ORIGINAL ARTICLE

# CT or Invasive Coronary Angiography in Stable Chest Pain

The DISCHARGE Trial Group


## ABSTRACT

### BACKGROUND

In the diagnosis of obstructive coronary artery disease (CAD), computed tomography (CT) is an accurate, noninvasive alternative to invasive coronary angiography (ICA). However, the comparative effectiveness of CT and ICA in the management of CAD to reduce the frequency of major adverse cardiovascular events is uncertain.

### METHODS

We conducted a pragmatic, randomized trial comparing CT with ICA as initial diagnostic imaging strategies for guiding the treatment of patients with stable chest pain who had an intermediate pretest probability of obstructive CAD and were referred for ICA at one of 26 European centers. The primary outcome was major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) over 3.5 years. Key secondary outcomes were procedure-related complications and angina pectoris.

### RESULTS

Among 3561 patients (56.2% of whom were women), follow-up was complete for 3523 (98.9%). Major adverse cardiovascular events occurred in 38 of 1808 patients (2.1%) in the CT group and in 52 of 1753 (3.0%) in the ICA group (hazard ratio, 0.70; 95% confidence interval [CI], 0.46 to 1.07; P=0.10). Major procedure-related complications occurred in 9 patients (0.5%) in the CT group and in 33 (1.9%) in the ICA group (hazard ratio, 0.26; 95% CI, 0.13 to 0.55). Angina during the final 4 weeks of follow-up was reported in 8.8% of the patients in the CT group and in 7.5% of those in the ICA group (odds ratio, 1.17; 95% CI, 0.92 to 1.48).

### CONCLUSIONS

Among patients referred for ICA because of stable chest pain and intermediate pretest probability of CAD, the risk of major adverse cardiovascular events was similar in the CT group and the ICA group. The frequency of major procedure-related complications was lower with an initial CT strategy. (Funded by the European Union Seventh Framework Program and others; DISCHARGE ClinicalTrials .gov number, NCT02400229.)


The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Dewey can be contacted at marc.dewey@charite.de or at the Department of Radiology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.

Drs. Maurovich-Horvat, Bosserdt, and Kofoed contributed equally to this article.

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In the diagnosis of obstructive coronary artery disease (CAD), computed tomography (CT) is an accurate, noninvasive alternative to invasive coronary angiography (ICA) in patients with stable chest pain and intermediate pretest probability for obstructive CAD.[1,2] ICA is the reference standard for the diagnosis of obstructive CAD and enables coronary revascularization during the same procedure. However, elective ICA is associated with rare but major procedure-related complications[3] and has been reported to reveal obstructive CAD in only 38 to 50% of the patients who are referred for the procedure in the United States[4] and Europe.[5]

CT has generated interest since it may rule out obstructive CAD in a noninvasive procedure with a low risk of adverse events as it identifies patients who are appropriate candidates for coronary revascularization.[6] As compared with an initial strategy of functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography), an initial CT strategy in patients with stable symptoms was associated with similar cardiovascular outcomes at 25 months in the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, which indicated equipoise between functional testing and CT.[7,8] In the SCOT-HEART (Scottish Computed Tomography of the Heart) trial, CT was added to standard care, which included functional testing, and was compared with standard care alone. The use of CT was associated with a significantly lower incidence of major adverse cardiovascular events, which were defined as death from CAD or nonfatal myocardial infarction at 4.8 years (hazard ratio, 0.59).[9] In two small randomized trials of CT as compared with ICA,[10,11] an initial CT strategy resulted in a lower number of invasive procedures, a higher percentage (75%) of coronary angiograms showing obstructive CAD, and similar clinical outcomes, which included hospitalization and revascularization.[12]

We conducted the DISCHARGE (Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease) trial to compare CT with ICA as an initial diagnostic imaging strategy for guiding the treatment of patients with stable chest pain who were clinically referred for ICA. Here, we report the comparative effectiveness of CT and ICA in preventing the primary outcome of major adverse cardiovascular events, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

## Methods

### Trial Design and Oversight

We conducted this multicenter, pragmatic, randomized superiority trial to compare CT with ICA in guideline-directed management of stable chest pain.[13-15] The trial design and methods have been published previously[16] and are described in the protocol (which includes the statistical analysis plan) and the Supplementary Appendix (both of which are available with the full text of this article at NEJM.org). In brief, this investigator-initiated, assessor-blinded, parallel-group trial was reviewed and approved by the ethics committee at Charit ñUniversit tsmedizin Berlin as the coordinating center, by the German Federal Office for Radiation Protection, and by local or national ethics committees. The trial was funded by the European Union Seventh Framework Program and others. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The second author and last author wrote the first draft of the manuscript (see the Study Organization section in the Supplementary Appendix).

### Patients and Randomization

Eligible patients were at least 30 years of age and were referred for ICA to one of 26 centers in 16 European countries because of stable chest pain with intermediate (10 to 60%) pretest probability of obstructive CAD. Referral for ICA with or without previous functional testing was in accordance with the European guidelines at the time of trial initiation.[13,15] The pretest probability of obstructive CAD was assessed after enrollment but before randomization with a contemporary calculator according to the patient s age, sex, and type of chest pain (Section S7 in the Supplementary Appendix). Clinical centers were informed by means of the Web-based enrollment system about whether the calculated pretest probability was within the eligible range. Exclusion criteria were the receipt of hemodialysis, an absence of sinus rhythm, and pregnancy.

Patients were randomly assigned in a 1:1 ratio to undergo either CT or ICA with the use of a Web-based system to ensure concealment of

group assignments after eligibility criteria had been checked. Block randomization used computer-generated and randomly permuted blocks of 4, 6, or 8, stratified according to center and the patient s sex with central assignment. All the patients provided written informed consent.

### TRIAL PROCEDURES

CT and ICA were performed at certified clinical centers (Section S9). CT with at least 64-slice technology was performed according to a 10-step guide and scanner-specific recommendations.[16] CT scans were interpreted by board-certified radiologists who had at least a level 2 qualification, according to the Society of Cardiovascular Computed Tomography or similar certification, and at least one reader had level 3 certification for cardiac CT laboratory leadership. ICA was performed according to contemporary guidelines by board-certified cardiologists.[17]

In the two groups, it was recommended that patients without obstructive CAD be discharged from the trial center back to their referring physician for further treatment; patients with obstructive CAD were treated according to guidelines.[13,15] Trial centers were provided with recommendations incorporating European guidelines on the management of stable CAD,[13] on cardiovascular disease prevention,[14] and on myocardial revascularization[15] (Sections S10 and S11). Decisions regarding treatment were made by members of local heart teams and referring physicians on the basis of results on CT and ICA. In the two groups, additional recommendations included risk-factor modification and secondary prevention,[13] according to guidelines regarding cardiovascular disease prevention.[14] A CT-based clinical management guideline was provided to participating trial centers.

### OUTCOMES

The primary outcome of major adverse cardiovascular events was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. In this pragmatic trial, we did not assess myocardial biomarkers for the detection of silent myocardial infarction or perform brain imaging for the detection of asymptomatic stroke after all procedures. Therefore, the trial protocol required that the primary outcome be symptomatic. Cardiovascular death was determined according to the criteria of the Cardiac Safety Research Consortium, myocardial infarction was determined according to the Third Universal Definition of myocardial infarction, and stroke was determined according to the updated definition for the 21st century (Section S12). Possible cardiovascular events were adjudicated by members of an independent clinical events committee, who were unaware of group assignments. We also evaluated an expanded primary outcome that was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, or major procedure-related complications.

Key secondary outcomes were major procedure-related complications occurring during or within 48 hours after CT or ICA or related tests or revascularization procedures. Complications of ICA or revascularization procedures that were performed after CT were attributed to the CT strategy and were classified according to the National Cardiovascular Data Registry CathPCI Registry Coder s Data Dictionary, version 4.4. Patient-reported outcomes included angina during the last 4 weeks of follow-up, the score on the visual-analogue scale of the European Quality of Lifeñ5 Dimensions (EQ-5D), and the score on the physical component summary of the Short-Form Health Survey (SF-12v2). Additional secondary outcomes were defined in the trial registration and statistical analysis plan but are not the topic of this article (Section S16).

### STATISTICAL ANALYSIS

We determined that the enrollment of 3546 patients would provide the trial with 80% power to detect a relative reduction in the annual risk of the primary outcome from 1.4% in the ICA group to 0.8% in the CT group, assuming an annual loss to follow-up of 5%. We used a sequential design in which one interim analysis was performed after the occurrence of 50 major adverse cardiovascular events. The two-sided P value was set at 0.05, with levels of 0.0052 for the interim analysis and 0.048 for the final analysis, according to the O BrienñFleming method. After review and approval by the European Commission, the enrollment period was extended from the planned 2 years to 3.5 years to enable the recruitment of the planned number of patients, and the median follow-up period was extended from 3 years to 3.5 years to maintain statistical power.

Analyses were performed in a modified inten-

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Computed Tomography (N=1808) | Invasive Coronary Angiography (N=1753) |
|---|---|---|
| Median age (IQR) yr | 61.3 (53.2 67.8) | 60.6 (53.0 67.4) |
| Female sex no. (%) | 1019 (56.4) | 983 (56.1) |
| Outpatient at time of enrollment no./total no. (%) | 1386/1752 (79.1) | 1327/1695 (78.3) |
| Type of chest pain no. (%) | | |
| Typical angina | 232 (12.8) | 275 (15.7) |
| Atypical angina | 843 (46.6) | 805 (45.9) |
| Nonanginal chest pain | 677 (37.4) | 634 (36.2) |
| Other | 56 (3.1) | 39 (2.2) |
| Median pretest probability of obstructive CAD (IQR) % | 36.6 (28.8 46.2) | 37.9 (29.5 46.5) |
| Category for ICA referral no./total no. (%) | | |
| Clinical constellation suggesting high event risk, particularly with inadequate response to medical treatment | 870/1802 (48.3) | 791/1745 (45.3) |
| Severe angina, particularly with inadequate response to medical treatment | 354/1802 (19.6) | 397/1745 (22.8) |
| Intermediate pretest probability of CAD or LVEF <50% without typical angina after functional testing showing ischemia | 277/1802 (15.4) | 275/1745 (15.8) |
| Low or intermediate event risk with inadequate response to medical treatment | 189/1802 (10.5) | 177/1745 (10.1) |
| Intermediate pretest probability or LVEF <50% without typical angina after nondiagnostic functional testing | 52/1802 (2.9) | 51/1745 (2.9) |
| Other‖ | 60/1802 (3.3) | 54/1745 (3.1) |
| Cardiovascular risk factor no./total no. (%)** | | |
| Arterial hypertension | 1102/1799 (61.3) | 1020/1745 (58.5) |
| Diabetes mellitus | 263/1799 (14.6) | 294/1742 (16.9) |
| Hyperlipidemia | 874/1799 (48.6) | 832/1742 (47.8) |
| ≥1 Functional test performed before assigned intervention no. (%) | 599 (33.1) | 606 (34.6) |
| Positive results | 277 (15.3) | 275 (15.7) |
| Negative results | 270 (14.9) | 280 (16.0) |
| Nondiagnostic | 52 (2.9) | 51 (2.9) |
| Score on EQ-5D visual-analogue scale | 67.8±17.4 | 66.5±17.5 |
| Score on SF-12v2 physical component summary | 44.1±9.1 | 43.4±9.3 |

* Plus minus values are means ±SD. CAD denotes coronary artery disease, ICA invasive coronary angiography, IQR interquartile range, and LVEF left ventricular ejection fraction.

All other patients were inpatients at the time of enrollment.

Patients were classified according to the type of chest pain at baseline before undergoing the assigned intervention (CT or ICA). The four types of chest pain were defined as follows. Typical angina was considered if the following three criteria were fulfilled: retrosternal chest discomfort, precipitation by exertion, and prompt relief (within 30 seconds to 10 minutes) by rest or nitroglycerin.[19] Patients who met two, one, or none of these three criteria were classified as having atypical angina, nonanginal chest pain or discomfort, and other chest pain or discomfort, respectively. Because all the trial patients were symptomatic with stable chest pain, the category of other was used for patients who did not have any of the three criteria as described.[20] A breakdown of the four types of chest pain in terms of positive, negative, and nondiagnostic functional test results is provided in Table S15, and the distribution of the six ICA referral categories for the four chest pain types is provided in Table S16.

Pretest probability of CAD was calculated with the use of an updated model of the Diamond and Forrester method, which is based on the patient s age, sex, and type of stable chest pain and was developed by the Collaborative Meta-Analysis of Cardiac CT Consortium.[1] Additional details are provided in Section S7.

Angiography referral categories are listed according to the European guidelines for the management of stable CAD.[13] A breakdown of the six referral categories (available for 1802 patients in the CT group and 1745 patients in the ICA group) regarding the median (IQR) pretest probability of obstructive CAD in the two randomization groups is provided in Table S17. In all referral categories, patients with a history of previous ICA or CT were eligible only if those results had been negative for obstructive CAD and the procedures had been conducted at

**Table 1. (Continued.)**

least 5 years before enrollment. Such previous negative results on ICA were reported for 66 of 1808 patients in the CT group (3.7%)and for 39 of 1753 patients (2.2%) in the ICA group; previous negative results on CT were reported for 9 of 1808 patients (0.5%) in the CT group and for 10 of 1753 patients (0.6%) in the ICA group.

‖ Other ICA referral categories included a lack of ability to undergo stress imaging (in 12 patients [0.7%] in the CT group and in 6 [0.3%] in the ICA group), an LVEF level of less than 50% and typical angina (in 15 patients [0.8%] and 21 patients [1.2%], respectively), the presence of mild symptoms with medical treatment with noninvasive risk stratification indicating a high event risk and consideration of revascularization for improvement of prognosis (in 27 patients [1.5%] and 18 patients [1.0%], respectively), inconclusive diagnosis on noninvasive testing or conflicting results from different noninvasive methods (in 5 patients [0.3%] and 8 patients [0.5%], respectively), and employment in a special profession, such as airplane pilot, due to regulatory issues (in 1 patient [0.1%] in each group).

** Additional cardiovascular risk factors are described in Table S2.

Functional testing before the assigned intervention was recorded at each clinical center; no time frame before enrollment was specified.

Scores on the European Quality of Life 5 Dimensions (EQ-5D) visual-analogue scale range from 0 to 100, with higher scores indicating better health status. Data were available for 1745 patients in the CT group and for 1684 in the ICA group.

The physical component summary of the Short-Form Health Survey (SF-12v2) was transformed to T scores from 0 to 100, with higher scores indicating higher functioning and 50 being the middle of the distribution. Data were available for 1754 patients in the CT group and for 1692 in the ICA group.

tion-to-treat population that included all the patients who had fulfilled the eligibility criteria, had undergone randomization, and had not withdrawn or been excluded before undergoing CT or ICA. Continuous variables are reported as means and standard deviations for normally distributed data and as medians and interquartile ranges for other continuous data; categorical variables are reported as numbers and percentages.

The primary outcome analysis included an estimation of the cumulative risk of major adverse cardiovascular events and a comparison of randomization groups with the use of the method of Fine and Gray.[18] In this analysis, death from noncardiovascular causes was taken into account as a competing risk, and proportionality was tested (and affirmed) by including in the model a time-dependent covariate with two-way interaction of the randomization group. We analyzed secondary outcomes using absolute frequencies and percentages in the description of subgroups and calculated hazard ratios and 95% confidence intervals in the comparisons of groups.[18] Event rates were calculated in percentages as the ratio of the number of events to the person-years at risk for the event. Because a plan to adjust for multiplicity of inferences was not prespecified, all secondary outcomes are reported as point estimates of effects with 95% confidence intervals. The widths of these intervals were not adjusted for multiple comparisons, and inferences drawn from these intervals may not be reproducible.

We performed a comparison of rates of angina in the last 4 weeks of follow-up as the dependent variable using a logistic generalized-estimating-equation model that took into account interactions between groups and prespecified subgroups. For the SF-12v2 and EQ-5D measures, we used linear mixed-effects models with a random intercept for the trial center as the sole random effect. For these analyses, the covariates were trial group, age, sex, angina type at baseline, time from baseline to follow-up, and (on the SF-12v2 and EQ-5D measures) the baseline of the dependent variable. We performed multiple imputation of missing patient-reported outcome data using the R package Multivariate Imputation by Chained Equations (MICE) algorithm, predictive-mean-matching imputation for missing data on metric variables, and logistic regression imputation for missing binary data.

In the total population and in subgroups, we calculated odds ratios to indicate effect sizes for patient-reported angina and hazard ratios to indicate effect sizes for time-to-event data. Sample-size estimation was performed with the use of nQuery, version 7.0, and the R package gsDesign for the group sequential design. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute); SPSS for Windows, version 26 (IBM); and the statistical programming language R, version 4.0.3.

## RESULTS

### PATIENTS

Between October 3, 2015, and April 12, 2019, a total of 3667 patients were enrolled at 26 centers (Table S1). Of these patients, 1833 were randomly assigned to the CT group and 1834 to the ICA group. A total of 3561 patients were included

**Table 2. Results of Diagnostic Strategy during Initial Management.***

| Result | Computed Tomography (N=1808) | Invasive Coronary Angiography (N=1753) |
|---|---|---|
| Median time from enrollment to initial intervention (IQR) days | 3 (0 14) | 12 (1 37) |
| Initial intervention no. (%) | | |
| CT | 1782 (98.6) | 31 (1.8) |
| ICA | 20 (1.1) | 1705 (97.3) |
| Did not have scheduled intervention | 6 (0.3) | 17 (1.0) |
| Diagnostic findings on assigned intervention no. (%) | | |
| Obstructive CAD: ≥50% stenosis | 465 (25.7) | 451 (25.7) |
| 1 vessel | 155 (8.6) | 181 (10.3) |
| 2 vessels | 59 (3.3) | 74 (4.2) |
| High-risk anatomy | 251 (13.9) | 196 (11.2) |
| Nonobstructive CAD: 1 49% stenosis | 655 (36.2) | 393 (22.4) |
| No sign of CAD | 573 (31.7) | 877 (50.0) |
| Nondiagnostic result | 103 (5.7) | 5 (0.3) |
| CT performed during initial management no. (%) | 1784 (98.7) | 35 (2.0) |
| ICA performed during initial management no. (%)‖ | 404 (22.3) | 1708 (97.4) |
| Type of access no./total no. (%) | | |
| Radial artery | 343/404 (84.9) | 1514/1708 (88.6) |
| Femoral artery | 56/404 (13.9) | 165/1708 (9.7) |
| Other artery or missing data** | 5/404 (1.2) | 29/1708 (1.7) |
| Invasive procedure performed during initial management no. (%) | | |
| PCI | 195 (10.8) | 253 (14.4) |
| CABG | 39 (2.2) | 62 (3.5) |

* Initial management was performed at the clinical centers after initial testing for example, ICA with immediate or staged percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG).
The time from enrollment to the initial intervention is a cumulative incidence estimate.
In this category, data were missing for 23 patients who did not undergo the scheduled intervention (6 in the CT group and 17 in the ICA group), 12 patients who had an incomplete intervention (3 and 9, respectively), 3 patients who had data that were not documented or were lost (2 and 1, respectively), and 1 patient in the CT group with a missing test finding.
CAD with high-risk anatomy was defined as any 3-vessel CAD or stenosis in the left main coronary artery, in the proximal left anterior descending coronary artery, or both.
A nondiagnostic result was defined as the presence of a relevant artifact on CT or poor opacification on CT or ICA that could conceal stenosis of 50% or more in a vessel with a reference diameter of at least 2 mm. Obstructive CAD in non-high-risk anatomy was detected in 6 patients in the CT group who were described as having nondiagnostic results with high-risk anatomy.

‖ Included in this category were patients in the CT group who had undergone ICA before CT (2 patients) and after CT (384 patients) and patients in the ICA group who had undergone CT before ICA (5 patients) and after ICA (3 patients).
Access through the radial artery was common (>85% of cases), since this procedure has been associated with fewer procedural complications than access through the femoral artery.

** Other ICA access was used in 25 patients with both radial and femoral artery access (4 and 21, respectively), 6 patients with brachial artery access (1 and 5, respectively), 1 patient in the ICA group with radial and brachial artery access, and 2 patients in the ICA group for whom access was not documented or data were lost.
Included in this category were PCI and CABG procedures that were performed during initial management. Revascularization procedures that were performed during initial management and follow-up were included in the time-to-event analyses. (Details are shown in Fig. S6B, S6C, and S6D.) Both PCI and CABG were performed during initial management in 3 patients in the CT group and 8 patients in the ICA group.

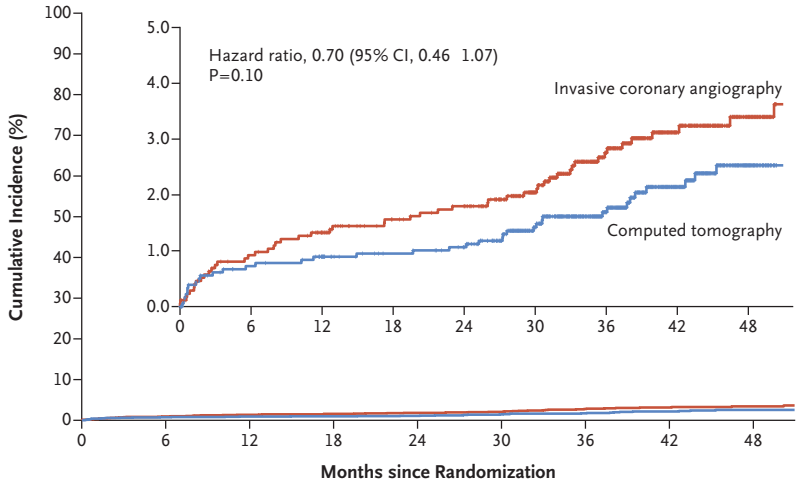


**Figure 1. Time-to-Event Curves for the Primary Composite Outcome.**

Shown is the cumulative incidence of the primary composite outcome of major adverse cardiovascular events, which included cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The inset shows the same data on an expanded y axis. The tick marks indicate censored data.

in the modified intention-to-treat analysis; adherence to the randomized assignments was 98.6% in the CT group and 97.3% in the ICA group (Fig. S1). The median follow-up was 3.5 years (interquartile range, 2.9 to 4.2), and complete follow-up for the primary outcome was obtained for 3523 patients (98.9%).

Table 1 presents the characteristics of the patients at baseline, which were similar in the two groups. (An expanded list of characteristics is provided in Table S2, and details regarding the representativeness of the trial population are provided in Table S3.) The mean (±SD) age of the patients was 60.1±10.1 years; 2002 of the 3561 patients were women (56.2%). Noninvasive functional testing was performed at the referral site or trial site before the assigned intervention (CT or ICA) in approximately one third of the patients. The use of cardiovascular medications at baseline, the type of patient-reported angina, and ICA referral categories were balanced between the two groups.

The median time from enrollment to the assigned intervention was 3 days in the CT group and 12 days in the ICA group (hazard ratio, 1.54; 95% confidence interval [CI], 1.44 to 1.65), which reflected typical wait times for elective testing (Table 2 and Fig. S2). The characteristics of the CT and ICA procedures were as specified in guidelines (Tables S4 and S5); the percentage of patients who had findings of obstructive CAD was 25.7% in each group. In the CT group, 404 patients underwent ICA during their initial treatment and were considered for the calculation of diagnostic yield; 293 patients (72.5%) were found to have obstructive CAD on ICA (Table S6).

### PRIMARY OUTCOME

Over a median follow-up of 3.5 years, the primary composite outcome of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 38 patients (2.1%) in the CT group and in 52 patients (3.0%) in the ICA group (hazard ratio, 0.70; 95% CI, 0.46 to 1.07; P=0.10) (Fig. 1 and Table 3). The results according to trial center are provided in Table S7. The resulting annual rate of major adverse cardiovascular events was 0.61% in the CT group and 0.86% in the ICA group. The results for the primary outcome in the prespecified subgroups were generally consistent with those in the overall population (Fig. S3). The

**Table 3. Primary and Secondary Outcomes.***

| Outcome | Computed Tomography (N=1808) | Invasive Coronary Angiography (N=1753) | Effect Size (95% CI) |
|---|---|---|---|
| **Primary outcome** | | | |
| Major adverse cardiovascular events no. (%) | 38 (2.1) | 52 (3.0) | 0.70 (0.46 to 1.07) |
| Nonfatal myocardial infarction | 23 (1.3) | 20 (1.1) | 1.11 (0.61 to 2.03) |
| Nonfatal stroke | 10 (0.6) | 20 (1.1) | 0.48 (0.23 to 1.03) |
| Cardiovascular death | 7 (0.4) | 14 (0.8) | 0.48 (0.20 to 1.20) |
| Expanded major adverse cardiovascular events no. (%) | | | |
| Cardiovascular death, myocardial infarction, stroke, transient ischemic attack, or major procedure-related complication | 50 (2.8) | 80 (4.6) | 0.60 (0.42 to 0.85) |
| Vascular death or myocardial infarction | 25 (1.4) | 24 (1.4) | 1.01 (0.58 to 1.77) |
| Cardiac death or myocardial infarction | 27 (1.5) | 30 (1.7) | 0.87 (0.52 to 1.46) |
| All-cause death, myocardial infarction, or stroke | 68 (3.8) | 83 (4.7) | 0.79 (0.57 to 1.09) |
| **Secondary outcomes** | | | |
| Major procedure-related complications during initial management no. (%) | 9 (0.5) | 33 (1.9) | 0.26 (0.13 to 0.55) |
| Nonfatal myocardial infarction | 3 (0.2) | 10 (0.6) | |
| Nonfatal stroke | 0 | 1 (0.1) | |
| Cardiac arrhythmia: ventricular tachycardia or fibrillation | 0 | 6 (0.3) | |
| Complication prolonging hospitalization by ≥24 hr‖ | 4 (0.2) | 11 (0.6) | |
| Dissection of coronary artery or aorta | 2 (0.1) | 2 (0.1) | |
| Cardiac arrest | 0 | 2 (0.1) | |
| Cardiac tamponade | 0 | 1 (0.1) | |
| Patient-reported outcome measures at follow-up** | | | |
| Angina in the past 4 wk no./total no. (%) | 152/1735 (8.8) | 125 /1671 (7.5) | 1.17 (0.92 to 1.48) |
| Health-related quality of life | | | |
| Score on EQ-5D visual-analogue scale | 71.8±16.4 | 71.1±16.7 | 0.31 (–0.76 to 1.38) |
| Score on SF-12v2 physical component summary | 48.4±8.7 | 47.8±8.7 | 0.26 (–0.27 to 0.78) |

* Plus minus values are means ±SD.
Effect sizes are hazard ratios except as marked.
Percentage results for major and expanded adverse cardiovascular events and major procedure-related complications are cumulative incidence estimates. Percentage results for individual major procedure-related complications are simple proportions.
According to the trial protocol, only symptomatic events were defined as major adverse cardiovascular events. As a result, only two silent myocardial infarctions that were detected as incidental findings were reported (one each by two trial centers during follow-up).
A detailed list of all major procedure-related complications in both groups and the relation to procedures is provided in Tables S8 through S12.
‖ Complications prolonging hospitalization included such events as cardiac arrhythmia and bleeding.
** For patient-reported outcomes, unadjusted percentages and means are listed. Estimates of odds ratios and mean differences were derived with the use of models with multiple imputation. Results for patient-reported outcomes at 1 year of follow-up are provided in Table S19.
The effect size is reported as an odds ratio.
Scores on the EQ-5D visual-analogue scale are included for 1395 patients in the CT group and for 1313 in the ICA group.
The effect size is the mean difference between groups.
Scores on the SF-12v2 physical component summary are included for 1392 patients in the CT group and for 1310 in the ICA group.

results for the components of the primary outcome are provided in Figure S4A, S4B, and S4C.

The expanded composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, or major procedure-related complications occurred in 50 patients (2.8%) in the CT group and in 80 patients (4.6%) in the ICA group (hazard ratio, 0.60; 95% CI, 0.42 to 0.85) (Fig. S4D). The incidences of other definitions of major adverse

cardiovascular events were similar in the two groups (Fig. S4E, S4F, and S4G); the detection of silent myocardial infarction in this pragmatic trial was uncommon.

### SECONDARY OUTCOMES

Overall, 42 major procedure-related complications occurred during initial management, of which 37 were associated with ICA and related intravascular procedures (7 in the CT group and 30 in the ICA group). These major complications related to ICA included 11 nonfatal myocardial infarctions and 1 nonfatal stroke. Of the 5 major complications not related to ICA, 1 was related to CT and 4 to coronary-artery bypass grafting (Tables S8 through S12). Because only 22.3% of the patients in the CT group underwent ICA during initial treatment, as compared with 97.4% in the ICA group, major procedure-related complications were less common in the CT group than in the ICA group (hazard ratio, 0.26; 95% CI, 0.13 to 0.55) (Table 3 and Fig. S5). The risk of major complications from ICA procedures was four times as high among the patients who had undergone revascularization as among those who had not undergone revascularization (4.2% vs. 0.9%) (Tables S10 and S11).

During the follow-up period, more patients in the CT group underwent additional functional tests than those in the ICA group (336 patients [18.6%] vs. 227 patients [12.9%]; hazard ratio, 1.49; 95% CI, 1.26 to 1.76) (Fig. S6A). The frequency of coronary revascularization procedures was lower in the CT group than in the ICA group (256 patients [14.2%] vs. 315 patients [18.0%]; hazard ratio, 0.76; 95% CI, 0.65 to 0.90) (Fig. S6B, S6C, and S6D). During the last 4 weeks of follow-up, angina was reported by less than 10% of the patients, and the incidence did not differ substantially between the two groups and was similar in most subgroups (Fig. S7). Quality-of-life outcomes that were assessed at follow-up were also similar in the two groups, and medical therapy did not differ substantially between groups at follow-up (Tables S13 and S14).

## DISCUSSION

In this multicenter, pragmatic, randomized trial of initial CT as compared with ICA for guiding the treatment of patients with stable chest pain, we found no significant difference in the primary outcome of major adverse cardiovascular events. The annual incidence of such events was lower than expected in the two groups, possibly due to improvements in the methods used to perform ICA and general improvements in cardiovascular care during the past few years. The CT strategy was associated with fewer major complications and revascularization procedures, and there were no substantial differences in the incidence of angina in the two groups at follow-up.

Our findings complement the results of two large trials ó the PROMISE[7] and SCOT-HEART trials[9] ó that compared CT with functional testing in patients with stable symptoms (Table S18). In both of those trials, investigators found that CT was as good as or better than functional testing as a preliminary evaluation before possible ICA. Our trial confirmed the safety of a CT-first strategy and showed results that were similar to those with ICA. CT identifies covert CAD, which may be of greatest value in patients with atypical symptoms.[21] In a large U.S. registry of almost 400,000 patients referred for ICA, such atypical symptoms were present in approximately 37% of the patients, of whom 25.2% had obstructive CAD.[4] In our trial, the incidence of obstructive CAD in the two groups (25.7% in each) was nearly the same as that reported in the registry, a finding that indicates similar clinical practice patterns in patients with atypical symptoms. In an update of the large U.S. registry, 56.5% of patients with suspected CAD underwent functional testing before being referred for ICA,[22] as compared with only 33.6% of our patients who underwent functional testing before referral.

All the patients in our trial had an intermediate pretest probability of obstructive CAD and were referred by the responsible physician for ICA according to European guidelines.[13] The rationale behind choosing this trial population was that intermediate-risk patients have been found to benefit the most from cardiac imaging.[6] We found that CT may be suitable for certain intermediate-risk patients with stable chest pain who are referred for ICA because they have a clinical constellation suggesting a high risk of cardiovascular events, abnormal or inconclusive results on functional testing, or persistent symptoms despite medical treatment.[3,6,23,24]

The use of ICA in just 22% of the patients in the CT group resulted in fewer major procedure-related complications in the CT group, an im-

portant outcome for the comparison of invasive and noninvasive management strategies.[25] The incidence of complications that were associated with ICA in our trial was similar to that in the registry.[26]

Freedom from angina and improvement in quality of life are key objectives in the treatment of patients with stable chest pain.[27] An initial invasive management strategy, as compared with a conservative strategy, had similar event rates but larger reductions in angina symptoms and improvements in quality of life, which persisted for 2 years in the COURAGE trial[27,28] and 3 years in the ISCHEMIA trial.[29,30] In our trial, we did not find evidence of differences in angina relief and quality of life between the CT strategy and the ICA strategy.

Strengths of our trial include the multicenter, pragmatic design, which enhances external validity. The adherence to the group assignments and the completeness of follow-up were high, and 56% of the patients were women. Our trial also has some important limitations. First, patients and their clinicians were necessarily aware of the group assignments, which might have influenced outcomes, especially patient-reported outcomes. Because we could not systematically identify silent events (especially procedure-related myocardial infarction or stroke), ascertainment bias might have favored the ICA group. Second, the incidence of nondiagnostic CT in this and previous trials was approximately 6%,[7,9] which indicates the need for continuous quality control of the conduct and interpretation of CT. Third, because this was a pragmatic trial, diagnostic imaging results informed, but did not mandate, management decisions, which might have resulted in a departure from guideline-based care. Finally, we do not present results for a comparison of the cost-effectiveness of CT and ICA, a factor that is a crucial component of decision making and that warrants rigorous analysis.

Overall, we found that a strategy of initial CT resulted in no significant difference in the incidence of major adverse cardiovascular events as compared with ICA but was associated with a lower risk of major procedure-related complications and revascularization procedures.

The views expressed in this article are those of the authors and do not necessarily represent the views of the European Commission.

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## APPENDIX

The authors full names and academic degrees are as follows: P l Maurovich-Horvat, M.D., Ph.D., M.P.H., Maria Bosserdt, Ph.D., Klaus F. Kofoed, M.D., D.M.Sc., Nina Rieckmann, Ph.D., Theodora Benedek, M.D., Ph.D., Patrick Donnelly, M.D., Jos Rodriguez-Palomares, M.D., Ph.D., Andrejs Erglis, M.D., Cyril Štěchovský, M.D., Gintare Šakalyte, M.D., Nada Čemerlić Adić, M.D., Matthias Gutberlet, M.D., Ph.D., Jonathan D. Dodd, M.D., Ignacio Diez, M.D., Gershan Davis, M.D., Elke Zimmermann, M.D., Cezary Kępka, M.D., Radosav Vidakovic, M.D., Ph.D., Marco Francone, M.D., Ph.D., Małgorzata Ilnicka-Suckiel, M.D., Ph.D., Fabian Plank, M.D., Ph.D., Juhani Knuuti, M.D., Rita Faria, M.D., Stephen Schr der, M.D., Colin Berry, M.D., Luca Saba, M.D., Balazs Ruzsics, M.D., Ph.D., Christine Kubiak, Ph.D., I aki Gutierrez-Ibarluzea, Ph.D., Kristian Schultz Hansen, Ph.D., Jacqueline M ller-Nordhorn, M.D., M.P.H., Bela Merkely, M.D., Ph.D., Andreas D. Knudsen, M.D., Ph.D., Imre Benedek, M.D., Ph.D., Clare Orr, M.D., Filipa Xavier Valente, M.D., Ph.D., Ligita Zvaigzne, M.D., Vojtěch Such nek, M.D., Laura Zajančkauskiene, M.D., Filip Adić, M.D., Michael Woinke, M.D., Mark Hensey, M.B., B.Ch., B.A.O., I igo Lecumberri, M.D., Erica Thwaite, M.D., Michael Laule, M.D., Mariusz Kruk, M.D., Aleksandar N. Neskovic, M.D., Ph.D., Massimo Mancone, M.D., Donata Kuśmierz, M.D., Gudrun Feuchtner, M.D., Mikko Pietil , M.D., Ph.D., Vasco Gama Ribeiro, M.D., Tanja Drosch, M.D., Christian Delles, M.D., Gildo Matta, M.D., Michael Fisher, M.D., Ph.D., B lint Szilveszter, M.D., Ph.D., Linnea Larsen, M.D., Ph.D., Mihaela Ratiu, M.D., Ph.D., Stephanie Kelly, B.Sc., Bruno Garcia del Blanco, M.D., Ph.D., Ainhoa Rubio, M.D., Zs fia D. Drobni, M.D., Birgit Jurlander, M.D., Ph.D., Ioana Rodean, M.D., Susan Regan, B.Sc., Hug Cu l-lar Calabria, M.D., Ph.D., Melinda Boussoussou, M.D., Thomas Engstr m, M.D., D.M.Sc., Roxana Hodas, M.D., Adriane E. Napp, Ph.D., Robert Haase, M.D., Sarah Feger, M.D., Lina M. Serna-Higuita, M.D., Konrad Neumann, Ph.D., Henryk Dreger, M.D., Matthias Rief, M.D., Viktoria Wieske, M.D., Melanie Estrella, Ph.D., Peter Martus, Ph.D., and Marc Dewey, M.D.

The authors affiliations are as follows: the Heart and Vascular Center (P.M.-H., B.M., B.S., Z.D.D., M. Boussoussou) and the Department of Radiology, Medical Imaging Center (P.M.-H.), Semmelweis University, Budapest, Hungary; the Departments of Radiology (M. Bosserdt, E.Z., A.E.N., R. Haase, S.F., M. Rief, V.W., M.E., M.D.) and Cardiology and Angiology (M.L., H.D.), the Institute of Public Health (N.R., J.M.-N.), and the Institute of Biometry and Clinical Epidemiology (K.N.), Charit ñUniversit tsmedizin Berlin, Freie

Universit t Berlin and Humboldt-Universit t zu Berlin and DZHK (German Center for Cardiovascular Research) Partner Site Berlin (H.D., M.D.), Berlin Institute of Health and Berlin University Alliance (M.D.), Berlin, the Departments of Radiology (M.G.) and Cardiology (M.W.), University of Leipzig Heart Center, Leipzig, the Department of Cardiology, Alb Fils Kliniken, G ppingen (S.S., T.D.), the Bavarian Cancer Registry, Bavarian Health and Food Safety Authority, Munich (J.M.-N.), and the Department of Clinical Epidemiology and Applied Biostatistics, Universit tsklinikum T bingen, T bingen (L.M.S.-H., P.M.) ó all in Germany; the Departments of Cardiology (K.F.K., A.D.K., T.E.) and Radiology (K.F.K., A.D.K.), Rigshospitalet, and the Department of Clinical Medicine, Faculty of Health and Medical Sciences (K.F.K., A.D.K., T.E., L.L., B.J.), and the Department of Public Health, Section for Health Services Research (K.S.H.), University of Copenhagen, Copenhagen, the Department of Cardiology, Herlev-Gentofte Hospital, Hellerup (L.L.), and the Department of Cardiology, Nordsjaellands Hospital, Hillerod (B.J.) ó all in Denmark; the Department of Internal Medicine, Clinic of Cardiology (T.B., R. Hodas), and the Department of Radiology and Medical Imaging (M. Ratiu), George Emil Palade University of Medicine, Pharmacy, Science, and Technology, County Clinical Emergency Hospital Targu Mures (T.B.), and the Center of Advanced Research in Multimodality Cardiac Imaging, CardioMed Medical Center (I.B., I.R.) ó all in Targu Mures, Romania; the Department of Cardiology, Southeastern Health and Social Care Trust, Belfast (P.D., C.O., S.K., S.R.), the Departments of Cardiology (G.D.) and Radiology (E.T.), Aintree University Hospital, the Department of Cardiology, Royal Liverpool University Hospital and the Institute for Cardiovascular Medicine and Science, Liverpool Heart and Chest Hospital (B.R., M. Fisher), and the Faculty of Health and Life Sciences, University of Liverpool (M. Fisher), Liverpool, Edge Hill University, Ormskirk (G.D.), the Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow (C.B., C.D.), and Golden Jubilee National Hospital, Clydebank (C.B.) ó all in the United Kingdom; the Departments of Cardiology (J.R.-P., F.X.V., B.G.B.) and Radiology (H.C.C.), Hospital Universitario Vall d Hebron, Institut de Recerca, Universitat Aut noma de Barcelona, Barcelona, Centro de Investigaci n Biom dica en Red, Madrid (J.R.-P., F.X.V., B.G.B.), the Departments of Cardiology (I.D., A.R.) and Radiology (I.L.), Basurto Hospital, Bilbao, Basque Foundation for Health Innovation and Research, Barakaldo, and the Basque Office for Health Technology Assessment, Vitoria-Gasteiz (I.G.-I.) ó all in Spain; the Departments of Cardiology (A.E.) and Radiology (L. Zvaigzne), Paul Stradins Clinical University Hospital, and the University of Latvia (A.E.) ó both in Riga, Latvia; the Departments of Cardiology (C.Š.) and Imaging Methods (V.S.), Motol University Hospital, Prague, Czech Republic; the Department of Cardiology, Medical Academy, Lithuanian University of Health Sciences, and the Department of Cardiology, Hospital of Lithuanian University of Health Sciences (G.Š., L. Zajančkauskiene) ó both in Kaunas, Lithuania; the Faculty of Medicine, University of Novi Sad, and the Department of Cardiology, Institute for Cardiovascular Diseases of Vojvodina, Novi Sad (N.Č.A., F.A.), and the Department of Cardiology, Internal Medicine Clinic, Clinical Hospital Center Zemun, and the Faculty of Medicine, University of Belgrade, Belgrade (R.V., A.N.N.) ó all in Serbia; the Departments of Radiology (J.D.D.) and Cardiology (M.H.), St. Vincent s University Hospital and School of Medicine, University College Dublin (J.D.D.), Dublin; the National Institute of Cardiology, Warsaw (C. Kępka, M.K.), and the Departments of Cardiology (M.I.-S.) and Radiology (D.K.), Provincial Specialist Hospital in Wroclaw, Wroclaw ó both in Poland; the Department of Clinical Internal, Anesthesiologic, and Cardiovascular Sciences, Sapienza University of Rome, Rome (M.M.), the Department of Biomedical Sciences, Humanitas University, and IRCCS Humanitas Research Hospital (M. Francone), Milan, and the Department of Radiology, University of Cagliari (L.S.), and the Department of Radiology, Azienda Ospedaliera Brotzu (G.M.), Cagliari ó all in Italy; the Department of Internal Medicine III, the Department of Cardiology (F.P.), and the Department of Radiology (G.F.), Innsbruck Medical University, Innsbruck, Austria; the Turku PET Center (J.K.) and Heart Center (M.P.), Turku University Hospital and University of Turku, and the Administrative Center, Health Care District of Southwestern Finland (M.P.) ó all in Turku, Finland; the Department of Cardiology, Centro Hospitalar de Vila Nova de GaiañEspinho, Vila Nova de Gaia, Portugal (R.F., V.G.R.); and the European Clinical Research Infrastructure NetworkñEuropean Research Infrastructure Consortium, Paris (C. Kubiak).

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