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ORIGINAL INVESTIGATIONS

Coronary CT Angiography in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome

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ABSTRACT

BACKGROUND In patients with non-ST-segment elevation acute coronary syndrome (NSTEACS), coronary pathology may range from structurally normal vessels to severe coronary artery disease.

OBJECTIVES The purpose of this study was to test if coronary computed tomography angiography (CTA) may be used to exclude coronary artery stenosis ≥50% in patients with NSTEACS.

METHODS The VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography in Patients With Acute Coronary Syndromes) trial (NCT02061891) evaluated the outcome of patients with confirmed NSTEACS randomized 1:1 to *very early* (within 12 h) or *standard* (48 to 72 h) invasive coronary angiography (ICA). As an observational component of the trial, a clinically blinded coronary CTA was conducted prior to ICA in both groups. The primary endpoint was the ability of coronary CTA to rule out coronary artery stenosis (≥50% stenosis) in the entire population, expressed as the negative predictive value (NPV), using ICA as the reference standard.

RESULTS Coronary CTA was conducted in 1,023 patients—*very early*, 2.5 h (interquartile range [IQR]: 1.8 to 4.2 h), n = 583; and *standard*, 59.9 h (IQR: 38.9 to 86.7 h); n = 440 after the diagnosis of NSTEACS was made. A coronary stenosis ≥50% was found by coronary CTA in 68.9% and by ICA in 67.4% of the patients. Per-patient NPV of coronary CTA was 90.9% (95% confidence interval [CI]: 86.8% to 94.1%) and the positive predictive value, sensitivity, and specificity were 87.9% (95% CI: 85.3% to 90.1%), 96.5% (95% CI: 94.9% to 97.8%) and 72.4% (95% CI: 67.2% to 77.1%), respectively. NPV was not influenced by patient characteristics or clinical risk profile and was similar in the *very early* and the *standard* strategy group.

CONCLUSIONS Coronary CTA has a high diagnostic accuracy to rule out clinically significant coronary artery disease in patients with NSTEACS. (J Am Coll Cardiol 2020;75:453-63) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CTA = computed tomography angiography

ECG = electrocardiography

ICA = invasive coronary angiography

NSTEACS = non-ST-segment elevation acute coronary syndrome

In patients with acute coronary syndrome (ACS), coronary pathology ranges from structurally normal vessels to non-obstructive atherosclerosis and severe obstructive coronary artery disease (CAD). Therefore, in current guidelines, the primary diagnostic pathway for optimal management of patients with clinically confirmed non-ST-segment elevation acute coronary syndrome (NSTEACS) is invasive coronary angiography (ICA) (1). In patients with at least 1 high-risk criterion (abnormal cardiac troponin compatible with myocardial infarction, dynamic electrocardiography [ECG] changes, or a Global Registry of Acute Coronary Events [GRACE] risk score >140), ICA is recommended to be performed quickly and within 24 h. Interestingly, in the randomized component of the VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography in Patients With Acute Coronary Syndromes) trial we recently reported that a strategy of very early invasive coronary evaluation within 12 h does not improve overall long-term clinical outcome compared with an invasive strategy conducted within 2 to 3 days (2).

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The goal of this diagnostic strategy is to either rule out coronary artery disease (CAD) and thereby terminate unnecessary antithrombotic medication or to identify patients potentially in need of revascularization. A routine invasive strategy in patients with NSTEACS, however, is associated with an increased risk of bleeding as a consequence of concurrent antithrombotic medical therapy (3). Consequently, in patients with NSTEACS without coronary anatomical indication for revascularization, the risk-benefit ratio of routine ICA may not be favorable.

Coronary computed tomography angiography (CTA) has evolved as a logistically simple, accurate, and low-risk noninvasive test to diagnose or rule-out CAD (1,4). The negative predictive value of coronary CTA has been reported to be especially high in a broad range of clinical presentations (5–8). Moreover, in low-risk patients presenting with acute chest pain in the emergency room, coronary CTA has proven valuable for early rule out of ACS (9,10). Nevertheless, in patients with NSTEACS, the diagnostic accuracy of coronary CTA to rule out hemodynamically significant CAD and/or to potentially identify patients in need of revascularization is unknown.

As a pre-planned observational component of the VERDICT trial, a clinically blinded coronary CTA was conducted prior to ICA to test the hypothesis that coronary CTA conducted before ICA may be used to rule out coronary artery stenosis ≥50% in patients presenting with NSTEACS and at least 1 high-risk criterion. The diagnostic performance of coronary CTA was evaluated and compared in patients scanned within 12 h and within 2 to 3 days after the diagnosis of NSTEACS was made.

METHODS

STUDY DESIGN. The VERDICT trial is a prospective, combined observational and randomized controlled multicenter trial. The randomized component of the trial assessed the optimal timing of invasive coronary management in patients with NSTEACS (2). In brief, patients randomized to the *very early* invasive

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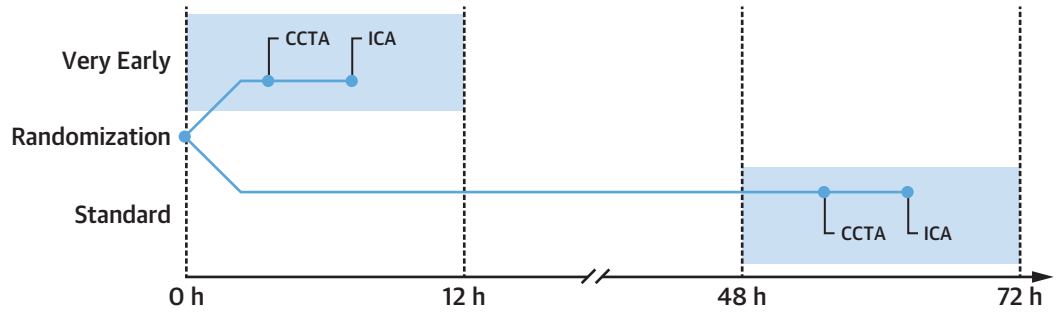
FIGURE 1 Study Design



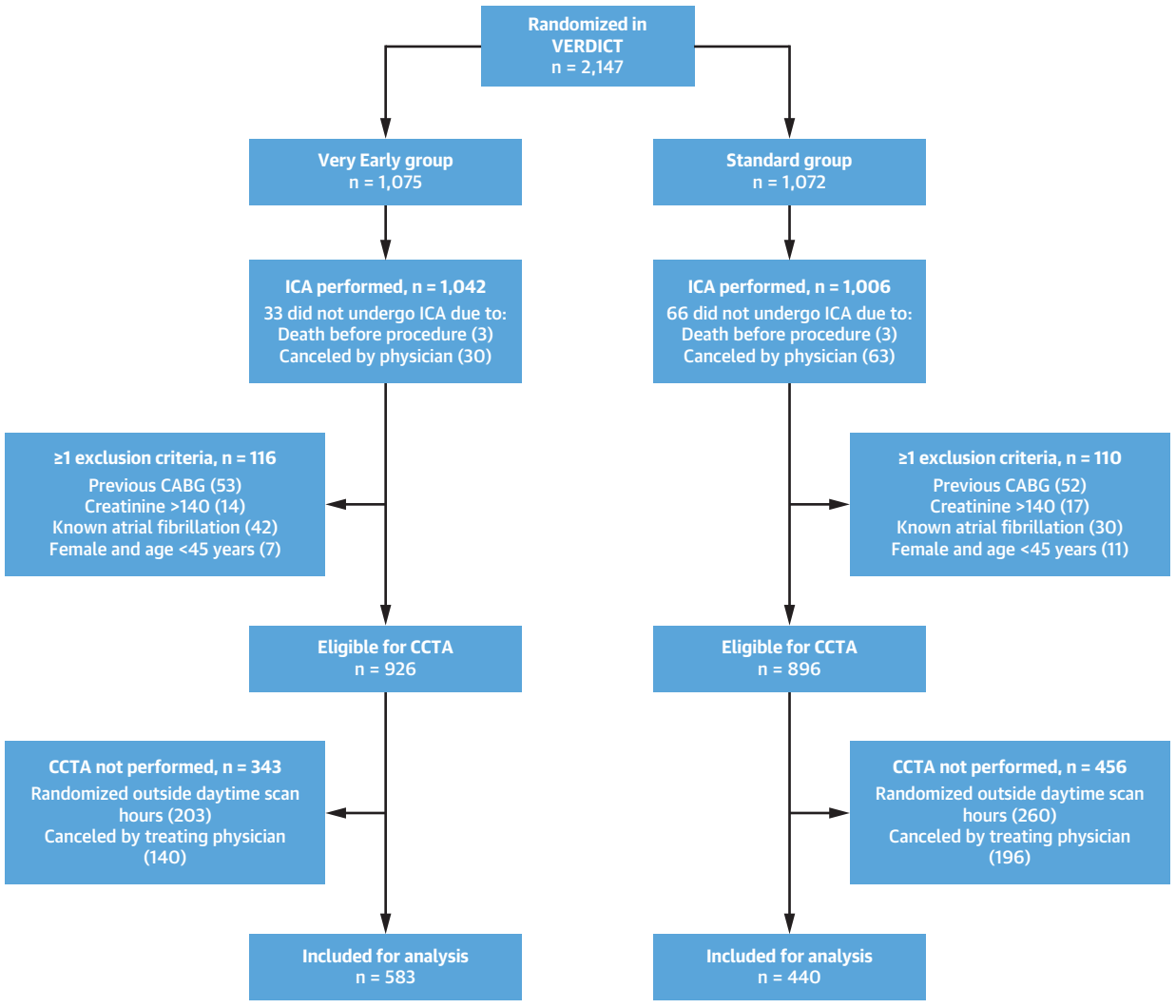
Patients in the VERDICT trial were, after diagnosis of non–ST-segment elevation acute coronary syndrome, randomized to a *very early* strategy with an invasive coronary angiography (ICA) performed within 12 h or a *standard* strategy with ICA performed within 48 to 72 h. A clinically blinded coronary computed tomographic angiography (CCTA) was performed before ICA in both groups to allow for subsequent assessment of diagnostic accuracy parameters.

strategy arm (within 12 h) were transferred immediately from the referring hospital to the invasive center for ICA, whereas patients randomized to the deferred invasive strategy arm (*standard*) were transferred within 48 to 72 h and subsequently underwent ICA. After transfer to the invasive center and prior to invasive examination, all patients underwent coronary CTA when logistically feasible (Figure 1). Coronary CTA findings remained blinded throughout the study period. The primary endpoint of this observational component was the negative predictive value of coronary CTA to rule out coronary artery stenosis ≥50%, using ICA as the reference standard. Secondary endpoints were diagnostic accuracy stratified by randomization groups and the frequency of nondiagnostic coronary CTA scans. The trial was conducted as a pragmatic clinical study embedded in routine clinical practice. The study was approved by the Danish National Committee on Health Research Ethics (Journal number H-4-2010-039) and the Danish Data Protection Agency (NCT02061891).

PARTICIPANTS. In 9 hospitals of the Capital Region of Copenhagen, Denmark, patients admitted with chest pain and suspected acute coronary syndrome were screened for inclusion (2). Patients in whom ICA was deemed clinically indicated and logistically possible within 12 h from time of diagnosis were offered participation in the study. Inclusion criteria were age ≥18 years, clinical suspicion of ACS, and at least 1 of the following high-risk criteria: 1) ECG changes indicating new ischemia (new ST-segment depression, horizontal or down sloping ≥0.05 mV in 2 consecutive leads, and/or T-wave inversion >0.01 mV in 2 leads with prominent R-wave or R/S ratio >1); and 2) an increase in coronary markers of ischemia (troponin). Exclusion criteria were pregnancy, patient inability to understand trial information, an indication for acute ICA (very high-risk NSTEACS) (1), expected survival <1 year, and known intolerance to platelet inhibitors, heparin, or x-ray contrast that could not be remedied medically. Furthermore, patients with previous coronary artery bypass grafting, creatinine >140 μmol/l, known atrial fibrillation, or women age <45 years of age were not considered eligible for coronary CTA. All included patients provided written informed consent.

PROCEDURES. Coronary computed tomography angiography. Image acquisition was performed using a 320-detector (Aquilion one, Vision Edition, Canon, Otawara, Japan) or a 64-detector (Brilliance, Phillips, the Netherlands) CT scanner, predominantly using a prospectively ECG-triggered protocol—a retrospectively gated protocol was used in patients with irregular or accelerated heart rhythms. Tube voltage was based on body mass index (BMI). Patients were pre-treated with oral metoprolol, and sublingual nitroglycerin was administered prior to contrast injection at the discretion of the treating physician. A noncontrast scan was performed prior to infusion of contrast. Intravenous contrast media (Visipaque, GE Healthcare, London, United Kingdom) was infused with a biphasic injection protocol followed by a saline chaser. Coronary CTA procedural data, including heart rate during the scan (beats/min), contrast volume (ml), and effective radiation dose in mSv, using a conversion factor of 0.014 mSv/mGy/cm, were recorded.

FIGURE 2 Study Flow Chart



Very early: invasive coronary angiography and possible revascularization within 12 h from time of diagnosis. *Standard*: invasive coronary angiography and possible revascularization within 48 to 72 h from time of diagnosis. Outside daytime scan hours were defined as working days after 4 PM and weekends. CABG = coronary artery bypass grafting; CCTA = coronary computerized tomography angiography; ICA = invasive coronary angiography; VERDICT = Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography in Patients With Acute Coronary Syndromes.

Following completion of the trial, all coronary CTAs were visually assessed in a core laboratory by consensus reading between 2 expert coronary CTA readers (J.J.L. and K.F.K.). Readers were blinded to both clinical data and randomization allocation. An external work station (Vitrea 2, version 6.9, Vital Images Inc., Minnetonka, Minnesota) was used. For each patient, CT image quality (diagnostic/non-diagnostic CT scans), presence and severity of CAD (≥50% and ≥70% diameter stenosis), and coronary artery calcium score (Agatston score) were evaluated in accordance with the Society of Cardiovascular Computed Tomography guidelines (11).

Invasive coronary angiography. ICA was performed according to guidelines and clinical practice at the respective invasive centers and assessment of coronary pathology was performed visually by the interventional cardiologist. Radiation dose ($Gy \cdot cm^2$) recorded in the cath suite was converted to mSv by a conversion factor of 0.18 $mSv \cdot Gy^{-1} \cdot cm^{-2}$.

Coronary angiography findings. For both coronary CTA and ICA, coronary pathology was assessed

according to the presence of a coronary stenosis in 1 or more coronary arteries (stenosis defined using ≥50% and ≥70% diameter stenosis thresholds) and by coronary vascular territory (≥50% diameter stenosis threshold), defined as: left main (LM), left anterior descending (LAD) including diagonal branches, left circumflex including marginal branches, and right coronary artery (RCA).

STATISTICAL ANALYSES. All results are calculated and reported according to Standards for Reporting Diagnostic Accuracy (12). Power calculations have previously been published (2). Continuous variables with normal distribution are presented as mean ± SD and compared using Student's *t*-test. Variables with non-normal distribution are presented as median (interquartile range [IQR]) and compared using Mann-Whitney *U* test. Discrete variables are presented as n (%) and compared using the Fisher exact test.

The primary analysis included categorization of all scanned patients into 3 groups according to coronary CTA findings: positive (≥1 coronary stenosis ≥50%), negative (normal or coronary stenosis <50%), or nondiagnostic. For the primary diagnostic accuracy analyses, the intention-to-diagnose principle was used, and patients with a nondiagnostic scan were considered as coronary CTA positives. An "interpretable only" analysis, excluding patients with a nondiagnostic coronary CTA, was also performed as well as an analysis excluding patients with a history of CAD, defined as previous AMI and/or percutaneous coronary intervention (PCI). In addition, an analysis applying a coronary stenosis threshold of ≥70% to define positive or negative coronary CTA was performed as well as an analysis assessing the diagnostic accuracy at the coronary vascular territory level. We created 2 × 2 contingency tables, including 95% confidence intervals (CIs), to calculate diagnostic performance estimates (negative predictive value [NPV], positive predictive value [PPV], sensitivity, specificity, and diagnostic accuracy [(true positives + true negatives)/(total number of patients)]) as well as negative and positive likelihood ratios. Receiver-operating characteristic curves were created to calculate the area under the curve. The CIs were used to compare the *very early* and *standard* group, and were calculated using the Wilson-Brown method.

Additionally, diagnostic accuracy was calculated according to the following subgroups: sex, age, BMI, history of cardiovascular disease, previous myocardial infarction, previous revascularization, diabetes, hypertension, smoking, chronic obstructive pulmonary disease, GRACE risk score, elevated troponins, ischemia in ECG, or computed tomography scanner type. Between subgroups, differences of accuracy variables were compared using the Fisher exact test with subsequent Bonferroni correction. Statistical analyses were conducted using the statistical program R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1 Clinical Characteristics

	All Patients (N = 1,023)	Very Early (n = 583)	Standard (n = 440)	p Value
Male	687 (67.2)	387 (66.4)	300 (68.2)	0.589
Age, yrs	61.9 ± 11.9	62.4 ± 11.8	61.2 ± 11.9	0.087
BMI, kg/m^2	26.9 ± 4.4	26.6 ± 4.4	27.2 ± 4.4	0.062
Diabetes	130 (12.7)	70 (12.0)	60 (13.6)	0.497
Prior smoker	370 (36.2)	210 (36.0)	160 (36.4)	0.962
Current smoker	342 (33.4)	202 (34.6)	140 (31.8)	0.377
Hypertension	491 (48.0)	268 (46.0)	223 (50.7)	0.153
Chronic obstructive pulmonary disease	130 (12.7)	70 (12.0)	60 (13.6)	0.497
Previous stroke	78 (7.6)	48 (8.2)	30 (6.8)	0.468
History of CV disease	245 (23.9)	126 (21.6)	119 (27.0)	0.052
Known valve disease	32 (3.1)	16 (2.7)	16 (3.6)	0.529
Previous AMI	149 (14.6)	73 (12.5)	76 (17.3)	0.041
Previous PCI	136 (13.3)	68 (11.7)	68 (15.5)	0.094
GRACE score >140	438 (42.8)	261 (44.8)	177 (40.2)	0.227
Elevated troponin	797 (77.9)	462 (79.2)	335 (76.1)	0.203
ECG with new ischemia	413 (40.4)	245 (42.0)	168 (38.2)	0.177

Values are n (%) or mean ± SD.

AMI = acute myocardial infarction; BMI = body mass index; CV = cardiovascular; ECG = electrocardiography; GRACE = Global Registry of Acute Coronary Events; PCI = percutaneous coronary intervention.

RESULTS

From November 2010 to June 2016, 2,147 patients were randomized in the VERDICT trial (**Figure 2**) and among 1,822 patients eligible for coronary CTA, coronary CTA was performed in 1,023 patients (56%), all of whom underwent ICA. Patient characteristics and ICA findings were similar in patients eligible for coronary CTA with (n = 1,023) and without (n = 799) coronary CTA performed (Online Appendix, Online Table 1). More patients underwent coronary CTA in the *very early* group compared with the *standard* group (583 vs. 440; p < 0.001). Clinical characteristics were similar between the 2 strategy groups, except for more patients having a history of previous acute myocardial infarction in the *standard* group (**Table 1**).

Time intervals and procedural data for coronary CTA and ICA for all patients and by randomization group are given in **Table 2**. Radiation dose, contrast volume, and heart rate during coronary CTA were similar in the 2 strategy groups. Median radiation dose in patients examined with 320-detector CT was

TABLE 2 Procedural Data for Coronary Computed Tomographic and Invasive Angiography

	All (N = 1,023)	Very Early (n = 583)	Standard (n = 440)	p Value
Coronary CTA				
Time to coronary CTA, h	9.3 (2.3–47.6)	2.5 (1.8–4.2)	59.0 (38.9–86.7)	<0.001
CT scanner type				
-320 slices	821 (80.3)	483 (82.8)	338 (76.8)	0.02
Contrast volume, ml	84.9 ± 14.6	84.5 ± 15.0	85.4 ± 14.0	0.313
Radiation dose, mSv	5.3 (3.4–10.4)	5.1 (3.3–10.2)	5.4 (3.5–10.8)	0.223
Heart rate, beats/min	63.6 ± 9.3	64.0 ± 9.3	63.0 ± 9.2	0.086
Invasive coronary angiography				
Time to ICA, h	15.0 (4.2–58.7)	4.7 (3.2–10.4)	65.0 (44.3–93.1)	<0.001
Time from coronary CTA to ICA, h	3.8 (2.9–5.9)	3.3 (2.7–4.8)	4.8 (3.3–7.0)	<0.001
Contrast volume, ml	66.2 ± 29.9	64.6 ± 29.3	68.3 ± 30.5	0.052
Radiation dose, mSv	2.3 (1.4–3.8)	2.16 (1.44–3.60)	2.52 (1.71–3.96)	0.003

Values are median (interquartile range), n (%), or mean ± SD.
CTA = computed tomography angiography; ICA = invasive coronary angiography.

4.6 mSv (IQR: 3.2 to 7.9 mSv) compared with 12.2 mSv (IQR: 10.7 to 13.2 mSv) in patients examined with 64-detector CT. ICA in the *standard* group was associated with a slightly higher radiation dose compared with the *very early* group (2.5 mSv vs. 2.2 mSv; $p < 0.003$).

Coronary CTA was positive for a coronary artery stenosis ≥50% in 705 (68.9%) patients, negative in 265 (25.9%) patients, and nondiagnostic in 53 (5.2%) patients (**Table 3**, top panel). Patients examined with 320-detector CT had a significantly lower proportion of nondiagnostic coronary CTA compared with patients examined with 64-detector CT (3.7%, 30 of 821 vs. 11.4%, 23 of 202; $p < 0.001$). ICA was positive for a coronary artery stenosis ≥50% in 690 patients (67.4%) and negative in 333 (32.6%) patients, and there was no difference between strategy groups (**Table 3**, lower panel).

TABLE 3 Coronary Angiographic Data for Coronary Computed Tomographic and Invasive Examinations

	All (N = 1,023)	Very Early (n = 583)	Standard (n = 440)	p Value
Coronary CTA				
No coronary stenosis ≥50%	265 (25.9)	137 (23.5)	128 (29.1)	0.051
Nondiagnostic scan	53 (5.2)	28 (4.8)	25 (5.7)	0.627
≥1 coronary stenosis ≥50%	705 (68.9)	418 (71.7)	287 (65.2)	0.032
1-vessel disease	292 (28.5)	179 (30.7)	113 (25.7)	0.0.91
2-vessel disease	257 (25.1)	138 (23.7)	119 (27.0)	0.246
3-vessel disease	156 (15.2)	101 (17.3)	55 (12.5)	0.042
Calcium score	165 (14–724)	198 (15–790)	132 (14–617)	0.112
Invasive coronary angiography				
No coronary stenosis ≥50%	333 (32.6)	181 (31.0)	152 (34.5)	0.265
≥1 coronary stenosis ≥50%	690 (67.4)	402 (69.0)	288 (65.5)	
1-vessel disease	380 (37.1)	215 (36.9)	165 (37.5)	0.890
2-vessel disease	165 (16.1)	99 (17.0)	66 (15.0)	0.443
3-vessel disease	145 (14.2)	88 (15.1)	57 (13.0)	0.378

Values are n (%) or median (interquartile range).

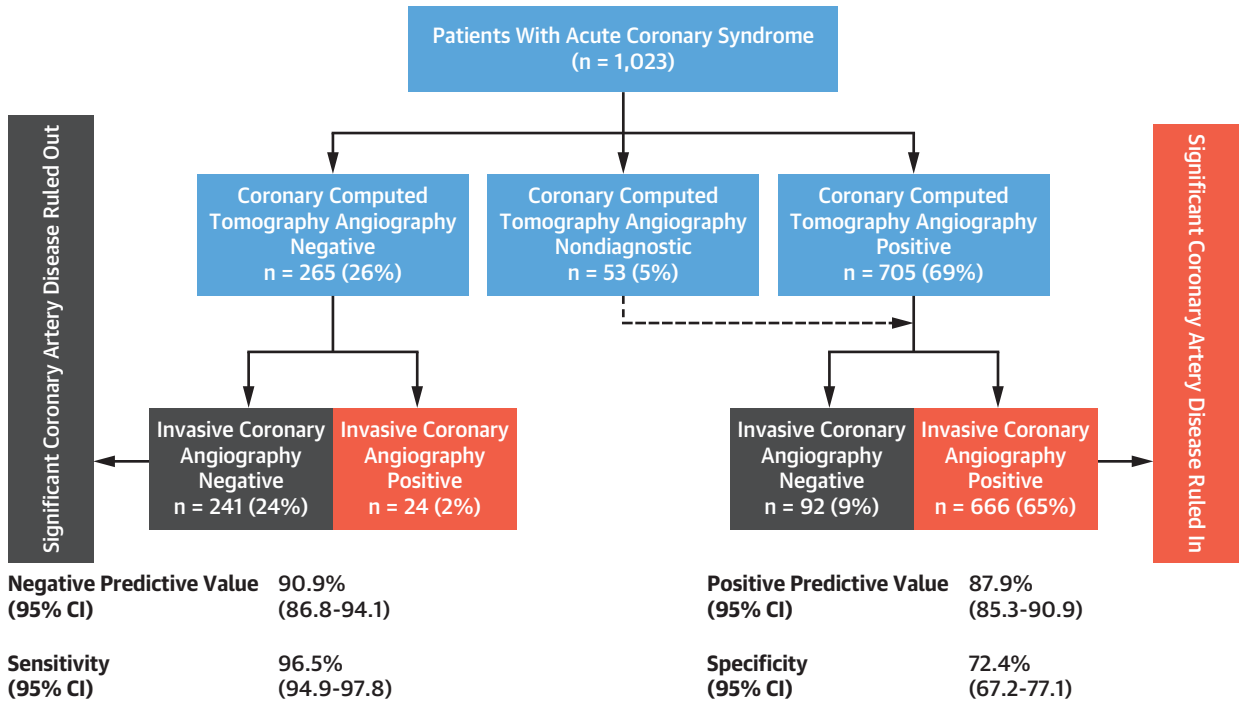
The primary endpoint is given in the **Central Illustration and Table 4**. The ability of coronary CTA to rule out the presence of a coronary artery stenosis ≥50%, as defined by the NPV, was 90.9% (95% CI: 86.8% to 94.1%). Coronary CTA was false negative in 24 patients (2.3%) as validated against ICA. All patients with a coronary lesion overlooked by coronary CTA had single-vessel disease, and the majority of lesions were located in small coronary segments with a luminal diameter of ≤2.5 mm. Only 3 patients (0.3%) with a false-negative coronary CTA had a lesion (as assessed with ICA) in a major vessel: 1 in the mid-right coronary artery, 1 in the mid-LAD, and 1 in the LM that was deemed nonsignificant by measurement of the fractional flow reserve (>0.80). NPV was consistent across subgroups (**Figure 3**, Online Table 2).

In the entire patient population, PPV, sensitivity, and specificity were 87.9% (95% CI: 85.3% to 90.1%), 96.5% (95% CI: 94.9% to 97.8%), and 72.4% (95% CI: 67.2% to 77.1%), respectively. Overall accuracy was 88.7% (95% CI: 86.6% to 90.5%) and area under the curve was 0.84 (95% CI: 0.82 to 0.87) (**Table 4**). coronary CTA falsely identified patients to have obstructive CAD in 92 (8.9%) patients, among whom 18.4% (17 of 92) had nondiagnostic CT scans (and thus deemed positive) and 20.7% (19 of 92) had previous coronary stenting. PPV was comparable in all subgroups, except with regard to sex, where women had a significantly lower PPV compared with men ($p < 0.001$) (**Figure 3**, Online Table 2). Sensitivity and specificity were also similar in all subgroups, except in patients with previous AMI, previous PCI, and elevated troponin. These patients had a significantly lower specificity ($p < 0.001$) (Online Table 2).

The secondary endpoint of NPV in the *very early* compared with the *standard* strategy group was not significantly different (**Table 4**). No difference in accuracy parameters was found between the *very early* and the *standard* group, except that sensitivity was slightly higher in the *very early* group.

When addressing diagnostic performance in the following subgroups: 1) patients with a diagnostic coronary CTA (53 patients with nondiagnostic scans excluded); and 2) patients without a previous history of CAD (181 patients excluded), the NPV was not affected compared with the overall population, but specificity increased to 76.0% and 76.6%, respectively (**Table 5**). Among 136 patients (13%) with previous

CENTRAL ILLUSTRATION **Diagnostic Accuracy of Coronary Computed Tomography Angiography Using Invasive Coronary Angiography as Reference Standard**



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Values in **parenthesis** are confidence intervals and are calculated by the Wilson-Brown method.

PCI, the NPV and sensitivity were high (91.7% and 99.1%), but the PPV and specificity were reduced to 84.7% and 36.7% (**Figure 3**, Online Table 2). In further subgroup analyses, NPV remained constant when using a discrimination threshold of ≥70% coronary stenosis (Online Table 3) and when assessing diagnostic performance at the coronary vascular territory level (Online Table 4).

DISCUSSION

In the VERDICT trial, we found that the diagnostic performance of coronary CTA to rule out or rule in significant CAD (≥50% coronary stenosis) in patients with NSTEACS was high, with a NPV of 90.9% and a PPV of 87.9% (**Central Illustration**). Furthermore, the diagnostic performance of coronary CTA was equally high when conducted within 2 to 3 h compared with 2 to 3 days of the clinical diagnosis of NSTEACS being made.

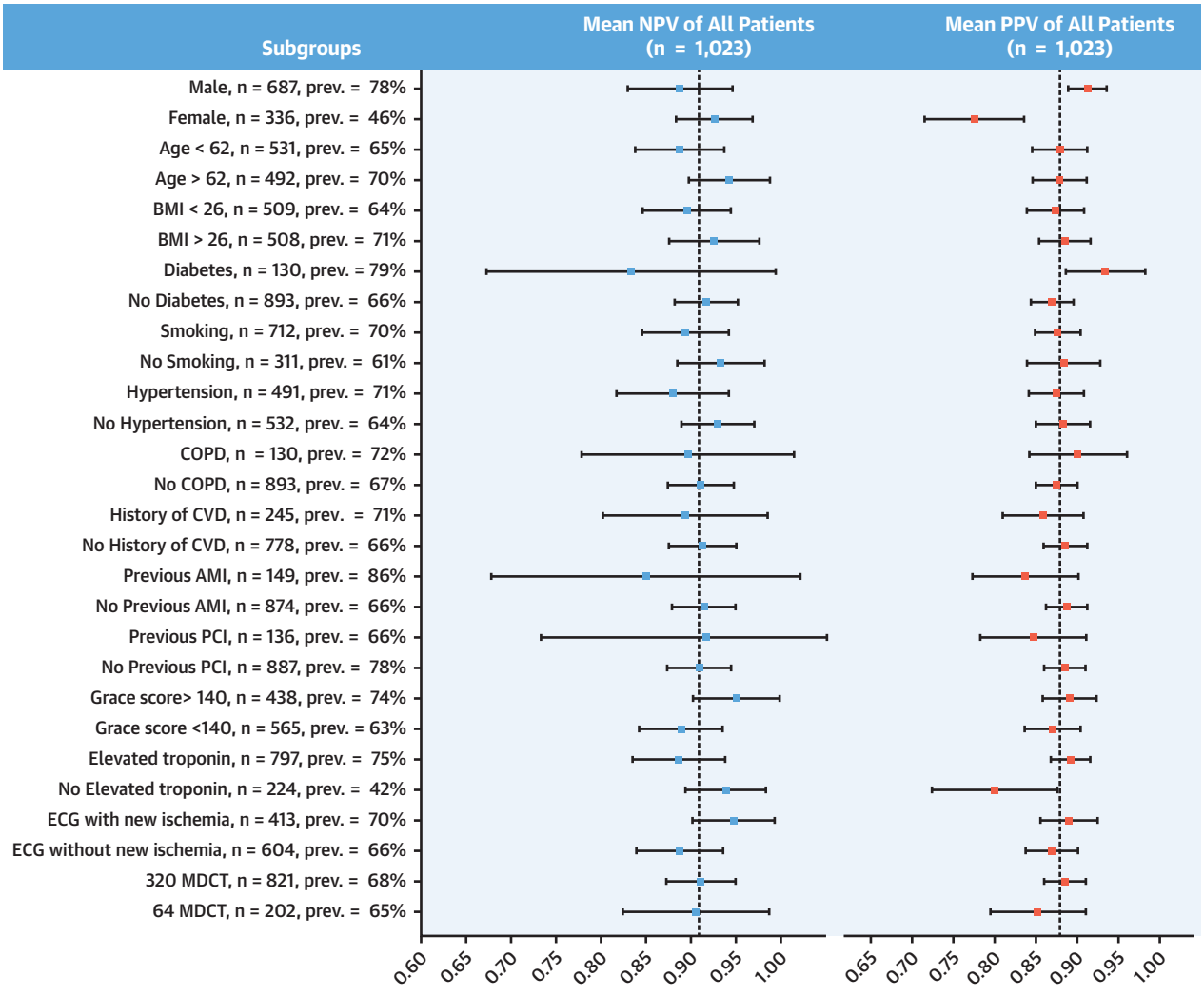
Coronary CTA is currently recommended for the clinical evaluation of patients with stable chest pain and an intermediate pre-test likelihood of CAD (4,13). This recommendation is based on coronary CTA diagnostic accuracy data using 64-detector CT technology in patients with stable angina with a disease prevalence from 10% to 63% (5,6,14). The reported negative and positive predictive values of these

TABLE 4 **Diagnostic Accuracy of Coronary Computed Tomography Angiography to Detect a Coronary Stenosis ≥50% by Invasive Coronary Angiography**

	All	Very Early	Standard
Number of patients	1,023	583	440
True negative	241	127	114
True positive	666	392	274
False negative	24	10	14
False positive	92	54	38
Negative predictive value, %	90.9 (86.8-94.1)	92.7 (87.0-96.4)	89.1 (82.3-93.9)
Positive predictive value, %	87.9 (85.3-90.1)	87.9 (84.5-90.8)	87.8 (83.7-91.2)
Sensitivity, %	96.5 (94.9-97.8)	97.5 (95.5-98.8)	95.1 (92.0-97.3)
Specificity, %	72.4 (67.2-77.1)	70.2 (62.9-76.7)	75.0 (67.3-81.7)
Negative likelihood ratio	0.05 (0.03-0.07)	0.04 (0.02-0.07)	0.06 (0.04-0.11)
Positive likelihood ratio	3.49 (2.93-4.16)	3.27 (2.61-4.09)	3.81 (2.89-5.02)
Accuracy, %	88.7 (86.6-90.5)	89.0 (86.2-91.4)	88.2 (84.8-91.0)
Area under curve	0.84 (0.82-0.87)	0.84 (0.80-0.87)	0.85 (0.81-0.89)

Values are n or as indicated (95% confidence intervals) calculated by the Wilson-Brown method.

FIGURE 3 **Negative and Positive Predictive Values of Coronary Computed Tomographic Angiography to Predict Invasive Coronary Artery Stenosis ≥50%**



The **dotted lines** represent the overall mean negative predictive value (NPV) and positive predictive value (PPV) for the entire population (n = 1,023). PPV in men compared with women was significantly higher ($p < 0.001$). Confidence intervals (CIs) were calculated by the Wilson-Brown method. AMI = acute myocardial infarction; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; ECG = electrocardiography; GRACE = Global Registry of Acute Coronary Events; MDCT = multidetector computed tomography; PCI = percutaneous coronary intervention; Prev. = prevalence of coronary stenosis ≥50 by invasive coronary angiography.

moderately sized studies were in the ranges of 83% to 99% and 64% to 91%, respectively. In the VERDICT trial, we examined 1,023 patients with NSTEACS primarily using 320-detector CT, and as such, to the best of our knowledge, our trial is the largest coronary CTA diagnostic accuracy study conducted so far. It might have been anticipated that a high disease prevalence among our patients with NSTEACS (67%) would result in a decline in the NPV of coronary CTA. Nevertheless, we found that the NPV of coronary CTA was >90%, concordant with previously reported results (6,15,16). The vast majority of patients with false negative coronary CTA results had CAD located in small side branches, suggesting that the NPV of coronary CTA to exclude clinically significant CAD is close to 100%. Whereas in patients with stable chest pain, high-severity CAD including LM stenosis, proximal LAD stenosis, and/or multivessel disease with impaired LV functions all have a Class I indication for revascularization (17), the specific

TABLE 5 Subgroup Diagnostic Accuracy Analysis for the Prediction of Coronary Stenosis ≥50% in Patients With a Diagnostic Coronary CTA and in Patients Without a History of Coronary Artery Disease

	Patients With a Diagnostic Coronary CTA (53 Patients With Nondiagnostic Coronary CTA Excluded)			Patients Without a History of CAD (181 Patients With CAD Excluded)		
	All	Very Early	Standard	All	Very Early	Standard
Number of patients	970	555	415	842	490	352
True negative	241	127	114	222	115	107
True positive	629	374	255	532	326	206
False negative	24	10	14	20	8	12
False positive	76	44	32	68	41	27
Negative predictive value, %	90.9 (86.8-94.1)	92.7 (87.0-96.4)	89.1 (82.3-93.9)	91.7 (87.5-94.9)	93.5 (87.6-97.2)	89.9 (83.0-94.7)
Positive predictive value, %	89.2 (86.7-91.4)	89.5 (86.2-92.2)	88.9 (84.6-92.2)	88.7 (85.9-91.1)	88.8 (85.2-91.9)	88.4 (83.6-92.2)
Sensitivity, %	96.3 (94.6-97.6)	97.4 (95.3-98.7)	94.8 (91.4-97.1)	96.4 (94.5-97.8)	97.6 (95.3-99.0)	94.5 (90.6-97.1)
Specificity, %	76.0 (70.9-80.6)	74.3 (67.0-80.6)	78.1 (70.5-84.5)	76.6 (71.2-81.3)	73.7 (66.1-80.4)	79.9 (72.1-86.3)
Negative likelihood ratio	0.05 (0.03-0.07)	0.04 (0.02-0.07)	0.07 (0.04-0.11)	0.05 (0.03-0.07)	0.03 (0.02-0.06)	0.07 (0.04-0.12)
Positive likelihood ratio	4.02 (3.30-4.89)	3.79 (2.93-4.89)	4.32 (3.18-5.88)	4.11 (3.34-5.06)	3.71 (2.85-4.83)	4.69 (3.34-6.58)
Accuracy, %	89.7 (87.6-91.5)	90.3 (87.5-92.6)	88.9 (85.5-91.8)	89.5 (87.3-91.5)	90.0 (87.0-92.5)	88.9 (85.2-92.0)
Area under curve	0.86 (0.84-0.89)	0.86 (0.82-0.89)	0.86 (0.83-0.90)	0.86 (0.84-0.89)	85.7 (82.1-89.2)	87.2 (83.4-90.9)

Values are n or as indicated (95% confidence intervals) calculated using the Wilson-Brown method. CAD was defined as previous acute myocardial infarction and/or percutaneous coronary intervention.

CAD = coronary artery disease; CTA = computed tomography angiography.

value of revascularizing smaller side branches is uncertain (17).

The frequency of a nondiagnostic CT scan in our study was 5.2%, which is marginally lower than what has previously been reported in a French multicenter study (6%) that included 746 patients with stable chest pain examined with 64-detector CT (8). This finding is most likely explained by the fact that the majority of patients in the VERDICT cohort were examined with 320-detector CT, in whom we recorded an even lower frequency of nondiagnostic coronary CTA (3.7%). Additionally, the high NPV in the VERDICT cohort was achieved at a substantially lower radiation dose (5.3 mSv) compared with earlier reports in patients with NSTEACS (10 to 21 mSv) (6,15,16), mainly as a consequence of a very low radiation dose recorded in patients examined with 320-detector CT. Furthermore, NPV was similar in patients examined within 2 h or 2 days of NSTEACS diagnosis, which is probably associated with the well-controlled heart rate at both time points in our study.

NPV was not influenced by patient characteristics or clinical risk profile. This finding is important, because the diagnostic performance of coronary CTA in patients with a GRACE risk score >140 is of substantial clinical interest, as we and others have found that early invasive evaluation and coronary revascularization especially in this subset of patients with NSTEACS may improve clinical outcome (2,18). The prevalence of significant CAD in patients with a GRACE risk score >140 was 74%, which is higher than the overall prevalence of disease in the entire cohort. Despite this, the NPV of coronary CTA was >95% in these patients. It therefore appears plausible that a coronary CTA conducted before ICA in patients with NSTEACS—regardless of clinical risk profile—might be used to identify patients with the highest likelihood of benefit from subsequent revascularization. The observational design of our study, however, does not allow a firmer conclusion, and future studies are needed to elucidate this concept further.

The ability of coronary CTA to rule in significant CAD, expressed as the PPV, was slightly lower than that of NPV. False positive findings by coronary CTA were frequently caused by nondiagnostic CT scans, which, in our study, were characterized as positive and/or by previous coronary stenting.

The findings of the VERDICT trial suggest that, in patients with NSTEACS, coronary CTA can be conducted within 2 h of clinical diagnosis to quickly identify patients in whom invasive evaluation will be futile. A diagnostic strategy using coronary CTA in patients with NSTEACS could, therefore, reduce the duration of antithrombotic medical therapy in patients without significant CAD and augment the risk-benefit ratio of this medical strategy. An early rule out of CAD in these patients could also improve patient flow in acute medical care facilities. Correspondingly, the efficiency of invasive catherization laboratories would be increased as only patients with

significant CAD identified by coronary CTA, and thus, a high likelihood of subsequent revascularization, would be admitted for invasive examination. However, a coronary CTA strategy in patients needing subsequent ICA and revascularization could entail an overall higher dose of radiation and contrast volumes. Overall clinical risk, however, may be negligible as contemporary CT technology is associated with a relatively low radiation dose (3.7 mSv for patients scanned with 320 multidetector CT in this study) and low contrast volumes when using low kV imaging (19). Furthermore, it appears likely that future integration of coronary CT data into PCI procedural planning, including CT-defined coronary lesion length and severity, extent of vessel/lesion calcification, vessel reference diameter, presence and extent of disease in side branches, and so on, would reduce invasive procedural time, radiation, and use of contrast (17,20).

STUDY LIMITATIONS. First, patients with impaired renal function, known atrial fibrillation, previous coronary artery bypass surgery, and women below the age of 45 years were not included in the study. Our findings may therefore not apply in these subsets of patients with NSTEACS.

Second, this was a pragmatic trial leaving the final decision to perform the research protocol-defined coronary CTA to the treating physician. Consequently, a sizable number of patients eligible for coronary CTA from the VERDICT cohort did not undergo coronary CTA. Clinical characteristics, risk profile, and subsequent invasive angiographic findings were, however, similar in patients with and without coronary CTA. It therefore appears likely that our findings may apply in similar all-comer NSTEACS populations.

Third, the coronary CTA component of the VERDICT trial was designed to determine the diagnostic accuracy of coronary CTA to identify coronary diameter stenoses ≥50% using a head-to-head comparison between coronary CTA and an ICA assessment. Therefore, the ability of coronary CTA to discriminate between invasively measured FFR-positive versus FFR-negative coronary stenoses cannot be assessed in our study. Nevertheless, it has previously been reported that absence of a coronary stenosis (≥50%) on coronary CTA rules out hemodynamically significant stenosis measured invasively by FFR, suggesting that our primary study endpoint would not have been different had systematic invasive FFR evaluation been conducted (21).

Functional assessment of intermediate coronary lesions using invasive FFR was encouraged but not mandatory in stable coronary lesions in the VERDICT trial. Consequently, the use of invasive FFR in our study may not reflect current clinical practice where invasive FFR may be more widespread. Further studies are needed to assess the clinical value of FFR in patients with NSTEACS, especially in light of recent advancements in computational fluid dynamics which allow for the noninvasive assessment of coronary pressure gradients based on coronary CTA imaging (22). These accuracy studies evaluated CT-based FFR in chronic CAD patients and reported a higher specificity and PPV when compared against anatomical evaluation alone. Future studies are needed to investigate if additional CT-based FFR can improve the ability of a coronary CTA-guided strategy to "rule in" hemodynamically significant CAD in patients with NSTEACS.

CONCLUSIONS

Coronary CTA may be used to rule out significant coronary artery disease in patients with NSTEACS and thus potentially guide patient management.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Current guidelines for management of patients with NSTEACS recommend invasive coronary angiography, although up to one-third of patients do not have significant coronary disease. Coronary CT angiography can accurately detect or exclude significant coronary disease in patients with NSTEACS.

TRANSLATIONAL OUTLOOK: Randomized trials of early coronary CT angiographically based management of patients with NSTEACS are needed to assess the impact of subsequent resource utilization and clinical outcomes.

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KEY WORDS acute coronary syndrome, cardiac CT, diagnostic accuracy, timing

APPENDIX For supplemental tables, please see the online version of this paper.