

Value of Myocardial Perfusion Assessment With Coronary Computed Tomography Angiography in Patients With Recent Acute-Onset Chest Pain



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ABSTRACT

OBJECTIVES The authors sought to perform a randomized controlled trial to evaluate the clinical efficacy of combined examination with coronary computed tomography angiography (CTA) and computed tomography perfusion imaging (CTP) compared to coronary CTA alone.

BACKGROUND Stress myocardial CTP may increase diagnostic specificity when added to coronary CTA in patients suspected of having ischemic heart disease.

METHODS Patients recently hospitalized for acute-onset chest pain, who had acute coronary syndrome had been ruled out by normal electrocardiograms, normal troponin levels, and relief of symptoms, and who had a clinical indication for outpatient noninvasive testing, were screened for inclusion in the CATCH-2 (Cardiac cT in the treatment of acute Chest pain 2) trial (NCT02014311). Patients were randomized 1:1 to examination with coronary CTA or coronary CTA+CTP. The primary endpoint was the frequency of coronary revascularization among patients referred for invasive coronary angiography (ICA) based on index computed tomography evaluation. Secondary endpoints were invasive procedural complications at index-related ICA, post-index cardiac death, hospital admittance because of recurrence of chest pain, unstable angina pectoris, or acute myocardial infarction, ICA, and revascularization.

RESULTS Among 300 patients allocated to the coronary CTA+CTP group, 41 (14%) were referred for ICA compared with 89 (30%) allocated to coronary CTA ($p < 0.0001$). The primary endpoint occurred in 50% of coronary CTA+CTP patients versus 48% of invasively examined patients ($p = 0.85$). The total number of revascularizations was significantly lower in the coronary CTA+CTP group compared to the coronary CTA group ($n = 20$ [7%] vs. $n = 42$ [14%]; $p = 0.0045$). At median follow-up of 1.5 years, the occurrence of secondary endpoints was similar in the 2 groups.

CONCLUSIONS A post-discharge diagnostic strategy of coronary CTA+CTP safely reduces the need for invasive examination and treatment in patients suspected of having ischemic heart disease. (Cardiac cT in the treatment of acute Chest pain 2—Myocardial CT Perfusion [CATCH2]; NCT02014311) (J Am Coll Cardiol Img 2018;11:1611–21)

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CT = computed tomography

CTA = computed tomography angiography

CTP = computed tomography perfusion imaging

FFR = fractional flow reserve

ICA = invasive coronary angiography

IHD = ischemic heart disease

Current guidelines recommend that patients with low-risk acute coronary syndrome (ACS) be examined using a diagnostic strategy similar to that applied to patients with stable angina pectoris (1-3). In some countries, including the United States, this may be performed during hospital admission; elsewhere it may be performed as part of a diagnostic work-up in the outpatient clinic. To identify patients from this group in whom coronary revascularization and optimal medical therapy may improve clinical outcome, assessment of coronary atherosclerotic burden or myocardial ischemia has been used, and a strategy combining invasive angiography with functional evaluation of coronary lesions appears to optimize coronary stenting (4).

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According to current guidelines, coronary computed tomography angiography (CTA) is a potential first-choice diagnostic test when examining patients suspected of having stable angina pectoris, as patients who had coronary CTA as part of the diagnostic work-up have clinical outcomes comparable to those examined with a functional diagnostic test alone (5,6). We recently reported improved clinical outcomes in patients with low-risk ACS using coronary CTA compared with a functional test (7).

Adenosine computed tomography myocardial perfusion imaging (CTP) has recently emerged as a novel noninvasive functional test, which may be performed in the same imaging session as a standard coronary CTA. Observational studies and meta-analyses have indicated an increase in the diagnostic accuracy of coronary CTA when combined with CTP (8-10). In addition, patients with a normal CTP seem to have a lower risk of cardiovascular events (11,12). However, the extent to which a combined anatomic and functional strategy of coronary CTA+CTP may improve the clinical outcome of patients with recent acute-onset chest pain and suspected ischemic heart disease (IHD) compared to coronary CTA alone is unknown.

We conducted the CATCH-2 (Cardiac cT in the treatment of acute CHest Pain 2) randomized

controlled trial (NCT02014311) to assess the potential clinical value of a diagnostic strategy combining coronary CTA and CTP compared to coronary CTA alone.

METHODS

STUDY DESIGN. The CATCH-2 trial is a prospective randomized controlled multicenter study comparing the clinical value of a diagnostic procedure including coronary CTA in combination with CTP compared with coronary CTA alone. The short-term goal of the diagnostic procedures was to triage patients for optimal clinical management: 1) referral for subsequent invasive coronary angiography (ICA) and potentially revascularization (for patients with significant coronary artery stenosis); 2) optimal medical therapy (for patients with nonobstructive IHD); or 3) providing patient information and counseling and evaluation for noncardiac chest pain (for patients with normal coronary arteries). The study was approved by the Danish National Committee on Health Research Ethics (Journal Number H-3-2013-065) and the Danish Data Protection Agency. Details of the study design have been published previously (13).

PARTICIPANTS. Consecutive patients discharged from 1 of 6 different hospitals in the Copenhagen Capital Region of Denmark after hospitalization for acute chest pain, in whom ACS had been ruled out by normal electrocardiograms, normal plasma troponin levels, and relief of symptoms, and for whom the treating cardiologist had found indication for further outpatient noninvasive testing, were screened for participation by review of electronic patient charts. Inclusion criteria were age at least 50 years, at least 1 risk factor for IHD, and referral for noninvasive cardiac examination at an outpatient clinic. After hospital discharge, eligible patients were contacted by a member of the CATCH-2 research team and offered participation in the study. All included patients provided written informed consent.

RANDOMIZATION, MASKING, AND CLINICAL MANAGEMENT

STRATEGY. Patients agreed to participate in the study were prospectively randomized 1:1 to coronary CTA or coronary CTA+CTP. Randomization was performed using an electronic case report form by means of

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permuted-block randomization and stratified by referring clinical site. The randomization was performed by the study personnel performing the enrollment. The person performing the randomization had no foreknowledge of the next treatment assignment on the randomization schedule.

Coronary CTA was conducted in an outpatient clinic at Rigshospitalet within 2 weeks of study inclusion. Coronary CTA images were analyzed immediately after acquisition by 2 independent readers who initially were blinded to group allocation by being presented with the coronary CTA images only. After the blinded coronary CTA analysis, the CTP images were presented to the readers when applicable. In the coronary CTA group, patients with $\geq 50\%$ stenosis in a coronary artery having a diameter ≥ 2 mm were referred for ICA in accordance with current guidelines (3). In the coronary CTA+CTP group, only patients with both $\geq 50\%$ stenosis in a coronary artery having a diameter of at least 2 mm and a corresponding reversible myocardial perfusion defect were referred for ICA. CTP was considered reversible if a perfusion defect was observed in the subendocardium or transmurally and was present only during adenosine stress. Furthermore, the perfusion defect has to correspond to the part of the myocardium supplied by the vessel in which $>50\%$ stenosis was observed on coronary CTA.

The invasive cardiologist performing the ICA was blinded to allocation group but was informed about which coronary artery territory (left anterior descending artery, circumflex artery, or right coronary artery) a stenosis had been identified by coronary CTA. Coronary revascularization and optimal medical therapy were prescribed by the invasive cardiologist, without involvement of the CATCH-2 research team.

Patients with coronary artery stenosis $<50\%$ and patients with no myocardial perfusion defect (irrespective of lesion severity) were not referred for ICA, but the referring physician from the appropriate hospital was advised by the CATCH-2 research team to commence or continue optimal medical therapy according to guidelines. In patients with normal coronary arteries, the referring physician was advised about the findings, and indication for noncardiac chest pain examinations was discussed.

PROCEDURES. Coronary computed tomography angiography. Coronary CTA was conducted using the Toshiba Aquilion ONE ViSION Edition 320-multidetector computed tomography (CT) scanner (Toshiba, Tokyo, Japan). Patients were given a beta-receptor blocking agent either orally or intravenously in order to reduce heart rate <65 beats/min

with appropriate considerations of blood pressure and weight. Sublingual nitroglycerine was administered immediately before coronary CTA. In patients undergoing CTP, intravenous adenosine (0.14 mg/kg/min) was administered for 5 min before the scan as previously described (13). Scheduled scan time for patients undergoing CTP was 15 min longer than for patients undergoing coronary CTA alone.

All images were transferred to a dedicated workstation using the commercially available software Vitrea version 6.4 (Vital Images, Minnetonka, Minnesota) for analysis. Coronary CTA images were analyzed and stenosis severity was categorized in accordance with the recommendations of the Society of Cardiovascular Computed Tomography as normal vessels, $<25\%$ stenosis, 25% to 49% stenosis, 50% to 69% stenosis, 70% to 99% stenosis, and occluded vessels (14). Furthermore, for all patients with at least 1 vessel having stenosis of at least 50%, the number of vessels with disease was registered. CTP analysis was conducted by visual assessment with slice thickness of 3 mm, average projection, and window/level setting of 300/150 HU, in accordance with methods previously suggested (15). Overlay images of coronary CTA and CTP were produced to determine the vessel supply to the myocardium. In patients with multivessel coronary artery disease, the specific anatomic location of the individual diseased vessel was tracked visually, and myocardial areas subtended by the vessel were inspected for absence/presence of perfusion abnormalities. Using this approach, we previously reported high intraobserver and interobserver agreement (16).

Invasive coronary angiography. ICA was performed within 4 weeks of coronary CTA according to standard practice, at either Rigshospitalet or Gentofte Hospital. The examining invasive cardiologist was required to perform fractional flow reserve (FFR) measurement for the guidance of revascularization, in accordance with aspects of patient safety, specific coronary anatomy, and clinical reliance in each patient case. Indication for coronary revascularization was determined by the treating invasive cardiologist in collaboration with the local heart team according to current guidelines (17). Coronary angiograms were independently adjudicated by 2 experienced ICA operators blinded to examination allocation to determine the presence of myocardium at risk for relative hypoperfusion defined as at least 1 of the following criteria: FFR determined invasively <0.80 , focal diameter stenosis $>70\%$, or diffuse atherosclerotic disease.

STUDY OUTCOMES. The invasive outcome measures of the study were: 1) referral rates for ICA; 2) frequency of invasive identification of myocardium at risk

for relative hypoperfusion in patients referred for ICA; 3) frequency of coronary revascularization among patients referred for ICA; and 4) total number of coronary revascularizations performed in the patient population. The primary endpoint of the study was the frequency of coronary revascularization among patients referred for ICA.

The secondary endpoints were: 1) hospital admission because of recurrent chest pain (duration >12 h) or acute myocardial infarction in addition to cardiac death (18); 2) new referrals for ICA (ICA not planned during index evaluation); 3) revascularization (percutaneous coronary intervention or coronary artery bypass graft); and 4) index procedure-related complications (death, bleeding according to the Bleeding Academic Research Consortium criteria [19], vascular complications, stroke, acute myocardial infarction). Secondary endpoints were recorded for at least >3 months post-index evaluation.

All primary and secondary endpoints were recorded by review of patients' electronic medical files. Secondary endpoints and physician-prescribed medication, in addition to status of cardiac symptoms, were recorded 3 months after randomization of the last included patient. The endpoints were recorded by personnel who were blinded to the treatment allocation. All endpoints were adjudicated by consensus among members of the CATCH-2 study group blinded to randomization.

Prescribed medication. Data on physician-prescribed medication were extracted from the Danish electronic medication registry. The following categories of medication were recorded: acetylsalicylic acid; short- and long-acting nitrates; beta-receptor blockers; calcium antagonists; and statins.

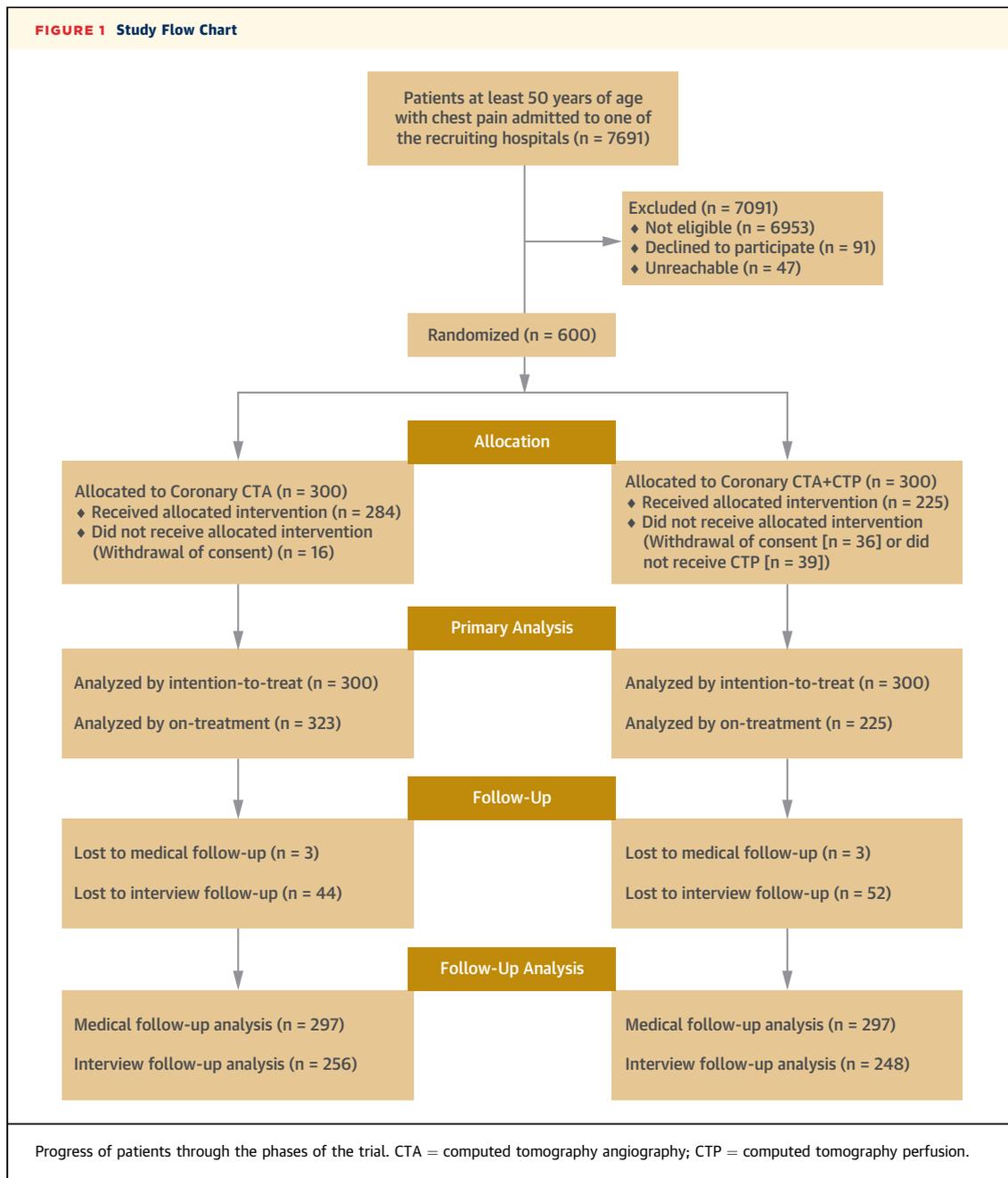
Status of cardiac symptoms. All patients included in the study were contacted by telephone to obtain information of possible recurrent chest pain and to classify the pain according to Canadian Cardiovascular Society guidelines (3). Contact with our patients was attempted at least 3 times during a time period of at least 2 weeks. Interviews were performed by 2 nurses trained in cardiology who were blinded to study group allocation. The questionnaire can be found in [Online Appendix A](#).

STATISTICAL ANALYSIS. Sample size calculations for the primary endpoint were conducted as previously described, partly based on observations made in our previous CATCH trial cohort (13,16). In brief, we estimated that by coronary CTA imaging alone, approximately 25% of patients included in the CATCH-2 trial would be referred for ICA, among whom 36% would have a false-positive test result, but

that the false-positive rate would be reduced to 20% when the coronary CTA+CTP approach was used. Based on these assumptions, we calculated that, with an expected dropout rate of 5% to 10%, a sample size of 600 patients would be needed (with 80% power and a 2-sided alpha level of 0.05). Both primary and secondary endpoints were analyzed on an intention-to-treat basis. In this analysis, patients who withdrew consent to undergo the CT examination were examined according to standard of care at their local hospital, in which case the examination performed was treated as the index test. We performed a supplementary on-treatment analysis for the primary endpoint, in which patients from the coronary CTA+CTP group who underwent only coronary CTA were transferred to the coronary CTA group, and patients who withdrew from the study were excluded. Patients who withdrew their consent before CT imaging were censored from the on-treatment analyses. We evaluated differences between group mean values using the Student *t* test for unpaired samples, and differences between proportions were compared using the Fisher exact test. Differences in cardiovascular events were assessed using Kaplan-Meier plots and compared using hazard ratios from Cox proportional hazards regression analysis. A nonrandom pattern of the residuals over time from the Cox analysis was ensured to test for the Cox proportional hazards assumption. Outcome for the Cox regression was recorded 3 months post trial termination, and the difference between the survival curves in treatment allocation groups was calculated for the entire follow-up period, as well as for the median follow-up time. Values of $p < 0.05$ were considered significant.

RESULTS

Inclusion in the CATCH-2 trial commenced in October 2013 and was terminated in March 2017. From the 6 participating hospitals in the Copenhagen Capital Region of Denmark, 7,691 patients were screened for trial eligibility. Of these patients, 6,953 were not eligible, and 138 could not be reached or declined to participate ([Figure 1](#), [Online Figure 1](#)). A total of 600 patients were included and randomized 1:1 to coronary CTA or coronary CTA+CTP. Median index hospitalization for patients was 1 day (range 1 to 6 days). After randomization, 16 patients from the coronary CTA group and 36 patients from the coronary CTA+CTP group withdrew their consent to undergo CT examination as randomized. In the coronary CTA+CTP group, 39 patients did not undergo CTP because of inability to tolerate adenosine ($n = 21$), safety restrictions defined by the research protocol



(n = 11), or logistic reasons (n = 7). Median time from hospital discharge to coronary CTA was 12 days. Mean radiation dose associated with CT was 5.8 ± 3.3 mSv in the coronary CTA group versus 10.9 ± 3.9 mSv in the coronary CTA+ CTP group ($p < 0.0001$). Status of prescribed medication was obtained for all but 6 patients, who died during the follow-up period of noncardiac causes (3 in each strategy group). Telephone interview data were obtained in 256 patients (85%) from the coronary CTA group and 248 patients (83%) from the coronary CTA+CTP group. Median

follow-up time after study randomization for the secondary endpoints was 17 months (range 3 to 40 months) for the coronary CTA group and 18 months (range 3 to 39 months) for the coronary CTA+CTP group.

Demographics of the patients showed equal distribution of all relevant data (Table 1). Demographics for patients in the on-treatment analysis are shown in Online Table 1. The distribution of patients with $\geq 50\%$ stenosis, $< 50\%$ stenosis, normal coronary arteries, and nondiagnostic examinations were

TABLE 1 Patient Demographics			
	Coronary CTA Group (n = 300)	Coronary CTA+CTP Group (n = 300)	p Value
Age, yrs	63.5 ± 8.8	62.9 ± 8.9	0.41
Male	144 (48)	154 (51)	0.46
BMI, kg/m ²	27.1 ± 4.5	27.1 ± 4.5	1.00
Caucasian	286 (95)	280 (93)	0.38
IHD risk factors			
Hypertension	165 (55)	172 (57)	0.62
Hypercholesterolemia	165 (55)	180 (60)	0.25
Diabetes	37 (12)	33 (11)	0.70
Family history of IHD	86 (29)	110 (37)	0.045
Smoking			
Active	70 (23)	79 (26)	0.45
Ever smokers	205 (68)	208 (69)	0.86
Pack years	29.9 ± 17.1	31.0 ± 18.4	0.45
Known IHD	45 (15)	43 (14)	0.91
Patients with stents	42 (14)	36 (12)	0.54
Previous stroke/TCI	23 (8)	19 (6)	0.63
Peripheral arterial disease	8 (3)	7 (2)	1.00
Chest pain classification			
Typical chest pain	158 (53)	145 (48)	–
Atypical chest pain	126 (42)	135 (45)	–
Noncardiac chest pain	16 (5)	20 (7)	–
Pre-test probability of IHD*			
Low risk	30 (10)	28 (9)	–
Intermediate risk	269 (90)	270 (90)	–
High risk	1 (0.3)	2 (1)	–
NYHA functional class			
I	91 (30)	92 (31)	–
II	49 (16)	45 (15)	–
III	26 (9)	28 (9)	–
IV	0 (0)	0 (0)	–

Values are mean ± SD or n (%). *According to the updated Diamond and Forrester risk score as recommended by European Society of Cardiology guidelines (3).
BMI = body mass index; CTA = computed tomography angiography; CTP = computed tomography perfusion; IHD = ischemic heart disease; NYHA = New York Heart Association; TCI = transient cerebral ischemia.

similar in the 2 groups (Figure 2 and Table 2). In the coronary CTA+CTP group, coronary CTA was normal and CTP was positive in 4 patients; 33 patients with positive coronary CTA had negative CTP.

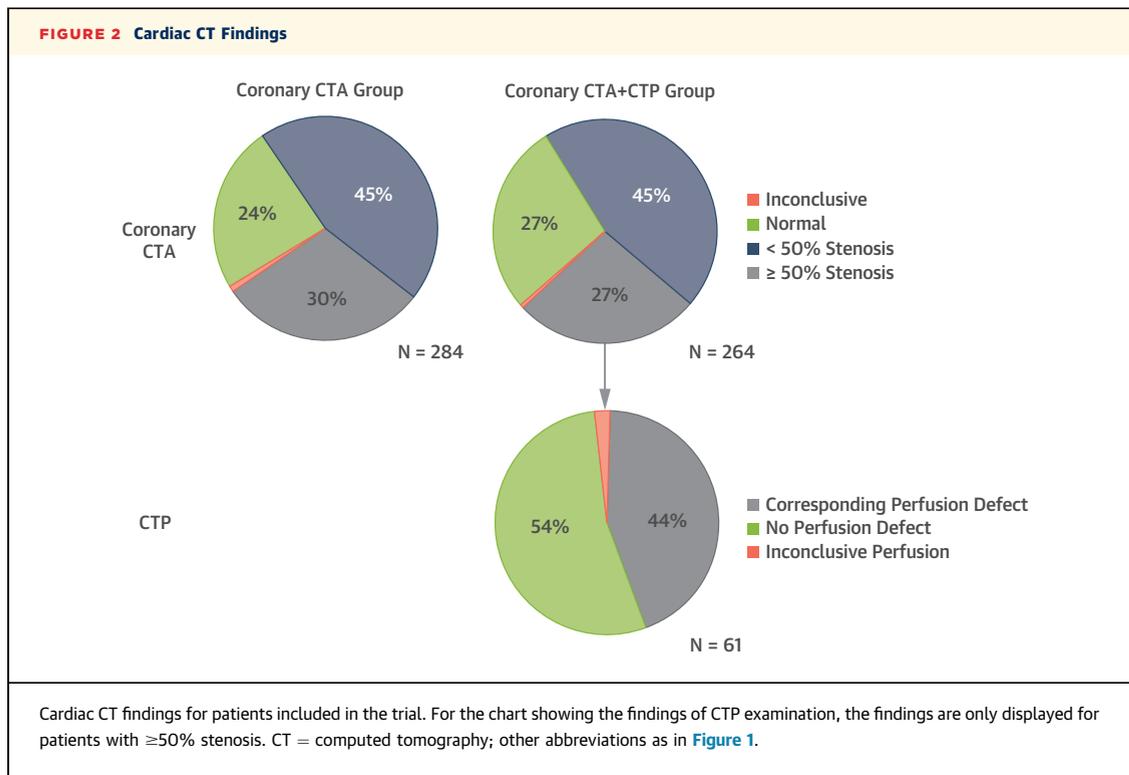
PRIMARY OUTCOME. Significantly fewer patients were referred for ICA in the coronary CTA+CTP group compared to the coronary CTA group (41 of 300 [14%] vs. 89 of 300 [30%]; $p < 0.0001$). All patients who underwent ICA did so exclusively as a consequence of CT findings according to the principles detailed in the Methods section (coronary CTA and coronary CTA+CTP). Median time from index coronary CTA to ICA was 31 days. One patient from each group did not undergo ICA (1 canceled by the treating physician because of patient's lack of symptoms, and 1 patient refused to undergo ICA). Among patients who

underwent ICA, invasive FFR assessment was conducted in 91% of patients in the coronary CTA group and 88% of patients in the coronary CTA+CTP group ($p = 0.76$). In the coronary CTA group, myocardium at risk for relative hypoperfusion was found in 60% (53 of 88) of the patients from the coronary CTA group versus 68% (27 of 40) of patients from the coronary CTA+CTP group ($p = 0.70$) (Figure 3A, Online Table 2).

No significant difference was observed in the occurrence of the primary endpoint in the 2 patient groups: 42 of 88 patients (48%) from the coronary CTA group versus 20 of 40 patients (50%) from the coronary CTA+CTP group ($p = 0.85$) (Figure 3A). Reasons for not undergoing revascularization despite the presence of myocardium at risk for relative hypoperfusion were low symptom burden ($n = 1$ from each group) and lesions unsuited for revascularization (all other patients). The total number of revascularizations was significantly lower in the coronary CTA+CTP group compared to the coronary CTA group ($n = 20$ [7%] vs. $n = 42$ [14%]; $p = 0.0045$). Patient management is summarized in Online Figure 2.

In the on-treatment analysis, not including the 52 patients who withdrew consent, significantly fewer patients were referred for ICA in the coronary CTA+CTP group compared to the coronary CTA group (29 of 225 [13%] vs. 101 of 323 [31%]; $p < 0.0001$). ICA findings are given in Online Table 3. Based on the independent ICA reading, significantly more patients from the coronary CTA+CTP group than from the coronary CTA group had myocardium at risk for relative hypoperfusion (23 of 28 [82%] vs. 57 of 100 [57%]; $p = 0.016$) (Figure 3B). The frequency of coronary revascularizations among patients referred for ICA was not significantly different between the 2 groups (17 of 28 [61%] from the coronary CTA+CTP group vs. 45 of 100 [45%] from the coronary CTA group; $p = 0.20$) (Figure 3B). Overall, in this population, significantly fewer patients from the coronary CTA+CTP group were revascularized compared to patients from the coronary CTA group (17 of 225 [8%] vs. 45 of 323 [14%]; $p = 0.020$). In a subanalysis that included only patients who had invasive FFR was performed, the true positive rate of coronary CTA+CTP was 90% versus a false-positive rate of 10%.

SECONDARY ENDPOINTS. Secondary endpoints are given in Table 3 and Online Table 4. No difference in hospitalization for chest pain, including acute myocardial infarction, was observed between the groups. Three patients from the coronary CTA group and 2 patients from the coronary CTA+CTP group were admitted with either unstable angina pectoris or



acute myocardial infarction. No patients died of a cardiovascular cause. A tendency toward a lower event rate was noted for the coronary CTA+CTP group (Figure 4). In a Cox proportional hazards regression analysis, we found a hazard ratio of 0.63 (95% confidence interval: 0.32 to 1.27; $p = 0.20$). After 18 months of follow-up, no difference in the event rate was observed between the groups ($p = 0.34$). No difference in referral rate for ICA or coronary revascularization was observed between the 2 groups.

CARDIAC SYMPTOMS AND PRESCRIBED MEDICATION. Post-discharge status of cardiac symptoms and prescribed medication were similar between groups (Online Figure 3). Freedom from angina pectoris was recorded in 94% of patients; 8% were taking nitroglycerin on a regular basis, and slightly more than 10% were taking some kind of antianginal medication. Acetylsalicylic acid and statins were prescribed with equal frequency in the coronary CTA and coronary CTA+CTP groups (Online Table 5).

DISCUSSION

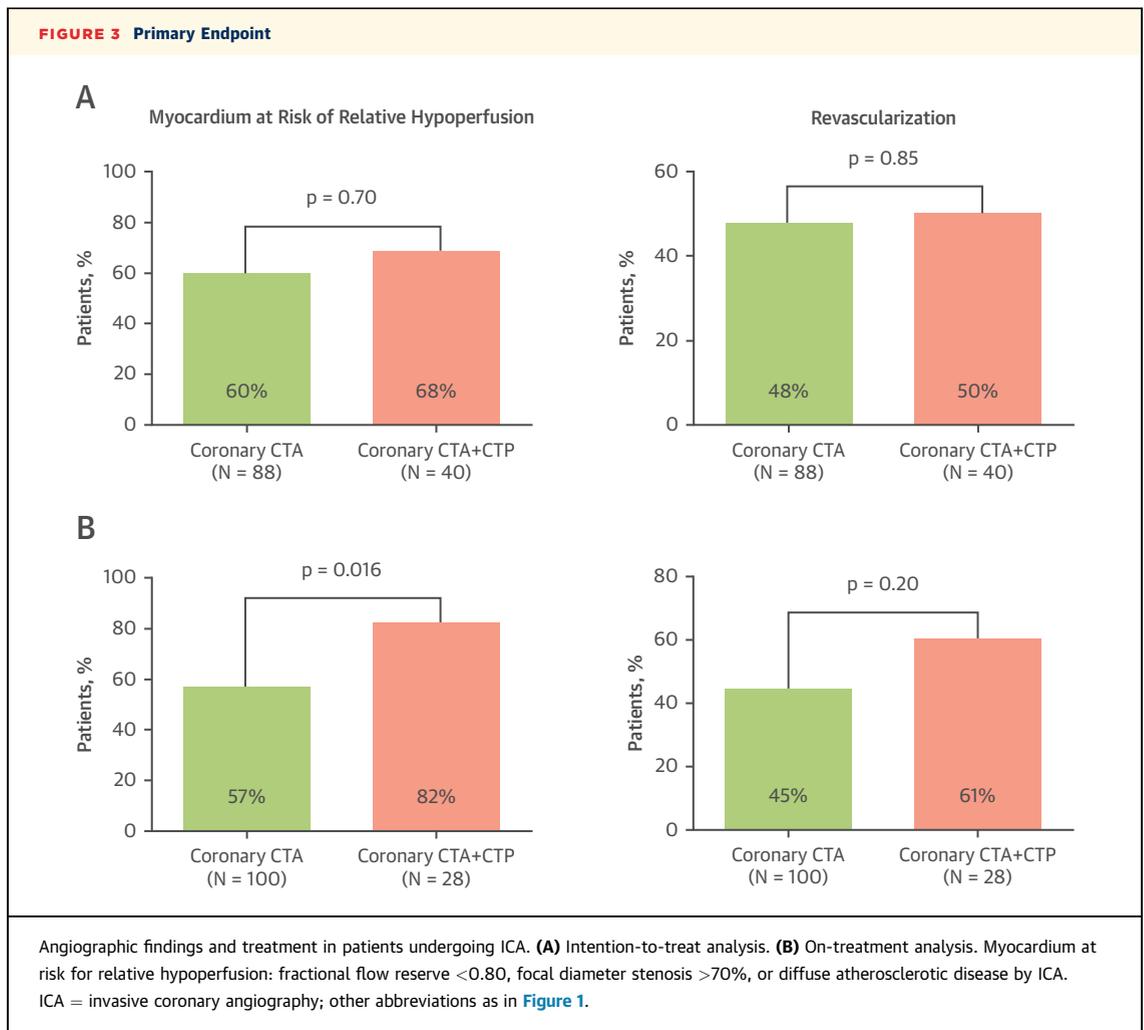
This is the first randomized trial to assess the clinical value of a combined coronary CTA and CTP examination as part of the post-discharge diagnostic work-up in patients with recent hospitalization for acute-onset chest pain, in whom ACS had been ruled out. The

combined strategy had no significant impact on our primary endpoint—the frequency of coronary revascularization among patients referred for ICA. However, addition of CTP to coronary CTA examination

TABLE 2 CT Findings

	Coronary CTA Group (n = 284)	Coronary CTA+CTP Group (n = 264/225*)	p Value
CAC score	58 (0-306)	38 (0-196)	0.38
Coronary CTA findings			0.18
Normal coronary vessels	68 (24)	72 (27)	—
<50% stenosis	127 (45)	118 (45)	—
$\geq 50\%$ stenosis	86 (30)	72 (27)	—
Affected vessels			
1-vessel disease	47 (17)	50 (19)	—
2-vessel disease	31 (11)	17 (6)	—
3-vessel disease	7 (2)	4 (2)	—
Left main stenosis	1 (0.4)	1 (0.4)	—
Inconclusive	3 (1)	2 (1)	—
CTP findings			
Normal	—	186 (83)	—
Reversible perfusion defect	—	31 (14)	—
Fixed perfusion defect	—	6 (3)	—
Inconclusive	—	2 (1)	—

Values are median (interquartile range) or n (%). *Coronary CTA findings are given for 264 patients whereas CTP findings are only given for 225 patients because all patients in the coronary CTA + CTP group did not have CTP performed.
 CAC = coronary artery calcium; CT = computed tomography; other abbreviations as in Table 1.



substantially reduced the number of patients referred for ICA and the total number of coronary revascularizations. However, within a median follow-up time of >17 months, similar frequencies of cardiac deaths, post-index revascularizations, and hospital

admittances due to recurrence of chest pain, unstable angina pectoris, and acute myocardial infarction were recorded in the 2 groups, indicating that the coronary CTA+CTP strategy was safe. Furthermore, the overall freedom from angina pectoris was high in both groups, and the use of antianginal medication was similar at follow-up.

The absence of statistical significance of our primary endpoint could potentially be related in part to the 15% dropout rate in the coronary CTA+CTP group, as patients did not complete CTP primarily because of the inability to tolerate the adenosine infusion, a proportion also previously reported (20). Using ICA as the gold standard, we estimated a 36% false-positive rate and found a 43% rate in the coronary CTA group, and respective values of 20% and 18% in the coronary CTA+CTP group by on-treatment analysis. The corresponding true-positive values of coronary CTA and coronary CTA+CTP with ICA as the reference were 57% and 82%, respectively, in our study,

TABLE 3 Post-Index Hospital Admittance

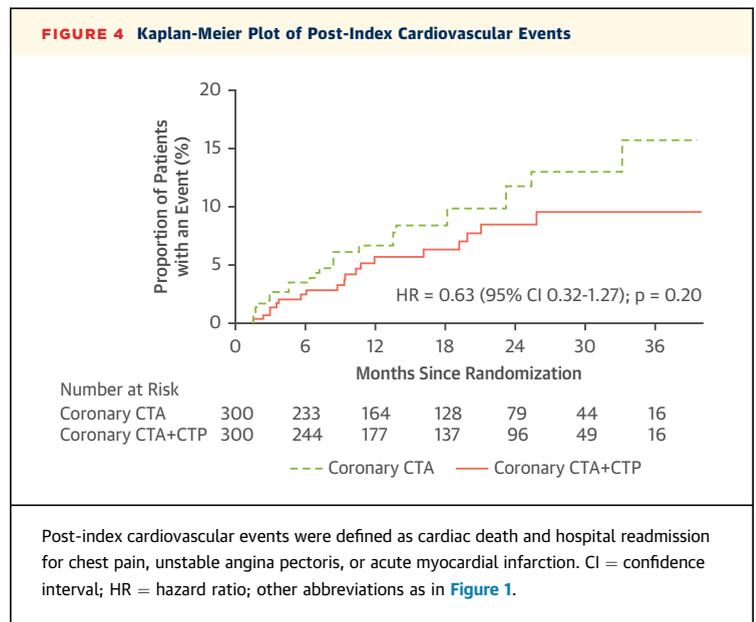
	Coronary CTA (n = 300)	Coronary CTA+CTP (n = 300)	p Value
Chest pain	24 (8.0)	18 (6.0)	0.42
Unstable angina pectoris	1 (0.3)	1 (0.3)	1.00
Acute myocardial infarction	2 (0.7)	1 (0.3)	1.00
Death, cardiovascular cause	0 (0.0)	0 (0.0)	—
Death, other cause	3 (1.0)	3 (1.0)	1.00
All	31 (10.0)	23 (8.0)	0.32

Values are n (%). Median follow-up time was 17 months (range 3 to 40 months) for the coronary CTA group and 18 months (range 3 to 39 months) for the coronary CTA+CTP group.
Abbreviations as in Table 1.

whereas the true-positive values using revascularization as the reference (our primary endpoint) were 45% and 61%, respectively, because a considerable number of patients were found unsuitable for revascularization. In addition, a lower number of patients than assumed in the pre-trial power calculations were referred for ICA in the coronary CTA+CTP group. Both factors may have reduced the statistical power of the primary endpoint analysis. This seems to be supported by a drop in statistical power from 80% predicted to 77% when the actual numbers of patients completing the study were applied in a post hoc power calculation. Subsequent indication for coronary revascularization was decided by members of the local heart team who were blinded to CATCH-2 trial allocation, who included multiple factors such as symptom burden, comorbidity, and technical procedural aspects in their decision-making.

Despite the lower number of coronary revascularizations in the coronary CTA+CTP group compared to the coronary CTA alone group, the rate of subsequent referral of study patients to hospitals for chest pain, unstable angina pectoris, and acute myocardial infarction was numerically lower albeit statistically insignificant in the coronary CTA+CTP group (Figure 4). By design, the diagnostic false-negative rate of CTP could not be assessed in our study, but the excellent clinical outcome suggests that this rate was rather low. Thus, the use of a coronary CTA+CTP-guided treatment strategy seemed safe and did not result in a delayed need for coronary revascularization. However, sample size calculations were only performed with regard to the primary endpoint, so safety by secondary endpoints and differences in long-term clinical outcome should be interpreted with caution. These findings concur with a recent meta-analysis assessing the effects of percutaneous coronary intervention and optimal medical therapy versus optimal medical treatment alone (20).

CLINICAL IMPLICATIONS. According to the current guidelines of the European Society of Cardiology, use of coronary CTA in symptomatic individuals is recommended as a first-choice test to rule out atherosclerotic coronary artery disease (3). When coronary atherosclerosis is identified by coronary CTA, different pathways may be taken depending on the specific angiographic findings, patient risk profile, and individual preference. These paths include direct referral for ICA, optimal medical therapy, and watchful waiting, or additional noninvasive ischemia testing to evaluate the clinical importance of the findings. The guidelines recommend that the specific choice of method for ischemia testing may be decided



based on patient suitability/preference, availability, and local expertise. In this context, CTP technology could be logistically advantageous because coronary CTA and CTP can be conducted within the same CT scan session. In the CATCH-2 study, we evaluated CTP as an adjunct to coronary CTA imaging to limit the fraction of patients in whom invasive coronary evaluation was necessary. Provided appropriate CT equipment and trained staff are available, our results suggest that coronary CTA in combination with CTP is valuable in the clinical management of patients with recent acute-onset chest pain. Nevertheless, future randomized controlled trials should explore the extent to which other modalities of myocardial perfusion imaging, including single-photon emission computed tomography, positron emission tomography, or magnetic resonance imaging, may achieve comparable or more cost-effective results. It would be especially helpful to assess the relative contribution of CT-FFR and CTP, which share the advantage that they can be conducted within the same examination. Although CT FFR does not entail additional radiation, it may be slightly less effective and require mandatory high image quality compared to CTP (21).

STUDY LIMITATIONS. CT perfusion imaging was performed using 320-multidetector technology, and our results might not apply if older or lower Z-coverage scanners are used. The treating interventional cardiologist was blinded to the detailed coronary CTA findings, which precluded a CT-based assessment of the technical feasibility of invasive intervention, specifically including aspects of

coronary vessel angulation, calcification, vessel tortuosity, presence of side branches, and bifurcations within the coronary lesions. How the knowledge of such CT information might have influenced clinical decisions made by the treating physicians is unknown. After index evaluation, long-term medical treatment strategy was the responsibility of the treating physician at each referring hospital. Consequently, the recommendations given by the CATCH-2 research team based on CT findings in terms of medical treatment were merely guidelines. Nevertheless, the prescribed medical treatment recorded at follow-up suggested a high degree of adherence to the CATCH-2 medical treatment recommendations.

CONCLUSIONS

A post-discharge diagnostic strategy of combined coronary CT angiography and CT myocardial perfusion imaging safely reduces the need for invasive coronary intervention while maintaining a low angina pectoris burden in patients with suspected IHD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

A combined approach using coronary CTA and CTP as a diagnostic strategy in patients with suspected IHD is safe and results in a decreased need for invasive investigation and treatment.

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: CTP should be considered a helpful diagnostic supplementary tool for coronary CTA in the clinical management of patients hospitalized because of acute-onset chest pain and subsequently referred for noninvasive diagnostic testing for IHD.

TRANSLATIONAL OUTLOOK: Although previous studies have demonstrated that the cardiovascular event rate of patients with normal CTP is low, long-term follow-up studies are warranted.

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KEY WORDS chest pain, ischemia, noninvasive imaging, outcome, revascularization

APPENDIX For supplemental tables and figures and Appendix A, please see the online version of this paper.