Supplementary Appendix

Supplement to: The DISCHARGE Trial Group. CT or invasive coronary angiography in stable chest pain. N Engl J Med. DOI: 10.1056/NEJMoa2200963

This appendix has been provided by the authors to give readers additional information about the work.

SUPPLEMENTARY APPENDIX

CT or Invasive Coronary Angiography in Stable Chest Pain

The DISCHARGE Trial Investigators

Funding

The trial was funded by the EU 7th Framework Programme (Grant ID no. 603266) and others

Trial Registration

ClinicalTrials.gov Identifier: NCT02400229

Additional information may be found at https://www.dischargetrial.eu.

Content

A. Study Organization

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M.D. conceived and initiated the project. M.D. and R. Haase jointly designed the project. M.D., A.E.N., M.B. and M.E. provided infrastructure and jointly supervised the project. M.D. and M.B. wrote the first draft of the manuscript. J.D.D., K.F.K., N.R. and M.E. further edited the manuscript. P.M. and K.N. performed the statistical analyses with contributions from N.R., L.M.H.-S. and M.B. P.M.-H., M.B., K.F.K, T.B., P.D., J.R.P., A.E., C.Š., G.Š., N.Č.A., M.G., J.D.D:, I.D., G.D., E.Z., C. Kępka, R.V., M. Francone, M.I.S., F.P., J.K., R.F., S.S., C.B., L.S., B.R., B.M., A. D.K., I.B., C.O., F.X.V., L. Zvaigzne, V.S., L. Zajančkauskienė, F.A., M.W., M.H., I.L., E.T., M.L., M.K, A.N.N., M.M., D. K., G.F., M.P., V.G.R., T.D., C.D., G.M., M. Fisher, B.S., L.L., M. Ratiu, S.K., B.G.B., A.R., Z.D.D., B.J., I.R., S.R., H.C.C., M.B., .T.E., R. Hodas, S.F., H.D., M. Rief, V.W., M.E. and M.D. organized and supervised patient inclusion and retrieval of clinical data, and provided input to study design and performance. All work package leaders of the DISCHARGE project (K.F.K., N.R., C. Kubiak, I.G.-I., K.S.H., J.M.-N., M.D.) provided intellectual input during the project and trial performance. The decision to publish was made by M.D. and the Dissemination Committee in agreement with all authors. All authors provided intellectual input to the manuscript and revised and edited the manuscript for critical content and approved the final version before submission for publication.

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S6. Data Management and Clinical Monitoring

S6.1 Data Management

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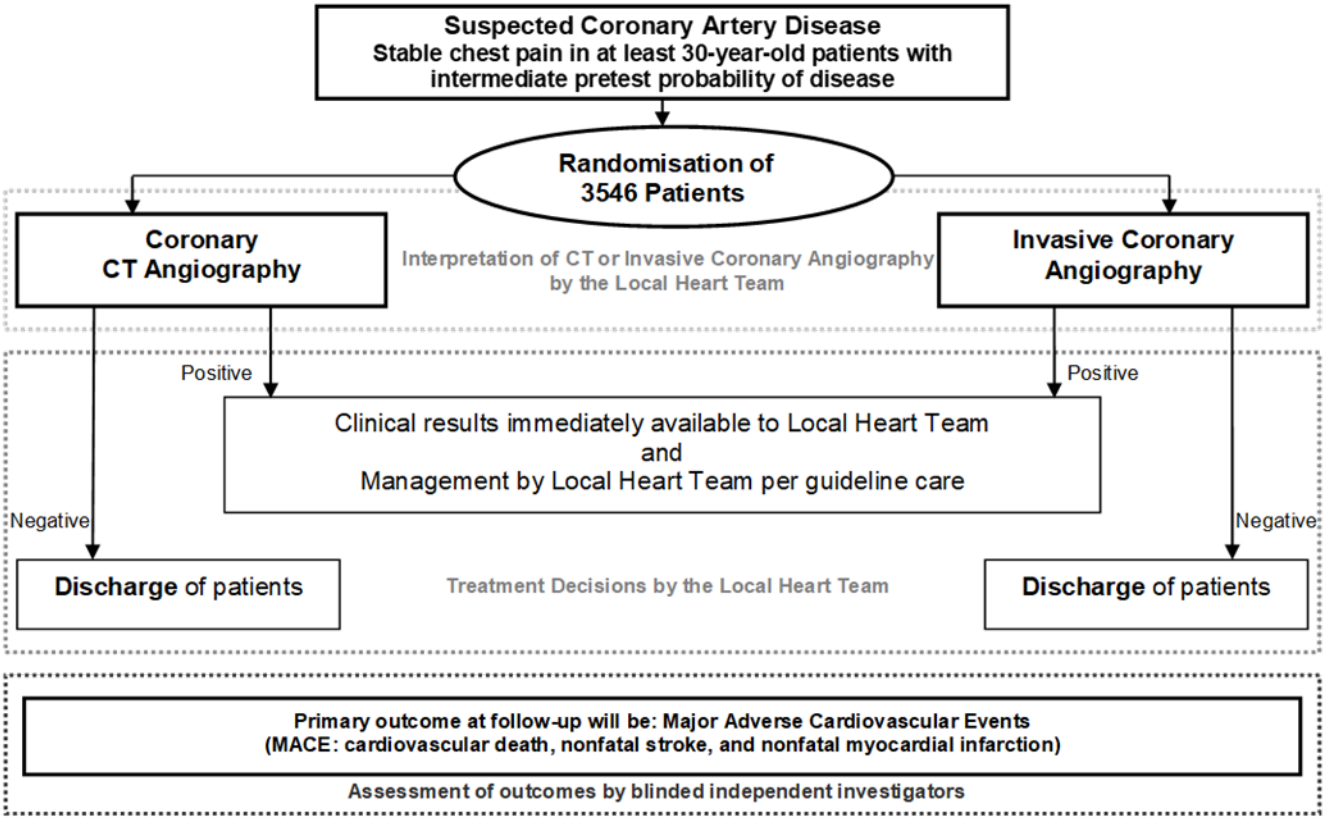
B. Supplementary Methods

A detailed description of the trial design and methods has previously been published (Napp AE et al. Eur Radiol 2017;27:2957–68).[1] Components of relevance for this report are summarized in the following sections.

S7. Overview of Trial Design

Methods Figure 1 Overview of Trial Design

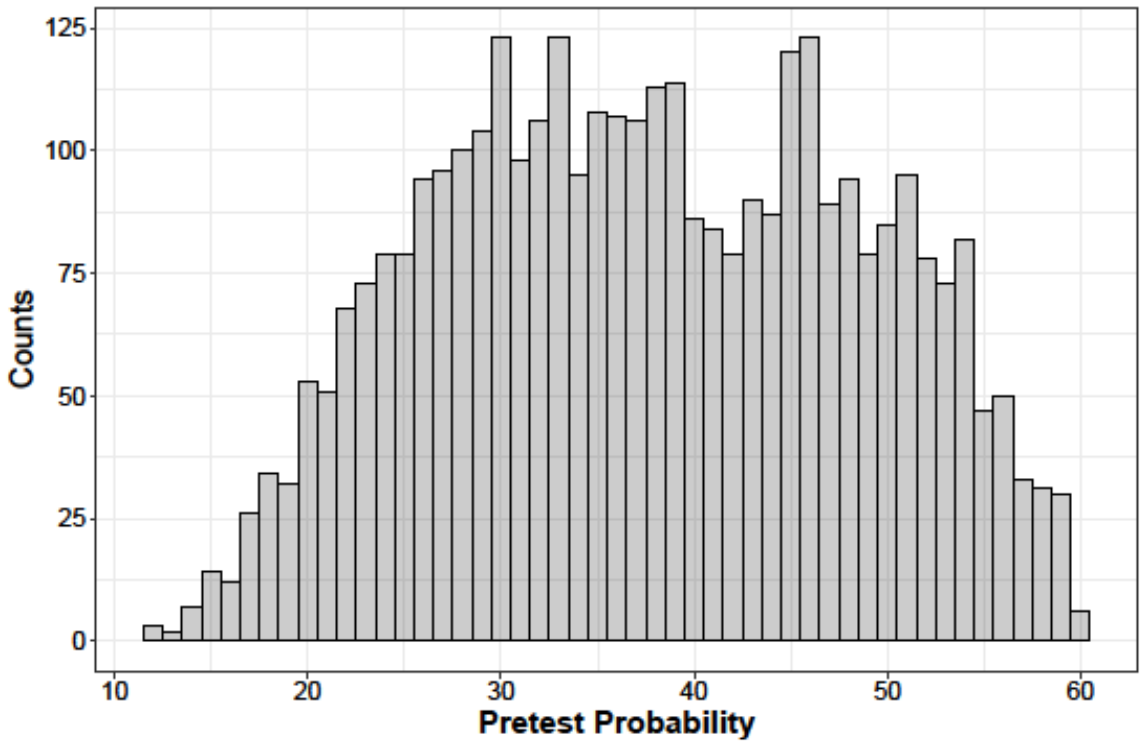


Reference: Napp AE et al Eur Radiol 2017;27:2957-68.[1]

Included patients were managed by local heart teams in both groups according to contemporary European guidelines including the European Guidelines on disease prevention, management of stable coronary artery disease, and myocardial revascularization applicable at the time of study conduct.* The number of randomized patients planned is slightly lower than the actual number of patients randomized in the trial since potential drop-out of patients was taken into account to reach the aimed required number of randomized patients. Intermediate pretest probability was defined as 10-60% because CT has shown the best diagnostic performance in differentiating presence versus absence of obstructive CAD in the 7-67% pretest probability range.[2] Individual calculation of pretest probability was not made available to clinical centers to avoid bias in recruiting subsequent patients, e.g., by not approaching patients who are thought not to be in the intermediate range. All patients included were in the intermediate pretest probability range (Methods Figure 2). The pretest probability calculation used in the DISCHARGE trial is made available in Methods Table 1, and estimates of the logistic regression model for pretest probability calculation are provided in Methods Table 2. Further information on the cardiovascular risk factor management approach specifically developed for the trial by Joep Perk is provided in Methods Figure 4. Additional information on CT-based management in the trial is provided in Methods Figure 5.

* European Guidelines References: Perk et al. 2012. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012) (European Heart Journal (2012) 33, 1635–1701),[3] Montalescot et al. 2013. ESC guidelines on the management of stable coronary artery disease (European Heart Journal (2013) 34, 2949–3003)[4] and Windecker et al. ESC/EACTS Guidelines on myocardial revascularization (European Heart Journal (2014) 35, 2541–2619).[5]

Methods Figure 2 Distribution of Pretest Probabilities of Obstructive CAD



All patients included in the DISCHARGE trial were in the intermediate pretest probability range defined as 10-60%. The above histogram shows the distribution of pretest probabilities of obstructive CAD with counts (numbers of patients) on the y-axis.

Methods Table 1 Calculation of Pretest Probabilities (in %) of Obstructive CAD

Age	Typical Angina		Atypical Angina		Nonanginal Chest Discomfort		Other Chest Discomfort	
years	Women	Men	Women	Men	Women	Men	Women	Men
30	28	48	13	26	12	25	10	22
35	31	52	15	29	14	28	12	25
40	34	55	17	33	16	32	13	28
45	38	59	19	36	18	35	15	31
50	41	63	21	40	21	38	18	34
55	45	66	24	43	23	42	20	38
60	49	69	27	47	26	46	23	41
65	53	73	30	51	29	50	25	45
70	56	76	34	55	32	53	28	49
75	60	78	37	58	36	57	32	52
80	64	81	41	62	39	61	35	56
85	67	83	44	65	43	64	39	60
90	70	85	48	69	47	68	42	63
95	73	87	52	72	50	71	46	67

The above table allows readers to reproduce calculation of individual pretest probabilities of obstructive CAD by age, gender, and chest pain type, as it was used in the DISCHARGE trial. The calculator was developed by the Collaborative Meta-Analysis of Cardiac CT (COME-CCT) Consortium.[2] The four types of chest pain were defined as follows. Typical angina was considered if all of the following three criteria were fulfilled: retrosternal chest discomfort, precipitation by exertion, and prompt relief (within 30 s – 10 min) by rest or nitroglycerin. Patients who met two, one, or none of these three criteria were classified as having atypical angina, nonanginal chest pain/discomfort, and other chest pain/discomfort, respectively. Because all patients included were symptomatic with stable chest, the category ‘other chest discomfort’ was used for patients not exhibiting any of the three criteria as described.

Methods Table 2 Estimates of the Logistic Regression Model for Pretest Probability of CAD

	Estimate (S.E.)	Odds Ratio (95% CI)
Age	0.035 (0.004)	1.04 (1.03–1.04)
Gender (male vs. female)	1.012 (0.075)	2.75 (2.37–3.19)
Symptoms*		
Typical angina	1.371 (0.127)	3.94 (3.07–5.05)
Atypical angina	0.275 (0.124)	1.32 (1.03–1.68)
Nonanginal chest discomfort	0.215 (0.142)	1.24 (0.94–1.64)
Other chest discomfort	Reference group	1.00
Model constant	–3.541 (—)	—
Variance of random intercept (τ^2) †	0.806 (0.898)	
BIC	5273.22	
Log likelihood	–2607.23	

S.E. denotes standard error, BIC Bayesian information criterion. The logistic regression model was developed by the COME-CCT Consortium and is based on data from 4416 patients with suspected CAD and stable chest pain included in the individual-patient data COME-CCT meta-analysis. Data used for developing the DISCHARGE pretest probability calculation were based on data from 55 prospective diagnostic accuracy studies with ICA as the reference standard. Individually calculated pretest probabilities were not made available to clinical centers in the DISCHARGE trial to avoid bias in recruiting subsequent patients, e.g., by not approaching patients thought not to be in the intermediate range.

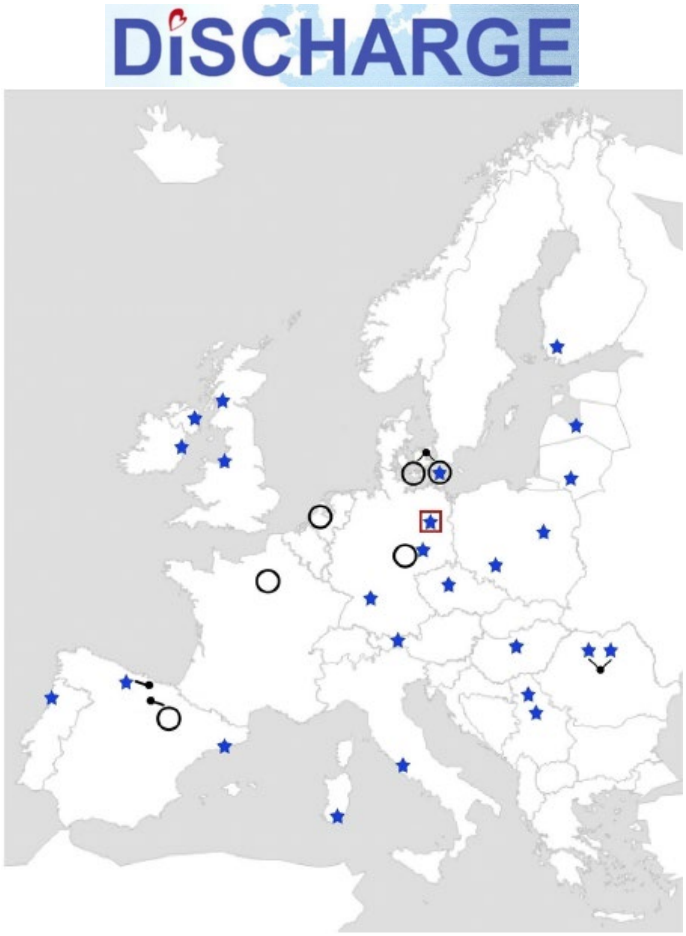
* Typical angina was present when all of the following three criteria were fulfilled: retrosternal chest discomfort, precipitation by exertion, and prompt relief (within 30 s – 10 min) by rest or nitroglycerin. Patients with two, one, or none of these three criteria were classified as having atypical angina, nonanginal chest discomfort, and other chest discomfort, respectively.

† Variance component estimate (τ^2) for the random intercept.

S8. Overview of Clinical Centers, Work Package Leaders, and Coordinator

The DISCHARGE consortium is a multinational group comprising a broad variety in geographical and economic differences throughout Europe.

Methods Figure 3 Overview of Clinical Centers, Work Package Leaders, and Coordinator



Reference: Napp AE et al. Eur Radiol 2017;27:2957–68.[1]

Black circles represent work package leaders and blue stars represent clinical centers (note that two centers are located in Liverpool). The red square stands for the coordinating center at Charité – Universitätsmedizin Berlin, which also functions as a clinical center and work package leader. The consortium consists of 31 partners in 18 countries, including 26 clinical centers in 16 European countries.

www.dischargetrial.eu

S9. Quality Control of Clinical Centers, Database Entry, and Monitoring

S9.1 Quality Control of Centers

Prior to enrollment of patients in the pragmatic randomized controlled trial, all participating clinical centers were required to undertake an observational pilot study to ensure appropriateness and high quality of data collection for pretest probability assessment (Feger et al, Eur Radiol 2020),[6] patient-reported outcome measures (Rieckmann et al, Health and Quality of Life Outcomes 2020),[7] and CT and ICA image acquisition and reconstruction (De Rubeis et al, Eur Radiol 2020).[8] Only centers certified in this observational pilot study before the randomized trial were allowed to participate in the DISCHARGE trial.

S9.2 Characteristics of Participating Centers

ICA procedural volume: Based on database queries performed at all centers for the EC grant application and prior to study initiation, the annual average number of clinical ICA procedures with the indication of stable chest pain per center was a mean of 1076 (min: 210, max: 3515).

CT procedural volume: Based on the above database queries, the annual average number of all cardiac CT procedures per center was a mean of 1213 (min: 120, max: 6800). To ensure a low proportion of nondiagnostic CT scans, the use of ≥ 64 slice CT scanners was mandatory.

S9.3 Required CT and ICA Quality Standards for Participating Sites

Invasive image acquisition and reading: According to contemporary clinical standards of each participating center, trained interventional cardiologists were responsible for performing appropriate invasive image projections for diagnostic ICA image acquisition. ICA coronary artery diameters were assessed according to clinical practice at each center using either visual assessment or quantitative coronary angiography according to the European guidelines (Windecker S et al, Eur Heart J 2014;35:2541–619).[5] Additional imaging modalities including intravascular ultrasound and/or optical coherence tomography were allowed at the discretion of the operator. Invasive fractional flow reserve (FFR) assessment could be conducted when deemed clinically indicated by the operator and according to local routine practice.

CT image acquisition and reading: CT images were acquired according to the "10–steps guide to performing cardiac CT" and scanner-specific guides developed by the DISCHARGE consortium.[1] Each CT was evaluated by two local readers at each center of whom at least one had to be certified as a level-2 reader according to the Society of Cardiovascular Computed Tomography or similar certification. At least one CT reader per center was required to have level-3 certification for cardiac CT lab leadership. Moreover, at least one reader from each site participated in one of two additional hands-on training course at Charité with interpretation of 100 CT cases with ICA correlation, from outside of this trial, as part of quality assurance and to improve skills and knowledge of readers (Zimmermann et al.).[9] For CT, it was recommended to use double oblique views, multi-planar reformations, and cross-sections in all coronary artery segments (Leipsic et al.).[10]

S9.4 Electronic Case Report Form for Database Entry, Image Transfer and Analysis

At the Coordinating Center of Clinical Studies at Charité (KKS Charité), a central web-based database was designed using an Electronic Data Capture system (EDC, SecuTrial ®). This system

was designed to operate according to the principle of online data capture and is compliant with the code of federal regulations (FDA 21 CFR Part 11) to ensure reliability of the recorded data. It allowed the documentation of study data in electronic case report forms (eCRF). The software was specially designed for the data entry according to Good Clinical Practice (GCP). This EDC system included the following major functions: system checks and plausibility, consistency and range checks, Query management tool, Audit Trail to log all activities, which are necessary and helpful for the data entry process. The system used a secured data connection (with Secure-Sockets-Layer protocol, SSL) enabling transfer of data from the participating clinical centers to the central database. Image data were transferred using AG Mednet and the core laboratory at Charité reviewed all CT image data using Vitrea workstations (Vital Images).

S9.5 Good Clinical Practice and Surveillance System of Clinical Centers

All clinical centers underwent pretrial training in good clinical practice, and on-site monitoring was conducted throughout the duration of the trial under the leadership of the European Clinical Research Infrastructures Network (ECRIN, https://ecrin.org/) and in collaboration with the coordination center of clinical studies at Charité (KKS Charité), Berlin, Germany, as specified in the DISCHARGE study protocol. The on-site monitoring activities for all countries (except Germany) were coordinated and delivered via a network of national hubs of academic clinical research centers and clinical trials units with professional staff working according to minimum standards as defined by ECRIN. All monitors were trained by the team of the KKS Charité (web-based online training) to guarantee consistent quality for monitoring at all centers. The monitors visited the clinical study centers on a regular basis during the study in a general risk-based approach. The monitors conducted a review of the ongoing study to verify adherence to the protocol and compliance with ICH-GCP and national regulations.

The SecuTrial ® system, which complies with Good Clinical Practice, was used. Furthermore, in DISCHARGE the safety surveillance system was adapted to the requirements of a pragmatic study and was based on documentation of (serious) adverse events (SAEs) and reporting of SAEs to the sponsor. Continuous medical assessment was performed by the sponsor together with the data safety and monitoring board (DSMB) to identify any risk for patients arising from study conduct or study procedures. With respect to the various SAE-reporting requirements of the different countries, SAEs were reported in compliance with applicable law.

The DISCHARGE consortium agreement required all investigators (including the authors) to protect the privacy of patients in their use of the study dataset.

S9.6 Study Database Quality Control

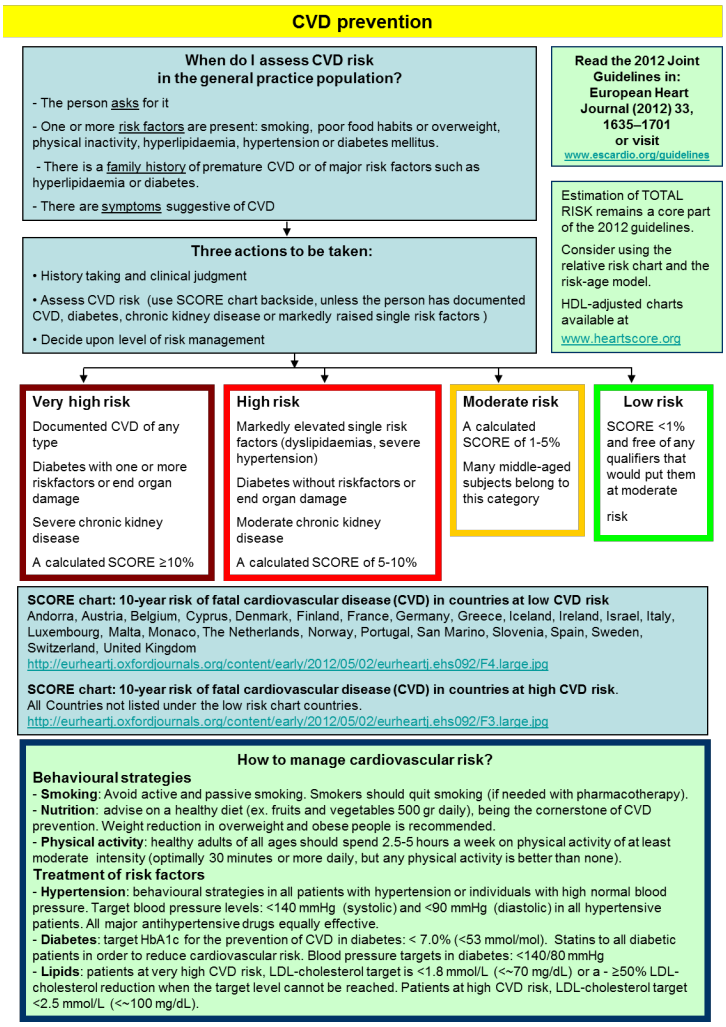
To verify data entries centrally, the coordination center of clinical studies at Charité (KKS Charité), Berlin, Germany, in collaboration with the coordinator team, carried out central remote monitoring by checking the electronic case report forms in the study-specific database using automated checks of plausibility, ranges, consistency, and data completeness to ensure high data quality.

S10. Recommendations for Patient Management and Risk Factor Modification in the DISCHARGE Trial

Following initial testing – either by ICA or CT – subsequent management decisions were made as described in the trial design and protocol,[1] according to the local heart team following contemporary guidelinesof the ESC/EACTS including additional functional testing, antianginal medication (Montalescot G et al, Eur Heart J 2013;34:2949–3003),[4] coronary revascularization (Windecker S et al, Eur Heart J 2014;35:2541–619),[5] and preventive treatment (Perk J et al ,Eur Heart J 2012;33:1635–701).[3]
As this was a pragmatic trial, variance between the recommendations and the actual proceeding was possible.

The recommendation for risk factor modification in the DISCHARGE trial was developed for the trial by Joep Perk (first author of the European Guidelines on cardiovascular disease prevention 2012)* and was recommended to patients in both groups (Methods Figure 4).

Methods Figure 4 Recommendations for Risk Factor Modification in the DISCHARGE Trial

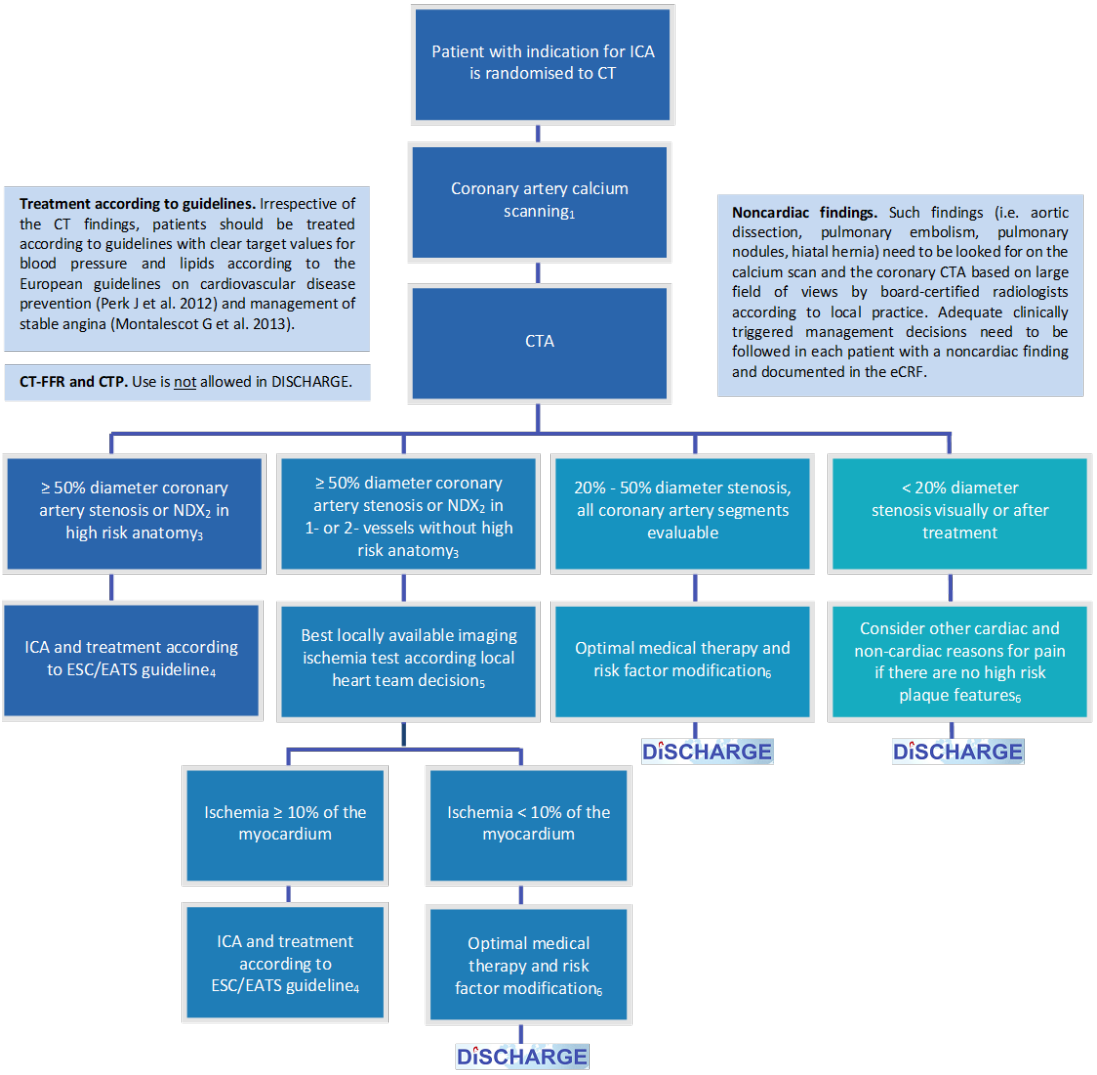


* Reference: Perk et al. 2012. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012) (European Heart Journal (2012) 33, 1635–1701).[3]

S11. CT-Based Management in the DISCHARGE Trial

In patients randomized to an initial CT-guided patient management a specific standard operating procedure was implemented according to the DISCHARGE study protocol.

Methods Figure 5 CT based Management in the DISCHARGE Trial



1. The coronary artery anatomic information from calcium scanning can be used to reduce the z-axis coverage of subsequent CTA by trimming the start and end according to individual patient anatomy to reduce exposure (Leschka S et al., AJR 2010; Zimmermann E et al., RoFo 2011). Calcium score calculation (Agatston AS et al., JACC 1990) should only be done after performing CTA in order to not obstruct the workflow. Even in high calcium scores CTA will always be done.
2. NDX (nondiagnostic segment) defined as: In a vessel with a reference diameter of ≥ 2 mm a relevant artifact (that could hide a ≥50% stenosis) is present.
3. High-risk anatomy defined as: LM stenosis ≥50% diameter reduction or proximal LAD stenosis ≥ 50% or 3-vessel disease (Windecker S et al., Eur Heart J 2014).
4. European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guideline (Windecker S et al., Eur Heart J 2014), see summarizing tables in "Revascularization in DISCHARGE".
5. Proceed to the best locally available imaging ischemia test (Shaw LJ et al., Circulation 2008), if not already done, to make a well informed decision about whether or not ischemia ≥10% of the myocardium corresponding to coronary stenosis seen on CTA is present (Hachamovitch R et al., Eur Heart J 2011).
6. The local heart team will determine risk factor modification (Montalescot J et al., Eur Heart J 2013; Perk J et al., Eur Heart J 2012). Risk factor modification and secondary prevention therapy should be considered if one of the following CT findings is seen: Agatston coronary artery calcium score of over 400 (Budoff MJ et al., JACC 2009; Greenland P et al., Circulation 2007) or high-risk plaque features such as low-attenuation noncalcified plaques (≤50 HU, this threshold might change with intraluminal enhancement, see plaque characterization document for details), a positive remodeling index ≥1.1 (calculated as the vessel cross-sectional area at the site of maximal stenosis divided by the average of proximal and distal reference segments' cross-sectional areas, Motoyama S et al., JACC 2009; Otsuka K et al., JACC Cardiovasc Imaging 2013) or the presence of a napkin-ring sign (non-calcified plaque with a central area of low CT attenuation that is apparently in contact with the lumen; and a ring-like higher attenuation plaque tissue surrounding this central area, Maurovich-Horvat P, et al. Nat Rev Cardiol 2014; Otsuka K et al. JACC Img 2013). For intensified risk factor modification please use the summary by Perk et al. "What is CVD prevention".

Reference: Napp et.al. 2017. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomized multicenter DISCHARGE trial (Eur Radiol (201) 27, 2957–2968).[1]

S12. Primary Outcome

The primary objective (or primary outcome measure) for evaluating CT vs. ICA is the occurrence of major adverse cardiovascular events (MACE) from randomization until follow-up (see ClinicalTrials.gov*). MACE were defined as a composite outcome as follows: cardiovascular death,[11] nonfatal myocardial infarction,[12] and nonfatal stroke.[13] Only symptomatic events were defined as MACE according to the study protocol.

The final analysis of MACE was performed after a median follow-up of 3.5 years after randomization to CT-guided management or to ICA-guided management in stable chest pain patients with intermediate pretest probability (10-60%) of obstructive CAD. An interim analysis of the primary outcome was prespecified in the study protocol and statistical analysis plan to be performed after the occurrence of 50 MACE, which was done but was not published.

* https://clinicaltrials.gov/ct2/show/study/NCT02400229

S12.1 Cardiovascular Death

The standardized definitions for cardiovascular and stroke end point events in clinical trials by the Cardiac Safety Research Consortium were implemented.[11] According to these definitions, cardiovascular death included death resulting from: acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular haemorrhage, death due to other cardiovascular causes.

S12.2 Nonfatal Myocardial Infarction

The third universal definition of myocardial infarction (MI) of the ESC/ACCF/AHA/WHF Task Force was implemented.[12] An event was defined as nonfatal if it did not cause the affected patient's death. All fatal events were recorded as cardiovascular death. The preferred biomarker for the MI definition was cardiac troponin I or T (cTn). If a cTn assay was not available, the best alternative was creatine kinase MB isoform (CKMB).

Myocardial infarction was classified, as indicated by the ESC/ACCF/AHA/WHF Task Force, into the following categories: spontaneous myocardial infarction (Type 1), myocardial infarction secondary to an ischemic imbalance (Type 2), myocardial infarction resulting in death when biomarker values were unavailable** (Type 3), myocardial infarction related to percutaneous coronary intervention (PCI, Type 4a) or related to stent thrombosis (Type 4b), and myocardial infarction related to coronary artery bypass grafting (CABG, Type 5).

** Myocardial infarction resulting in death was recorded as cardiovascular death.

S12.3 Nonfatal Stroke

The definition of stroke by the AHA/ASA[13] was used. Similar to acute myocardial infarction, only symptomatic events were defined as MACE. As explained above, silent stroke was treated as an incidental finding. Ischemic stroke was defined as an episode of neurological dysfunction caused by focal infarction of the central nervous system (CNS). Nonfatal stroke was classified, as indicated by the AHA/ASA Task Force, into the following categories: hemorrhagic infarction, cerebral

hemorrhage (intracerebral hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage), and cerebral venous thrombosis.

A detailed description and information on the definitions of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke is provided in the current version of the study protocol, the statistical analysis plan, and the original articles.

S13. Major Procedure-Related Complications

To identify and document procedure-related complications in both randomization groups, center investigators contacted patients by phone at least 48 hours after the last diagnostic or revascularization procedure of the initial management, and if the patient could not be contacted, center personnel contacted relatives, referring physicians, and responsible general practitioners. The list of major procedure-related complications followed the definitions of the CAD-Man trial (Dewey et al. BMJ 2016)[14] and was predefined in the study protocol as follows:

- Death
- Nonfatal myocardial infarction
- Nonfatal stroke
- Further complications prolonging hospitalization by at least 24 hours
- Dissection (coronary, aorta)
- Cardiogenic shock
- Cardiac tamponade
- Retroperitoneal bleeding
- Cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation)
- Cardiac arrest

S14. Patient Management Outcomes

Patient management data were recorded using a dedicated questionnaire sent by the principal investigators and his/her team at each clinical center at the first and second follow-up at 1 year and a median of 3.5 years after randomization, respectively. This follow-up data acquisition was monitored using a structured contact log protocol.

- Proportion of first ICAs showing obstructive coronary artery disease in both groups, i.e., the diagnostic yield of ICA in the two groups
- Additional noninvasive or invasive functional tests: the rate of functional tests following the initial tests was analyzed to detect differences in management between the two groups. Additional functional tests recorded included invasive fractional flow reserve (FFR) and best locally available noninvasive ischemia imaging test.
- Preventive medical therapy at a median follow-up of 1 and 3.5 years.
- Coronary revascularization (PCI and CABG): the proportion of patients undergoing coronary revascularization was analyzed to detect differences in management between randomization groups.

S15. Patient-Reported Outcomes

Patient-reported outcome measures were collected using a questionnaire at prerandomization and follow-up postrandomization, which was monitored using a structured contact log protocol.

Exertional and nonexertional chest pain was assessed using the short version of the Rose questionnaire[15], and occurrence of self-reported angina in the last 4 weeks before follow-up was the primary angina outcome to analyze if angina had resolved at follow-up.

Quality of life was assessed at baseline (prior to randomization) and follow-up and included the European Quality of Life–5 Dimensions (EQ-5D-3L) utility index score and visual analogue scale,[16] the Short Form (SF) 12v2,[17] and the Hospital Anxiety and Depression Scale.[18] The visual analogue scale (VAS) of the EQ-5D, i.e., self-reported assessment of one's overall health, and the physical component summary score of the SF-12, which has shown to be associated with chest pain types,[7] were the quality of life measures of primary interest at follow-up according to the statistical analysis plan. Although all quality-of-life outcomes are of a secondary nature, the VAS (EQ5D) and the physical component score (PCS) of the SF12v2 were defined as variables of primary interest (prespecified principal patient-reported QOL outcomes in the statistical analysis plan).

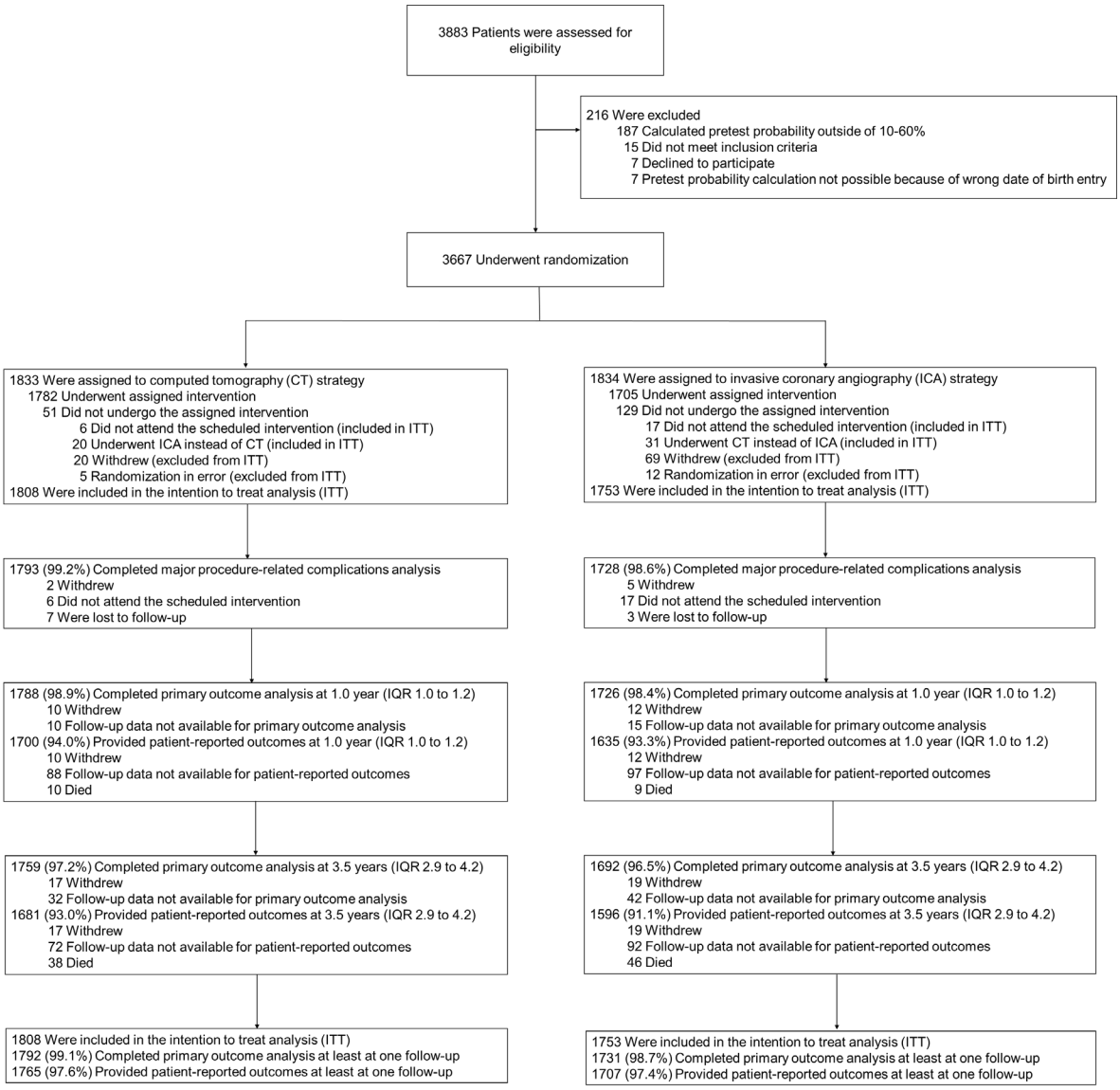
S16. Trial Registration and Additional Secondary Outcomes

The trial was registered at https://clinicaltrials.gov/ct2/show/NCT02400229 and included 127 secondary outcomes before the start of recruitment and the study design was published.[1] The Statistical Analysis Plan (SAP) details the statistical approaches used for the primary and secondary outcomes and additional secondary analysis defined after start of recruitment but before data unblinding on December 10, 2021. Additional secondary outcomes were defined in the trial registration and SAP but were not analyzed at the time of this report of the primary outcome. The focus of the primary outcome manuscript is to compare MACE and other major outcomes such as major procedure-related complications as well as patient management outcomes and patient-reported outcomes. Minor outcomes such as minor adverse cardiovascular events (MICE) are not the focus of this publication and will be included in secondary publications.

C. Supplementary Results

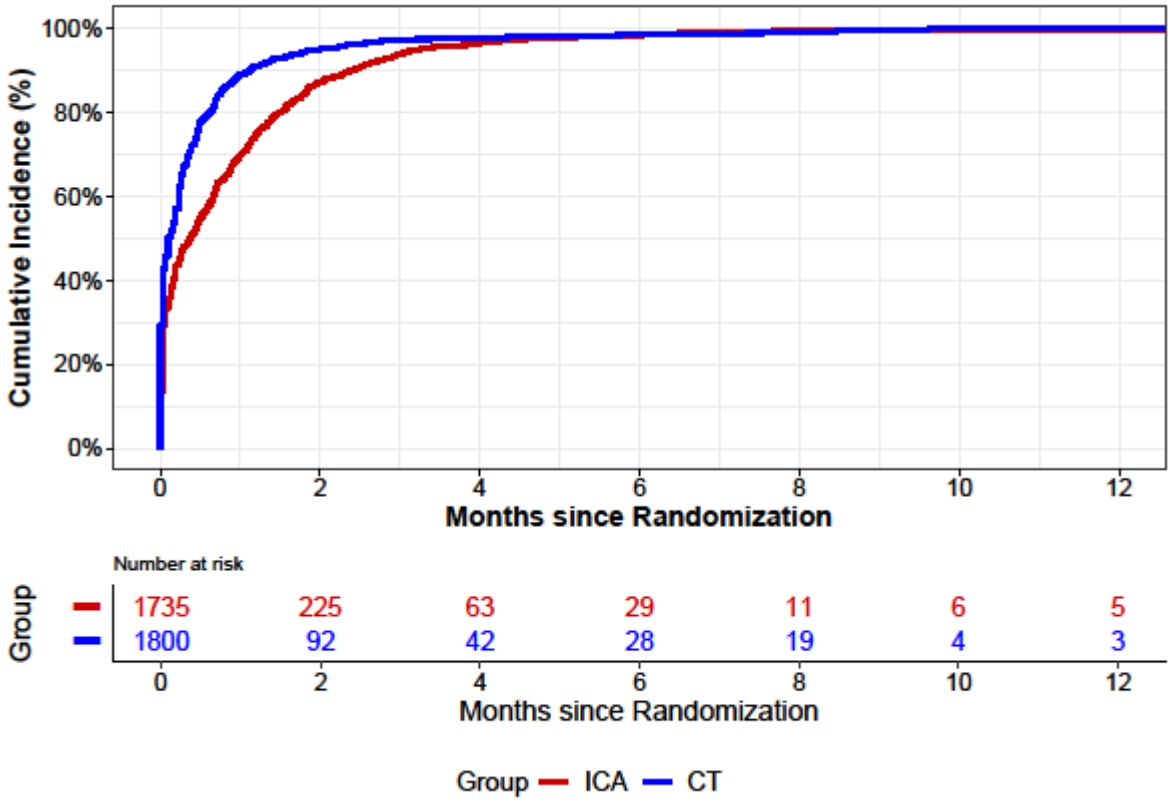
S17. Supplementary Results Figures

Figure S1. Enrollment, Randomization, and Follow-up



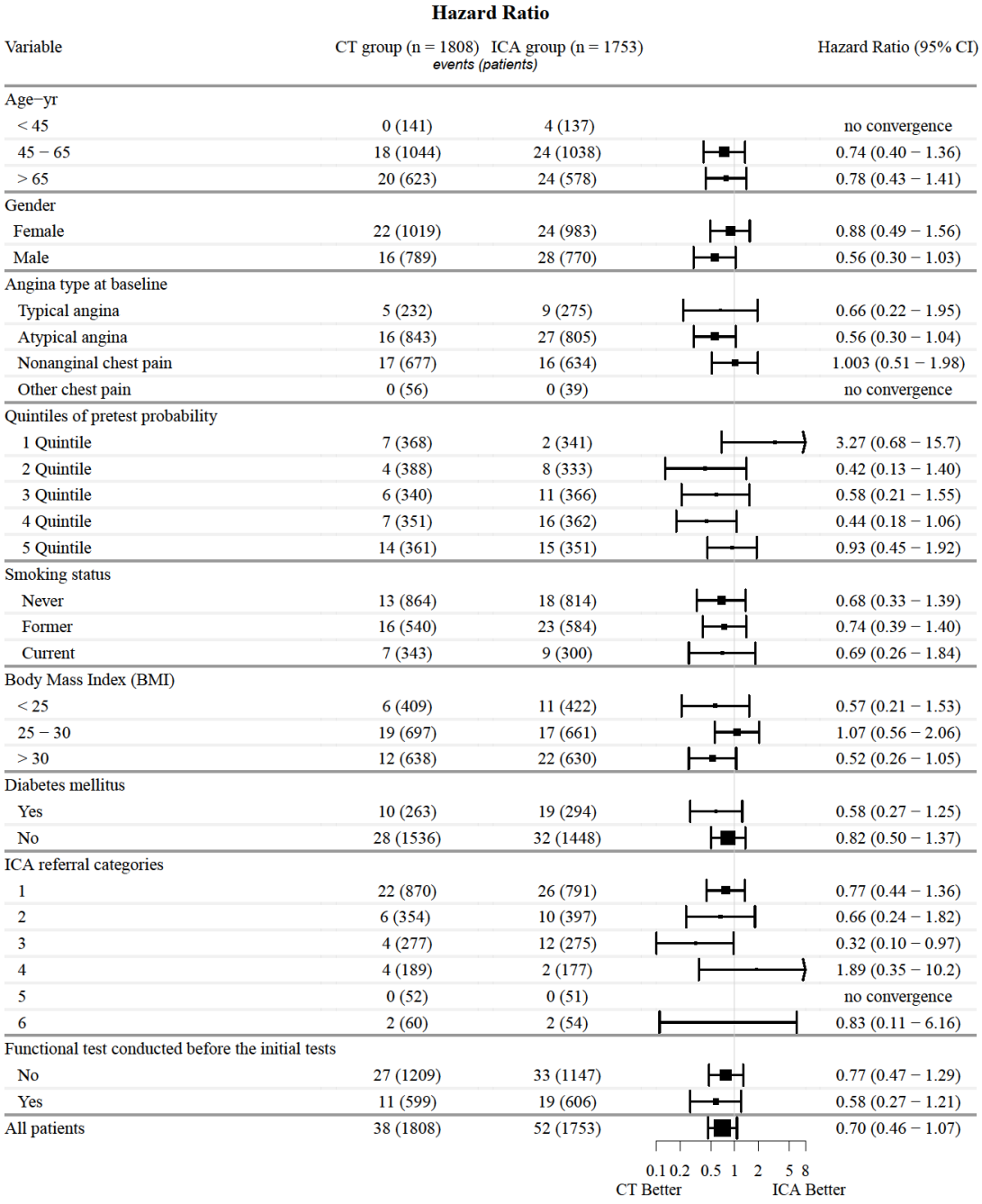
A total of 3667 patients were enrolled, 1833 were randomized to the CT group and 1834 to the ICA group. In the CT group, 20 patients (1%) withdrew consent and 5 were randomized in error (0.3%); the corresponding numbers in the ICA group were 69 (3.8%) and 12 (0.7%). These patients were not included in the modified intention-to-treat population because only baseline characteristics would have been available, no initial tests were performed, and the collection of test or follow-up data on outcomes would not have been allowed. Overall, 3561 stable chest pain patients were randomly assigned and included in the modified intention-to-treat population: 1808 were assigned to the CT group and 1753 to the ICA group. Of these, a total of 1782 patients (98.6%) in the CT group and 1705 patients (97.3%) in the ICA group underwent their assigned test. Twenty patients (1.1%) assigned to CT underwent ICA as the initial test and 31 patients (1.7%) assigned to ICA underwent CT as the initial test; these patients were included in the modified intention-to-treat population. In the CT group, 2 patients withdrew consent before major procedure-related complications analysis, 8 patients withdrew consent until follow-up at 1.0 year, and an additional 7 patients withdrew consent until follow-up at 3.5 years (overall: 17 patients); the corresponding numbers in the ICA group were, 5, 7, and 7 (overall: 19 patients). These patients were included in the modified intention-to-treat population and in the time-to-event analyses until the last available date and were censored thereafter. Follow-up for the primary outcome and patient-reported outcomes was performed after a median of 1.0 year and 3.5 years. Primary outcome analysis was complete at least at one follow-up for 99.1% of patients in the CT group (1792/1808) and 98.7% of patients in the ICA group (1731/753); the corresponding numbers for the patient-reported outcomes were 97.6% in the CT group and 97.4% in the ICA group.

Figure S2. Cumulative Incidence Curves for Time to Initial Test



The median time from enrollment to the initial test was 3 days in the CT group and 12 days in the ICA group (hazard ratio, 1.54; 95% CI, 1.44 to 1.65).

Figure S3. Subgroup Analyses for MACE



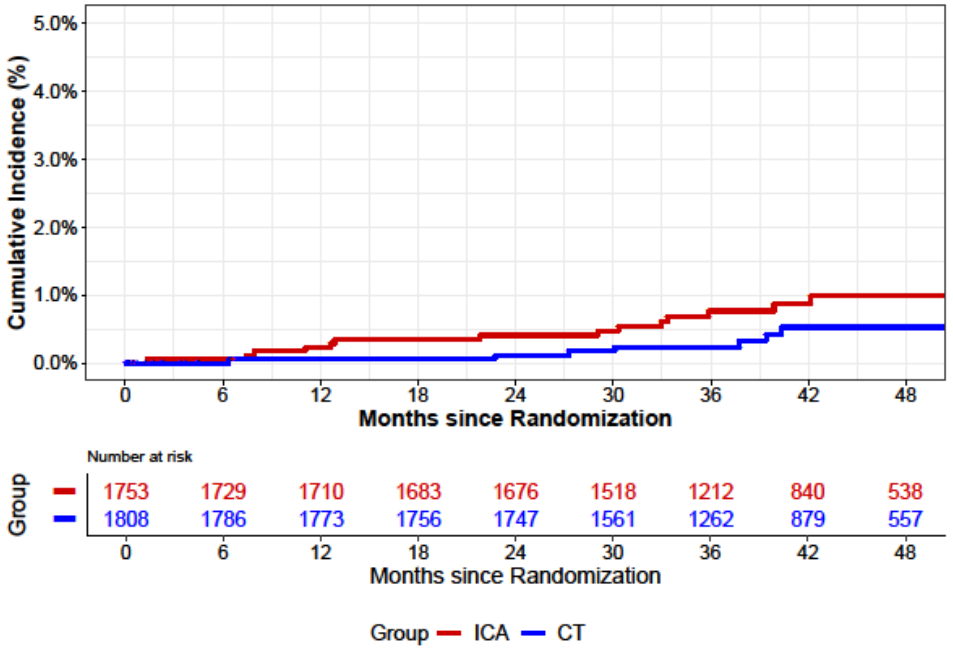
The results for the primary outcome in the prespecified subgroups were consistent with those in the overall study population with no differences except a possible advantage of CT in patients referred with intermediate pretest probability and functional testing showing ischemia (ICA referral category 3). All exploratory subgroup analyses of the primary outcome (MACE) prespecified in Table 3 of the SAP were included in the above subgroup analysis with the exception of CT plaque characteristics, which are only available for the CT group and will be further investigated and published in a separate study. In addition, a reviewer requested a post-hoc analysis to be included regarding the two referral strategies for ICA in our trial: 1) direct referral for ICA without a functional test conducted before the initial tests (CT or ICA) versus 2) functional test done before the initial tests (CT or ICA). These two subgroups were added as a post-hoc analysis. ICA referral categories: 1) Clinical constellation suggesting high event risk, particularly if symptoms were inadequately responding to medical treatment, 2) Severe angina, particularly if symptoms were inadequately responding to medical treatment, 3) Intermediate pretest probability or LVEF <50% without typical angina following functional testing showing ischemia, 4) Low or intermediate event risk if symptoms were inadequately responding to medical treatment, 5) Intermediate pretest probability or LVEF <50% without typical angina following nondiagnostic functional testing, 6) other.

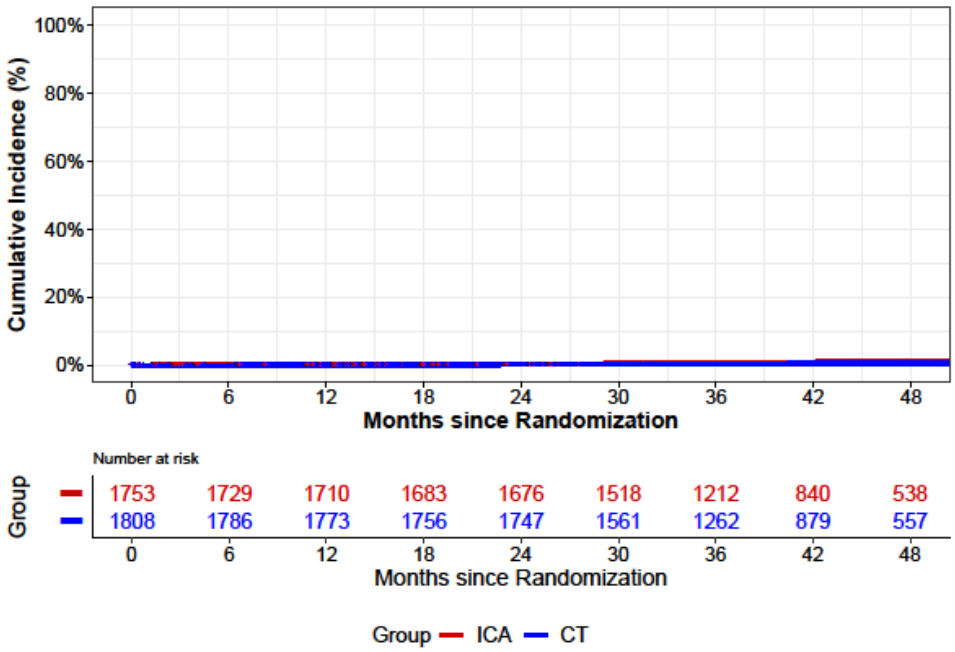
Figure S4. Cumulative Incidence Curves for Secondary Composites of MACE

The results for each of the components of the primary outcome (cardiovascular death, nonfatal stroke nonfatal myocardial infarction) are shown in panels A-C. The secondary expanded MACE composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, transient ischemia attack, or major procedure-related complication was seen less often in the CT group (hazard ratio, 0.60; 95% CI, 0.42 to 0.85, panel D). Rates of other secondary composite definitions of MACE (vascular death or myocardial infarction (D), cardiac death or myocardial infarction (E), all-cause death, myocardial infarction, or stroke (F)) were similar in the two groups.

A Cumulative incidence curves for cardiovascular death

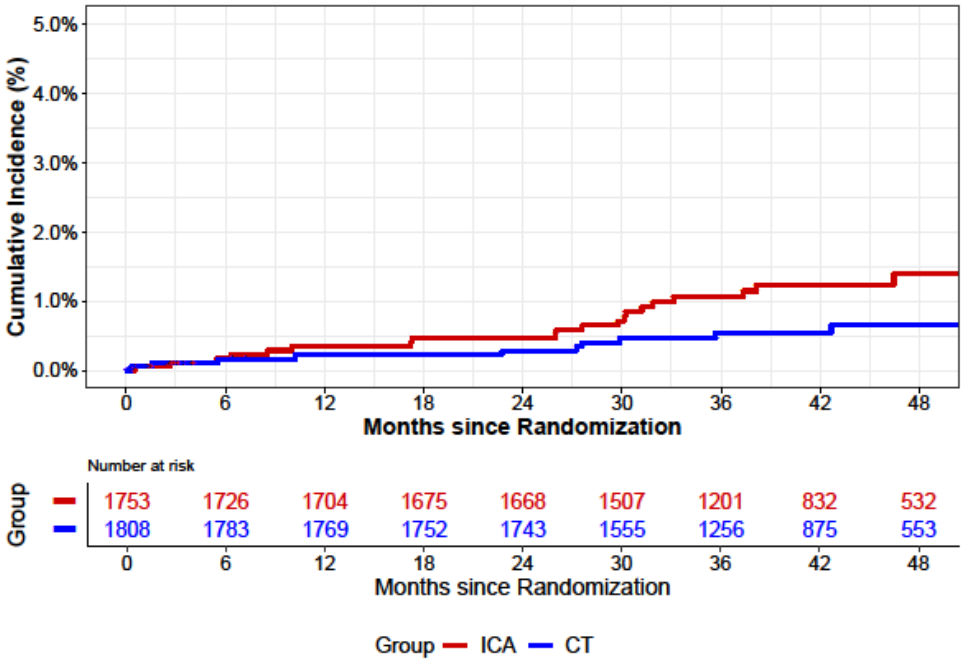
Hazard ratio (95% CI) 0.48 (0.20 – 1.20)

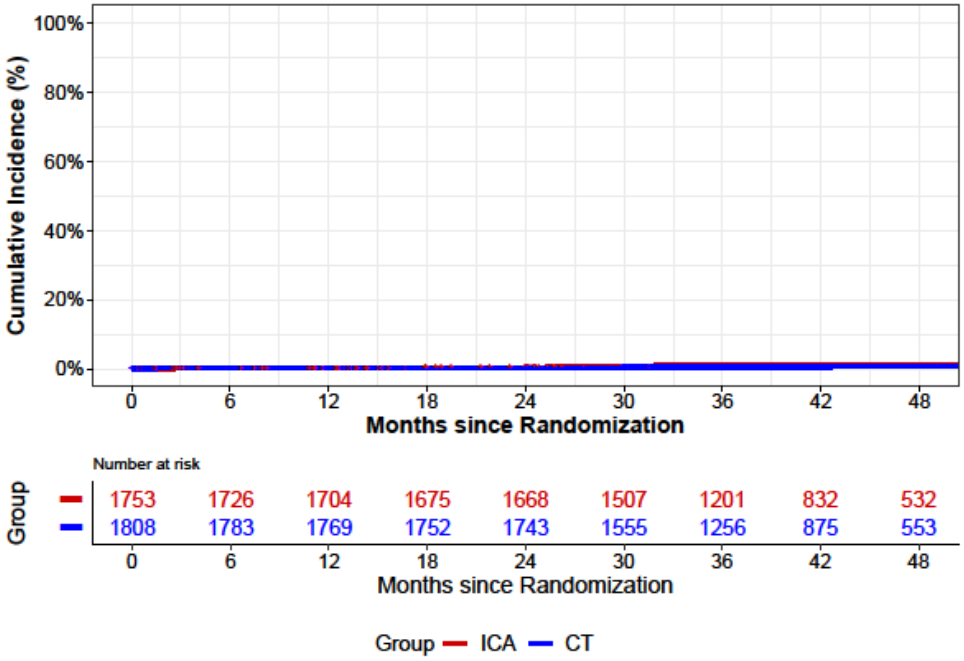




B Cumulative incidence curves for nonfatal stroke

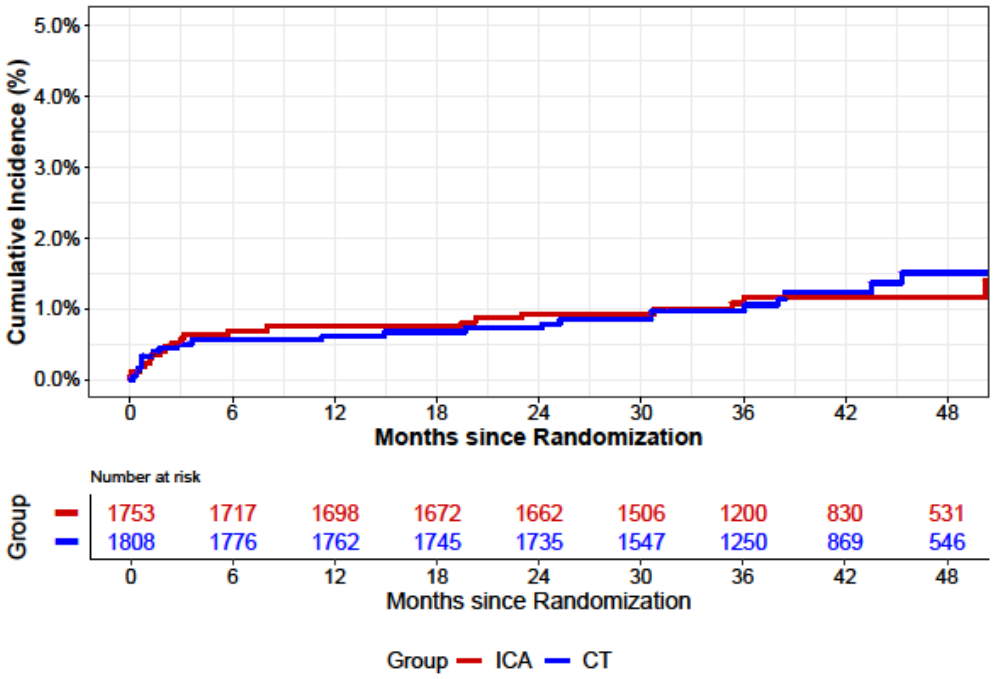
Hazard ratio (95% CI) 0.48 (0.23 – 1.03)

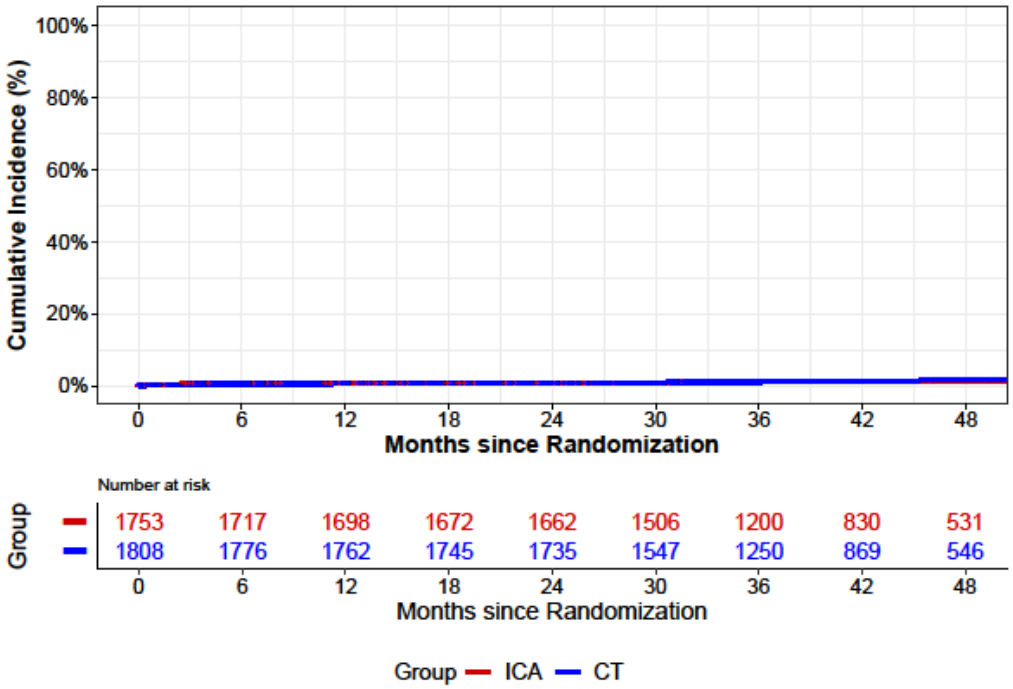




C Cumulative incidence curves for nonfatal myocardial infarction

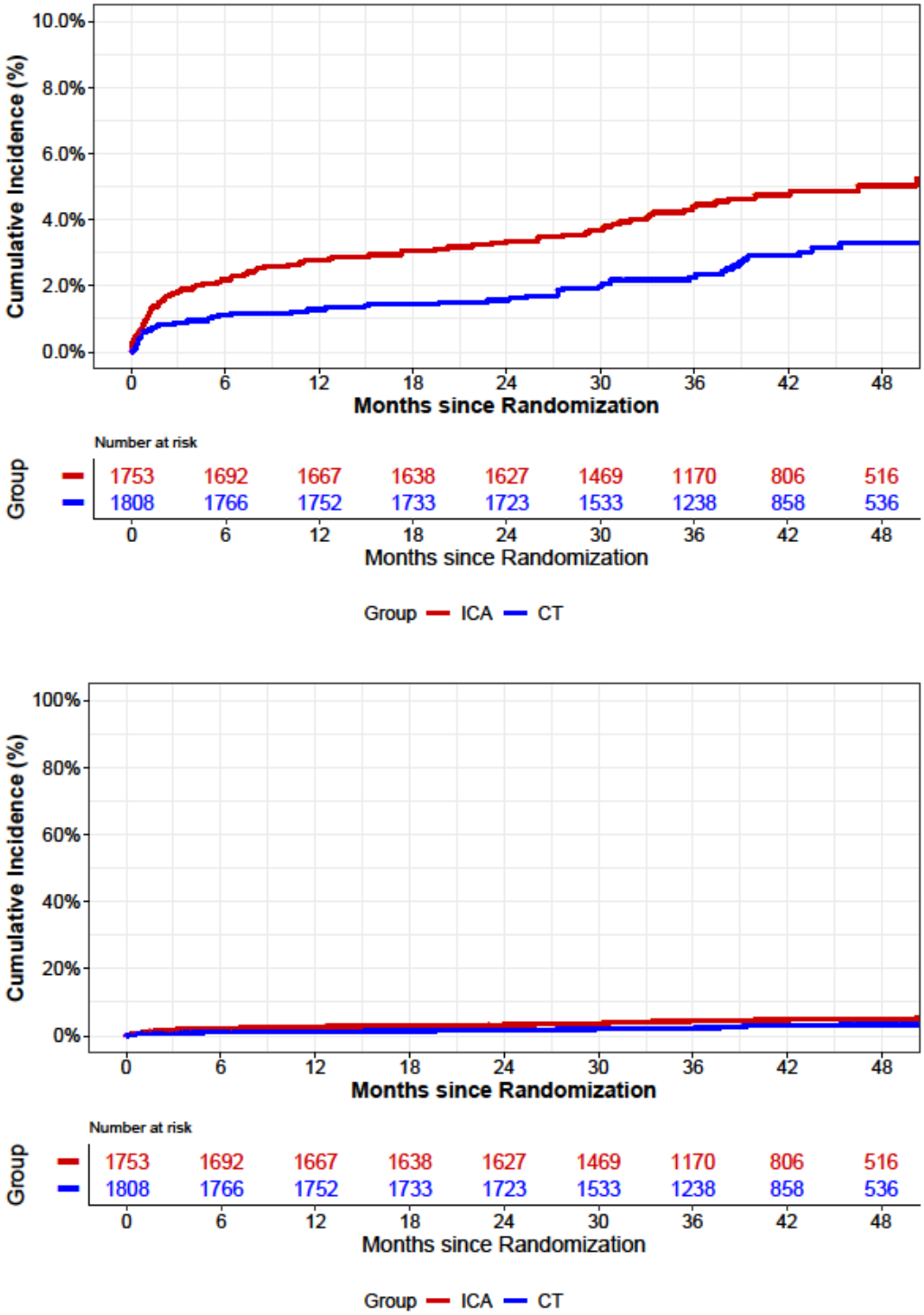
Hazard ratio (95% CI) 1.11 (0.61 – 2.03)





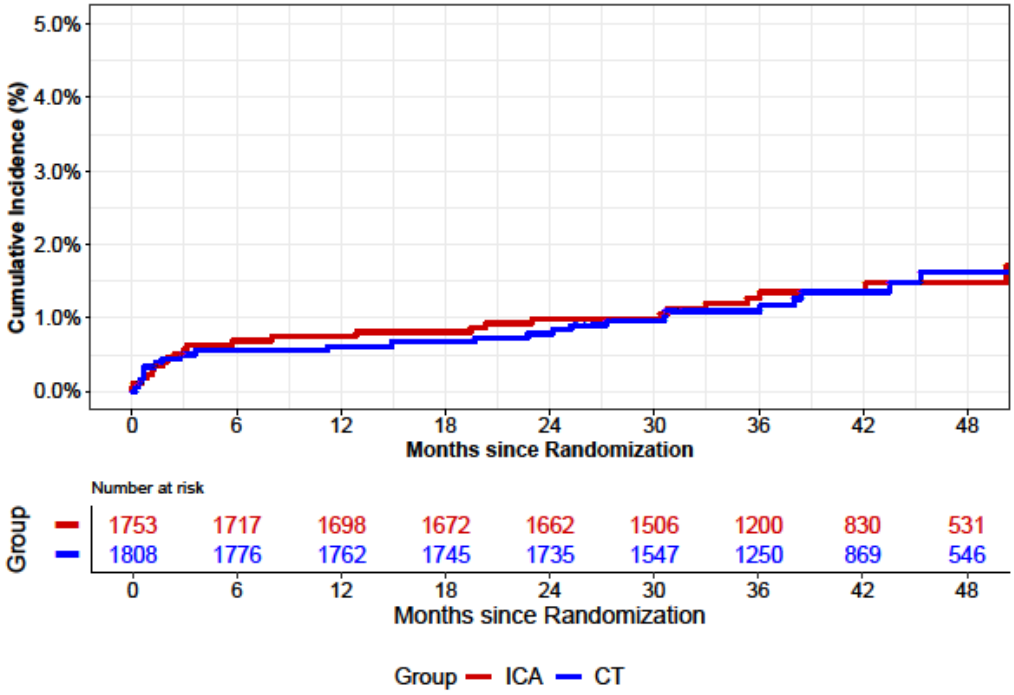
D Cumulative incidence curves for the secondary expanded MACE composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, transient ischemia attack, or major procedure-related complication

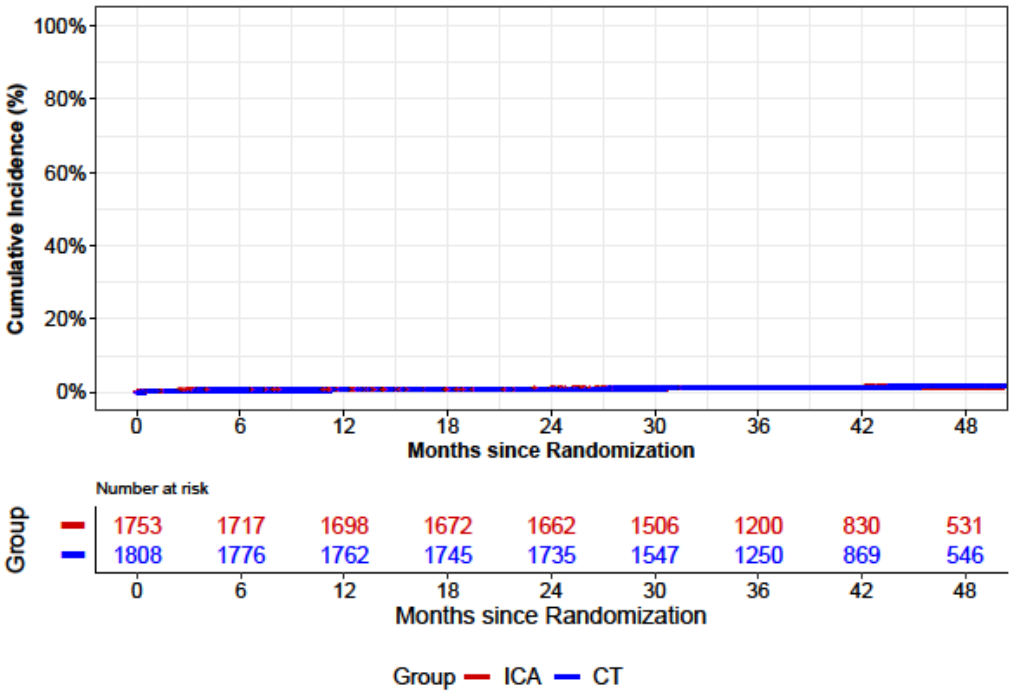
Hazard ratio (95% CI) 0.60 (0.42 – 0.85)



E Cumulative incidence curves for vascular death or myocardial infarction

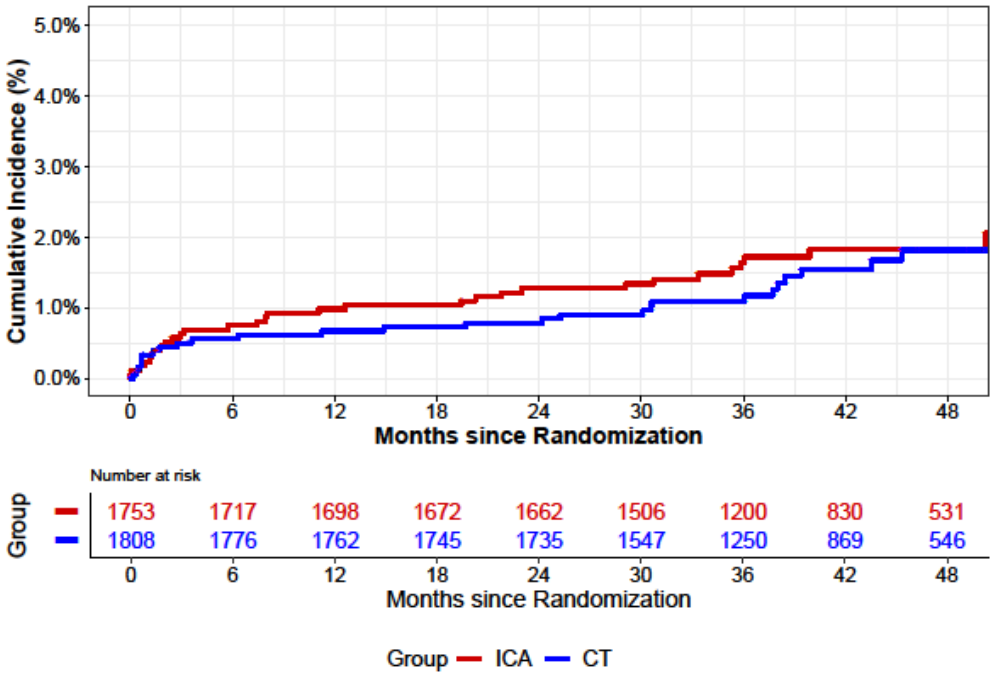
Hazard ratio (95% CI) 1.01 (0.58 – 1.77)

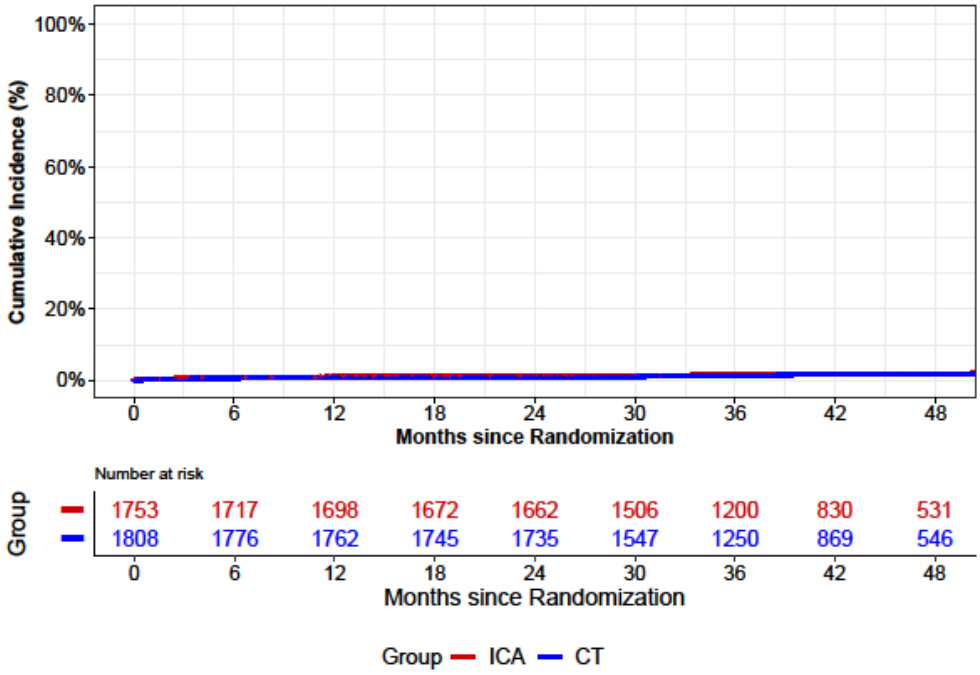




F Cumulative incidence curves for cardiac death or myocardial infarction

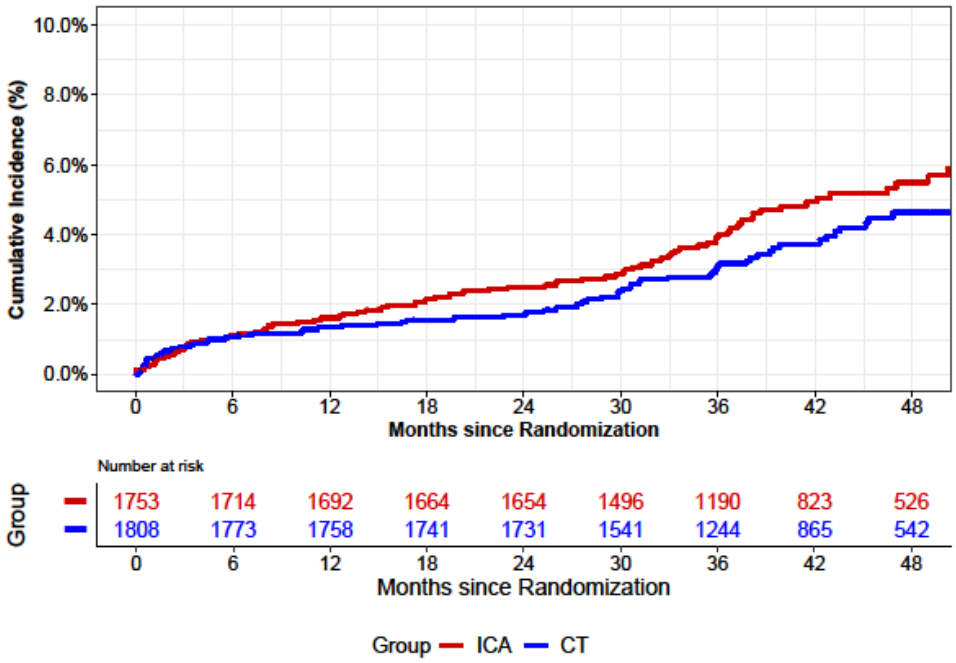
Hazard ratio (95% CI) 0.87 (0.52 – 1.46)





G Cumulative incidence curves for all-cause death, myocardial infarction, or stroke

Hazard ratio (95% CI) 0.79 (0.57 – 1.09)



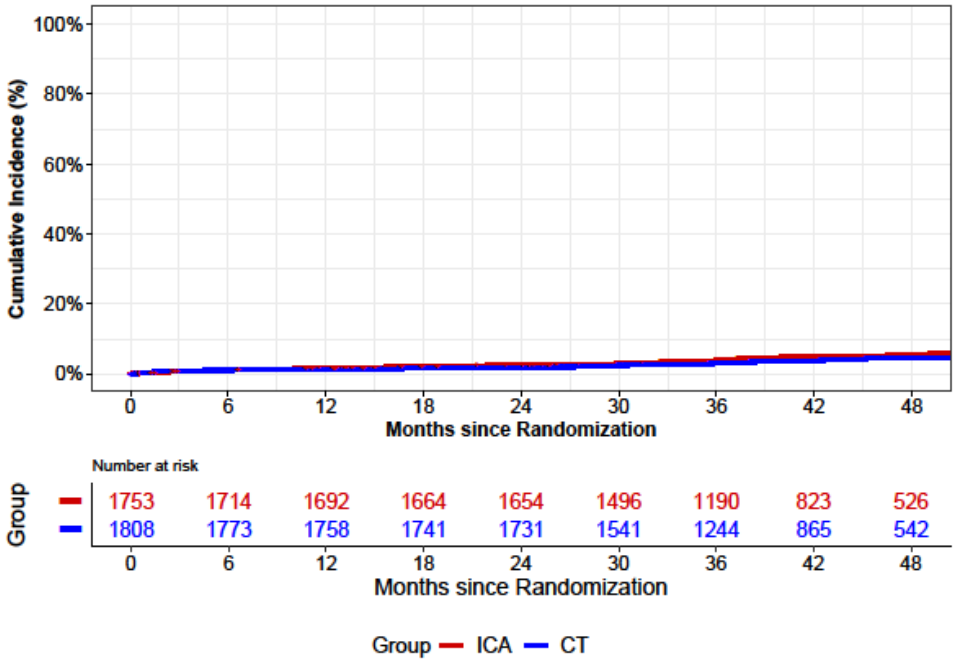


Figure S5. Cumulative Incidence Curves for Major Procedure-Related Complications

Cumulative risk of major procedure-related complications. Note that events keep accumulating at 2 months and beyond because approximately 10% of patients in the ICA group underwent the initial test 2 months after enrollment (Fig. S1), and complications also include those of related tests and procedures during initial management. The inset (top) show the same data on an enlarged y-axis. Hazard Ratio, 0.26 (0.13–0.55).

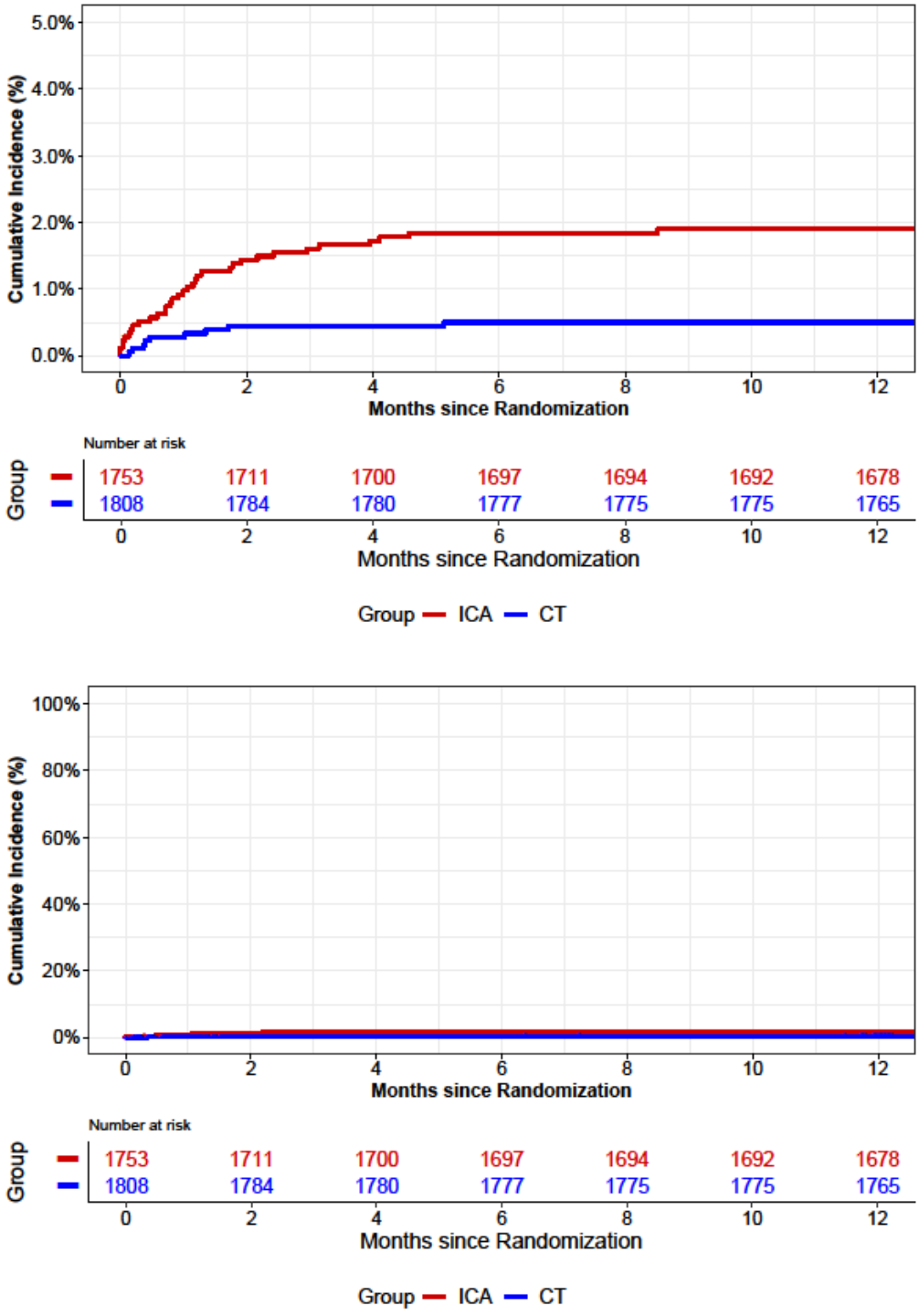
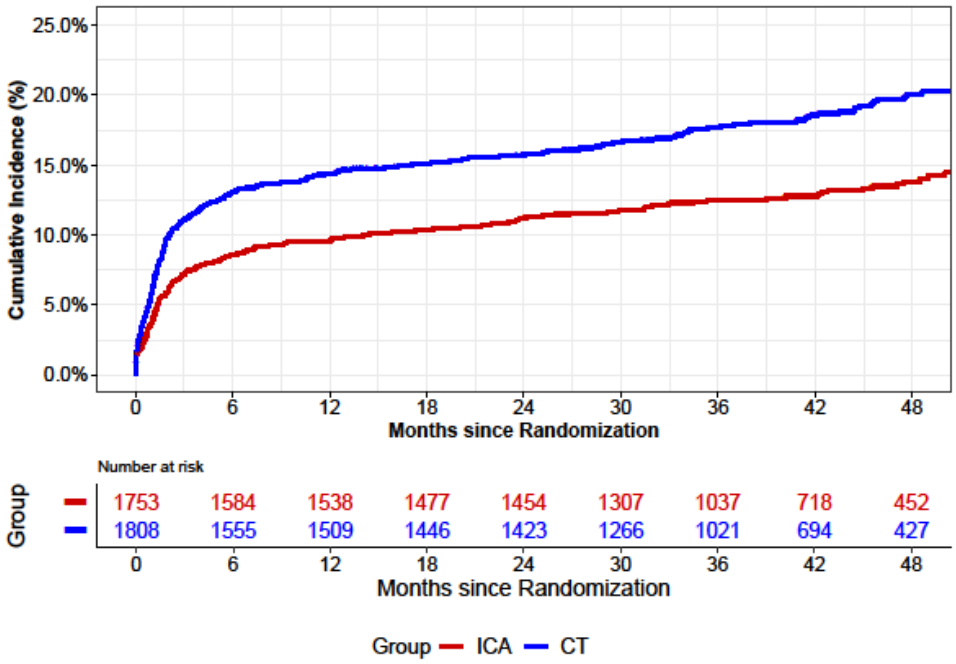


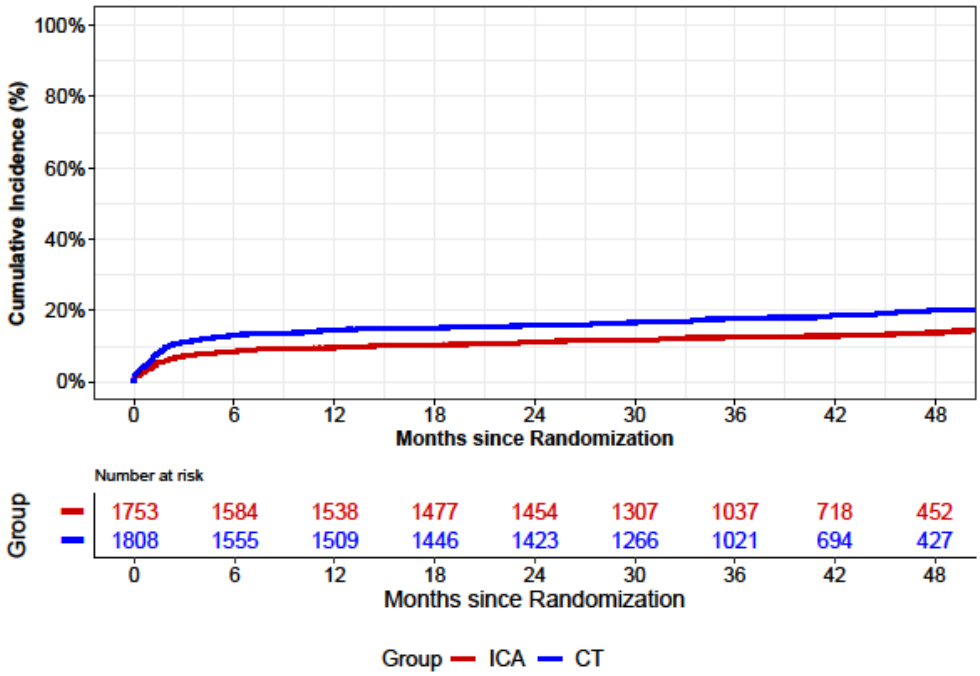
Figure S6. Cumulative Incidence Curves for Secondary Outcomes

Patients in the CT group had more additional functional tests than patients in the ICA group (A) and fewer coronary revascularizations (B-D).

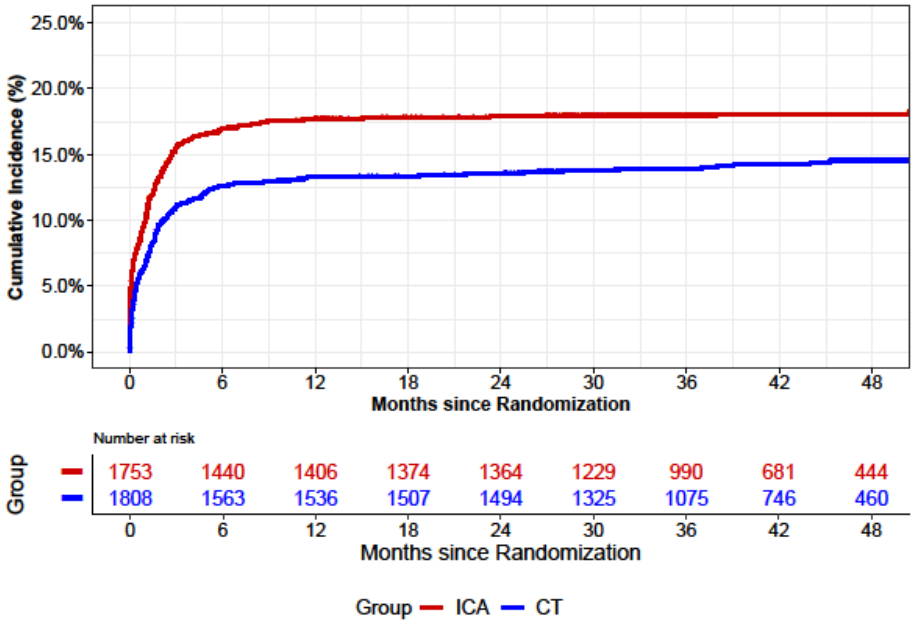
A Cumulative Incidence Curves for Additional Functional Tests

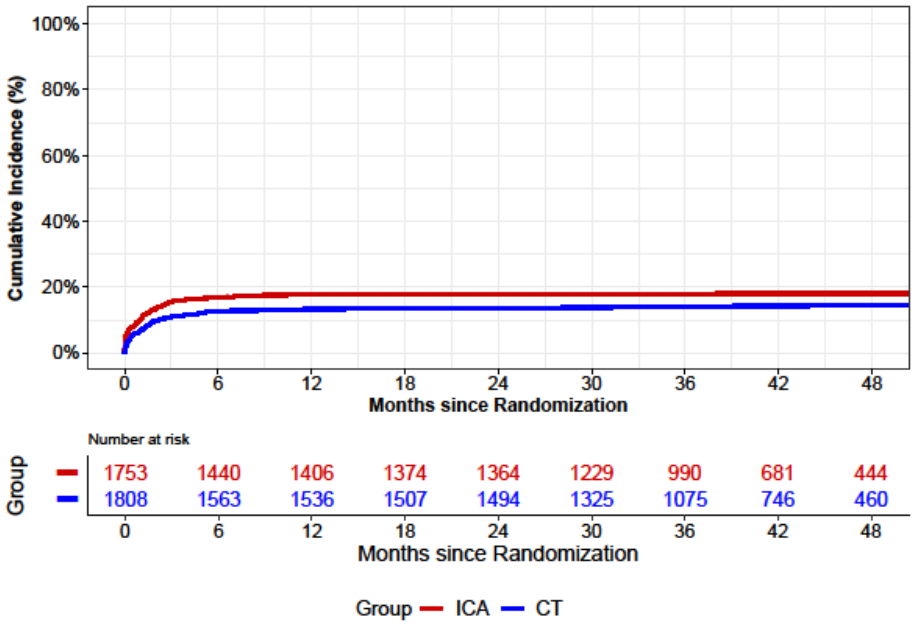
Hazard ratio (95% CI) 1.49 (1.26 – 1.76)





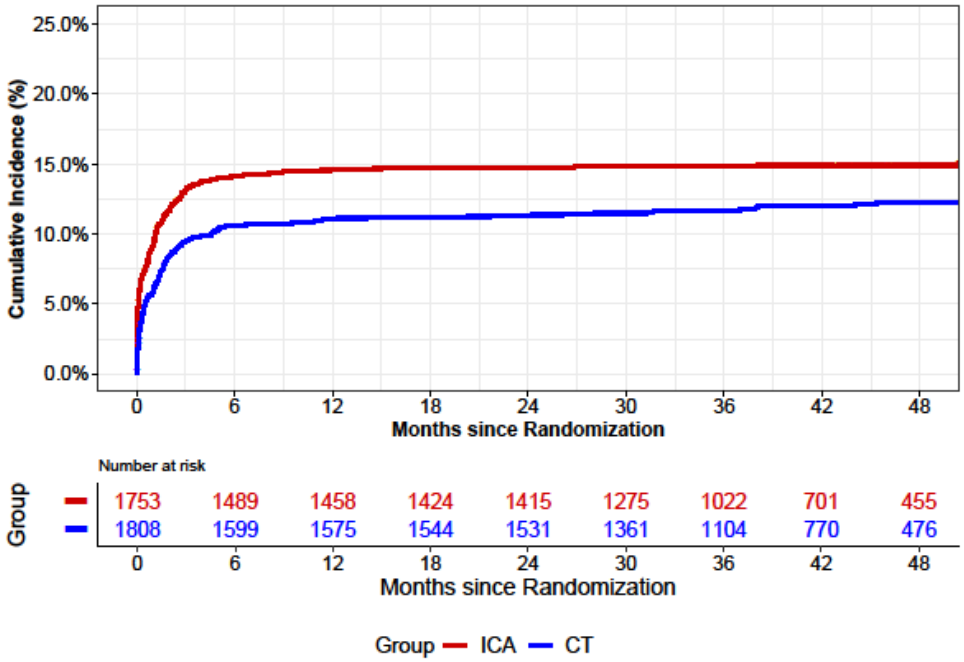
B Cumulative Incidence Curves for Coronary Revascularization
Hazard ratio (95% CI) 0.76 (0.65 – 0.90)

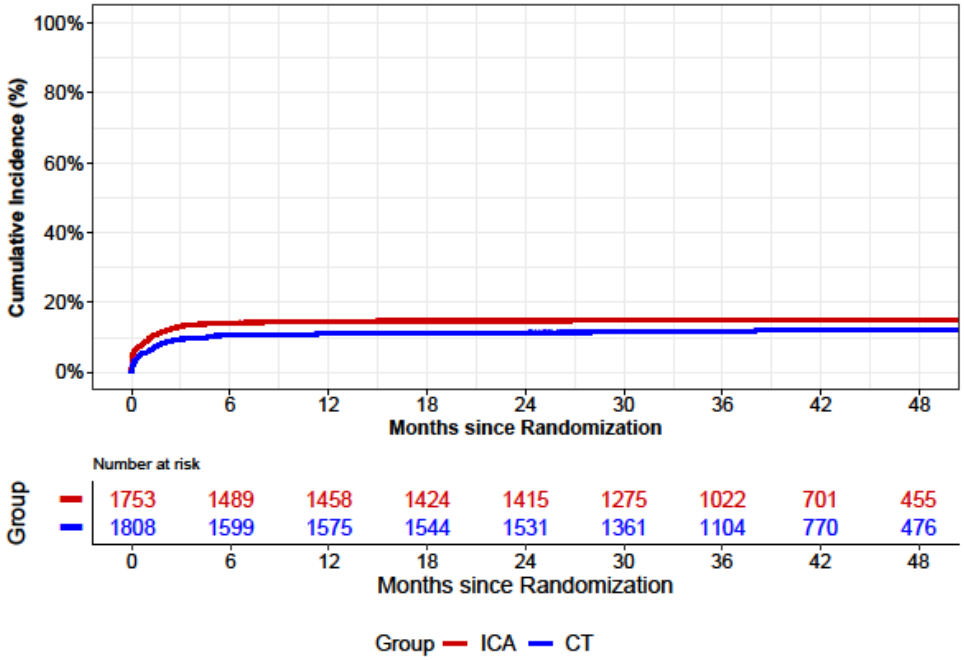




C Cumulative Incidence Curves for Percutaneous Coronary Intervention

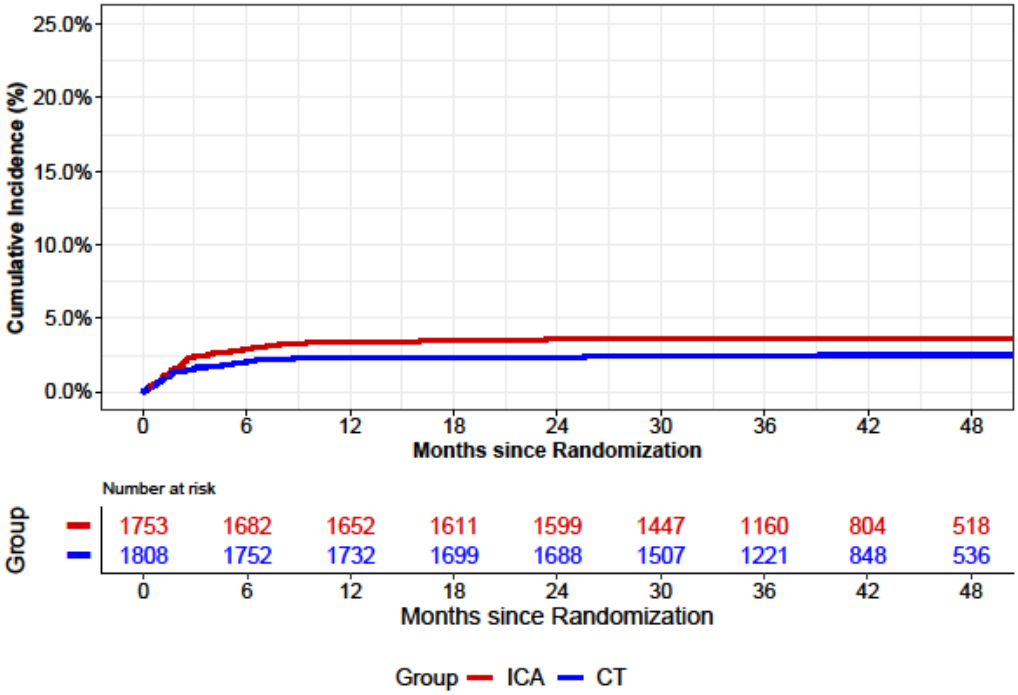
Hazard ratio (95% CI) 0.78 (0.65 – 0.93)





D Cumulative Incidence Curves for Coronary Artery Bypass Grafting

Hazard ratio (95% CI) 0.67 (0.46 – 0.99)



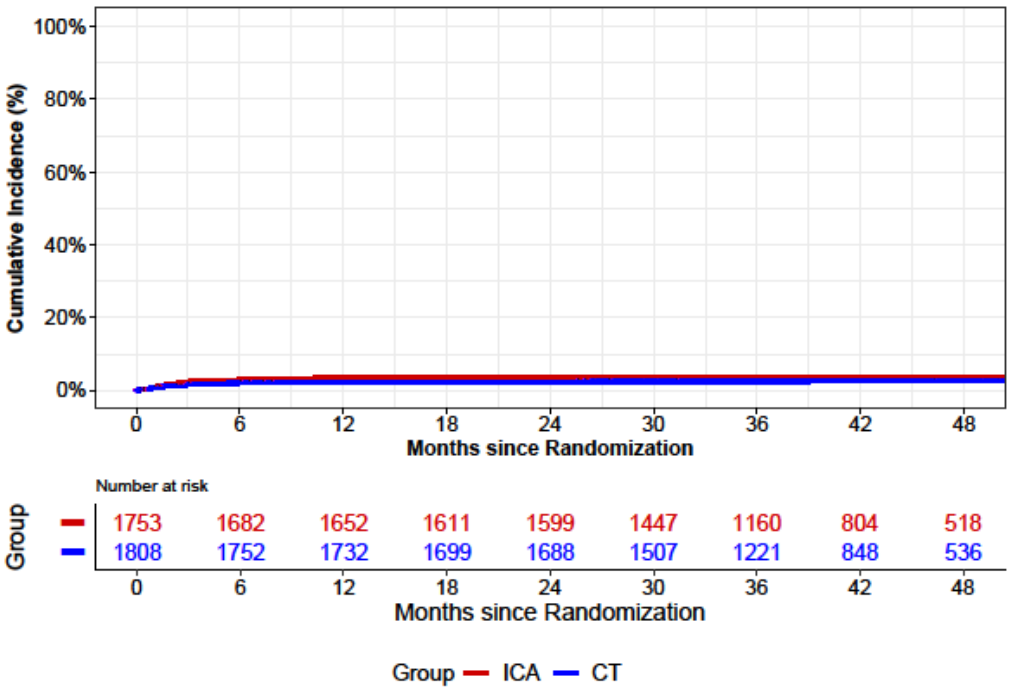
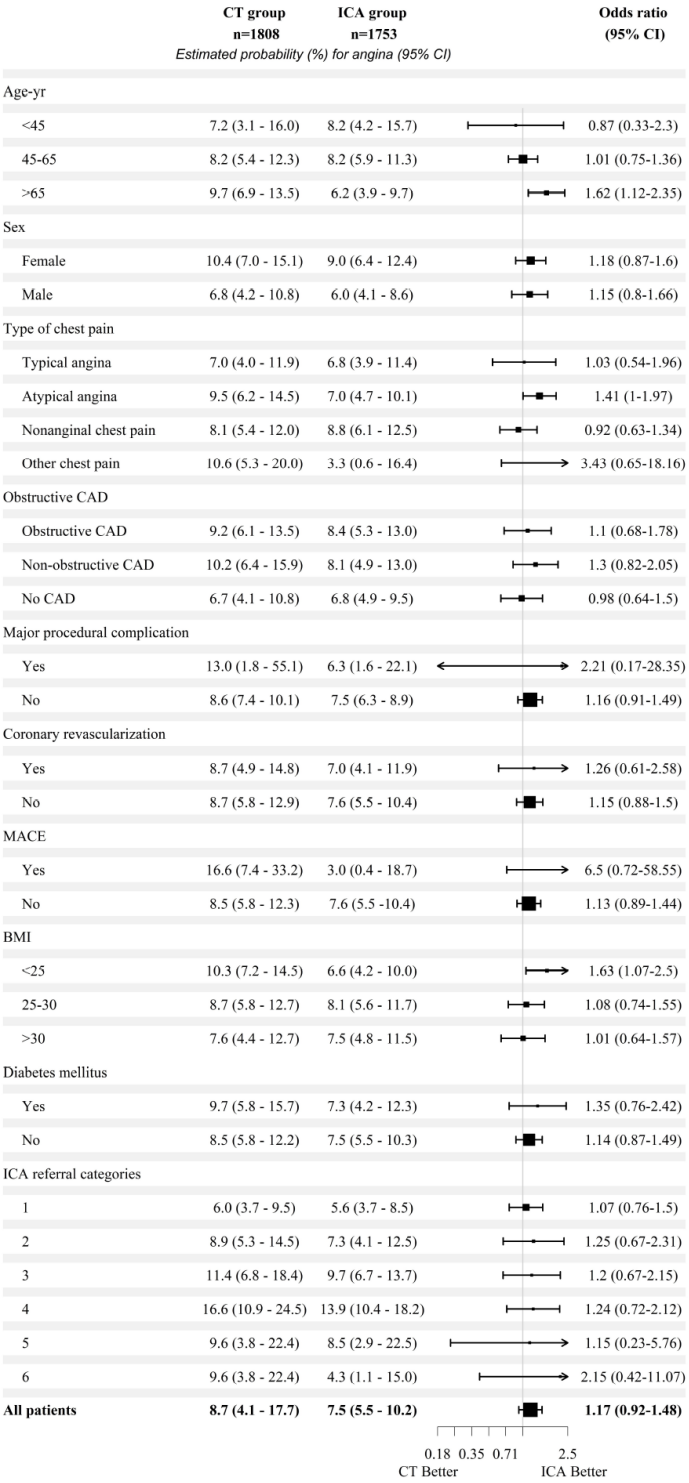


Figure S7. Subgroup Analyses for Angina in the Last 4 Weeks Before Follow-up



Subgroup analysis for angina in the last 4 weeks before follow-up at median 3.5 years (IQR, 2.9-4.2). All estimates are adjusted and missing values were treated using multiple imputation. All exploratory subgroup analyses of the secondary outcome angina prespecified in Table 8 of the SAP were included in the above subgroup analysis. ICA referral categories: 1) clinical constellation suggesting high event risk, particularly if symptoms were inadequately responding to medical treatment, 2) severe angina, particularly if symptoms were inadequately responding to medical treatment, 3) intermediate pretest probability or LVEF <50% without typical angina following functional testing showing ischemia, 4) low or intermediate event risk if symptoms were inadequately responding to medical treatment, 5) intermediate pretest probability or LVEF <50% without typical angina following nondiagnostic functional testing, 6) other.

S18. Supplementary Results Tables

Table S1. Patient Enrollment per Study Center

Study center	Assessed for eligibility	Excluded		Not included in ITT		CT Group		ICA Group	
		N	%	N	%	N	%	N	%
Semmelweis University, Budapest, Hungary	522	9	2	4	1	256	50	253	50
Rigshospitalet, University of Copenhagen, Denmark	505	35	7	10	2	234	51	226	49
Cardio Med Medical Center, Tirgu Mures, Rumania	356	1	0	11	3	176	51	168	49
Southeastern Health and Social Care Trust, Belfast, United Kingdom	247	10	4	12	5	116	52	109	48
Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona Spain	223	10	4	2	1	104	49	107	51
Paul Stradins Clinical University Hospital, Riga, Latvia	198	6	3	8	4	94	51	90	49
Motol University Hospital, Prague, Czech Republic	156	11	7	0	0	72	50	73	50
Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania	151	1	1	7	5	74	52	69	48
Institute for Cardiovascular Diseases of Vojvodina, Novi Sad, Sremska Kamenica, Serbia	184	41	22	1	1	70	49	72	51
University of Leipzig Heart Centre, Leipzig, Germany	132	0	0	9	7	64	52	59	48
St. Vincent's University Hospital, Dublin, Ireland	143	15	10	7	5	62	51	59	49
Basurto Hospital, Bilbao Spain	110	2	2	4	4	51	49	53	51
Aintree University Hospital, Liverpool, United Kingdom	123	21	17	1	1	50	50	51	50
University of Medicine, Pharmacy, Science and Technology "G.E.Palade", Tirgu Mures, Rumania	82	0	0	1	1	42	52	39	48
Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany	94	8	9	7	7	43	54	36	46
National Institute of Cardiology, Warsaw, Poland	77	0	0	2	3	37	49	38	51
Clinical Hospital Center Zemun, Faculty of Medicine, University of Belgrade, Belgrade, Serbia	88	14	16	1	1	37	51	36	49
Sapienza University of Rome, Rome, Italy	78	0	0	7	9	36	51	35	49
Wojewodzki Szpital Specjalistyczny We Wroclawiu, Wroclaw, Poland	76	2	3	4	5	38	54	32	46
Innsbruck Medical University, Innsbruck, Austria	70	6	9	0	0	31	48	33	52
Turku University Hospital and University of Turku, Turku, Finland	61	0	0	0	0	30	49	31	51
Centro Hospitalar de Vila Nova de Gaia/ Espinho, Vila Nova de Gaia, Portugal	60	10	17	1	2	25	51	24	49
ALB FILS KLINIKEN GmbH, Goeppingen, Germany	44	1	2	1	2	22	52	20	48
University of Glasgow, Glasgow, United Kingdom	48	7	15	0	0	20	49	21	51
University of Cagliari, Cagliari, Italy	32	3	9	2	6	14	52	13	48
Royal Liverpool University Hospital, Liverpool, United Kingdom	23	3	13	4	17	10	63	6	38
Total	**3883**	**216**	**6**	**106**	**3**	**1808**	**51**	**1753**	**49**

Table S2. Expanded Baseline Characteristics

Characteristics	CT Group (N=1808)	ICA Group (N=1753)
Cardiovascular risk factors – no./total no. (%)		
Peripheral artery disease	24/1799 (1.3)	25/1745 (1.4)
Valve disease	94/1799 (5.2)	95/1745 (5.4)
Stroke	47/1799 (2.6)	44/1745 (2.5)
Transient ischemic attack (TIA)	32/1799 (1.8)	35/1745 (2.0)
Prolonged ischemic neurological deficit (PRIND)	2/1799 (0.1)	3/1745 (0.2)
Carotid artery disease	38/1799 (2.1)	44/1745 (2.5)
Family history of premature CAD (female)	321/1012 (31.7)	337/979 (34.4)
Family history of premature CAD (male)	194/787 (24.7)	211/766 (27.5)
Pulmonary risk factors – no./total no. (%)		
Asthma	123/1799 (6.8)	91/1742 (5.2)
Chronic obstructive pulmonary disease	72/1799 (4.0)	81/1742 (4.6)
Cigarette smoking – no./total no. (%)		
Current smokers	343/1747 (19.6)	300/1698 (17.7)
Former smokers	540/1747 (30.9)	584/1698 (34.4)
Never smoked	864/1747 (49.5)	814/1698 (47.9)
Median body mass index (IQR) *	28.3 (25.3–31.6) (n=1744)	28.2 (25.1–31.6) (n=1713)
Cardiovascular medications – no./total no. (%)		
Statin	808/1795 (45.0)	787/1742 (45.2)
Antiplatelet agent	857/1795 (47.7)	884/1742 (50.7)
Beta-blocker	753/1795 (41.9)	740/1742 (42.5)
Nitrates	203/1795 (11.3)	190/1742 (10.9)
Calcium antagonist	368/1795 (20.5)	349/1742 (20.0)
Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker	868/1795 (48.4)	799/1742 (45.9)
Angina intensity – no./total no. (%)†		
Low intensity (0-3)	370/1797 (20.6)	335/1744 (19.2)
Moderate intensity (4-6)	878/1797 (48.9)	923/1744 (52.9)
High intensity (7-10)	549/1797 (30.6)	486/1744 (27.9)
Do you currently have a partner? – no./total no. (%)		
Yes	1371/1777 (77.2%)	1282/1712 (74.9%)
No	406/1777 (22.8%)	430/1712 (25.1%)
What is your legal marital status? – no./total no. (%)		
Married or in a registered partnership.	1200/1776 (67.6%)	1132/1706 (66.4%)
Divorced or with registered partnership that was legally dissolved (not remarried or in new registered partnership).	242/1776 (13.6%)	248/1706 (14.5%)
Widowed or with registered partnership that ended with death of partner (not remarried or in new registered partnership).	204/1776 (11.5%)	192/1706 (11.3%)
Never married and never in a registered partnership.	130/1776 (7.3%)	134/1706 (7.9%)
About how many years of education have you completed, whether full-time or part-time? – no./total no. (%)		

0–4 years	64/1771 (3.6%)	62/1715 (3.6%)
5–8 years	281/1771 (15.9%)	271/1715 (15.8%)
9–12 years	817/1771 (46.1%)	792/1715 (46.2%)
≥ 13 years	609/1771 (34.4%)	590/1715 (34.4%)
Work status – no./total no. (%)		
Employed	736/1768 (41.6%)	677/1712 (39.5%)
Unemployed	70/1768 (4.0%)	110/1712 (6.4%)
Retired	715/1768 (40.4%)	696/1712 (40.7%)
Fulfilling domestic tasks	77/1768 (4.4%)	60/1712 (3.5%)
Permanently disabled	44/1768 (2.5%)	38/1712 (2.2%)
Other	126/1768 (7.1%)	131/1712 (7.7%)
What is your average monthly net income in Euros? (IQR)	625 (300-1519)	620 (295-1500)
Over the past 12 months what has been your typical exposure to other people's smoke? – no./total no. (%)		
No exposure	1045/1613 (64.8%)	1036/1569 (66.0%)
Less than one hour exposure per week	317/1613 (19.7%)	314/1569 (20.0%)
One or more hours of second-hand smoke exposure per week	251/1613 (15.6%)	219/1569 (14.0%)
During the last 12 months, about how often did you drink any alcoholic beverage? – no./total no. (%)		
<1 time per month	663/1748 (37.9%)	671/1699 (39.5%)
<1 time per week	227/1748 (13.0%)	218/1699 (12.8%)
1–2 times per week	256/1748 (14.6%)	240/1699 (14.1%)
3–4 times per week	161/1748 (9.2%)	141/1699 (8.3%)
5–6 times per week	67/1748 (3.8%)	45/1699 (2.6%)
Daily	91/1748 (5.2%)	95/1699 (5.6%)
No drinker	283/1748 (16.2%)	289/1699 (17.0%)
Nutrition – no./total no. (%)		
Do you eat salty food or snacks one or more times a day:		
Yes	747/1737 (43.0%)	707/1682 (42.0%)
No	990/1737 (57.0%)	975/1682 (58.0%)
Do you eat fruit one or more times daily:		
Yes	1474/1748 (84.3%)	1423/1700 (83.7%)
No	274/1748 (15.7%)	277/1700 (16.3%)
Do you eat vegetables one or more times daily:		
Yes	1526/1746 (87.4%)	1468/1700 (86.4%)
No	220/1746 (12.6%)	232/1700 (13.6%)
Do you eat meat and/or poultry one or more times daily:		
Yes	1039/1745 (59.5%)	1030/1697 (60.7%)
No	706/1745 (40.5%)	667/1697 (39.3%)

* Body mass index is the weight in kilograms divided by the square of the height in meters. TIA is defined as an ischemic neurologic deficit that persists for less than 24 hours while PRIND is defined as an ischemic neurologic deficit that persists for longer than 24 hours and resolves after 2-3 weeks.

† Angina intensity was assessed based on the description of the strongest episode of pain on a rating scale ranging from 0 to 10 (with 0 being no pain at all and 10 being the most severe pain you can imagine).

Table S3. Representativeness of the study group*	
Disease, problem, or condition under investigation	Participants referred for invasive coronary angiography (ICA) to 26 European centers with stable chest pain and 10-60% probability of CAD.
Special considerations related to	
Gender	56% of participants were female.
Age	Participants younger than 30 years were excluded from the study. There was no upper age limit for inclusion. 58% of participants were 45-65 years old, 34% were older than 65 years, and 8% of participants were younger than 45 years.
Ethnicity	The study population was typical for a European patient cohort with 99% being Caucasian, 0.3% Asian, 0.2% Indian, and 0.1% Black.
Countries	Participants were from 16 countries and included all European regions (North: Denmark, Latvia, Finland; Central: Germany, Austria; East: Czech Republic, Hungary, Lithuania, Poland, Romania, Serbia; South: Italy, Portugal, Spain; West: United Kingdom, Ireland)
Continental region	44% of participants were from Eastern Europe, followed by 20% of participants from Northern Europe, 14% of participants from Western Europe, 13% of participants from Southern Europe, and 8% of participants from Central Europe.
Overall representativeness of this trial	The study is representative of participants referred for ICA with stable chest pain and intermediate pretest probability of CAD (10-60%)
Income level	Patients included in the study cohort reported a personal monthly income of 623.6 (300.0–1504.2) Euros.
Marital status	67% of participants were married or in a registered partnership, 14% were divorced or reported a registered partnership that was legally dissolved, 11% were widowed or with registered partnership that ended with death of partner, 8% were never married and never in a registered partnership.
Employment status	41% of participants were employed, 40% of participants were retired, 5% of participants were unemployed, 4% of participants fulfilled domestic tasks, and 2% of participants reported to be permanently disabled.

* The DISCHARGE consortium is a multinational, European research group investigating a patient population with a broad variety of characteristics in the DISCHARGE trial due to geographical and economical differences throughout Europe.

Table S4. CT Procedure Characteristics		
Characteristics	**CT Group (N=1784/1808)**	**ICA Group (N=35/1753)**
Patient Preparation		
Intravenous access for contrast agent – no./total no.		
Cubital fossa	1635/1781 (91.8%)	34/35 (97.1%)
Back of hand	63/1781 (3.5%)	0
Forearm	79/1781 (4.4%)	0
Other*	4/1781 (0.2%)	1/35 (2.9%)
Prescan Medication – no./total no.		
Hydration performed	81/1781 (4.5%)	0
Isotonic solution	40/1781 (2.2%)	0
ACC (acetylcysteine)	0	0
Sodium hydrogen carbonate	1/1781 (0.1%)	0
Other†	41/1781 (2.3%)	0
Median Prescan Heart Rate in beats per minute (IQR)	66 (60-75)	68 (60-73)
Patients with data – no./total no.	1781/1781 (100%)	35/35 (100%)
Oral Heart Rate-Lowering Therapy– no./total no.		
Oral beta blockers	1312/1781 (73.7%)	22/35 (62.9%)
Metopropol	1232/1781 (69.2%)	20/35 (57.1%)
Other‡	80/1781 (4.5%)	2/35 (5.7%)
Ivabradine	51/1781 (2.9%)	1/35 (2.9%)
Calcium channel blockers	3/1781 (0.2%)	0
Nitroglycerine		
Nitroglycerine – no./total no.	1722/1781 (96.7%)	33/35 (94.3%)
Mode of administration – no./total no.		
Spray	1418/1781 (79.6%)	31/35 (88.6%)
Capsule	304/1781 (17.1%)	2/35 (5.7%)
Contrast Agent		
Median amount of contrast agent for CTA in ml (IQR)	84.0 (68.0–95.0)	80.0 (66.5–95.0)
Patients with data – no./total no.	1735/1781 (97.4%)	25/35 (71.4%)
Bolus tracking – no./total no.	1768/1781 (99.3%)	35/35 (100%)
Test bolus – no./total no.	13/1781 (0.7%)	0
Amount of contrast agent for test bolus in ml	10.0 (10.0-13.7)	n/a
Median Heart Rate during CT in beats per minute (IQR)	57.0 (51.7-62.4)	61.0 (55.8-64.5)
Patients with data – no./total no.	1202/1781 (67.5%)	10/35 (28.6%)
CTA scan mode – no./total no.		
Prospective	1151/1781 (64.6%)	22/35 (62.9%)
Retrospective	630/1781 (35.4%)	13/35 (37.1%)
Median Dose-Length Product for Calcium Score in mGy cm (IQR)	51.7 (32.1-77.0)	49.8 (30.2-69.9)
Patients with data – no./total no.	1760/1781 (98.8%)	17/35 (48.6%)
Median Dose-Length Product for bolus tracking or test bolus in mGy cm (IQR)	10.0 (6.8-16.2)	12.0 (9.0-16.1)
Patients with data – no./total no.	1654/1781 (92.8%)	17/35 (48.6%)
Median Dose-Length Product for CTA in mGy cm (IQR)	249.4 (155.0-394.0)	293.3 (135.0-426.5)

Patients with data – no./total no.	1777/1781 (99.7%)	32/35 (91.4%)
Median Dose-Length Product for the entire CT procedure in mGy cm (IQR)	330.0 (220.0-481.0)	332.5 (183.0-463.5)
Median effective radiation dose for the entire CT procedure in mSv (IQR)§	5.6 (3.7-8.2)	5.7 (3.1-7.9)
Patients with data – no./total no.	1778/1781 (99.8%)	32/35 (91.4%)

* Other included unknown (3/1781 (0.2%)) and wrist (1/1781 (0.06%)).

† Other was always oral hydration (41/1781).

‡ Other included bisoprolol (CT group: 54/1781 (3.0%); ICA group: 2/35 (5.7%)), atenolol (CT group: 16/1781 (0.9%); ICA group: (0)), carvedilol (CT group: 3/1781 (0.2%); ICA group: (0)), propranolol (CT group: 2/1781 (0.1%); ICA group: (0)), nebivolol (CT group: 2/1781 (0.1%); ICA group: (0)), unknown (CT group: 2/1781 (0.1%); ICA- group: (0)) and esmolol (CT group: 1/1781 (0.05%); ICA group: (0)).

§ Converted from the dose-length product to effective radiation dose using a k factor of 0.017 mSv/(mGy×cm).

Table S5. ICA Procedure Characteristics

Characteristics	CT Group (N=404/1808)	ICA Group (N=1708/1753)
Fast-acting nitrate – no./total no. (%)	171/404 (42.3%)	667/1706 (39.8%)
Fast-acting nitrate for right coronary artery	143/404 (35.4%)	605/1706 (35.4%)
Fast-acting nitrate for left main artery	153/404 (37.9%)	650/1706 (38.1%)
Left ventriculography – no./total no. (%)	23/404 (5.7%)	65/1706 (3.8%)
Median contrast agent amount for diagnostic ICA, excluding left ventriculography, excluding PCI, in ml (IQR)	70.0 (50.0-100.0)	62.0 (46.0-86.0)
Patients with data – no./total no. (%)	357/404 (88.4%)	1633/1706 (95.7%)
Median Dose-Area Product (DAP) for diagnostic part, $Gycm^2$ (IQR)	20.5 (10.5-38.1)	17.1 (9.4-31.2)
Patients with data – no./total no. (%)	342/404 (84.7%)	1655/1706 (97.0)
Fractional flow reserve – no./total no. (%)	51/404 (12.6%)*	71/1706 (4.2%)*
Intravascular ultrasound – no./total no. (%)	4/404 (1.0%)	7/1706 (0.4%)
Optical coherence tomography – no./total no. (%)	1/404 (0.2%)	1/1706 (0.1%)
Percutaneous coronary intervention (PCI) – no./total no. (%)	156/404 (38.6%)*	182/1706 (10.7%)*
Contrast agent amount for entire procedure (including PCI) ml	100.0 (60.0-200.0)*	70.0 (50.0-100.0)*
Patients with data – no./total no. (%)	390/404 (96.5%)	1667/1706 (97.7%)
Median Dose-Area Product (DAP) for entire ICA procedure (including PCI), $Gycm^2$ (IQR)	29.9 (13.8-61.1)*	18.4 (10.0-36.0)*
Median effective radiation dose for entire ICA procedure (including PCI), mSv (IQR)†	6.6 (3.0-13.4)*	4.1 (2.2-7.9)*
Patients with data – no./total no. (%)	394/404 (97.5%)	1699/1706 (99.6%)

* There was a significantly higher proportion of ICA with PCI and consequently also more use of fractional flow reserve, larger contrast agent amounts and radiation dose used for ICA in the CT group because more patients undergoing ICA in the CT group had obstructive CAD (72.5%) as compared with the ICA group (26.2%) (Table S6).

† Converted from the dose-area product to effective radiation dose using a factor of 0.22 mSv/(Gy×cm^2).

Table S6. CT and ICA Findings in Patients with Both Tests during Initial Management		
Outcome	**CT Group (N = 1808)**	**ICA Group (N= 1753)**
Underwent CT and ICA – no./total no. (%)	386/1808 (21.3 %)	8/1753 (0.5%)
Coronary artery disease defined by CT		
Obstructive coronary artery disease (≥ 50%) by CT – no./total no. (%)	334/386 (86.5%)	3/8 (37.5%)
Findings on ICA		
Obstructive coronary artery disease (≥ 50%) with high-risk anatomy – no./total no. (%)	147/334 (44.4%)	
Obstructive coronary artery disease (≥ 50%) without high-risk anatomy – no./total no. (%)	116/334 (34.7%)	3/3 (100%)
Nonobstructive coronary artery disease (1-49%) – no./total no. (%)	54/334 (16.2%)	0
No signs of coronary artery disease – no./total no. (%)	16/334 (4.8%)	0
Nondiagnostic – no./total no. (%)	1/334 (0.3%)	0
Data not available due to an incomplete test or data not documented – no./total no. (%)	0	0
Obstructive coronary artery disease (≥ 50%) with high-risk anatomy by CT – no./total no. (%)	222/386 (57.5%)	2/8 (25.0%)
Findings on ICA		
Obstructive coronary artery disease (≥ 50%) with high-risk anatomy – no./total no. (%)	131/222 (59.0%)	2/2 (100%)
Obstructive coronary artery disease (≥ 50%) without high-risk anatomy – no./total no. (%)	40/222 (18.0%)	0
Nonobstructive coronary artery disease (1-49%) – no./total no. (%)	39/222 (17.6%)	0
No signs of coronary artery disease – no./total no. (%)	11/222 (5.0%)	0
Nondiagnostic – no./total no. (%)	1/222 (0.4%)	0
Data not available due to an incomplete test or data not documented – no./total no. (%)	0	0
Obstructive coronary artery disease (≥ 50%) without high-risk anatomy by CT – no./total no. (%)	112/386 (29.0%)	1/8 (12.5%)
Findings on ICA		
Obstructive coronary artery disease (≥ 50%) with high-risk anatomy – no./total no. (%)	16/112 (14.3%)	0
Obstructive coronary artery disease (≥ 50%) without high-risk anatomy – no./total no. (%)	76/112 (67.9%)	1/1 (100%)
Nonobstructive coronary artery disease (1-49%) – no./total no. (%)	15/112 (13.4%)	0
No signs of coronary artery disease – no./total no. (%)	5/112 (4.5%)	0
Nondiagnostic – no./total no. (%)	0	0
Data not available due to an incomplete test or data not documented – no./total no. (%)	0	0

Nonobstructive coronary artery disease by CT (1-49%) – no./total no. (%)	9/386 (2.3%)	1/8 (12.5%)
Findings on ICA		
Obstructive coronary artery disease (≥ 50%) with high-risk anatomy – no./total no. (%)	0	0
Obstructive coronary artery disease (≥ 50%) without high-risk anatomy – no./total no. (%)	0	0
Nonobstructive coronary artery disease (1-49%) – no./total no. (%)	4/9 (44.4%)	0
No signs of coronary artery disease – no./total no. (%)	5/9 (55.6%)	0
Nondiagnostic – no./total no. (%)	0	0
Data not available due to an incomplete test or data not documented – no./total no. (%)	0	1/1 (100%)
No signs of coronary artery disease by CT – no./total no. (%)	2/386 (0.5%)	4/8 (50.0%)
Findings on ICA		
Obstructive coronary artery disease (≥ 50%) with high-risk anatomy – no./total no. (%)	0	0
Obstructive coronary artery disease (≥ 50%) without high-risk anatomy – no./total no. (%)	0	0
Nonobstructive coronary artery disease (1-49%) – no./total no. (%)	0	1/4 (25.0%)
No signs of coronary artery disease – no./total no. (%)	2/2 (100%)	1/4 (25.0%)
Nondiagnostic – no./total no. (%)	0	0
Data not available due an incomplete test or data not documented – no./total no. (%)	0	2/4 (50.0%)
Nondiagnostic CT– no./total no. (%)	41/386 (10.6%)	0
Findings on ICA		
Obstructive coronary artery disease (≥ 50%) with high-risk anatomy – no./total no. (%)	9/41 (21.9%)	0
Obstructive coronary artery disease (≥ 50%) without high-risk anatomy – no./total no. (%)	13/41 (31.7%)	0
Nonobstructive coronary artery disease (1-49%) – no./total no. (%)	6/41 (14.6%)	0
No signs of coronary artery disease – no./total no. (%)	13/41 (31.7%)	0
Nondiagnostic – no./total no. (%)	0	0
Data not available due to an incomplete test or data not documented – no./total no. (%)	0	0
Diagnostic yield of ICA* – no./total no. (%)	293/404 (72.5%)	448/1708 (26.2%)

* The diagnostic yield of ICA defined as the proportion of obstructive coronary arteries found on ICA in both randomization groups. Note that a total of 404 patients in the CT group underwent ICA during initial management and were considered for the calculation of the diagnostic yield of ICA and that 386 patients in the CT group underwent both CT and ICA.

Table S7. Major Adverse Cardiovascular Events (MACE) per Study Center				
Study Center	**CT Group**		**ICA Group**	
	MACE	**Total**	**MACE**	**Total**
Semmelweis University, Budapest, Hungary	7	256	7	253
Rigshospitalet, University of Copenhagen, Denmark	6	234	7	226
Cardio Med Medical Center, Tirgu Mures, Rumania	0	176	3	168
Southeastern Health and Social Care Trust, Belfast, United Kingdom	2	116	2	109
Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona Spain	7	104	6	107
Paul Stradins Clinical University Hospital, Riga, Latvia	1	94	2	90
Motol University Hospital, Prague, Czech Republic	0	72	2	73
Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania	1	74	1	69
Institute for Cardiovascular Diseases of Vojvodina, Novi Sad, Sremska Kamenica, Serbia	1	70	1	72
University of Leipzig Heart Centre, Leipzig, Germany	1	64	4	59
St. Vincent's University Hospital, Dublin, Ireland	1	62	1	59
Basurto Hospital, Bilbao Spain	0	51	0	53
Aintree University Hospital, Liverpool, United Kingdom	2	50	3	51
University of Medicine, Pharmacy, Science and Technology "G.E.Palade", Tirgu Mures, Rumania	0	42	1	39
Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany	1	43	1	36
National Institute of Cardiology, Warsaw, Poland	1	37	3	38
Clinical Hospital Center Zemun, Faculty of Medicine, University of Belgrade, Belgrade, Serbia	1	37	0	36
Sapienza University of Rome, Rome, Italy	0	36	1	35
Wojewodzki Szpital Specjalistyczny We Wroclawiu, Wroclaw, Poland	1	38	1	32
Innsbruck Medical University, Innsbruck, Austria	2	31	0	33
Turku University Hospital and University of Turku, Turku, Finland	1	30	0	31
Centro Hospitalar de Vila Nova de Gaia/ Espinho, Vila Nova de Gaia, Portugal	1	25	1	24
ALB FILS KLINIKEN GmbH, Goeppingen, Germany	1	22	1	20
University of Glasgow, Glasgow, United Kingdom	0	20	2	21
University of Cagliari, Cagliari, Italy	0	14	1	13
Royal Liverpool University Hospital, Liverpool, United Kingdom	0	10	1	6
Total	**38**	**1808**	**52**	**1753**

Table S8. Major Procedure-Related Complications and Relationship to Procedures in the Two Groups		
ITT analysis in both groups	**CT Group (N=1793/1808)**	**ICA Group (N= 1728/1753)**
Major procedure-related complications during initial management - no./total no. (%)	9/1793 (0.5%)	33/1728 (1.9%)
Nonfatal myocardial infarction – no./total no. (%)	3/1793 (0.2%)	10/1728 (0.6%)
Nonfatal stroke – no./total no. (%)	0	1/1728 (0.1%)
Death – no./total no. (%)	0	0
Cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation) – no./total no. (%)	0	6/1728 (0.3%)
Further complications prolonging hospitalization by at least 24 h – no./total no. (%)	4/1793 (0.2%)	11/1728 (0.6%)
Cardiac arrhythmia (other than ventricular tachycardia, ventricular fibrillation)	2/1793 (0.1%)	0
Closure or injury of vessels	1/1793 (0.06%)	1/1728 (0.06%)
Skin tissue and nerve injuries	0	2/1728 (0.1%)
Allergoid contrast agent reaction	0	1/1728 (0.06%)
Hematoma at the puncture site	0	3/1728 (0.2%)
Angina without infarction	0	1/1728 (0.06%)
Allergic reaction (other than contrast agent)	0	1/1728 (0.06%)
Bradycardia	1/1793 (0.06%)	0
Secondary bleeding at the puncture site - no./total no. (%)	0	1/1728 (0.06%)
Bleeding (hematoma)	0	1/1728 (0.06%)
Dissection (coronary, aorta) – no./total no. (%)	2/1793 (0.1%)	2/1728 (0.1%)
Cardiogenic shock – no./total no. (%)	0	0
Retroperitoneal bleeding – no./total no. (%)	0	0
Cardiac arrest – no./total no. (%)	0	2/1728 (0.1%)
Cardiac tamponade – no./total no. (%)	0	1/1728 (0.06%)
Relationship to procedures*		
CT – no./total no. (%)	1/9 (11.1%)	0
ICA without PCI – no./total no. (%)	1/9 (11.1%)	15/33 (45.5%)
ICA with PCI – no./total no. (%)	6/9 (66.7%)	15/33 (45.5%)
CABG – no./total no. (%)	1/9 (11.1%)	3/33 (9.1%)
Functional test – no./total no. (%)	0	0

* Results shown here are absolute values and are different from the cumulative incidences (Table 3). Major procedure-related complications were more likely related to ICA with PCI than to ICA without PCI (4% [20 of 500 ICA procedures with PCI] vs. 0.9% [16 of 1784 ICA procedures without PCI]). Further details of major procedure-related complications and their relationship to procedures performed in the two groups are given on the following pages.

Table S9. Major Procedure-Related Complications Related to CT Procedures		
ITT analysis in both groups	**CT Group**	**ICA Group**
At least one CT	1782	35
Nonfatal myocardial infarction – no./total no. (%)	0	0
Nonfatal stroke – no./total no. (%)	0	0
Death – no./total no. (%)	0	0
Cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation) – no./total no. (%)	0	0
Further complications prolonging hospitalization by at least 24 h – no./total no. (%)	1/1782 (0.05%)	0
Cardiac arrhythmia (other than ventricular tachycardia, ventricular fibrillation)	0	0
Closure or injury of vessels	0	0
Skin tissue and nerve injuries	0	0
Allergoid contrast agent reaction	0	0
Hematoma at the puncture site	0	0
Angina without infarction	0	0
Allergic reaction (other than contrast agent)	0	0
Bradycardia	1/1782 (0.05%)	0
Secondary bleeding at the puncture site	0	0
Bleeding (hematoma)	0	0
Dissection (coronary, aorta) – no./total no. (%)	0	0
Retroperitoneal bleeding – no./total no. (%)	0	0
Cardiogenic shock – no./total no. (%)	0	0
Cardiac arrest – no./total no. (%)	0	0
Cardiac tamponade	0	0
Total – no./total no. (%)	**1/1782 (0.05%)**	**0**

Table S10. Major Procedure-Related Complications Related to ICA Procedures without PCI		
ITT analysis in both groups	**CT Group**	**ICA Group**
At least one ICA procedure without PCI	252	1532
Nonfatal myocardial infarction – no./total no. (%)	1/252 (0.4%)	0
Nonfatal stroke – no./total no. (%)	0	1/1532 (0.06%)
Death – no./total no. (%)	0	0
Cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation) – no./total no. (%)	0	4/1532 (0.3%)
Further complications prolonging hospitalization by at least 24 h – no./total no. (%)	0	7/1532 (0.5%)
Cardiac arrhythmia (other than ventricular tachycardia, ventricular fibrillation)	0	0
Closure or injury of vessels	0	1/1532 (0.06%)
Skin tissue and nerve injuries	0	2/1532 (0.1%)
Allergoid contrast agent reaction	0	1/1532 (0.06%)
Hematoma at the puncture site	0	2/1532 (0.1%)
Angina without infarction	0	0
Allergic reaction (other than contrast agent) - no./total no. (%)	0	1/1532 (0.06%)
Bradycardia	0	0
Secondary bleeding at the puncture site	0	0
Bleeding (hematoma)	0	0
Dissection (coronary, aorta) – no./total no. (%)	0	1/1532 (0.06%)
Retroperitoneal bleeding – no./total no. (%)	0	0
Cardiogenic shock – no./total no. (%)	0	0
Cardiac arrest – no./total no. (%)	0	1/1532 (0.06%)
Cardiac tamponade	0	0
Total – no./total no. (%)	**1/252 (0.4%)**	**15/1532 (1.0%)**

Table S11. Major Procedure-Related Complications Related to ICA Procedures with PCI		
ITT analysis in both groups	**CT Group**	**ICA Group**
At least one ICA with PCI	231	269
Nonfatal myocardial infarction – no./total no. (%)	1/231 (0.4%)	9/269 (3.3%)
Nonfatal stroke – no./total no. (%)	0	0
Death – no./total no. (%)	0	0
Cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation) – no./total no. (%)	0	2/269 (0.7%)
Further complications prolonging hospitalization by at least 24 h	3/231 (1.3%)	2/269 (0.7%)
Cardiac arrhythmia (other than ventricular tachycardia, ventricular fibrillation)	2/231 (0.9%)	0
Closure or injury of vessels	1/231 (0.4%)	0
Skin tissue and nerve injuries	0	0
Allergoid contrast agent reaction	0	0
Hematoma at the puncture site	0	1/269 (0.4%)
Angina without infarction	0	1/269 (0.4%)
Allergic reaction (other than contrast agent)	0	0
Bradycardia	0	0
Secondary bleeding at the puncture site	0	0
Bleeding (hematoma)	0	0
Dissection (coronary, aorta) – no./total no. (%)	2/231 (0.86%)	1/269 (0.4%)
Retroperitoneal bleeding – no./total no. (%)	0	0
Cardiogenic shock – no./total no. (%)	0	0
Cardiac arrest – no./total no. (%)	0	1/269 (0.4%)
Cardiac tamponade – no./total no. (%)	0	0
Total – no./total no. (%)	**6/231 (2.6%)**	**15/269 (5.6%)**

Table S12. Major Procedure-Related Complications Related to CABG Procedures		
ITT analysis in both groups	**CT Group**	**ICA Group**
At least one CABG procedure	41	56
Nonfatal myocardial infarction – no./total no. (%)	1/41 (2.4%)	1/56 (1.8%)
Nonfatal stroke – no./total no. (%)	0	0
Death – no./total no. (%)	0	0
Cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation) – no./total no. (%)	0	0
Further complications prolonging hospitalization by at least 24 h – no./total no. (%)	0	1/56 (1.8%)
Cardiac arrhythmia (other than ventricular tachycardia, ventricular fibrillation)	0	0
Closure or injury of vessels	0	0
Skin tissue and nerve injuries	0	0
Allergoid contrast agent reaction	0	0
Hematoma at the puncture site	0	0
Angina without infarction	0	0
Allergic reaction (other than contrast agent)	0	0
Bradycardia	0	0
Secondary bleeding at the puncture site	0	0
Bleeding (hematoma)	0	1/56 (1.8%)
Dissection (coronary, aorta) – no./total no. (%)	0	0
Retroperitoneal bleeding – no./total no. (%)	0	0
Cardiogenic shock – no./total no. (%)	0	0
Cardiac arrest – no./total no. (%)	0	0
Cardiac tamponade – no./total no. (%)	0	1/56 (1.8%)
Total – no./total no. (%)	**1/41 (2.4%)**	**3/56 (5.4%)**

Table S13. Cardiovascular Medications at a Median of 1.0 year (IQR 1.0 to 1.2)		
	CT Group (N=1808)	**ICA Group (N=1753)**
Statin	933/1739 (53.7)	891/1661 (53.6)
Antiplatelet agent	814/1739 (46.8)	820/1661 (49.4)
Beta-blocker	725/1739 (41.7)	728/1661 (43.8)
Nitrates	131/1739 (7.5)	125/1661 (7.5)
Calcium antagonist	391/1739 (22.5)	387/1661 (23.3)
Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker	861/1739 (49.5)	791/1661 (47.6)

Table S14. Cardiovascular Medications at a Median of 3.5 years (IQR 2.9 to 4.2)		
Characteristics	**CT Group (N=1808)**	**ICA Group (N=1753)**
Statin	802/1608 (49.8)	756/1549 (48.8)
Antiplatelet agent	687/1608(42.7)	680/1549 (43.8)
Beta-blocker	695/1608 (43.2)	675/1549 (43.6)
Nitrates	107/1608 (6.7)	103/1549 (6.5)
Calcium antagonist	379/1608 (23.6)	372/1549 (24.0)
Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker	816/1608 (50.7)	769/1549 (49.6)

Table S15. Type of Chest Pain in Relation to Functional Test Results before the Initial Tests		
	CT Group (N=1808)	**ICA Group (N=1753)**
Type of chest pain – no./total no. (%)		
Typical angina – no./total no. (%)	232/1808 (12.8)	275/1753 (15.7)
Positive functional tests	37/232 (15.9)	60/275 (21.8)
Negative functional tests	37/232 (15.9)	37/275 (13.5)
Nondiagnostic functional tests	10/232 (4.3)	8/275 (2.9)
Atypical angina – no./total no. (%)	843/1808 (46.6)	805/1753 (45.9)
Positive functional tests	115/843 (13.6)	99/805 (12.3)
Negative functional tests	133/843 (15.8)	155/805 (19.3)
Nondiagnostic functional tests	26/843 (3.1)	27/805 (3.4)
Nonanginal chest pain – no./total no. (%)	677/1808 (37.4)	634/1753 (36.2)
Positive functional tests	114/677 (16.8)	108/634 (17.0)
Negative functional tests	93/677 (13.7)	82/634 (12.9)
Nondiagnostic functional tests	16/677 (2.4)	16/634 (2.5)
Other chest pain – no./total no. (%)	56/1808 (3.1)	39/1753 (2.2)
Positive functional tests	11/56 (19.6)	8/39 (20.5)
Negative functional tests	7/56 (12.5)	6/39 (15.4)
Nondiagnostic functional	0	0

Table S16. Type of Chest Pain in Relation to ICA Referral Categories

	CT Group (N=1808)	ICA Group (N=1753)
Typical angina – no./total no. (%)	232/1808 (12.8)	275/1753 (15.7)
Clinical constellation suggesting high event risk, particularly if symptoms were inadequately responding to medical treatment	95/232 (40.9)	88/275 (32.0)
Severe angina, particularly if symptoms were inadequately responding to medical treatment	68/232 (29.3)	93/275 (33.8)
Intermediate pretest probability or LVEF <50% without typical angina following functional testing showing ischemia	37/232 (15.9)	60/275 (21.8)
Low or intermediate event risk if symptoms were inadequately responding to medical treatment	15/232 (6.5)	20/275 (7.3)
Intermediate pretest probability or LVEF <50% without typical angina following nondiagnostic functional testing	10/232 (4.3)	8/275 (2.9)
Other	5/232 (2.2)	6/275 (2.2)
Atypical angina – no./total no. (%)	843/1808 (46.6)	805/1753 (45.9)
Clinical constellation suggesting high event risk, particularly if symptoms were inadequately responding to medical treatment	436/843 (51.7)	390/805 (48.4)
Severe angina, particularly if symptoms were inadequately responding to medical treatment	179/843 (21.2)	212/805 (26.3)
Intermediate pretest probability or LVEF <50% without typical angina following functional testing showing ischemia	115/843 (13.6)	99/805 (12.3)
Low or intermediate event risk if symptoms were inadequately responding to medical treatment	58/843 (6.9)	51/805 (6.3)
Intermediate pretest probability or LVEF <50% without typical angina following nondiagnostic functional testing	26/843 (3.1)	27/805 (3.4)
Other	26/843 (3.1)	22/805 (2.7)
Nonanginal chest pain – no./total no. (%)	677/1808 (37.4)	634/1753 (36.2)
Clinical constellation suggesting high event risk, particularly if symptoms were inadequately responding to medical treatment	308/677 (45.5)	293/634 (46.2)
Severe angina, particularly if symptoms were inadequately responding to medical treatment	97/677 (14.3)	84/634 (13.2)
Intermediate pretest probability or LVEF <50% without typical angina following functional testing showing ischemia	114/677 (16.8)	108/634 (17.0)
Low or intermediate event risk if symptoms were inadequately responding to medical treatment	114/677 (16.8)	106/634 (16.7)
Intermediate pretest probability or LVEF <50% without typical angina following nondiagnostic functional testing	16/677 (2.4)	16/634 (2.5)
Other	27/677 (4.0)	23/634 (3.6)
Other chest pain – no./total no. (%)	56/1808 (3.1)	39/1753 (2.2)
Clinical constellation suggesting high event risk, particularly if symptoms were inadequately responding to medical treatment	31/56 (55.4)	20/39 (51.3)
Severe angina, particularly if symptoms were inadequately responding to medical treatment	10/56 (17.9)	8/39 (20.5)
Intermediate pretest probability or LVEF <50% without typical angina following functional testing showing ischemia	11/56 (19.6)	8/39 (20.5)
Low or intermediate event risk if symptoms were inadequately responding to medical treatment	2/56 (3.6)	0
Intermediate pretest probability or LVEF <50% without typical angina following nondiagnostic functional testing	0	0
Other	2/56 (3.6)	3/39 (7.7)

Table S17. Median Pretest Probability of Obstructive CAD in the ICA Referral Categories		
	CT Group (N=1808)	**ICA Group (N=1753)**
Clinical constellation suggesting high event risk, particularly if symptoms were inadequately responding to medical treatment – no./total no. (%)	870/1802 (48.3)	791/1745 (45.3)
Median pretest probability of obstructive CAD (IQR) – %	35.9 (29.0–45.9)	37.1 (30.1–45.8)
Severe angina, particularly if symptoms were inadequately responding to medical treatment – no./total no. (%)	354/1802 (19.6)	397/1745 (22.8)
Median pretest probability of obstructive CAD (IQR) – %	38.8 (29.8–47.9)	39.4 (31.3–48.2)
Intermediate pretest probability or LVEF <50% without typical angina following functional testing showing ischemia – no./total no. (%)	277/1802 (15.4)	275/1745 (15.8)
Median pretest probability of obstructive CAD (IQR) – %	37.5 (28.7–45.4)	40.7 (29.0–47.4)
Low or intermediate event risk if symptoms were inadequately responding to medical treatment – no./total no. (%)‡	189/1802 (10.5)	177/1745 (10.1)
Median pretest probability of obstructive CAD (IQR) – %	37.3 (27.0–46.7)	36.1 (27.9–43.6)
Intermediate pretest probability or LVEF <50% without typical angina following nondiagnostic functional testing – no./total no. (%)	52/1802 (2.9)	51/1745 (2.9)
Median pretest probability of obstructive CAD (IQR) – %	34.9 (27.3–46.1)	34.1 (27.5–40.7)
Other – no./total no. (%)	60/1802 (3.3)	54/1745 (3.1)
Median pretest probability of obstructive CAD (IQR) – %	33.1 (26.3–43.0)	37.1 (28.8–47.4)

Table S18. Comparison of PROMISE, SCOT-HEART and DISCHARGE Trials Regarding Baseline Characteristics of Patients, Management, and Main Results*

	PROMISE	SCOT-HEART	DISCHARGE
Comparator	CT vs. functional testing	CT plus standard care vs. standard care	CT vs. ICA
Inclusion criteria	Symptomatic outpatients without diagnosed CAD whose physicians believed that nonurgent, noninvasive cardiovascular testing was necessary for the evaluation of suspected CAD	Stable chest pain patients referred by a primary care physician to an outpatient cardiology clinic	Stable chest pain, suspected CAD, at least 30 years of age referred for ICA with intermediate (10-60%) pretest probability of obstructive CAD
Exclusion criteria	- Unstable hemodynamic status or arrhythmias that required urgent evaluation for suspected acute coronary syndrome - History of CAD or evaluation for CAD within the previous 12 months - Clinically significant congenital, valvular, or cardiomyopathic heart disease - Any reason that the patient could not be randomly assigned to either group safely	- Known severe renal failure - Previous recruitment to the trial - Major allergy to iodinated contrast agent - Pregnancy - Acute coronary syndrome within 3 months	- Patients on hemodialysis - No sinus rhythm - Pregnancy - Any medical condition giving rise to concern that participation might not be in the best interest of health - Participation in any other study
Baseline characteristics of patients			
Age, mean (SD), yr	60.8 (8.3)	57.1 (9.7)	60.1 (10.1)
Women – no./total no. (%)	5270/10,003 (52.7)	1821/4146 (43.9)	2002/3561 (56.2)
Pretest probability of obstructive CAD, mean (SD)	53.4% (21.4)†	17% (12)‡	37.7% (10.8)§
Primary presenting symptom stable chest pain– no./total no. (%)	7272/9996 (72.7)	4146/4146 (100)	3561/3561 (100)
Had known CAD– no./total no. (%)	0	372/4142 (9.0)	0
Body mass index, mean (SD)	30.5 (6.1)	29.7 (5.9)	28.8 (5.2)
Cardiovascular risk factors – no./total no. (%)			
Arterial hypertension	6501/10,003 (65.0)	1395/4105 (34.0)	2122/3544 (59.9)
Diabetes mellitus	2144/10,003 (21.4)	444/4146 (10.7)	557/3544 (15.7)
Hyperlipidemia	6767/10,002 (67.7)	2176/4142 (52.5)	1706/3544 (48.1)
Cardiovascular medications – no./total no. (%)			
Statin	4389/9569 (45.9)	1786/4142 (43.1)	1595/3541 (45.0)
Antiplatelet agent	4280/9569 (44.7)	1993/4142 (48.1)	1741/3541 (49.2)
Beta-blocker	2399/9569 (25.1)	1357/4142 (32.8)	1492/3541 (42.1)

Angiotensin-converting enzyme inhibitor or Angiotensin-receptor blocker	4194/9569 (43.8)	685/4142 (16.5)	1667/3541 (47.1)
Nitrates		1160/4142 (28.0)	393/3537 (11.1)
Calcium antagonist		377/4142 (9.1)	717/3537 (20.3)
Diagnostic			
CT diagnostic findings in CT group – no./total no. (%)			
Obstructive CAD	517/4840 (10.7)	452/1778 (25.4)	465/1808 (25.7)
Nonobstructive CAD		672/1778 (37.8)	655/1808 (36.2)
No signs of CAD		654/1778 (36.8)	573/1808 (31.7)
Nondiagnostic	299/4677 (6.4)	5% had nondiagnostic quality	103/1808 (5.7)
ICA diagnostic findings in CT group – no./total no. (%)			
Obstructive CAD	439/609 (72.1)		293/404 (72.5)
Nonobstructive CAD			66/404 (16.3)
No signs of CAD			44/404 (10.9)
Nondiagnostic			1/404 (0.2)
Main results			
Definition of MACE	Composite of death, myocardial infarction, hospitalization for unstable angina or major procedural complication	Composite of death from coronary heart disease or nonfatal myocardial infarction	Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke
Significance for primary end point definition of MACE between groups	P = 0.75 Hazard ratio 1.04, 95% CI (0.83–0.29)	P = 0.004 Hazard ratio 0.59, 95% CI (0.41–0.84)	P = 0.10 Hazard ratio 0.70, 95% CI (0.46–1.07)
Proportion of major procedure-related complications	Similar (0.08% vs. 0.1%)	No major adverse events occurred among the 1778 patients undergoing CT	Higher in ICA group (0.5% vs. 1.9%)
Diagnostic yield of ICA (rate of ICA showing obstructive CAD)	Higher in CT group (72.1% vs. 47.5%)		Higher in CT group (72.5% vs. 26.2%)
Proportion of revascularizations	Higher in CT group at 90 days (6.2% vs. 3.2%)	Similar at 4.8 years (12.9% vs. 13.5%)	Higher in ICA group at 3.5 years (14.2% vs. 18.0%)
Median follow-up duration	25 months	4.8 years	3.5 years
Patient-reported outcome measures and differences between groups			
Difference in angina frequency at 6 months (95% CI)	Similar 0.2 (-0.4 to 0.9)	Higher in CT group -1.55 (-2.85 to -0.25)	
Difference in angina frequency at 12 months (95% CI)	Similar -0.1 (-0.7 to 0.5)		Similar angina in the last 4 weeks (10.0% vs. 8.4%)

Difference in angina frequency at 24 months (95% CI)	Similar -0.2 (-0.8 to 0.4)		
Difference in angina frequency at median 3.5 yr (IQR, 2.9-4.2)			Similar angina in the last 4 weeks (8.8% vs. 7.5%)
Difference in quality of life at 6 months (95% CI)	Similar (Quality of life scale) 0.2 (-1.2 to 0.9)	Better in standard care group SF-12v2: -3.48 (-4.95 to 2.01)	
Difference in quality of life at 12 months (95% CI)	Similar (Quality of life scale) -0.5 (-1.5 to 0.6)		Similar EQ-5D: -0.20 (-1.25 to 0.86) SF-12v2: 0.12 (-0.37 to 0.61)
Difference in quality of life at 24 months (95% CI)	Similar (Quality of life scale) -0.2 (-1.3 to 0.9)		
Difference in quality of life at median 3.5 yr (IQR, 2.9-4.2)			Similar EQ-5D: 0.31 (-0.76 to 1.38) SF-12v2: 0.26 (-0.27 to 0.78)

*All three trials - PROMISE, SCOT-HEART and DISCHARGE - compared diagnostic strategies in patients with stable symptoms. All three trials used CT to guide patient management in the intervention group.[19, 20] The PROMISE trial compared CT with functional testing, the SCOT-HEART trial compared CT added to standard care with standard care alone, which included functional testing, and the DISCHARGE trial compared CT with ICA.[19, 20] In DISCHARGE, patients were clinically referred for direct ICA, which thus formed the control group. Similar to SCOT-HEART, which enrolled patients referred to a recent-onset chest pain clinic, DISCHARGE patient inclusion required current stable chest pain at baseline.[19, 20] The SCOT-HEART trial had similar rates of obstructive CAD (25%) and nonobstructive CAD (38%) by CT as the DISCHARGE trial. The rate of nondiagnostic CT tests was similar in the PROMISE (6.4%), the SCOT-HEART (5%), and the DISCHARGE trial (5.7%).[21,22] The PROMISE trial found no statistically significant difference in MACE (composite of death, myocardial infarction, hospitalization for unstable angina or major procedural complication) between the two groups, with a hazard ratio of 1.04 at 25-month follow-up. The SCOT-HEART trial found statistically significantly reduced rates of MACE (composite of death from coronary heart disease or nonfatal myocardial infarction) with a hazard ratio of 0.59 at 4.8 years. The DISCHARGE trial found no statistically significant difference in MACE (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) between the two groups with a hazard ratio of 0.70.[19, 20] Annual rates of MACE of 0.61% in the CT group and 0.86% in the ICA group were lower than expected (0.8% and 1.4%) which may be due improvements in the methods used to perform ICA and general improvements in cardiovascular care including medications since planning of the study. The annual rate of MACE defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the CT group (0.61%) in the DISCHARGE trial was similar to the rate of this MACE definition used as a secondary end point in the SCOT-HEART trial (0.63%).[20] Major procedural complications in the PROMISE trial were rare and similar in both groups (0.08% vs. 0.1%), with no major procedure-related complications among the 4733 patients undergoing CT.[19] Procedural complications of CT were also rare in SCOT-HEART and no major complication occurred in the 1778 patients undergoing CT. In the DISCHARGE trial, the proportion of major procedural complications was higher in the ICA group than in the CT group (0.5% vs. 1.9%).[21,23] The diagnostic yield of ICA, i.e., the proportion of ICA showing obstructive CAD, was higher in the CT group than in the functional testing group of the PROMISE trial (72.1% vs. 47.5%) and the diagnostic yield of ICA was higher in the CT group than in the ICA group of the DISCHARGE trial (72.5% vs. 26.2%). In the PROMISE trial, the CT group had more coronary revascularizations (6.2% vs. 3.2%) at 90 days.[19] In the SCOT-HEART trial, coronary revascularization rates were initially higher than in the standard care group while overall rates were similar (12.9% vs. 13.5%) at 4.8 years.[20] In the DISCHARGE trial, the ICA group had more revascularizations (14.2% vs. 18.0%) than the CT group at median 3.5 years. In a large subgroup of 5985 patients from the PROMISE trial in whom a battery of angina and quality of life instruments were collected at baseline and at 6, 12, and 24 months, patient-reported outcomes similarly improved in the CT and the functional testing group.[24] Patients randomized to CT supplementing standard care in SCOT-HEART had smaller improvements in physical limitations, angina frequency, and quality of life at 6 months, which were attributed to the more common detection of previously undiagnosed nonobstructive CAD in the CT group. DISCHARGE found no reduction in MACE but similar patient-reported outcomes when a CT strategy, followed by functional testing and ICA if needed, was compared with an ICA strategy.[25]

† Combined Diamond and Forrester and Coronary Artery Surgery Study risk score.

‡ Predicted 10-yr coronary heart disease risk.

§ According to an updated Diamond and Forrester model.

Table S19. Patient-Reported Outcomes at 1.0 Year*			
Outcomes	**CT Group (N=1808)** events (estimated percentage)	**ICA Group (N=1753)**	**Effect Size (95% CI)**
After follow-up at 1.0 year†			
Angina in the last 4 weeks – no. (%)			
Yes	178/1784 (10.0)	145/1724 (8.4)	Odds Ratio, 1.20 (0.97–1.49)
Health-related quality of life			
EQ-5D visual analogue scale score‡	70.4±18.6 (n=1592)	69.9±18.1 (n=1521)	Mean Difference, -0.2017 (-1.253–0.869)
SF-12v2 Physical component summary score§	46.7±8.9 (n=1551)	46.1±9.1 (n=1489)	Mean Difference, 0.12 (-0.37–0.610)

* Plus–minus values are means±SD. CT denotes computed tomography, ICA invasive coronary angiography, EQ-5D European Quality of Life–5 Dimensions, and SF-12v2 Short Form (SF)-12v2. Patient-reported outcome measures at a median of 3.5 years (IQR, 2.9-4.2) are provided in Table 3.

† Unadjusted percentages and means±SD are displayed. Estimates of odds ratios and mean differences were derived using models with multiple imputation.

‡ On the European Quality of Life–5 Dimensions (EQ-5D) visual analogue scale, scores range from 0–100, with higher scores indicating better health status.

§ The Short Form (SF)-12v2 physical component summary scores were transformed to t-scores (0-100) with higher scores indicating better functioning and 50 being the middle of the distribution.

D. Supplementary Appendix References

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