



This is an Accepted Manuscript version of the article published originally by Radiological Society of North America, accepted for publication in the journal:

Radiology

This version may differ from the original in pagination and typographic details. When using, please cite the original.

AUTHOR(S)

Sykes, R., Collison, D., Merkely, B., Kofoed, K. F., Donnelly, P., Rodríguez-Palomares, J., Erglis, A., Veselka, J., Šakalytė, G., Ađić, N. Č., Gutberlet, M., Dodd, J. D., Diez, I., Davis, G., Zimmermann, E., Kępk, C., Vidakovic, R., Francone, M., ... Ilnicka-Suckiel, M.

TITLE

Effect of Body Mass Index on Effectiveness of CT versus Invasive Coronary Angiography in Stable Chest Pain: The DISCHARGE Trial

YEAR

2024

DOI

10.1148/radiol.230591

CITATION

Sykes, R., Collison, D., Merkely, B., Kofoed, K. F., Donnelly, P., Rodríguez-Palomares, J., Erglis, A., Veselka, J., Šakalytė, G., Ađić, N. Č., Gutberlet, M., Dodd, J. D., Diez, I., Davis, G., Zimmermann, E., Kępk, C., Vidakovic, R., Francone, M., ... Ilnicka-Suckiel, M. (2024). Effect of Body Mass Index on Effectiveness of CT versus Invasive Coronary Angiography in Stable Chest Pain: The DISCHARGE Trial. *Radiology*, 310(2). <https://doi.org/10.1148/radiol.230591>

VERSION

Accepted Manuscript

LICENSE

In Copyright © 2024 Radiology

Full Title Page

Association between Body Mass Index and Clinical Outcomes in Suspected Coronary Artery Disease – DISCHARGE Trial.

Authors: DISCHARGE Trial Group[‡].

Robert Sykes*¹, Damien Collison*^{1,2}, Bela Merkely³, Klaus F. Kofoed^{4,5}, Patrick Donnelly⁶, José Rodríguez-Palomares^{7,8}, Andrejs Erglis^{9,10}, Josef Veselka¹¹, Gintarė Šakalytė^{12,13}, Nada Čemerlić Adić^{14,15}, Matthias Gutberlet¹⁶, Jonathan D. Dodd^{17,18}, Ignacio Diez¹⁹, Gershan Davis^{20,21}, Elke Zimmermann²², Cezary Kępką²³, Radosav Vidakovic^{24,25}, Marco Francone^{26,27}, Małgorzata Ilnicka-Suckiel²⁸, Fabian Plank²⁹, Juhani Knuuti³⁰, Rita Faria³¹, Stephen Schröder³², Colin Berry^{1,2}, Luca Saba³³, Balazs Ruzsics^{34,35}, Nina Rieckmann³⁶, Christine Kubiak³⁷, Kristian Schultz Hansen³⁸, Jacqueline Müller-Nordhorn³⁹, Pál Maurovich-Horvat^{3,40}, Andreas D. Knudsen^{4,5}, Imre Benedek⁴¹, Clare Orr⁶, Filipa Xavier Valente^{7,8}, Ligita Zvaigzne⁴², Martin Horváth¹¹, Antanas Jankauskas^{43,44}, Filip Adić^{14,15}, Michael Woinke⁴⁵, Stephen Keane⁴⁶, Iñigo Lecumberri⁴⁷, Erica Thwaite⁴⁸, Michael Laule⁴⁹, Mariusz Kruk²³, Aleksandra Zivanic²⁴, Massimo Mancone⁵⁰, Donata Kuśmierz⁵¹, Gudrun Feuchtner⁵², Mikko Pietilä^{53,54}, Vasco Gama Ribeiro³¹, Tanja Drosch³², Christian Delles¹, Michele Porcu⁵⁵, Michael Fisher^{34,35,56}, Tamás Bárány³, Charlotte Sørum⁵⁷, Rosca Aurelian⁵⁸, Stephanie Kelly⁶, Bruno Garcia del Blanco^{7,8}, Ainhoa Rubio¹⁹, Bálint Szilveszter³, Jawdat Abdulla⁵⁹, Ioana Rodean⁴¹, Susan Regan⁶, Hug Cuéllar Calabria⁶⁰, Milán Vecsey-Nagy³, Birgit Jurlander⁶¹, Roxana Hodas⁶², Sarah Feger²², Mahmoud Mohamed²², Lina M. Serna-Higuaita⁶⁵, Konrad Neumann⁶⁶, Henryk Dreger^{49,63}, Matthias Rief²², Viktoria Wieske²², Maros Ferencik⁶⁷, Melanie Estrella²², Maria Bosserd²², Peter Martus⁶⁵, Theodora Benedek^{**62,68}, Marc Dewey^{**22,63,64,69,70}.

*Joint first authors: contributed equally. **Joint senior authors: contributed equally.

[‡]The complete list of authors and affiliations is provided in the supplement.

Corresponding author:

Professor Marc Dewey, Heisenberg Professor of Radiology, Charité – Universitätsmedizin Berlin
Campus Mitte. Charitéplatz 1, 10117 Berlin, Germany. Corresponding author email address:

Marc.Dewey@charite.de; telephone: +49 30 450527353.

Funding Statement: This study was funded by grants from the EU-FP7 Framework Program (FP 2007-2013, EC-GA 603266) to MD and others (Berlin Institute of Health (grant from Digital Health Accelerator); British Heart Foundation (Centre of Research Excellence RE/18/6/34217); Rigshospitalet, University of Copenhagen (grant and nonfinancial support); and German Research Foundation (grants from Radiomics Priority Programme: DE 1361/19-1 [428222922] and 20-1 [428223139] in SPP2177/1) and grants from the BIOQIC graduate program (GRK 2260/1 [289347353]). The DISCHARGE trial is associated with and endorsed by DZHK (German Centre for Cardiovascular Research and we greatly acknowledge this collaborative network.

Article Type

Original research

Word Count: Abstract – 298; Main – 2,748

Data Sharing Statement: Data collected for our study will be made available to others in the form of partial data sets including individual participant data that underlie the results reported in this article after deidentification (text, tables, figures and appendices). Study center individual patient data will not be disclosed because of the possibility of re-identification of patients. Researchers who wish to access data should send an email to discharge.eu@charite.de. To gain access, requestors will have to sign a data sharing agreement. Data availability will begin 12 months after publication and end 3 years after publication. Data will be shared with researchers who provide a methodologically sound proposal approved by the Dissemination Committee of the DISCHARGE trial. The study proposal must include: The proposed study's overview, rationale, aims and analysis methods, plans for dissemination of results and names of those wishing to access data, and how is the data going to be stored and for how long. Proposals must not infringe the rights of the DISCHARGE investigators to perform their predefined primary and secondary outcomes analyses and publications as laid out in the Consortium Agreement with the European Commission and listed at <https://clinicaltrials.gov/>

ct2/show/NCT02400229 or the Statistical Analysis Plan. Data will principally be made available for individual participant data for systematic reviews and meta-analysis. To be eligible for a request, IPD meta-analyses need to be registered on PROSPERO, have a study protocol that follows the PRISMA-P guideline and checklist, and will publish their results following the PRISMA-IPD statement. If the proposal is for collaborative analysis of data from several trials, the DISCHARGE trialists request to be considered as authors based on the proportion of patients provided for such an analysis and according to ICMJE authorship criteria.

Abbreviated Title page

Association between Body Mass Index and Clinical Outcomes in Suspected Coronary Artery Disease – DISCHARGE Trial

Article type: original research

Summary Statement

Body mass index does not influence major adverse cardiovascular events and major procedure-related complications in patients with suspected coronary artery disease investigated by CT compared with invasive coronary angiography.

Key Results

- At a median follow-up of 3.5 years, the effects across body mass index groups of CT vs. invasive coronary angiography were comparable for major adverse cardiovascular events;
- Expanded major adverse cardiovascular events and major procedural complications were lower with a CT-first strategy.
- This suggests that body mass index does not influence the overall benefit of CT over invasive coronary angiography, reducing the 3.5-year expanded major adverse cardiovascular events events and major procedural complications.

List of Abbreviations

BMI, body mass index; CAD, coronary artery disease; HR, hazard ratio; ICA, invasive coronary angiography; MACE, major adverse cardiovascular events; OR, odds ratio; TIA, transient ischemic attack.

Abstract

Background. Recent trials support the role of cardiac CT (CT) in the evaluation of symptomatic patients with suspected coronary artery disease (CAD).

Purpose. To investigate the comparative effectiveness of CT to invasive coronary angiography (ICA) by body mass index (BMI) category in patients with stable chest pain.

Materials and Methods. This is a prespecified subgroup analysis of the pragmatic, multicenter, prospective, randomized DISCHARGE study of CT vs ICA in patients with suspected CAD (ClinicalTrials.gov number, NCT02400229). The primary endpoint was MACE including cardiovascular death, nonfatal myocardial infarction, or stroke. A key secondary endpoint was an expanded MACE composite including transient ischemic attack and major procedure-related complications.

Results. Among 3457 of 3561 participants with complete data enrolled between October 3, 2015, and April 12, 2019, 831 (24.0%), 1358 (39.3%) and 1268 (36.7%) had a BMI < 25, between 25 and 30 and > 30 kg/m², respectively. No interaction was found between CT, ICA and BMI for MACE ($P = 0.29$), the expanded MACE composite ($P = 0.25$), or major procedure-related complications ($P = 0.60$). At a median follow-up of 3.5 years (25th-75th percentile 2.9-4.2), in participants with BMI > 30 kg/m², the CT group had fewer nonfatal strokes (1 (0.2%) vs 8 (1.3%); HR 0.12 (95% CI, 0.02–0.97); $P = 0.05$) than participants in the ICA group. Expanded MACE composite events (16 (2.5%) vs 30 (4.7%); HR 0.51 (95% CI, 0.28–0.93); $P = 0.03$) and major procedure-related complications during initial management were less frequent in the CT compared to ICA group in all BMI subgroups.

Conclusion. There was no significant difference in outcomes between CT and invasive coronary angiography across the three BMI subgroups. Our findings support evidence that BMI does not influence the overall benefit of CT over invasive coronary angiography, on expanded MACE and major procedure-related complications.

Trial Registration: ClinicalTrials.gov number, NCT02400229.

Funding Statement: This study was funded by grants from the EU-FP7 Framework Program (FP 2007-2013, EC-GA 603266 in HEALTH.2013.2.4.2-2) to MD and others (Berlin Institute of Health (grant from Digital Health Accelerator); British Heart Foundation (Centre of Research Excellence

RE/18/6/34217); Rigshospitalet, University of Copenhagen (grant and nonfinancial support); and German Research Foundation (grants from Radiomics Priority Programme: DE 1361/19-1 [428222922] and 20-1 [428223139] in SPP2177/1), GUIDE-IT (DE 1361/24-1), Berlin University Alliance (GC_SC_PC 27), Berlin Institute of Health (Digital Health Accelerator) and grants from the BIOQIC graduate program (GRK 2260/1 [289347353]). The DISCHARGE trial is associated with and endorsed by DZHK (German Centre for Cardiovascular Research and we greatly acknowledge this collaborative network.

Introduction

Obesity is a major risk factor for ischemic heart disease and is commonly found in patients presenting with stable chest pain (1). Obesity-related multimorbidity negatively impacts on cardiovascular and all-cause morbidity and mortality (2). Obesity often limits exercise tolerance but also reduces the reliability of imaging methods, complicating the diagnostic workup of stable chest pain and potentiating suboptimal management of these high-risk patients (1,3). During invasive management using femoral artery access, extremes of body weight increase the likelihood of bleeding complications (4–6). Body weight extremes are also associated with vascular complications following femoral artery access, and radial artery access is now recommended in clinical guidelines (6,7).

DISCHARGE was a prospective, multicenter, international, pragmatic clinical trial investigating the comparative effectiveness of the management of patients with stable chest pain and an indication for invasive coronary angiography (ICA) using either cardiac CT or ICA. During a median of 3.5 years follow-up, major adverse cardiovascular events (MACE) were similar in the two groups (8). The influence of body mass index (BMI) on the comparative effectiveness of these strategies is uncertain.

Prior investigations have demonstrated that BMI exerts a detrimental influence on the quality of cardiac CT images (9). The DISCHARGE trial presents a unique opportunity to investigate a CT-first vs an ICA-first test strategy and clinical outcomes, stratified by BMI, across a median follow-up period of 3.5 years. The pre-established endpoint of interest is the comparative efficacy of CT-based initial assessment versus ICA-based initial assessment, categorized by BMI at baseline.

Materials and Methods

Study Design and Participants

The study design, methods and statistical analysis plan have been published previously, and further detail is provided in the Supplement (8,10). Briefly, DISCHARGE was an investigator-initiated, pragmatic, assessor-blinded, randomized, multicenter trial of the comparative effectiveness of CT-guided versus ICA-guided management in patients with stable chest pain and a calculated intermediate pretest probability of obstructive coronary artery disease (CAD) referred for ICA. The study was funded by the European Union (EU-FP7 Framework Programme) and conducted at 26 clinical centers in 16 European countries following standard operating procedures under strict quality control according to good clinical practice. The study was approved by local or national ethics committees responsible for each participating center. The study was conducted and reported according to the CONSORT standards.

Patients aged 30 years and above, clinically referred for ICA because of stable chest pain in accordance with the European Society of Cardiology guidelines, were eligible for inclusion if they had a calculated intermediate clinical pre-test probability (10-60%) of obstructive CAD and no prior history of coronary revascularization (11–14). Exclusion criteria were hemodialysis, non-sinus rhythm and pregnancy. All participants provided written informed consent.

Randomization and Study Procedures

Participants were randomly allocated using a web-based block randomization system (SecuTrial ®) to either initial CT or initial ICA (ICA group) on a 1:1 basis. The CT and ICA protocols are described in the Supplement. Participants and physicians could not be blinded to the study assignment. Obstructive coronary disease was defined as at least one $\geq 50\%$ coronary artery luminal diameter stenosis, and defined as high-risk anatomy in the presence of 3-vessel CAD, left main stem or proximal left anterior descending artery obstructive CAD. Management recommendations followed contemporary guidelines as described in the study design and protocol (10–13). Patient management decisions were made by the local study site heart team members and referring physicians based on the CT and ICA reports. Participants randomized to CT as the initial test

underwent subsequent management according to the DISCHARGE CT-guided strategy protocol (8). In both randomization groups, participants without obstructive CAD by ICA or CT were discharged back to the referring physician, and participants with obstructive CAD were managed according to guidelines (11,12,15). Further recommendations included prescription of anti-anginal medication, additional invasive or noninvasive functional testing and coronary revascularization as appropriate. It was recommended that participants in both randomized groups be treated to target values for blood pressure, glycemia and lipids according to European guidelines on cardiovascular disease prevention (11).

CT and ICA protocol

CT was performed using at least 64-slice CT scanners following a 10-step acquisition guide and scanner-specific recommendations to identify coronary artery disease (10). ICA was performed at each participating center by trained interventional cardiologists (10,15). CT was evaluated by experienced local readers with SCCT level II or III certification.

Primary and Secondary Endpoints

The primary endpoint of this prespecified BMI analysis was major adverse cardiovascular events (MACE) as outlined in Table 3 of the statistical analysis plan, indicated on <https://clinicaltrials.gov/ct2/show/NCT02400229> (item 125), and defined as a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke(8). Events were adjudicated by independent assessors blinded to the study group assignment.

Key secondary endpoints included an expanded MACE composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack (TIA) or major procedure-related complication (as defined in the Supplement) occurring during or within 48 hours after CT, ICA or related tests. Complications were classified according to the NCDR®CathPCI Registry®v4.4 Coder's Data Dictionary. The CONSORT Extension for Harms was adhered to(16).

Statistical Analysis

The sample size estimation of the trial and statistical analysis plan has been published previously and was calculated to compare ICA vs CT-guided management to the first occurrence of a MACE(8,10). In this prespecified analysis, we assessed the associations of BMI category (< 25

kg/m², 25-30 kg/m² and > 30 kg/m²) at baseline with the primary and secondary outcomes of the DISCHARGE trial as well as interactions between BMI category and study arms. A *post hoc* power calculation for the primary outcome, MACE, was done using the R software version 4.1 (package powerSurvEpi). The power calculation was based on a Cox proportional hazard regression test for a fixed sample of 3,457 participants in the DISCHARGE trial (ICA/BMI ≤ 30 kg/m²: 1083, CT/ BMI ≤ 30 kg/m²: 1106, ICA/ BMI > 30 kg/m²: 630, CT/BMI > 30 kg/m²: 638. For MACE, which occurred in a total of 87 participants, a quotient of HR of 0.285 was required to achieve 80% power.

Categorical variables were compared using the Chi-square or Fisher's exact test. Continuous variables were compared using the independent samples Student's t-test (or analysis of variance test for 3-group comparisons) or the Mann-Whitney U-test for nonparametric data (or Kruskal-Wallis test for 3-group comparisons). Ordinal variables were compared using the linear-by-linear association test.

A subdistribution Cox proportional hazard model was used to test the heterogeneity of the effect of CT/ICA across BMI subgroups. The models included the variables initial-CT/initial-ICA strategy, BMI groups and the interaction between test type (CT/ICA) and BMI groups. Subgroup analyses were conducted to investigate the influence of BMI on initial-CT/initial-ICA strategy. Participants were as assigned to one of three BMI categories: < 25 kg/m², 25-30 kg/m² and > 30 kg/m². Results are reported as hazard ratios and 95% confidence intervals. Multivariable logistic regression analysis evaluated the relationship between major procedure-related complications, BMI and randomized group (CT vs ICA). Odds ratio (OR) and 95% confidence intervals (CI) were estimated.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc.), SPSS for Windows version 26 (IBM) and the statistical programming language R version 4.0.3. Statistical significance was defined as a two-sided P value of less than 0.05, applying adjustment for multiple hypothesis testing as appropriate. All analyses were performed on the intention-to-treat population.

Results

Baseline Characteristics

Figure 1 provides a flowchart of participants included in this analysis. Of 3,561 participants, 3,457 with complete data were included in this pre-specified analysis^{8,19}. Among these, 24.0% (831) had a BMI < 25 kg/m², 39.3% (1358) had a BMI between 25-30 kg/m², and 36.7% (1268) had a BMI > 30 kg/m² (Table 1). BMI was associated with increased age, female sex, and higher pretest probability of CAD. There was a higher prevalence of hypertension and diabetes mellitus and cardiovascular medications with increasing BMI whereas cigarette smoking status was associated with a lower BMI.

Noninvasive functional tests performed before the assigned intervention were undertaken less often in participants with a higher BMI, particularly in those with BMI > 30 kg/m², and the proportion of positive tests was lower (Table 1). Health-related quality of life reflected by the Physical Component Score of the SF12v2 questionnaire was lower with increasing BMI.

Comparison of Diagnostic Strategies during Initial Care

Compared to the CT group, the time from enrolment to initial test (days) was longer in the ICA group, and this difference was consistent across the three BMI subgroups (Table 2). Differences in diagnostic findings between CT and ICA groups were largely consistent across the BMI subgroups. Nondiagnostic findings were more common in the CT-guided group, and this was the case in each of the BMI categories (< 25 kg/m² – ICA: 0.20% vs. CT: 5.10%; 25-30 kg/m² – ICA: 0.30% vs. CT 4.00%; > 30 kg/m² – ICA: 0.30% vs. CT: 7.10%).

Clinical Outcomes

No significant interaction between CT, ICA and BMI was found with respect to MACE ($P = 0.29$), the expanded MACE secondary endpoint ($P = 0.25$) or major procedure-related complications ($P = 0.60$). During the study period, 87 MACE and 126 expanded MACE events were observed. The 3.5-year cumulative incidence of expanded MACE was 2.2% and 3.3% in the initial-CT and initial-ICA group, respectively. The incidence of MACE and expanded MACE at 3 and 4 years was greater in the ICA-first strategy/BMI subgroup < 25 kg/m² (MACE – 3 years: ICA: 2.26% vs CT: 0.99%, 4

years: ICA: 2.99% vs. CT: 1.84%; Expanded MACE – 3 years: ICA 4.65% vs. CT: 1.74%, 4 years: ICA: 5.38% vs. CT: 3.05%) and the ICA-first strategy/ BMI subgroup > 30 kg/m² (MACE – 3 years: ICA: 3.35% vs CT: 1.31%, 4 years: ICA: 4.10% vs. CT: 2.26%; Expanded MACE – 3 years: ICA: 5.39% vs. CT: 2.98%) ([Appendix Tables 1 and 2](#)).

The results for the primary and secondary endpoints stratified by BMI and randomization group (n = 3,457) are shown in [Table 3](#) and [Figure 2](#). For the primary endpoint, MACE, the overall HR (as reported previously) for CT compared to ICA was 0.57 (95% CI: 0.21 – 1.53, *P* = 0.26), with no significant interaction between BMI groups and strategy effect (*P* values for interaction = 0.29 and 0.90, respectively) ([Appendix Table 3](#))(8). Similarly, the effect of the CT-first strategy compared to the ICA-first strategy was consistent across BMI subgroups for all composites of MACE, nonfatal myocardial infarction (*P* for interaction = 0.50 and 0.58) and cardiovascular death (*P* for interaction = 0.81 and 0.17).

For the expanded MACE composite, in participants with BMI ≥ 30 kg/m², the HR suggested a benefit for initial CT compared to initial ICA (HR: 0.51; 95% CI: 0.28 – 0.93); however, there was no evidence of an association between CT-first/ICA-first strategy, BMI groups and expanded MACE composite events (*P* values for interaction = 0.25 and 0.92).

Major procedure-related complications during initial management were less frequent in the CT compared to ICA group (HR: 0.25; 95% CI: 0.06 – 0.80, *P* = 0.034). There was no evidence that the effect differed across subgroups (low BMI (< 25 kg/m²) subgroup (n (%); (3 (0.7%) vs 12 (2.9%); HR: 0.25; 95% CI: (0.06 – 0.80)), BMI 25–30 kg/m² subgroup (5 (0.7%) vs 12 (1.8%); HR: 0.39; 95% CI: (0.12 – 1.06) and BMI > 30 kg/m² subgroup (1 (0.2%) vs 9 (1.4%); HR: 0.11; 95% CI: (0.01 – 0.58) (*P* values for interaction 0.60 and 0.49) ([Figure 3](#) and [Appendix Tables 3 and 4](#)).

Discussion

In this prespecified analysis, we found no evidence of effect heterogeneity between CT- versus invasive coronary angiography guided management in participants with suspected coronary artery disease, regarding the risk of expanded major adverse cardiovascular events and major procedural

complications according to body mass index subgroups. However, in the group with a body mass index $> 30 \text{ kg/m}^2$, CT-guided management was associated with a lower incidence of nonfatal strokes and the expanded major adverse cardiovascular events secondary endpoint (including transient ischemic attacks and major procedure-related complications) compared with invasive coronary angiography.

This clinical trial involved comparisons of initial invasive versus noninvasive management strategies. Cardiac CT is considered a safe gatekeeper to ICA with fewer complications, and is preferred by patients, but BMI-related effects on MACE have not previously been explored (8,17–20). BMI can adversely affect image quality during ICA or cardiac CT, and direct comparisons between techniques have not previously been described (21). Although cardiovascular risk scores were similar, clinically obese people (BMI $> 30 \text{ kg/m}^2$) had higher rates of hypertension and diabetes, which has been reported to increase the likelihood and severity of bleeding complications following invasive management, especially when using femoral artery access compared with radial artery access (22,23). In the DISCHARGE trial, the CT-first strategy reduced the need for invasive management as only 22% of the participants in the CT group subsequently underwent invasive management (8). Furthermore, radiographic image quality may be affected in patients with extremes of BMI, limiting diagnostic accuracy and increasing the technical difficulty of percutaneous intervention. The rate of nondiagnostic CT scans in participants with BMI $> 30 \text{ kg/m}^2$ in the DISCHARGE trial was 7.1% compared with 4.0% in the BMI 25-30 kg/m^2 group, and 5.1% in participants with a BMI $< 25 \text{ kg/m}^2$.

The obesity paradox has previously been described in patients undergoing percutaneous coronary interventions (24). Obese patients may have a higher symptom burden at baseline and be younger than patients with a normal or lower BMI. The present analysis also revealed that obesity was associated with a greater proportion of high-risk clinical constellations including poor responses to medical therapy. Despite this, the number of percutaneous interventions performed between groups by BMI status was not significantly different. The nutritional status of younger obese patients and greater baseline muscle mass may offer some protection from MACE compared with older patients and those with below-normal BMI (25). However, considering traditional risk factors for adverse

cardiovascular events, obese patients were more likely to be hypertensive and insulin resistant as demonstrated in this analysis. The PROMISE trial performed a subanalysis of increasing obesity, calculated risk and outcomes and observed that, despite higher baseline risk characteristics, obese participants had a lower proportion of obstructive CAD compared to those with BMI < 30 kg/m², which translated to lower rates of adverse outcomes in obese participants (26,27). The PROMISE trial also further evaluated metabolic phenotypes in participants with and without obesity. The subanalysis observed that metabolic syndrome without obesity was associated with a greater prevalence of CAD than obesity without additional metabolic syndrome (28). Participants in the prospective Scottish Computed Tomography of the HEART (SCOT-HEART) trial with non-alcohol-related hepatic steatosis had higher BMI than those without, and the participants exhibited similar risk profiles to our analysis, with increased co-morbidity of hypertension and diabetes (29). However, despite higher prevalence of CAD in participants with hepatic steatosis, there was no difference in the rate of subsequent myocardial infarction at five years.

In the DISCHARGE trial, participants with a high BMI (> 30 kg/m²), CT-guided management was associated with a halving of the risk of the expanded MACE composite endpoint including transient ischemic attacks and major procedure-related complications. However, in participants with a low BMI (< 25 kg/m²), the odds of major procedure-related complications during initial management were four-fold lower in the CT-guided group. Invasive management by femoral or radial artery access can be technically more challenging in patients with low BMI, and a higher risk of procedure-related complications in this group has been previously described (6). Conversely, noninvasive imaging can be technically challenging in obese individuals. In our study, compared with ICA-guided management, obese participants were more likely to have nondiagnostic results following cardiac CT (7.1% vs 0.3%). This may reflect the technical challenges of achieving optimal image quality in obese individuals undergoing coronary CT.

Our study has several limitations. This analysis was conducted using prespecified BMI categories (< 25 kg/m², 25-30 kg/m² and BMI > 30 kg/m²), and therefore the analysis did not specifically assess outcomes in patients who were underweight (BMI < 18.5 kg/m²) (30). BMI was

not measured during follow-up, and may vary over time. As previously discussed (8), the event rate in DISCHARGE was lower than originally expected, potentially effecting prespecified secondary analyses.

In conclusion, BMI does not influence the overall benefit of CT-guided management compared to ICA-guided management on the risk of major procedural complications and expanded MACE. Overall, the results support the preferred use of an initial CT-guided management in all BMI subgroups of patients who have stable chest pain and an intermediate pretest probability of obstructive CAD.

Acknowledgements: We thank the clinical staff supporting the trial in the clinical centers and the core laboratories at Charité, Harold C Sox for his leadership of the external advisory board, the members of the external advisory board, the data safety and monitoring board, and the clinical events committee, as well as all participants who took part in the study.

Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: funding from the EU-FP7 Framework Program. KFK, MBosserdt, PMH, NR, TB, PD, JRP, AE, CS, GS, FA, MG, JDD, ID, GD, EZ, CKępka, RV, MFrancone, MIS, FP, JK, RF, SS, CB, LS, BR, CKubiak, KSH, JMN, BM, TSJ, IB, FXV, LZ, VS, LZ, MC, MW, SK, IL, ET, MK, ANN, MM, GF, MP, VGR, TD, CD, BL, MFischer, BS, PES, MRatiu, SK, BGB, CKragelund, IR, SR, HCC, MBoussoussou, TE, RH, AEN, RH, SF, MMAM, KN, HD, MR, VW, ME, and MD received grants from the European Commission during the conduct of the study [DISCHARGE trial (EC-GA 603266 in HEALTH.2013.2.4.2-2)]. KFK received grants and nonfinancial support from Rigshospitalet, University of Copenhagen, during the conduct of the study and grants from AP Møller og hustru Chastine McKinney Møllers Fond, the Danish Heart Foundation, the Danish Agency for Science, Technology and Innovation by the Danish Council for Strategic Research, and the Health Insurance Company Denmark and unrestricted research grants from Canon Medical Corporation and GE Healthcare outside the submitted work. PMH is a shareholder of Neumann Medical Ltd outside the submitted work. NR is principal investigator for grants (no own salary) from the German Ministry of Education and Research (NAVICARE

01GY1911) outside the submitted work. TB has received grants from the Romanian Ministry of European Funds the Romanian Government and the European Union outside the submitted work. GS has received payments or honorariums from Amgen, Astra Zeneca, Bayer, Berlin Chemie Menarini Baltic, Clinical Financial Service, IQVIA, Novartis Baltics, Sanofi Aventis, and Servier Pharma; received support for attending meetings or travel from Servier and Novartis; and participated on data safety monitoring boards or advisory boards for Boehringer Ingelheim outside the submitted work. GS is fellow of the ECS and is involved in the Lithuanian Society of Cardiology, the Lithuanian Heart Association, and the Lithuanian Hypertension Society. MG has received payments or honorariums from Bayer, Siemens, Bracco, and the German Roentgen Society (DRG) to the institution outside the submitted work. MG is a member of the Scientific Committee of the ESCR and member of the Committee of the Working Group on Cardiovascular Imaging of the German Roentgen Society (DRG). EZ has received grants from the Deutsche Forschungsgemeinschaft (Radiomics in SPP 2177/1) outside the submitted work. JK has received speaker fees from GE Healthcare, Merck, Lundbeck, Bayer, Boehringer-Ingelheim, and Pfizer and personal fees for study protocol review from AstraZeneca and GE Healthcare outside the submitted work. JK is chair of the European Society of Cardiology guidelines on chronic coronary syndrome; the work is on a voluntary basis and only remuneration of travel expenses occurs. The University of Glasgow, which employs CB, who has no personal contracts and receives no payments outside of his employment, has received in kind support for research from AstraZeneca, grant and in kind support for research and R&D consultancy funding from Abbott Vascular, a grant from GSK, in kind support for research and R&D consultancy funding from HeartFlow, educational funding from Menarini, R&D consultancy funding from Novartis, and in kind support for research from Siemens, outside the submitted work; furthermore, the University of Glasgow received research funding from the British Heart Foundation (RE/18/6/34217). BM has received personal fees from Biotronik, Medtronic, and Abbott and grants from Boston Scientific outside the submitted work. IB has received grants from the Romanian Ministry of European Funds, the Romanian Government, and the European Union outside the submitted work. MC has received direct payments from Abbott Vascular as lecturer, workshop participant as operator, and lecturer, Astra Zeneca as lecturer, and Boehringer Ingelheim, as well as payment to the institution from the

National Science Center (Poland) outside the submitted work. MK has a granted patent (EP3157444B1) and pending patents (WO2015193847A1, WO2013060883A4). CD has received grants from the British Heart Foundation (Centre of Research Excellence RE/18/6/34217) during the conduct of the study. PES has received consulting fees from Novo Nordisk outside the submitted work. MR has received grants from the Deutsche Forschungsgemeinschaft (Radiomics in SPP 2177/1) outside the submitted work. TE has received personal fees from Abbott and Bayer outside the submitted work. MD has received grant support from the German Research Foundation (DFG) [Graduate Program on Quantitative Biomedical Imaging (BIOQIC, GRK 2260/1, DFG project number: 289347353), the DFG Priority Programme Radiomics (DFG project number: 402688427) for the investigation of coronary plaque and coronary flow (DE 1361/19-1 [DFG project number: 428222922] and DE 1361/20-1 [DFG project number: 428223139] in SPP 2177/1), the GUIDE-IT project on data sharing of medical imaging trials (DE 1361/24-1 [DFG project number: 495697118]), the Quantitative Cardiovascular Imaging (QCI) meeting (DE 1361/22-1), and the Future of Medical Imaging meeting (DE 1361/28-1)], and grants from Berlin Institute of Health (Digital Health Accelerator) during the conduct of the study; grants from German Research Foundation (DFG) [Heisenberg Program (DE 1361/14-1, DFG project number: 213705389), Fractal Analysis of Myocardial Perfusion (DE 1361/18-1, DFG project number: 392304398)] and grants from Berlin University Alliance (GC_SC_PC 27) outside the submitted work MD is European Society of Radiology (ESR) Publications Chair (2022-2025); and the opinions expressed in this article are the author's own and do not represent the view of ESR. Per the guiding principles of ESR, the work as Publications Chair is on a voluntary basis and only remuneration of travel expenses occurs. MD is also the editor of Cardiac CT, published by Springer Nature, and offers hands-on courses on CT imaging (www.ct-kurs.de). Institutional master research agreements exist with Siemens, General Electric, Philips, and Canon. The terms of these arrangements are managed by the legal department of Charité – Universitätsmedizin Berlin. MD holds a joint approved patent with Florian Michallek on dynamic perfusion analysis using fractal analysis (EPO 2022 EP3350773A1, and USPTO 2021 10,991,109).

References

1. Cortez RM, Okoshi MP, Okoshi K. A Review of the Roles and Limitations of Noninvasive Imaging Methods for Investigating Cardiovascular Disease in Individuals with Obesity. *Med Sci Monit Int Med J Exp Clin Res.* 2022;28:e937362. doi: 10.12659/MSM.937362.
2. Pollack LM, Wang M, Leung MYM, Colditz G, Herrick C, Chang S-H. Obesity-related multimorbidity and risk of cardiovascular disease in the middle-aged population in the United States. *Prev Med.* 2020;139:106225. doi: 10.1016/j.ypmed.2020.106225.
3. Bigvava T, Zamani SM, Pieske-Kraigher E, Gebker R, Pieske B, Kelle S. Prognostic value of non-invasive stress testing for coronary artery disease in obese patients. *Expert Rev Cardiovasc Ther.* 2015;13(12):1325–1332. doi: 10.1586/14779072.2015.1102054.
4. Kim M, Kim M-A, Kim H-L, et al. Body mass index and the risk of low femoral artery puncture in coronary angiography under fluoroscopy guidance. *Medicine (Baltimore).* 2018;97(9):e0070. doi: 10.1097/MD.00000000000010070.
5. Berry C, Kelly J, Cobbe SM, Eteiba H. Comparison of femoral bleeding complications after coronary angiography versus percutaneous coronary intervention. *Am J Cardiol.* 2004;94(3):361–363. doi: 10.1016/j.amjcard.2004.04.036.
6. Cox N, Resnic FS, Popma JJ, Simon DI, Eisenhauer AC, Rogers C. Comparison of the risk of vascular complications associated with femoral and radial access coronary catheterization procedures in obese versus nonobese patients. *Am J Cardiol.* 2004;94(9):1174–1177. doi: 10.1016/j.amjcard.2004.07.088.

7. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165. doi: 10.1093/eurheartj/ehy394.
8. DISCHARGE Trial Group, Maurovich-Horvat P, Bossert M, et al. CT or Invasive Coronary Angiography in Stable Chest Pain. *N Engl J Med*. 2022;386(17):1591–1602. doi: 10.1056/NEJMoa2200963.
9. Dewey M, Vavere AL, Arbab-Zadeh A, et al. Patient characteristics as predictors of image quality and diagnostic accuracy of MDCT compared with conventional coronary angiography for detecting coronary artery stenoses: CORE-64 Multicenter International Trial. *AJR Am J Roentgenol*. 2010;194(1):93–102. doi: 10.2214/AJR.09.2833.
10. Napp AE, Haase R, Laule M, et al. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. *Eur Radiol*. 2017;27(7):2957–2968. doi: 10.1007/s00330-016-4620-z.
11. Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949–3003. doi: 10.1093/eurheartj/eh296.
12. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special

- contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35(37):2541–2619. doi: 10.1093/eurheartj/ehu278.
13. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33(13):1635–1701. doi: 10.1093/eurheartj/ehs092.
 14. Haase R, Schlattmann P, Gueret P, et al. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data. *BMJ*. 2019;365:11945. doi: 10.1136/bmj.11945.
 15. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol*. 1999;33(6):1756–1824. doi: 10.1016/s0735-1097(99)00126-6.
 16. Ioannidis JPA, Evans SJW, Gøtzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004;141(10):781–788. doi: 10.7326/0003-4819-141-10-200411160-00009.
 17. Dewey M, Rief M, Martus P, et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. *BMJ*. 2016;355:i5441. doi: 10.1136/bmj.i5441.

18. Bosserd M, Feger S, Rief M, et al. Performing Computed Tomography Instead of Invasive Coronary Angiography: Sex Effects in Patients With Suspected CAD. *JACC Cardiovasc Imaging*. 2020;13(3):888–889. doi: 10.1016/j.jcmg.2019.10.014.
19. Schönenberger E, Martus P, Bosserd M, et al. Kidney Injury after Intravenous versus Intra-arterial Contrast Agent in Patients Suspected of Having Coronary Artery Disease: A Randomized Trial. *Radiology*. Radiological Society of North America; 2019;292(3):664–672. doi: 10.1148/radiol.2019182220.
20. DISCHARGE Trial Group. Comparative effectiveness of initial computed tomography and invasive coronary angiography in women and men with stable chest pain and suspected coronary artery disease: multicentre randomised trial. *BMJ*. British Medical Journal Publishing Group; 2022;379:e071133. doi: 10.1136/bmj-2022-071133.
21. Gorenai V, Schönermark MP, Hagen A. CT coronary angiography vs. invasive coronary angiography in CHD. *GMS Health Technol Assess*. 2012;8:Doc02. doi: 10.3205/hta000100.
22. Andersen K, Bregendahl M, Kaestel H, Skriver M, Ravkilde J. Haematoma after coronary angiography and percutaneous coronary intervention via the femoral artery frequency and risk factors. *Eur J Cardiovasc Nurs*. 2005;4(2):123–127. doi: 10.1016/j.ejcnurse.2005.02.003.
23. Hayıroğlu Mİ, Çınar T, Bıçakçı B, et al. Predictors of femoral hematoma in patients undergoing elective coronary procedure: a trigonometric evaluation. *Int J Cardiovasc Imaging*. 2018;34(8):1177–1184. doi: 10.1007/s10554-018-1339-8.

24. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol.* 2002;39(4):578–584. doi: 10.1016/s0735-1097(01)01802-2.
25. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. *Diabetes Care.* 2013;36 Suppl 2:S276-281. doi: 10.2337/dcS13-2023.
26. Litwin SE, Coles A, Hill CL, et al. Discordances between predicted and actual risk in obese patients with suspected cardiac ischaemia. *Heart Br Card Soc.* 2020;106(4):273–279. doi: 10.1136/heartjnl-2018-314503.
27. Litwin SE, Coles A, Pagidipati N, et al. Effects of obesity on noninvasive test results in patients with suspected cardiac ischemia: Insights from the PROMISE trial. *J Cardiovasc Comput Tomogr.* 2019;13(4):211–218. doi: 10.1016/j.jcct.2019.03.010.
28. Kammerlander AA, Mayrhofer T, Ferencik M, et al. Association of Metabolic Phenotypes With Coronary Artery Disease and Cardiovascular Events in Patients With Stable Chest Pain. *Diabetes Care.* 2021;44(4):1038–1045. doi: 10.2337/dc20-1760.
29. Carter J, Heseltine TD, Meah MN, et al. Hepatosteatosis and Atherosclerotic Plaque at Coronary CT Angiography. *Radiol Cardiothorac Imaging.* 2022;4(2):e210260. doi: 10.1148/ryct.210260.
30. CDC. Assessing Your Weight. *Cent. Dis. Control Prev.* 2022. <https://www.cdc.gov/healthyweight/assessing/index.html>. Accessed October 29, 2022.

Table 1. Baseline characteristics stratified by BMI group and initial test strategy (CT vs ICA)

	< 25 kg/m ²	25-30 kg/m ²	> 30 kg/m ²	P value	< 25 kg/m ²		25-30 kg/m ²		> 30 kg/m ²	
	(n=831)	(n=1358)	(n=1268)		CT (n=409)	ICA (n=422)	CT (n=697)	ICA (n=661)	CT (n=638)	ICA (n=630)
Age	60.8 (10.8)	60.7 (10.1)	59.0 (9.68)	<0.001 ^{Anova}	61.0 (11.1)	60.6 (10.6)	60.9 (9.99)	60.6 (10.2)	58.8 (9.89)	59.2 (9.46)
Women	532 (64.0%)	695 (51.2%)	713 (56.2%)	<0.001 ^{Chi2}	262 (64.1%)	270 (64.0%)	344 (49.4%)	351 (53.1%)	375 (58.8%)	338 (53.7%)
Men	299 (36.0%)	663 (48.8%)	555 (43.8%)		147 (35.9%)	152 (36.0%)	353 (50.6%)	310 (46.9%)	263 (41.2%)	292 (46.3%)
In- and outpatients at time of trial enrollment										
Inpatients	202 (24.3%)	304 (22.4%)	224 (17.7%)	<0.001 ^{Chi2}	89 (21.8%)	113 (26.8%)	163 (23.4%)	141 (21.3%)	111 (17.4%)	113 (17.9%)
Outpatients	600 (72.2%)	1013 (74.6%)	1011 (79.7%)		304 (74.3%)	296 (70.1%)	514 (73.7%)	499 (75.5%)	514 (80.6%)	497 (78.9%)
Missing	29 (3.5%)	41 (3.0%)	33 (2.6%)		16 (3.9%)	13 (3.1%)	20 (2.9%)	21 (3.2%)	13 (2.0%)	20 (3.2%)
Pretest probability‡	36.8 (11.0)	38.5 (10.9)	37.3 (10.5)	<0.001 ^{Chi2}	36.5 (11.0)	37.0 (11.0)	38.6 (11.0)	38.3 (10.8)	36.4 (10.6)	38.2 (10.4)
Type of chest pain										
Typical angina	119 (14.3%)	161 (11.9%)	205 (16.2%)	0.023 ^{Chi2}	50 (12.2%)	69 (16.4%)	73 (10.5%)	88 (13.3%)	96 (15.0%)	109 (17.3%)
Atypical angina	392 (47.2%)	618 (45.5%)	593 (46.8%)		199 (48.7%)	193 (45.7%)	321 (46.1%)	297 (44.9%)	295 (46.2%)	298 (47.3%)
Nonanginal chest pain	299 (36.0%)	539 (39.7%)	437 (34.5%)		150 (36.7%)	149 (35.3%)	275 (39.5%)	264 (39.9%)	230 (36.1%)	207 (32.9%)
Other chest pain	21 (2.5%)	40 (2.9%)	33 (2.6%)		10 (2.4%)	11 (2.6%)	28 (4.0%)	12 (1.8%)	17 (2.7%)	16 (2.5%)
ICA referral categories§										
Clinical constellation suggesting high event risk, particularly with inadequate response to medical treatment	341 (41.0%)	612 (45.1%)	652 (51.4%)	<0.001 ^{LL}	172 (42.1%)	169 (40.0%)	322 (46.2%)	290 (43.9%)	335 (52.5%)	317 (50.3%)
Severe angina, particularly with inadequate response to medical treatment	165 (19.9%)	274 (20.2%)	293 (23.1%)		79 (19.3%)	86 (20.4%)	128 (18.4%)	146 (22.1%)	138 (21.6%)	155 (24.6%)
Intermediate pretest probability of CAD or LVEF < 50% without typical angina after functional testing showing ischemia	156 (18.8%)	222 (16.3%)	157 (12.4%)		80 (19.6%)	76 (18.0%)	105 (15.1%)	117 (17.7%)	83 (13.0%)	74 (11.7%)
Low or intermediate event risk with inadequate response to medical treatment	100 (12.0%)	156 (11.5%)	104 (8.2%)		47 (11.5%)	53 (12.6%)	88 (12.6%)	68 (10.3%)	52 (8.2%)	52 (8.3%)
Intermediate pretest probability or LVEF < 50% without typical angina after nondiagnostic functional testing	32 (3.9%)	41 (3.0%)	29 (2.3%)		12 (2.9%)	20 (4.7%)	20 (2.9%)	21 (3.2%)	19 (3.0%)	10 (1.6%)
Other¶	35 (4.2%)	44 (3.2%)	31 (2.4%)		18 (4.4%)	17 (4.0%)	29 (4.2%)	15 (2.3%)	11 (1.7%)	20 (3.2%)
Missing	2 (0.2%)	9 (0.7%)	2 (0.2%)		1 (0.2%)	1 (0.2%)	5 (0.7%)	4 (0.6%)	0 (0%)	2 (0.3%)
Cardiovascular risk factors										

Hypertension	382 (46.0%)	806 (59.4%)	883 (69.6%)	<0.001 ^{Chi}	196 (47.9%)	186 (44.1%)	422 (60.5%)	384 (58.1%)	447 (70.1%)	436 (69.2%)
Missing	0 (0%)	4 (0.3%)	2 (0.2%)		0 (0%)	0 (0%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Diabetes mellitus	72 (8.7%)	186 (13.7%)	283 (22.3%)	<0.001 ^{Chi}	35 (8.6%)	37 (8.8%)	84 (12.1%)	102 (15.4%)	133 (20.8%)	150 (23.8%)
Missing	3 (0.4%)	4 (0.3%)	2 (0.2%)		0 (0%)	3 (0.7%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Hyperlipidemia	383 (46.1%)	652 (48.0%)	630 (49.7%)	0.27 ^{Chi}	203 (49.6%)	180 (42.7%)	329 (47.2%)	323 (48.9%)	313 (49.1%)	317 (50.3%)
Missing	0 (0%)	3 (0.2%)	2 (0.2%)		0 (0%)	0 (0%)	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Peripheral artery disease	16 (1.9%)	16 (1.2%)	15 (1.2%)	0.27 ^{Chi}	7 (1.7%)	9 (2.1%)	9 (1.3%)	7 (1.1%)	6 (0.9%)	9 (1.4%)
Valve disease	50 (6.0%)	72 (5.3%)	64 (5.0%)	0.61 ^{Chi}	19 (4.6%)	31 (7.3%)	42 (6.0%)	30 (4.5%)	31 (4.9%)	33 (5.2%)
Missing	0 (0%)	4 (0.3%)	2 (0.2%)		0 (0%)	0 (0%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Stroke	21 (2.5%)	39 (2.9%)	29 (2.3%)	0.63 ^{Chi}	11 (2.7%)	10 (2.4%)	24 (3.4%)	15 (2.3%)	10 (1.6%)	19 (3.0%)
Missing	0 (0%)	4 (0.3%)	2 (0.2%)		0 (0%)	0 (0%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Transient ischemic attack (TIA)	18 (2.2%)	22 (1.6%)	26 (2.1%)	0.60 ^{Chi}	9 (2.2%)	9 (2.1%)	12 (1.7%)	10 (1.5%)	11 (1.7%)	15 (2.4%)
Missing	0 (0%)	4 (0.3%)	2 (0.2%)		0 (0%)	0 (0%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Prolonged ischemic neurological deficit	1 (0.1%)	4 (0.3%)	0 (0%)	0.136 ^{Chi}	0 (0%)	1 (0.2%)	2 (0.3%)	2 (0.3%)	0 (0%)	0 (0%)
Missing	0 (0%)	4 (0.3%)	2 (0.2%)		0 (0%)	0 (0%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Carotid artery disease	21 (2.5%)	31 (2.3%)	27 (2.1%)	0.84 ^{Chi}	8 (2.0%)	13 (3.1%)	19 (2.7%)	12 (1.8%)	10 (1.6%)	17 (2.7%)
Missing	0 (0%)	4 (0.3%)	2 (0.2%)		0 (0%)	0 (0%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Family history of premature CAD (women)	156/532 (29.3%)	243/692 (35.1%)	249/712 (35.0%)	0.059 ^{Chi}	74/262 (28.2%)	82/270 (30.4%)	119/342 (34.8%)	124 (350) (35.4%)	122/374 (32.6%)	127/338 (37.6%)
Family history of premature CAD (men)	80/299 (26.8%)	180/662 (27.2%)	140/554 (25.3%)	0.742 ^{Chi}	33/147 (22.4%)	47/152 (30.9%)	89/352 (25.3%)	91/310 (29.4%)	69/263 (26.2%)	71/291 (24.4%)
Missing	0 (0%)	4 (0.3%)	2 (0.2%)		0 (0%)	0 (0%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Pulmonary risk factors										
Asthma	52 (6.3%)	81 (6.0%)	74 (5.8%)	0.92 ^{Chi}	27 (6.6%)	25 (5.9%)	48 (6.9%)	33 (5.0%)	42 (6.6%)	32 (5.1%)
Chronic obstructive pulmonary disease	47 (5.7%)	43 (3.2%)	59 (4.7%)	0.016 ^{Chi}	24 (5.9%)	23 (5.5%)	14 (2.0%)	29 (4.4%)	32 (5.0%)	27 (4.3%)
Missing	3 (0.4%)	4 (0.3%)	2 (0.2%)		0 (0%)	3 (0.7%)	3 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Cigarette smokers										
Current smokers	198 (23.8%)	232 (17.1%)	206 (16.2%)	<0.001 ^{Chi}	103 (25.2%)	95 (22.5%)	134 (19.2%)	98 (14.8%)	104 (16.3%)	102 (16.2%)
Former smokers	224 (27.0%)	459 (33.8%)	409 (32.3%)		103 (25.2%)	121 (28.7%)	228 (32.7%)	231 (34.9%)	189 (29.6%)	220 (34.9%)
Never smoked	382 (46.0%)	635 (46.8%)	605 (47.7%)		189 (46.2%)	193 (45.7%)	319 (45.8%)	316 (47.8%)	320 (50.2%)	285 (45.2%)
Missing	27 (3.2%)	32 (2.4%)	48 (3.8%)		14 (3.4%)	13 (3.1%)	16 (2.3%)	16 (2.4%)	25 (3.9%)	23 (3.7%)

Cardiovascular medications										
Statin	351 (42.2%)	612 (45.1%)	593 (46.8%)	0.118 ^{Chi}	182 (44.5%)	169 (40.0%)	308 (44.2%)	304 (46.0%)	290 (45.5%)	303 (48.1%)
Antiplatelet agent	384 (46.2%)	653 (48.1%)	667 (52.6%)	0.009 ^{Chi}	179 (43.8%)	205 (48.6%)	321 (46.1%)	332 (50.2%)	331 (51.9%)	336 (53.3%)
Beta-blocker	301 (36.2%)	561 (41.3%)	600 (47.3%)	<0.001 ^{Chi}	160 (39.1%)	141 (33.4%)	277 (39.7%)	284 (43.0%)	297 (46.6%)	303 (48.1%)
Nitrates	79 (9.5%)	146 (10.8%)	162 (12.8%)	0.054 ^{Chi}	48 (11.7%)	31 (7.3%)	71 (10.2%)	75 (11.3%)	80 (12.5%)	82 (13.0%)
Calcium antagonist	117 (14.1%)	278 (20.5%)	301 (23.7%)	<0.001 ^{Chi}	57 (13.9%)	60 (14.2%)	138 (19.8%)	140 (21.2%)	158 (24.8%)	143 (22.7%)
Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker	294 (35.4%)	629 (46.3%)	708 (55.8%)	<0.001 ^{Chi}	151 (36.9%)	143 (33.9%)	343 (49.2%)	286 (43.3%)	348 (54.5%)	360 (57.1%)
Missing	1 (0.1%)	6 (0.4%)	3 (0.2%)		0 (0%)	1 (0.2%)	4 (0.6%)	2 (0.3%)	2 (0.3%)	1 (0.2%)
Functional test performed before assigned intervention	298 (35.9%)	491 (36.2%)	390 (30.8%)	0.007 ^{Chi}	143 (35.0%)	155 (36.7%)	241 (34.6%)	250 (37.8%)	201 (31.5%)	189 (30.0%)
Positive results	156 (18.8%)	222 (16.3%)	157 (12.4%)	0.003 ^{Chi}	80 (19.6%)	76 (18.0%)	105 (15.1%)	117 (17.7%)	83 (13.0%)	74 (11.7%)
Negative results	110 (13.2%)	228 (16.8%)	204 (16.1%)		51 (12.5%)	59 (14.0%)	116 (16.6%)	112 (16.9%)	99 (15.5%)	105 (16.7%)
Nondiagnostic results	32 (3.9%)	41 (3.0%)	29 (2.3%)		12 (2.9%)	20 (4.7%)	20 (2.9%)	21 (3.2%)	19 (3.0%)	10 (1.6%)
Physical component score (SF12v2)	44.7 (9.47)	44.4 (8.85)	42.4 (9.22)	<0.001 ^{ANOVA}	44.5 (9.65)	44.9 (9.29)	45.0 (8.52)	43.6 (9.15)	42.7 (9.19)	42.1 (9.25)

Values are means (SDs) unless otherwise stated. CT = computed tomography angiography, ICA = invasive coronary angiography. , Chi = Chi-square test,

ANOVA = analysis of variance, LL: linear-by-linear association test.

‡ Calculated pretest probability of CAD using an automated calculation tool(14) integrated into a web-based system of the electronic case report forms, which applied an updated model of the Diamond and Forrester method using patients' age, gender, and type of stable chest pain.

§ ICA referral categories were defined according to the European guidelines for management of stable CAD(11).

|| Other ICA referral categories included a lack of ability to undergo stress imaging (4 in patients with BMI < 25 kg/m² (CT: 4 vs ICA: 0), 7 in patients with 25-30 kg/m² (CT:5 vs ICA:2) and 7 in patients with BMI > 30 kg/m² (CT:3 vs ICA: 4), an LVEF level of < 50% and typical angina (15 in patients with BMI < 25 kg/m² (CT: 8 vs ICA: 7), 10 in patients with 25-30 kg/m² (CT:4 vs ICA:6) and 10 in patients with BMI > 30 kg/m² (CT:2 vs ICA: 8), presence of mild symptoms with medical treatment and noninvasive risk stratification indicating a high event risk and consideration of revascularization for improvement of prognosis (10 in

patients with BMI < 25 kg/m² (CT: 4 vs ICA: 6), 21 in patients with 25-30 kg/m² (CT: 16 vs ICA: 5) and 12 in patients with BMI > 30 kg/m² (CT: 6 vs ICA: 6), inconclusive diagnosis on noninvasive testing or conflicting results from different noninvasive methods (5 in patients with BMI < 25 kg/m² (CT: 1 vs ICA: 4), 3 in patients with 25-30 kg/m² (CT: 0 vs ICA: 2), and employment in a special profession, such as airplane pilot, due to regulatory issues (one patient with BMI < 25 kg/m² (CT: 1 vs ICA: 0), one in patients with 25-30 kg/m² (CT: 0 vs ICA: 1) and 0 in patients with BMI > 30 kg/m² (CT: 0 vs ICA: 0).

Table 2. Comparison of diagnostic strategies during initial care.

	< 25 kg/m ²			25-30 kg/m ²			> 30 kg/m ²		
	CT (N=409)	ICA (N=422)	P value	CT (N=697)	ICA (N=661)	P value	CT (N=638)	ICA (N=630)	P value
Time from enrollment to initial test [median (IQR)] (days) *	4.00 (0-14)	11.0 (1-37)	<0.001 ^{KW}	3.00 (0-13)	11.0 (1-37)	<0.001 ^{KW}	3.00 (0-14)	11.0 (1-36)	<0.001 ^{KW}
Did not have scheduled intervention	0 (0%)	4 (0.9%)		1 (0.1%)	6 (0.9%)		4 (0.6%)	5 (0.8%)	
Diagnostic findings on assigned intervention §			<0.001 ^{Fis}			<0.001 ^{Fis}			<0.001 ^{Fis}
Obstructive CAD: ≥50% stenosis	99 (24.2%)	97 (23.0%)		191 (27.4%)	182 (27.5%)		161 (25.2%)	163 (25.9%)	
1 vessel	25 (6.1%)	38 (9.0%)		65 (9.3%)	73 (11.0%)		59 (9.2%)	67 (10.6%)	
2 vessels	18 (4.4%)	16 (3.8%)		20 (2.9%)	23 (3.5%)		21 (3.3%)	32 (5.1%)	
High-risk anatomy †	56 (13.7%)	43 (10.2%)		106 (15.2%)	86 (13.0%)		81 (12.7%)	64 (10.2%)	
Nonobstructive CAD: 1-49% stenosis	136 (33.3%)	84 (19.9%)		276 (39.6%)	146 (22.1%)		226 (35.4%)	158 (25.1%)	
No sign of CAD	152 (37.2%)	234 (55.5%)		199 (28.6%)	322 (48.7%)		199 (31.2%)	298 (47.3%)	
Nondiagnostic results ‡	21 (5.1%)	1 (0.2%)		28 (4.0%)	2 (0.3%)		45 (7.1%)	2 (0.3%)	
Missing §	1 (0.2%)	6 (1.4%)		3 (0.4%)	9 (1.4%)		7 (1.1%)	9 (1.4%)	
CT performed during initial management	407 (99.5%)	9 (2.1%)	<0.001 ^{Fis}	689 (98.9%)	13 (2.0%)	<0.001 ^{Chi}	626 (98.1%)	9 (1.4%)	<0.001 ^{Chi2}
ICA performed during initial management	82 (20.0%)	408 (96.7%)	<0.001 ^{Chi}	169 (24.2%)	645 (97.6%)	<0.001 ^{Chi}	142 (22.3%)	619 (98.3%)	<0.001 ^{Chi}
Radial artery	72 (87.8%)	351 (86.0%)		135 (79.9%)	563 (87.3%)		125 (88.0%)	566 (91.4%)	
Femoral artery	9 (11.0%)	50 (12.3%)		31 (18.3%)	71 (11.0%)		16 (11.3%)	43 (6.9%)	
Other artery or missing data **	1 (1.2%)	7 (1.7%)		3 (1.8%)	11 (1.7%)		1 (0.7%)	10 (1.6%)	
PCI during initial management	39 (9.5%)	56 (13.3%)	0.114 ^{Chi}	79 (11.3%)	105 (15.9%)	0.018 ^{Chi}	72 (11.3%)	88 (14.0%)	0.176 ^{Chi}
CABG during initial management	7 (1.7%)	11 (2.6%)	0.52 ^{Chi}	23 (3.3%)	28 (4.2%)	0.44 ^{Chi}	8 (1.3%)	23 (3.7%)	0.010 ^{Chi}

Values are means (SDs) unless otherwise stated. IQR = interquartile range, CT = computed tomography angiography, ICA = invasive coronary angiography, CI = confidence interval, CAD = coronary artery disease.

*Time to initial test results are cumulative incidence estimates.

†High-risk anatomy CAD was defined by the initial test as any 3-vessel CAD or left main coronary artery stenosis or proximal left anterior descending coronary artery stenosis or any combination of these.

‡Nondiagnostic test was defined as a relevant artifact in CT or poor opacification in CT or ICA that could conceal a $\geq 50\%$ stenosis in a vessel with a reference diameter of ≥ 2 mm without an obstructive coronary artery stenosis elsewhere in the same patient. Patients were recommended to undergo further testing in case of nondiagnostic initial test results.

§ Data missing: did not attend initial test (4 in patients with BMI < 25 kg/m² (CT: 0 vs ICA: 4), 7 in patients with 25-30 kg/m² (CT:1 vs ICA:6), and 9 in patients with BMI > 30 kg/m² (CT:4 vs ICA: 5), incomplete test (2 in patients with BMI < 25 kg/m² (CT: 0 vs ICA: 2), 4 in patients with 25-30 kg/m² (CT:1 vs ICA:3), and 5 in patients with BMI > 30 kg/m² (CT:2 vs ICA: 3), data not documented or lost (1 in patients with BMI < 25 kg/m² (CT: 1 vs ICA: 0), 0 in patients with 25-30 kg/m² (CT:0 vs ICA:0), and 2 in patients with BMI > 30 kg/m² (CT:1 vs ICA: 1), and test findings missing (0 in patients with BMI < 25 kg/m² (CT: 0 vs ICA: 0), 0 in patients with 25-30 kg/m² (CT:0 vs ICA:0), and 1 in patients with BMI > 30 kg/m² (CT:1 vs ICA: 0).

**Other access for ICA included: radial and femoral artery access (6 in patients with BMI < 25 kg/m² (CT: 1 vs ICA: 5), 10 in patients with 25-30 kg/m² (CT:3 vs ICA:7), and 8 in patients with BMI > 30 kg/m² (CT:0 vs ICA: 8), brachial artery access (1 in patients with BMI < 25 kg/m² (CT: 0 vs ICA: 1), 3 in patients with 25-30 kg/m² (CT:0 vs ICA:3), and 2 in patients with BMI > 30 kg/m² (CT:1 vs ICA: 1), radial and brachial artery access (1 in patients with BMI < 25 kg/m² (CT: 0 vs ICA: 1), 0 in patients with 25-30 kg/m² (CT:0 vs ICA:0), and 0 in patients with BMI > 30 kg/m² (CT:0 vs ICA: 0), and data on arterial access not

documented or lost (0 in patients with BMI < 25 kg/m² (CT: 0 vs ICA: 0), 1 in patients with 25-30 kg/m² (CT:0 vs ICA:1), and 1 in patients with BMI > 30 kg/m² (CT:0 vs ICA: 1).

Three subgroup analyses were prespecified to assess heterogeneity between CT/ICA intervention and BMI. The existence of an interaction between BMI and CT/ICA intervention was assessed using a subdistribution Cox proportional hazards model incorporating terms for the main effect of BMI, CT/ICA intervention, and the interaction between BMI and CT/ICA intervention. If a significant interaction was observed, the association between BMI and initial care was further evaluated in different subgroups, adjusting for multiplicity to avoid type 1 error.

Table 3. Primary, secondary endpoints stratified by BMI and randomization group (n = 3,457)

	< 25 kg/m ² (n = 831)			25 – 30 kg/m ² (n = 1358)			> 30 kg/m ² (n = 1268)			P for interaction [†]
	CT (n=409)	ICA (n=422)	Effect Size* (95% CI)	CT (n=697)	ICA (n=661)	Effect Size* (95% CI)	CT (n=638)	ICA (n=630)	Effect Size* (95% CI)	
<i>Primary endpoint</i>										
Major adverse cardiovascular events (MACE)	6 (1.5%)	11 (2.6%)	0.57 (0.21 – 1.53)	19 (2.7%)	17 (2.6%)	1.07 (0.56 – 2.06)	12 (1.9%)	22 (3.5%)	0.52 (0.26 – 1.05)	0.29
Nonfatal myocardial infarction	4 (1.0%)	2 (0.5%)	2.06 (0.38 – 11.2)	9 (1.3%)	8 (1.2%)	1.08 (0.42 – 2.80)	10 (1.6%)	8 (1.3%)	1.21 (0.48 – 3.04)	0.79
Nonfatal stroke	0	8 (2.0%)	No convergence	8 (1.1%)	4 (0.6%)	1.92 (0.57 – 6.40)	1 (0.2%)	8 (1.3%)	0.12 (0.02 – 0.97)	No convergence
Cardiovascular death	2 (0.5%)	2 (0.5%)	1.04 (0.15 – 7.40)	4 (0.6%)	5 (0.8%)	0.77 (0.21 – 2.87)	1 (0.2%)	7 (1.1%)	0.14 (0.02 – 1.11)	0.23
Expanded MACE composite including TIA and major procedure-related complications	10 (2.4%)	21 (5.1%)	0.48 (0.23 – 1.04)	23 (3.3%)	26 (3.9%)	0.84 (0.48 – 1.47)	16 (2.5%)	30 (4.7%)	0.51 (0.28 – 0.93)	0.38
Vascular death or myocardial infarction	4 (1.0%)	3 (0.7%)	1.37 (0.31 – 6.12)	11 (1.6%)	8 (1.2%)	1.32 (0.53 – 3.28)	10 (1.6%)	11 (1.7%)	0.87 (0.37 – 2.04)	0.77
Cardiac death or myocardial infarction	6 (1.5%)	3 (0.7%)	2.09 (0.52 – 8.39)	10 (1.4%)	13 (2.0%)	0.74 (0.32 – 1.68)	11 (1.7%)	12 (1.9%)	0.88 (0.39 – 1.99)	0.42

All-cause death, myocardial infarction or stroke	10 (2.4%)	20 (4.9%)	0.51 (0.24 – 1.09)	31 (4.4%)	29 (4.4%)	1.01 (0.61 – 1.68)	24 (3.8%)	32 (5.0%)	0.74 (0.43 – 1.25)	0.31
Major procedure-related complications during initial management (odds ratios CI 95%)	3 (0.7%)	12 (2.9%)	0.25 (0.06 – 0.80)	5 (0.7%)	12 (1.8%)	0.39 (0.12 – 1.06)	1 (0.2%)	9 (1.4%)	0.11 (0.01 – 0.58)	0.49

CT = computed tomography, ICA = invasive coronary angiography.

*Effect sizes are hazard ratios except as marked

†P for interaction: BMI (< 25 = -0.5, 25 – 30 = 0 and > 35 = 0.5)

‡A complete list of all major procedure-related complications and their relationship is provided in supplementary table 3-4 in appendix

The primary outcome hazard ratio results for MACE have been reported previously(8). Three subgroup analyses were prespecified to assess heterogeneity between CT/ICA intervention and BMI. The existence of an interaction between BMI and CT/ICA intervention was assessed using a subdistribution Cox proportional hazards model incorporating terms for the main effect of BMI, CT/ICA intervention, and the interaction between BMI and CT/ICA intervention. If a significant interaction was observed, the effect of BMI on MACE was further evaluated in different subgroups, adjusting for multiplicity to avoid type 1 error.

Figure Legend

Figure 1. Flowchart.

The prespecified analysis was performed in intention-to-treat population. For 3457 of 3561 patient included in the ITT data on smoking was available.

Figure 2. Time-to-event curves.

(A) Time-to-event curves for primary endpoint (MACE). (B) Time-to-event curves for secondary expanded MACE endpoint (cardiovascular death, myocardial infarction, stroke, transient ischemic attack, or major procedure-related complication).

(A) At a median follow-up of 3.5 years, no statistical significance was found between CT vs ICA and BMI on MACE (BMI < 25 kg/m²: HR 0.57; 95% CI: 0.21 – 1.53; BMI between 25-30 kg/m²: HR 1.07; 95% CI: 0.56 – 2.06; BMI > 30 kg/m²: HR 0.52; 95% CI: 0.26 – 1.05); P for interaction = 0.29)(8).

(B) At a median follow-up of 3.5 years, in patients with BMI > 30 kg/m², CT was associated with lower number of expanded MACE (HR 0.51; 95% CI: 0.28 – 0.93; CT: 2.5%; 16/638 vs. ICA: 4.7% 30/630). However, no interaction was found between CT and ICA for any BMI subgroup (p for interaction = 0.25).

Figure 3. Hazard ratios of primary and secondary endpoints comparing CT vs ICA stratified by BMI.

In the CT group, the proportion of major procedure-related complication was lower in patients with BMI < 25 kg/m² (HR 0.25; 95% CI 0.06 – 0.80; CT: 0.7%; 3/409 vs ICA: 2.9%; 12/422) and > 30 kg/m² (HR 0.11; 95% CI 0.01 – 0.58; CT: 0.2%; 1/638 vs ICA: 1.4%; 9/630) compared with ICA. This included a reduction in the occurrence of nonfatal stroke in the BMI >30kg/m² group (HR 0.12; 95% CI 0.02 – 0.97; CT 0.2%; 1/638 vs ICA: 1.3%; 8/630). However, no significant interaction was found between CT/ICA and BMI (major procedure-related complications P value for interaction=0.60 and 0.49, nonfatal stroke, P value for interaction does not converge).