTP), and significantly higher than for CTP alone (p = 0.004 vs. CTA–CTP). CTA had a negative predictive value of 94% with CTP providing added information on the hemodynamic significance of stenosis (Table 2). For CAC score ≥400; diagnostic performance of combined imaging was superior to CTA (p = 0.003 vs. CTA–CTP) and CTP (p = 0.006 vs. CTA–CTP) alone.

3.3. Patients with known coronary artery disease

Patients with zero calcium score were poorly represented (n = 8) (Table 3). In known CAD patients stratified by a CAC score of 1–399; combined CTA–CTP had a comparable AUC to CTA (p = 0.474) and CTP (p = 0.241). For the group with a calcium score of ≥400, AUC for combined imaging was 79 (67–92), for CTA it was 68 (54–79, p = 0.043 vs. CTA–CTP) and for CTP, the AUC was 75 (61–85, p = 0.311 vs. CTA–CTP), respectively. In patients with CAC score ≥400, CTA was

Table 3
AUCs and point characteristics of CTA, CTP and combined CTA–CTP in individuals with history of CAD.

Group	CTA alone	CTP alone	CTA–CTP
Calcium score = 0 (n = 8, 12.5% disease)			
n/a (numbers too small)			
Calcium score = 1–399 (n = 77, 33.8% disease)			
AUC	74 (63–83)	62 (51–73)	64 (55–81)
Sensitivity	92 (75–99)	65 (44–83)	46 (27–67)
Specificity	29 (17–44)	43 (29–58)	51 (37–65)
PPV	40 (28–53)	37 (23–52)	32 (18–50)
NPV	88 (64–99)	71 (52–86)	65 (48–79)
Calcium score = 400 + (n = 58, 39.7% disease)			
AUC	74 (61–85)	50 (37–63)	66 (57–85)
Sensitivity	100 (85–100)	70 (47–87)	61 (39–80)
Specificity	0 (0–10)	23 (10–40)	31 (17–49)
PPV	40 (27–53)	37 (23–53)	37 (22–54)
NPV	n/a	53 (27–79)	55 (32–77)

Table 4
AUCs and point characteristics of CTA, CTP and combined CTA–CTP in high-risk/known CAD population (n = 228[a]) detecting the gold standard of ≥50% stenosis by quantitative invasive angiography with corresponding SPECT summed stress score ≥1.

Group	CTA alone	CTP alone[b]	CTP alone[c]	CTA–CTP
Calcium score = 0 (n = 15, 20.0% disease)				
AUC	92 (68–100)	72 (45–92)		100 (100–100)
Sensitivity	100 (29–100)	100 (29–100)		67 (9–99)
Specificity	75 (43–95)	50 (21–79)		75 (43–95)
PPV	50 (12–88)	33 (7–70)		40 (5–85)
NPV	100 (66–100)	100 (54–100)		90 (56–100)
Calcium score = 1–399 (n = 117, 46.2% disease)				
AUC	74 (65–81)	71 (62–79)	71 (62–79)	77 (69–86)
Sensitivity	85 (73–93)	91 (80–97)	41 (28–55)	87 (75–95)
Specificity	41 (29–54)	30 (19–43)	90 (80–96)	40 (28–53)
PPV	55 (44–66)	53 (42–63)	79 (59–92)	55 (44–66)
NPV	76 (59–89)	79 (58–93)	64 (53–74)	78 (60–91)
Calcium score = 400 + (n = 95, 61.1% disease)				
AUC	75 (65–83)	78 (68–86)	78 (68–86)	86 (78–94)
Sensitivity	100 (94–100)	97 (88–100)	90 (79–96)	97 (88–100)
Specificity	0 (0–9)	11 (3–25)	57 (39–73)	16 (6–32)
PPV	61 (51–71)	63 (52–73)	76 (65–86)	64 (53–74)
NPV	n/a[d]	67 (22–96)	78 (58–91)	75 (35–97)

[a] One patient has missing coronary calcium score.
[b] Point characteristics are defined using CTP cut-off of SSS ≥ 2.
[c] Point characteristics are defined using optimal CTP cut-off of SSS ≥ 9 (CAC score 1–399) and SSS ≥ 6 (CAC score ≥ 400). For CAC score = 0, numbers are too small to analyze (n = 3).
[d] NPV unavailable for CTA alone as all patients were considered positive by CTA.

abnormal in all patients, with CTP providing incremental ability to discriminate between flow-obstructing and non-flow-obstructing stenoses.

3.4. High risk/known CAD

Given that the baseline characteristics and prevalence of disease were similar in both sub-groups, high risk CAD and known CAD patients were analyzed together. In the subgroup with a CAC score of 1–399; the AUC for CTA–CTP was not significantly different than CTA alone ($p = 0.275$ vs. CTA–CTP) but was superior to CTP alone ($p = 0.037$ vs. CTA–CTP). In the subgroup with a CAC score of ≥400 ($n = 95$), diagnostic performance of CTA–CTP 86 (78–94) was higher than that of CTA 75 (65–83, $p < 0.001$ vs. CTA–CTP) as well as CTP 78 (68–86, $p = 0.020$ vs. CTA–CTP) alone (Fig. 2, Table 4). For Agatston score thresholds of ≥600 and ≥1000, combined CTA–CTP had a higher diagnostic accuracy than CTA and CTP, although the differences were not statistically significant given the diminishing sample sizes (Online supplement — Table A).

4. Discussion

By stratifying the CORE320 population by pre-test probability of coronary artery disease and calcium scoring, we have demonstrated the following: 1) Among high risk patients and those with known CAD, CTP provides incremental diagnostic value over CTA alone in differentiating flow-obstructing stenosis from non-obstructive CAD. 2) Combined CTA–CTP imaging compared to individual CTA and CTP scanning has improved diagnostic performance in the high-risk/known CAD population, particularly for patients with Agatston score greater than 400. 3) Diagnostic performance of CTP alone was not equivalent or superior to combined CTA–CTP in assessing flow-limiting stenosis in high-risk/known CAD patients with severe coronary calcification.

4.1. Role of CTP in the low/intermediate risk population

For patients with low/intermediate risk pre-test probability of CAD, CTA demonstrated an excellent negative predictive value and CTP provided incremental functional information in defining flow-obstructive stenosis in patients with CAC score ≥ 400. In patients with CAC score <400, incremental diagnostic benefit of CTP over CTA was not statistically significant, thereby underlining the benefit of CTA as an excellent "rule out" test in this population subgroup. Consistent with the current consensus, CTA could serve as a "gatekeeper" to determine the indication of perfusion imaging. This of course is applicable to a rest–stress imaging protocol, which more closely resembles the clinical practice where CTP is triggered by "abnormal" CTA with at least moderate severity of coronary stenosis or equivocal CTA.

4.2. Role of CTP in high risk and known CAD patients

The diagnostic accuracy of CTP alone was equivalent to that of CTA in determining flow-obstructing stenosis defined using QCA and SPECT. In these patients, CTA was abnormal (≥50% stenosis) in all individuals while CTP provided additional information on the hemodynamic significance of the coronary stenosis. Among those with CAC score less than 400; the diagnostic performance of combined CTA–CTP was not superior to CTA alone highlighting the implications of accurate anatomic assessment of CAD. If the objective of CTA is to exclude obstructive CAD, a high negative predictive value is required; however, given the high prevalence of CAD in this group, the emphasis is on how to obtain combined anatomic–physiologic information on a stenosis to aid in the decision-making and establish its prognostic relevance.

While the diagnostic performance of CTA to detect obstructive stenosis in the high risk and known CAD population is reduced, registration of a concurrent perfusion deficit in the vessel territory suspicious of stenosis results in a diagnosis with significantly increased degree of confidence. Additional information on lesion location, plaque characteristics, degree of remodeling, and contrast opacification patterns are also advantageous in the management of patients with CAD in this group.

4.3. Role of CTP in patients with severe coronary calcification

In patients with severe coronary calcification, CTP had equivalent diagnostic accuracy to CTA. CTA was abnormal in all patients with CAC score ≥400; however, CTP provided incremental accuracy for detecting hemodynamically significant stenosis. The diagnostic performance of CTP alone was inferior to combined CTA–CTP imaging, therefore undermining the independent role of CTP as a solo imaging modality providing comprehensive anatomic–physiologic information in this subgroup. Therefore, both studies are recommended when CT is being considered for patients who meet the reported calcium scoring thresholds.

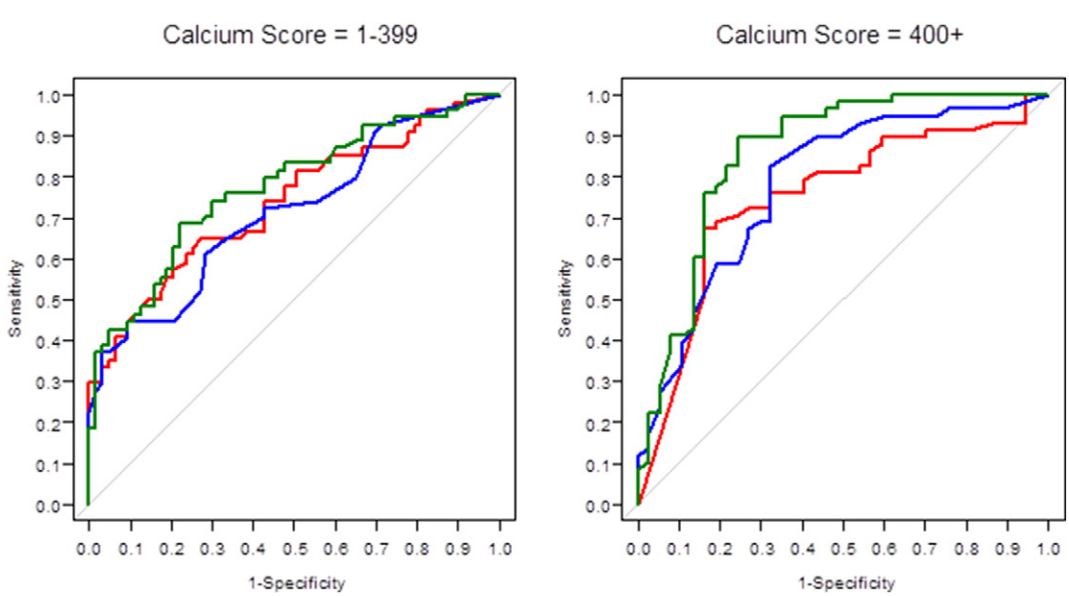

Fig. 2. ROC curves for CTA (red), CTP (blue) and combined CTA–CTP (green) in high risk/known CAD population stratified by coronary calcium score.

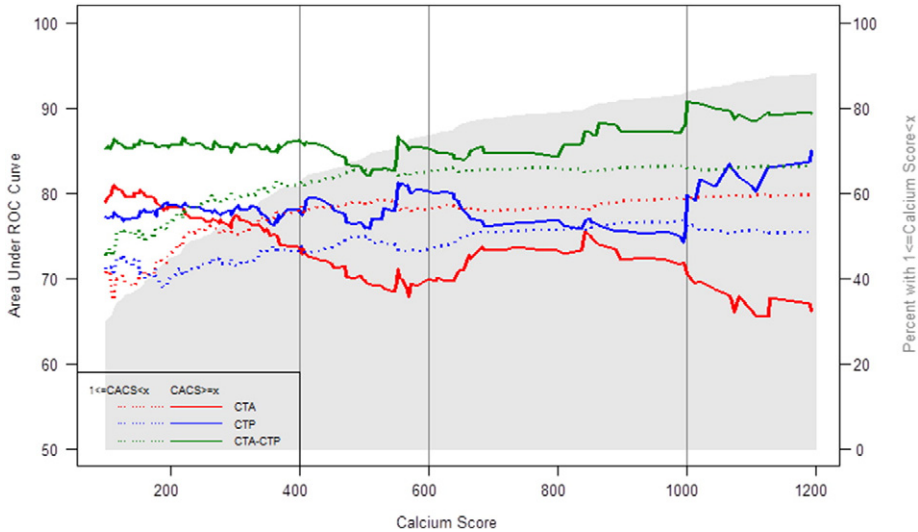

Fig. 3. AUCs for CTA (red), CTP (blue) and combined CTA–CTP (green) with changing coronary calcium score threshold demonstrating higher AUCs for combined CTA–CTP across severity spectra of CAC score. Solid lines indicate AUC in subgroup with calcium score above a particular CAC score threshold; dashed lines indicate AUC in subgroup with non-zero calcium score below the specified threshold. For e.g. with CAC score cut-off of 600, AUCs in a population with CAC score of less than 600 for CTA (red), CTP (blue) and combined CTA–CTP (green) are 78, 73 and 83 respectively. Similarly, AUCs in a population with CAC score above 600 for CTA (red), CTP (blue) and combined CTA–CTP (green) are 70, 80, and 85, respectively. Gray shade represents the percentage of population below a specific CAC score cut-off.

4.4. Is there a CAC score threshold beyond which CTP is equivalent to combined imaging?

While the diagnostic accuracy of CTA–CTP over CTA was limited in patients with CAC score <400, analyses utilizing different CAC score thresholds of 400, 600, and 1000 revealed that combined CTA–CTP better differentiated flow-obstructing stenosis compared to CTP alone (p-values not significant for threshold of 600 and 1000). Fig. 3 displays the predictive power of CTA, CTP and CTA–CTP for subgroups above (solid lines) and below (dashed lines) varying CAC thresholds, excluding patients with a zero calcium score. The analyses indicate that combined CTA–CTP is consistently superior to either individual test modality regardless of stratification based on CAC. Among patients with an Agatston score of ≥1000, the diagnostic performance of CTA declines and that of CTP increases, but the combined CTA–CTP imaging remains superior. CTP alone had inferior diagnostic accuracy compared to combined imaging (CTA–CTP) across all severity spectra of coronary artery calcification (Fig. 4).

Combined imaging may be challenging in view of establishing an incremental diagnostic value that influences therapeutic strategies. Usually, an adjunctive scan is performed if the result of initial modality is equivocal or if additional information is necessary to define therapeutic targets. In such cases, individual's pre-test likelihood of CAD and CAC score may be helpful in determining the diagnostic approach. Given its excellent NPV, CTA should be performed first in the patients with CAC score <400 with low, intermediate, and high likelihood of CAD;

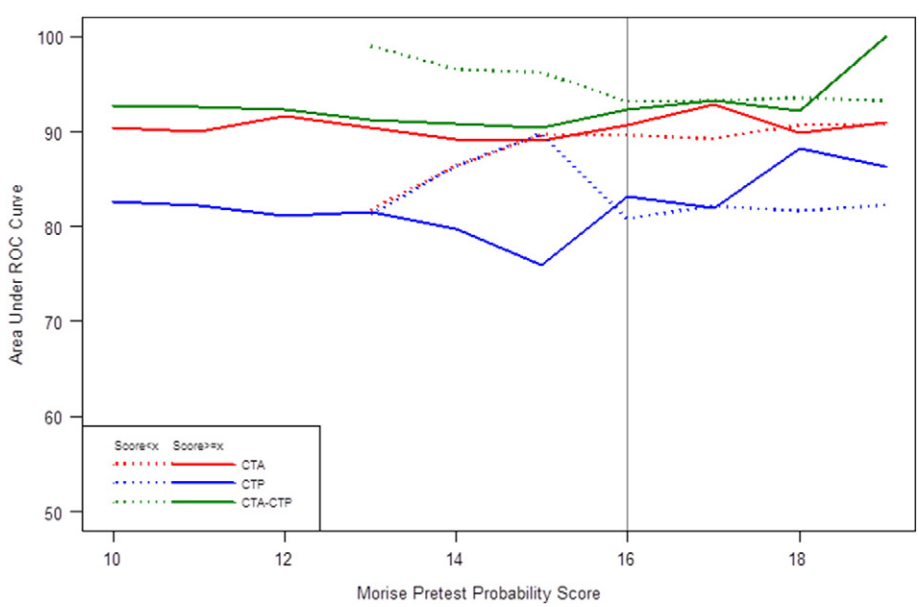

Fig. 4. AUCs for CTA (red), CTP (blue) and combined CTA–CTP (green) in participants without known CAD with changing Morise's pretest score threshold demonstrating higher AUCs for combined CTA–CTP across severity of pre-test probability. Solid lines indicate AUC in subgroup with pre-test probability (Morise's score) score above a particular Morise pre-test probability score threshold; dashed lines indicate AUCs in subgroup below a Morise pre-test probability score threshold.

followed by perfusion imaging in those with obstructive CAD in CTA. Conversely, in cases with high pre-test likelihood or established CAD with CAC score ≥400, starting with perfusion imaging may be a valid approach, with anatomic imaging being triggered by an abnormal, equivocal or suboptimal perfusion testing.

5. Study limitations

Despite comprehensive characterization of the study population, the enrolment of patients in the CORE320 trial, driven by clinical indication of invasive coronary angiography, points towards inclusion of patients with higher prevalence of CAD. The low-risk patient population was under-represented in our analyses. Although we attempted to stratify the study population utilizing an established pre-test probability score, we may not have accounted for certain factors influencing post-test probability [25]. Furthermore, categorization of study participants based on pre-test probability of CAD and CAC score restricts the sample size in each subgroup, limiting the power of the analyses. These issues may be relevant in the high risk/known CAD group with CAC score thresholds of 600 and 1000. The exclusion of segments with prior stent may result in lower quantitative estimation of CAC score. As such, the detailed analyses on the incremental diagnostic accuracy of CTA–CTP for evaluation of stented segments and its implication based on stent diameter, improvement in non-diagnostic rates, and predictive values were beyond the scope of the paper.

Dual imaging modality entails risk of higher radiation dose and is an important consideration during diagnostic evaluation of an individual. While stress echocardiography or stress cardiac magnetic resonance imaging does not involve additional radiation exposure, it is difficult to implement as a "hybrid" imaging modality limited by logistical inconvenience and lack of data on diagnostic utility. In the CORE320 study, mean radiation estimate for CTA–CTP (8.63 mSv) was significantly lower than SPECT imaging (10.48 mSv) and diagnostic catheter angiography (11.63 mSv) [26].

In summary, our results emphasize that the incremental diagnostic accuracy of CTP over CTA persists in patients across severity spectra of pre-test probability of CAD and coronary artery calcification. Importantly, in low–intermediate as well as high-risk/known CAD patients with severe coronary calcification (CAC score ≥ 400), combined CTA–CTP had better diagnostic accuracy than CTP or CTA alone. This work thus clarifies the dichotomy regarding whether CTP alone has equivalent diagnostic accuracy compared to combined CTA–CTP in the subgroup of population with severe coronary calcification. Overall, the current study supports the combination of CTA–CTP in patients with "abnormal" CTA (≥50% stenosis) and/or severe coronary calcification undergoing diagnostic CT imaging for the evaluation of coronary artery disease.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.05.110.

Conflict of interest

Dr. Ravi K. Sharma is a recipient of a post-doctoral research grant by Unijules Life Sciences Ltd., India.

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