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COMPUTED TOMOGRAPHY

Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial

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Abstract

Objectives More than 3.5 million invasive coronary angiographies (ICA) are performed in Europe annually. Approximately 2 million of these invasive procedures might be reduced by noninvasive tests because no coronary intervention is performed. Computed tomography (CT) is the most accurate noninvasive test for detection and exclusion of coronary artery disease (CAD). To investigate the comparative effectiveness of CT and ICA, we designed the European pragmatic multicentre DISCHARGE trial funded by the 7th Framework Programme of the European Union (EC-GA 603266).

Methods In this trial, patients with a low-to-intermediate pretest probability (10–60 %) of suspected CAD and a clinical indication for ICA because of stable chest pain will be randomised in a 1-to-1 ratio to CT or ICA. CT and ICA findings guide subsequent management decisions by the local heart teams according to current evidence and European guidelines.

Results Major adverse cardiovascular events (MACE) defined as cardiovascular death, myocardial infarction and stroke as a composite endpoint will be the primary outcome measure. Secondary and other outcomes include cost-

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effectiveness, radiation exposure, health-related quality of life (HRQoL), socioeconomic status, lifestyle, adverse events related to CT/ICA, and gender differences.

Conclusions The DISCHARGE trial will assess the comparative effectiveness of CT and ICA.

Key Points

- *Coronary artery disease (CAD) is a major cause of morbidity and mortality.*
- *Invasive coronary angiography (ICA) is the reference standard for detection of CAD.*
- *Noninvasive computed tomography angiography excludes CAD with high sensitivity.*
- *CT may effectively reduce the approximately 2 million negative ICAs in Europe.*
- *DISCHARGE addresses this hypothesis in patients with low-to-intermediate pretest probability for CAD.*

Keywords Computed tomography · Angiography · Invasive coronary angiography · Adverse events · Comparative effectiveness

Introduction

Coronary artery disease (CAD) is the leading cause of death in high-income countries, and the World Health Organisation predicts that cardiovascular diseases will become the main cause of death in low- and middle-income countries by 2030 [1]. Invasive coronary angiography (ICA) is the reference standard for the diagnosis of CAD and allows immediate intervention if indicated in the case of stenosis. However, only 38–40 % of the patients undergoing ICA in Europe [2] and the USA [3] actually have obstructive CAD (defined as at least 50 % coronary diameter stenosis). ICA involves relatively rare but considerable risks for patients such as death, myocardial infarction and stroke [4, 5]. An effective noninvasive test to rule out CAD would be pivotal to reduce the approximately 2 million annual ICAs in Europe that yield negative results [2]. Coronary computed tomography (CT), including coronary calcium score and CT angiography, is the most accurate noninvasive diagnostic imaging strategy for CAD [6, 7] and recommended by current guidelines at low to intermediate pretest probability [8]. Yet, in clinical routine, ICA is still often performed in such patients leading to overdiagnosis. It should also be noted that CT is highly cost-effective, thus promising the greatest societal benefit [9, 10]. With its high sensitivity of ca. 95 % [6, 7], it is the best noninvasive option to exclude CAD in patients with an intermediate pretest probability of CAD [11], e.g. patients with equivocal stress test results [12]. However, CT is not reimbursed by all European national health systems. CT applied as the first-line imaging modality to determine further workup may result in early and safe

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discharge of the majority of patients with intermediate risk of CAD and stable chest pain.

Only two published randomised trials in patients with stable chest pain and suspected CAD were published so far: PROMISE [13] and SCOT-HEART [14]. However, these two trials did not compare CT and ICA but CT with functional testing and standard care, respectively. Thus, we designed the multicentre DISCHARGE trial (Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies). This pragmatic randomised controlled trial (PRCT) will ultimately compare the effectiveness of CT and ICA by randomly evaluating CT versus ICA in patients with stable chest pain and low-to-intermediate pretest probability of CAD who have a clinical indication for ICA.

Study design

Registration and study website

Ethical approval for the PRCT and the pilot study was obtained at the coordinating site (EA1/294/13) and from the German Federal Office for Radiation Protection (Z5-2246/2-2014-001). Based on this, all other clinical partners received ethical approval for the PRCT and, if required by national law, also for the pilot study. Thirty partners participate (Fig. 1) and the study website is available at https://www.dischargetrial.eu. The DISCHARGE trial was registered at https://www.clinicaltrials.gov/ct2/show/NCT02400229 on 15 January 2015.

Study protocol and key study features

The study protocol (Appendix 1) was developed in accordance with the WHO recommendation (http://www.who.int/rpc/research_ethics/format_rp/en/) and with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [15, 16]. The SPIRIT checklist and the WHO checklist are available in Appendices 2 and 3, respectively. Over a period of 2 years, patients with stable chest pain and a pretest probability of CAD of 10–60 % who are indicated to undergo ICA will be randomised to CT or ICA. Chest pain will be assessed using the Rose angina questionnaire [17]. In both groups, patients with negative test results will be discharged and patients with positive test results (at least one obstructive coronary stenosis of at least 50 %) will undergo management by the local heart teams according to guidelines and guided by CT or ICA and noninvasive imaging ischaemia tests. Plaque features and coronary artery calcium scores will be evaluated by CT at each clinical site to guide local decisions about further

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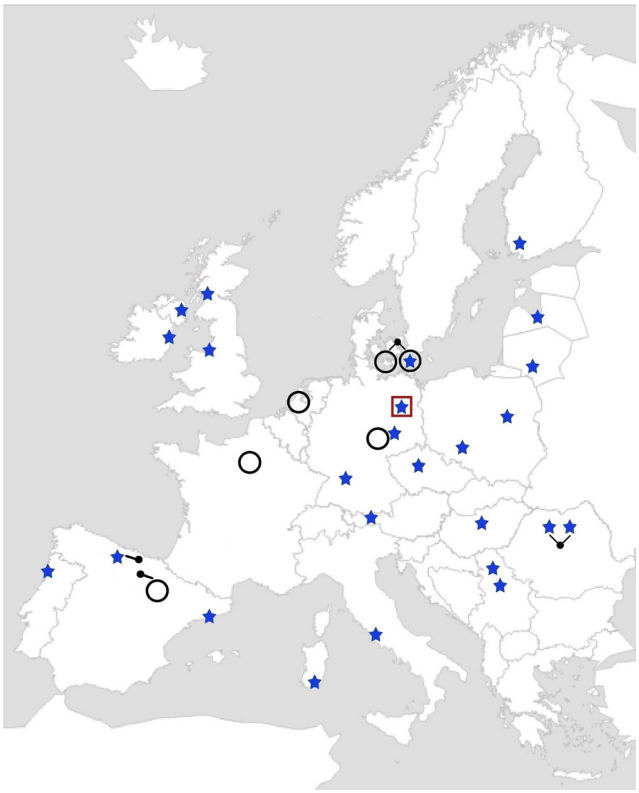

Fig. 1 Regional distribution of clinical sites (*blue stars*), work package leaders (*black circles*) and the coordinating site (*red square*), which also functions as a clinical site and work package leader. The consortium consists of 30 partners in 18 countries, including 25 clinical sites in 16 European countries

patient management including optimal medical therapy and intensified risk factor modification [18]. Feedback for each examination is given by the core lab at Charité where image quality, stenosis, plaque characteristics and noncardiac findings will be assessed. Follow-up for up to 4 years is planned.

Pragmatic versus explanatory trials

Explanatory trials are concerned with the question of how and why an intervention works under ideal circumstances [19, 20]. In contrast, for generating high-quality evidence for decision-makers, the pragmatic approach addresses practical questions about the risks, benefits and costs of an intervention as they occur in everyday clinical practice [19]. Therefore, they help facilitate decision-making about whether certain diagnostic procedures or therapies should be used more widely by analysing their effectiveness.

Pragmatic trial design

In the DISCHARGE trial, CT-directed clinical management will constitute the intervention group and ICA-directed clinical management will be the control group. Thus, a two-group randomised study approach is utilised and a pragmatic design will be followed to generate practical and usable outcomes for clinical decision-making (Fig. 2). By doing so, it will allow an optimal comparative effectiveness evaluation as a pragmatic trial design is considered most adequate according to comparative effectiveness research methodology for generating credible and relevant evidence [19–21]. How DISCHARGE specifically meets the criteria for a pragmatic randomised controlled trial (PRCT) is shown in detail in Fig. 2 by reference to each of the ten domains of PRECIS (Fig. 3) [21].

Primary outcome, secondary outcomes and other outcomes

The primary outcome, the main secondary outcomes and other outcomes are described below and consider gender aspects. All outcomes are included in Appendix 1 and Table 1.

Primary outcome

The primary outcome is the occurrence of major adverse cardiovascular events (MACE). It is a composite endpoint consisting of cardiovascular death, myocardial infarction and stroke. This primary outcome in different composites, e.g. only myocardial infarction and cardiovascular death, will also be analysed as a secondary outcome.

Secondary outcomes

Minor cardiovascular events

Minor cardiovascular events (MICE) are also a composite endpoint. They include coronary revascularisation (at least 1 month after initial ICA in order to remove test-driven outcomes), peripheral artery revascularisation, hospitalisation for chest pain/discomfort, emergency department visit for chest pain/discomfort, transient ischaemic attack and congestive heart failure.

Procedural complications

Major procedural complications are a composite endpoint and include death, stroke, myocardial infarction and other complications if they lead to a hospital stay of at least 24 h. Complications not leading to this prolonged stay, e.g. slight bleeding or mild allergic reactions, are classified as minor.

Health-related quality of life (HRQoL)

HRQoL encompasses individual perceptions of physical and mental health as well as functional capacities in everyday life. HRQoL will be assessed using established generic questionnaires, which have been validated previously in all languages

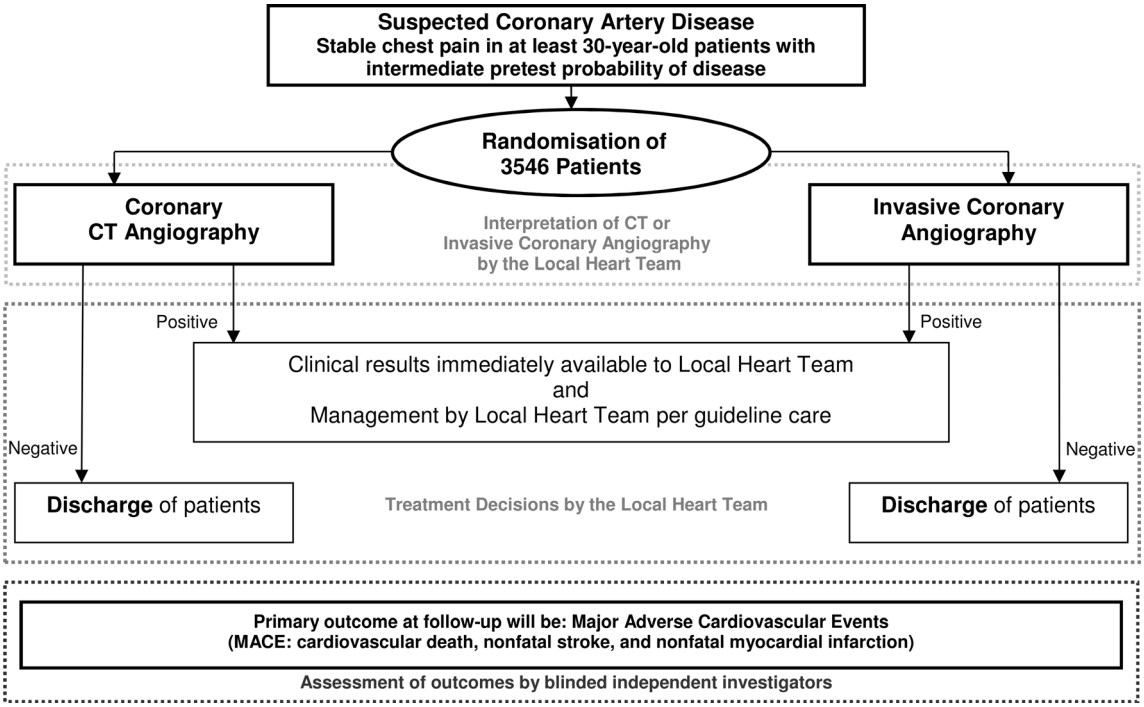

Fig. 2 Design of the DISCHARGE pragmatic randomised controlled trial. The design illustrates the pragmatic approach. Invasive coronary angiography will be performed according to the regular procedure. Cardiac CT will be performed using the 10-step guide for cardiac CT and scanner-specific protocols, but will also remain within an approved range. Patients with positive findings will be treated according to guideline care as decided by the local heart team. Patients with negative findings will be discharged

of the participating sites and will be completed by participants at baseline (prior to randomisation) and at each follow-up: the Short Form (SF)-12v2, [23] the EuroQoL (EQ-5D-3 L) [24] and the Hospital Anxiety and Depression Scale (HADS) [25].

Cost-effectiveness

Expected costs concerning diagnostic tests, treatments and handling of adverse events are calculated by using an analytic decision tree model [26]. The main analysis is the calculation of the incremental cost-effectiveness ratio (ICER) which focuses on differences between the two study groups in baseline costs plus treatment costs of MACE according to differences in the occurrence of MACE. Additional ICERs address serious adverse events (SAEs), adverse events (AEs) as well as mortality due to incidental and non-cardiovascular findings, applying adequate definitions of costs [27]. Downstream treatments after CT/ICA such as medication, further coronary diagnoses and interventions will be recorded. A cost-utility analysis, addressing health-related quality of life, will also be conducted.

Radiation and EU CT quality criteria

Image quality and radiation exposure in all patients will be assessed and monitored. The experience gained will be used to develop guidance on acquisition protocols and radiation protection that will be published as EU CT quality criteria. For this purpose, a guideline on how to generally perform cardiac CT (a 10-step guide) was developed at Charité with input from the DISCHARGE consortium and complemented by scanner-specific protocols.

Other outcomes

Other outcomes consist of analyses within the CT and ICA group, European differences and the development of a novel pretest probability calculator.

Quality assurance

Pilot study

In order to prepare the PRCT with high quality, e.g. image quality, all clinical sites performed a pilot study prior to the initiation of patient randomisation for the main study. The pilot study included 60 anonymised patients at each site with suspected CAD who were at least 30 years of age and had a clinical indication for CT or ICA (30 CT/30 ICA). Patients were excluded according to the criteria in Table 2. The pilot study design was similar to that of an anonymised observational study without randomisation and pretest probability calculation. This enabled a faster recruitment rate and was

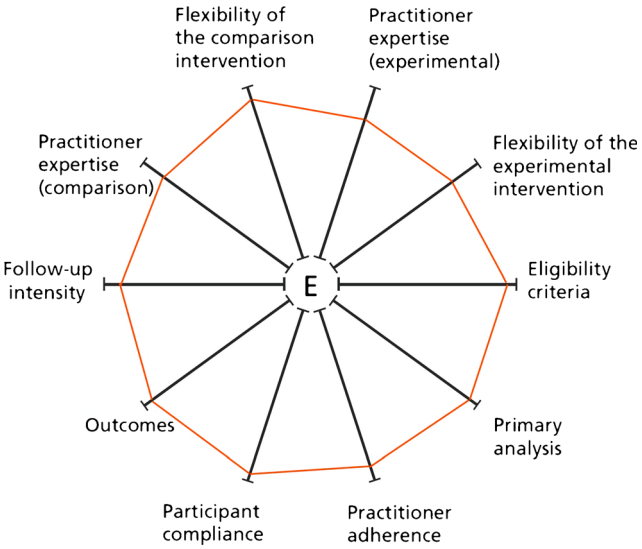

Fig. 3 Evaluation of the DISCHARGE PRCT design according to the 10 PRECIS domains. The DISCHARGE PRCT is essentially designed towards the pragmatic (external) end of the explanatory–pragmatic continuum of the ten domains, thus primarily investigating and addressing effectiveness, usual care, and implications for decision-making. An example is the practitioner expertise: readers of CT datasets will have to have at least a level II training certificate from the Society of Cardiovascular Computed Tomography (SSCT) or similar certification. At least one cardiac CT reader is required to have certification for cardiac CT lab leadership (SCCT level III or similar); moreover, a 1-week hands-on training in 100 cardiac CT cases with correlation to ICA was provided at Charité for at least one reader from each participating site before the start of the trial (www.ct-kurs.de) as part of the quality assurance programme [22]. ICA is applied by the full range of practitioners; no specification exists concerning their expertise or level of training

sufficient to collect data for microcosting and HRQoL. The pretest calculator will be validated through the pilot study.

Methods against bias

Bias will be reduced mainly because the patient population under investigation is eligible for randomisation to either CT or ICA at all sites. Blinding patients to the groups (CT or ICA) is not possible. Allocation concealment and equal allocation to the two trial arms will be ensured by block randomisation with central assignment. In addition, patients at each clinical site will be stratified according to gender to minimise covariate imbalance [29].

Clinical monitoring and clinical data management

On-site clinical monitoring will be carried out by European Clinical Research Infrastructure Network (ECRIN) in collaboration with KKS Charité and the coordinator team. Clinical monitoring will also be done centrally by checking the electronic case report forms in the study-specific database. (Serious) adverse events will also be entered in the database, and reporting procedures to meet legal requirements have been defined. This database is compliant with Good Clinical Practice and was specially designed for remote data entry to store and manage all study data. Automated checks for plausibility, ranges, consistency and data completeness ensure high quality of the data. These data will be prepared and exported for statistical and other analyses.

Statistics

This study was designed to show superiority of CT with respect to MACE. The primary outcome is the MACE incidence after a maximum follow-up of 4 years after CT or ICA. These time-to-event data will be analysed using a proportional hazard model adjusted for age, sex and other confounding factors such as education. For sensitivity analysis, a Cox proportional hazards model with random effects [30, 31] (frailty model) using the freely available software R [32] will be applied. This model is used to take into account variability between sites and unobserved heterogeneity. This unobserved heterogeneity might result e.g. from differences in therapeutic adherence within each centre (Table 3). These frailty models assume a continuous distribution for random effects. This assumption might be too strong. Thus a semiparametric mixture model [33] will be developed for time-to-event data within this project. Since MACE are potentially recurrent, a random effects model offers the additional advantage that it is also suitable for recurrent events. Again, potential confounding factors such as age, education, gender or smoking will be adjusted for in the analysis. Missing values for confounding factors are likely to occur, and will be dealt with using multiple imputation methods [34]. The statistical analysis will be performed centrally without influencing local decisions during the trial (Table 4).

The sample size estimation for the DISCHARGE PRCT is outlined in Appendix 1.

Study management

The coordinator is Professor Marc Dewey from the Department of Radiology at Charité – Universitätsmedizin Berlin. Coordination of the DISCHARGE project is facilitated by a core lab for CT and ICA and a central management team at Charité. The project manager of DISCHARGE is Adriane Napp, MSc, from the Department of Radiology at Charité. The governance structure is shown in Fig. 4 and described in Appendix 1.

Table 1 Primary outcome, secondary and other outcomes

Outcome	Topic
Primary	Composite endpoint: major cardiovascular event (MACE) consisting of cardiovascular death, myocardial infarction and stroke
Secondary	MACE in different composites
	MACE in subgroups
	Composite endpoint: minor cardiovascular events (MICE) include coronary revascularisation (at least 1 month after initial ICA in order to remove test-driven outcomes), peripheral artery revascularisation, hospitalisation for chest pain/discomfort, emergency department visit for chest pain/discomfort, transient ischaemic attack and congestive heart failure
	Influence of computed tomography angiography and invasive coronary angiography on angina pectoris
	Procedural complications in the computed tomography angiography and invasive coronary angiography group
	Procedural complications of invasive coronary angiography in the computed tomography angiography and invasive coronary angiography group
	Comparison of incidental findings in computed tomography angiography and invasive coronary angiography group and potential benefits and harms of findings
	Patient acceptance/preference
	Radiation exposure in the computed tomography angiography and invasive coronary angiography group
	Cost-effectiveness analysis
	Socioeconomic status, quality of life and lifestyle
	Gender analysis
Other	Analysis of differences in Europe
	Computed tomography angiography and invasive coronary angiography image-based outcomes
	Computed tomography image-based outcomes: image quality
	Computed tomography image-based outcomes: heart rate and dose
	Computed tomography image-based outcomes: plaques
	Invasive coronary angiography outcomes
	Planned cross-over in accordance with management recommendations
	Imaging ischaemia tests
	Comparison of pretest probability calculators
	Predictive value of DISCHARGE calculator
	Development of novel pretest probability calculator

For details see https://clinicaltrials.gov/ct2/show/NCT02400229

Secondary outcomes are those that arise from the direct comparison of the two groups

Discussion

The objectives, methods and design outlined above are unique in that the DISCHARGE trial will assess the comparative effectiveness of CT versus that of ICA in patients with stable chest pain and a clinical indication for ICA based on a low-to-intermediate pretest probability of disease. The primary outcome is MACE and further secondary and other outcomes have been defined prospectively (Table 1).

Thus far, only one single-centre study (CAD-Man) compared CT with ICA in a randomised fashion [36]. This study assessed procedural complications of CT and ICA in a randomised design in 340 patients, and it is expected that approximately 80–90 % of patients in DISCHARGE will not have obstructive CAD and can be discharged immediately. DISCHARGE goes beyond the assessment of clinical safety, which was done in CAD-Man, by analysing clinical effectiveness in terms of MACE observed during clinical follow-up (Fig. 5).

Two large multicentre randomised studies in patients with suspected CAD based on stable chest pain or chest pain of recent onset have been published so far. The SCOT-HEART study included 4146 patients and found a (nonsignificant) reduction in fatal and nonfatal myocardial infarction after 1.7 years in the CT group, indicating that CT may have benefits in patients with recent onset angina. This was supported by a common reclassification of disease by CT in comparison to standard of care and relevant changes in clinical management, e.g. withholding or prescribing medication [14]. The SCOT-HEART trial also showed that CT leads to more

Table 2 Eligibility criteria for the DISCHARGE trial

Inclusion criteria	Exclusion criteria
• Patients with suspected* coronary artery disease with stable** chest pain and intermediate pretest probability (10–60 %)*** of CAD clinically referred for ICA	• Patient is or was on haemodialysis
• Patients at least 30 years of age	• No sinus rhythm or pregnancy
• Written informed consent	• Any medical condition that raises concern that participation is not in the best interest of health (e.g. extensive comorbidities)

* Patients with known (or treated) CAD by CT or ICA will not be eligible. Patients who had no CAD, defined as at least one coronary stenosis with at least 50 % diameter reduction, on prior CT or ICA will only be eligible if the examination was done at least 5 years before the inclusion date

** "Stable chest pain" is defined as *not* being

- acute

(= first appearance within the last 48 h) or

- instable angina pectoris

(= (a) first appearance with Canadian Cardiovascular Society Angina Grading Scale (CCS) Class III or IV,

(b) progressive with at least 1 CCS Class to at least CCS Class III or, now at rest for at least 20 min)

*** It will be assessed using a pretest calculator integrated into the electronic case report form that uses age, gender and the patient's clinical presentation of stable chest pain to calculate pretest probability of disease. It was developed on the basis of the results of the CoMe-CCT project ("Collaborative Meta-analysis of Cardiac CT"; www.coronaryrisk.org) [28]

appropriate use of ICA but is more expensive than standard care [37]. For calculating costs, SCOT-HEART used reimbursement in Scotland. After a mean follow-up of 25 months, the PROMISE trial in 10,003 patients found no difference between CT and functional testing in the combined endpoint, which included death, myocardial infarction, hospitalisation for unstable angina, and major procedural complications [13]. This may relate to the composite nature of the endpoint which, contrary to recommendations [38], reflected both safety (e.g. complications) and effectiveness (e.g. deaths). The events combined in this endpoint clearly differ in clinical relevance, e.g. hospitalisation for unstable angina versus death. Thus a secondary analysis of PROMISE, at best with longer follow-up if funded by the National Institutes of Health (NIH), with regard to the composite of cardiovascular death, myocardial infarction and stroke might better reflect the capabilities of CT [39]. Additionally, statin therapy initiated after plaque detection on CT may reduce mortality but only after longer follow-up than currently reported for SCOT-HEART and PROMISE [40]. A randomised study mainly recruiting in Korea, the CONSERVE study, is also investigating CT versus ICA in a randomised design and is currently recruiting patients (NCT01810198). CONSERVE is potentially biased by the financial support provided by a medical technology company. Also, MACE is defined to incorporate additional events such as rehospitalisation for angina, which may dilute the results for the harder outcomes such as cardiovascular death, for which the planned patient number may not be sufficient. In conclusion, it is still open as to whether CT might be a valuable noninvasive alternative in certain situations where coronary angiography is already indicated [39]. This highlights the importance of the planned DISCHARGE study.

The radiation exposure of CT is lower than that of ICA using most recent technology [41]. But because of additional ICA examinations following positive CTs, the overall radiation exposure might be increased in a subgroup of the patients randomised to CT. Thus, the study was approved by the German Federal Office for Radiation Protection. Since plaque characterisation is included and scanners using 64 slices or up to 320 rows are part of the centres' technology, average

Table 3 Power calculations

Power	Total N	N_1	N_2	E	Survival CT	Survival ICA	Hazard ratio
0.80	3546	1773	1773	99	0.9920	0.9986	0.570
0.98	3546	1773	1773	106	0.9920	0.9983	0.460
0.73	3546	1773	1773	104	0.9914	0.9986	0.612
0.96	3546	1773	1773	112	0.9914	0.9983	0.495

N_1, N_2 number of randomised patients to the CT and the ICA groups, E number of events

Table 4 Statistical plan for interim analysis

Analysis	*E*(vents)	*Z*	Nominal *p*	Spend
Interim	50	2.80	0.0026	0.0026
Final	100	1.98	0.0240	0.0224
Total				0.0250

A symmetric two-sided group sequential design with 80 % power and 2.5 % type I error was used, and calculations were performed with R package gsDesign [35]

effective doses of 5–10 mSv can be expected. The large sample size of DISCHARGE is an important advantage that will allow us to draw representative conclusions about the radiation exposure.

The DISCHARGE trial has some limitations. It is a multicentre study conducted in Europe based on funding provided by the European Union (grant agreement no. 603266). Therefore, other regions of the world cannot be represented in the study. Second, the CT arm of the study is more explanatory than the ICA arm, which is almost entirely pragmatic. The DISCHARGE trial will include patients with a clinical indication for ICA because of suspected CAD with low-to-intermediate probability. Low-to-intermediate probability is defined as 10–60 % and will be estimated in all individuals eligible for the study using a pretest probability calculator derived from data obtained in the individual-patient data meta-analysis COME-CCT [28]. Patients with lower or higher probability of CAD are less likely to benefit from CT since positive and negative predictive values are reduced in these patient groups, respectively [11]. Still, this should be explored in the future since some studies have shown potential in such groups when comparing CT with exercise ECG [42] or standard care [43]. Patients are excluded from the DISCHARGE trial if they are or were on haemodialysis, are pregnant or not in sinus rhythm. These very limited exclusion criteria reflect

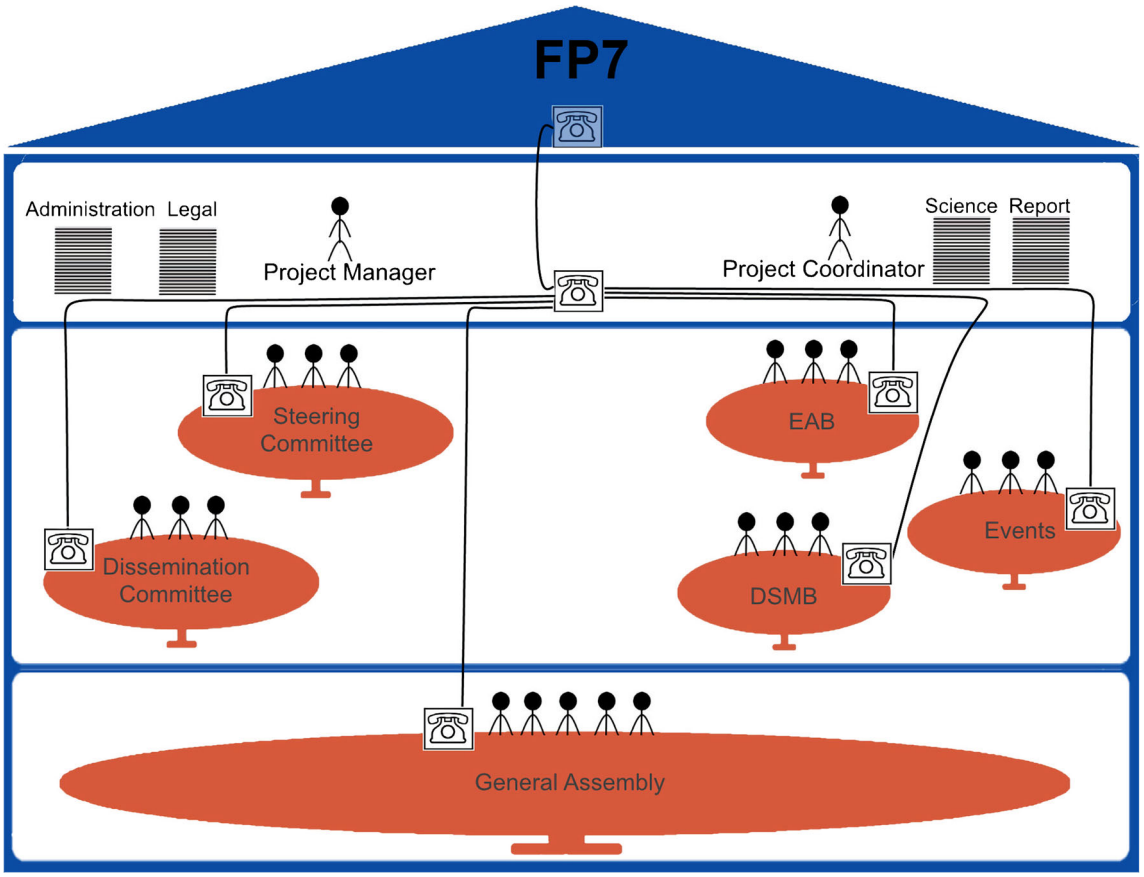

Fig. 4 Governance structure. *FP7* 7th Framework Programme of the European Union, *EAB* external advisory board, *DSMB* data safety monitoring board, *CEC* clinical events committee. The coordinator, the project manager and their team form the project management office. They are the intermediaries between the consortium and the European Commission. The communication lines are in between them and the general assembly and the boards and committees. All information is sent out by the project management office. The general assembly includes all partners and has empowered the steering committee (SC) to provide advice or decisions when issues arise that go beyond the scope of the responsible party. Detailed rules and procedures have been laid down in the dissemination policies which are governed by the dissemination committee (DC). All investigators and researchers, including the ones in a junior position, are encouraged to submit their publications and presentations to the DC. The EAB gives continuous guidance for all aspects of the project, the CEC assesses the occurrence of MACE and the DSMB evaluates the safety risks and potential harms for the study participants by reviewing all serious adverse events

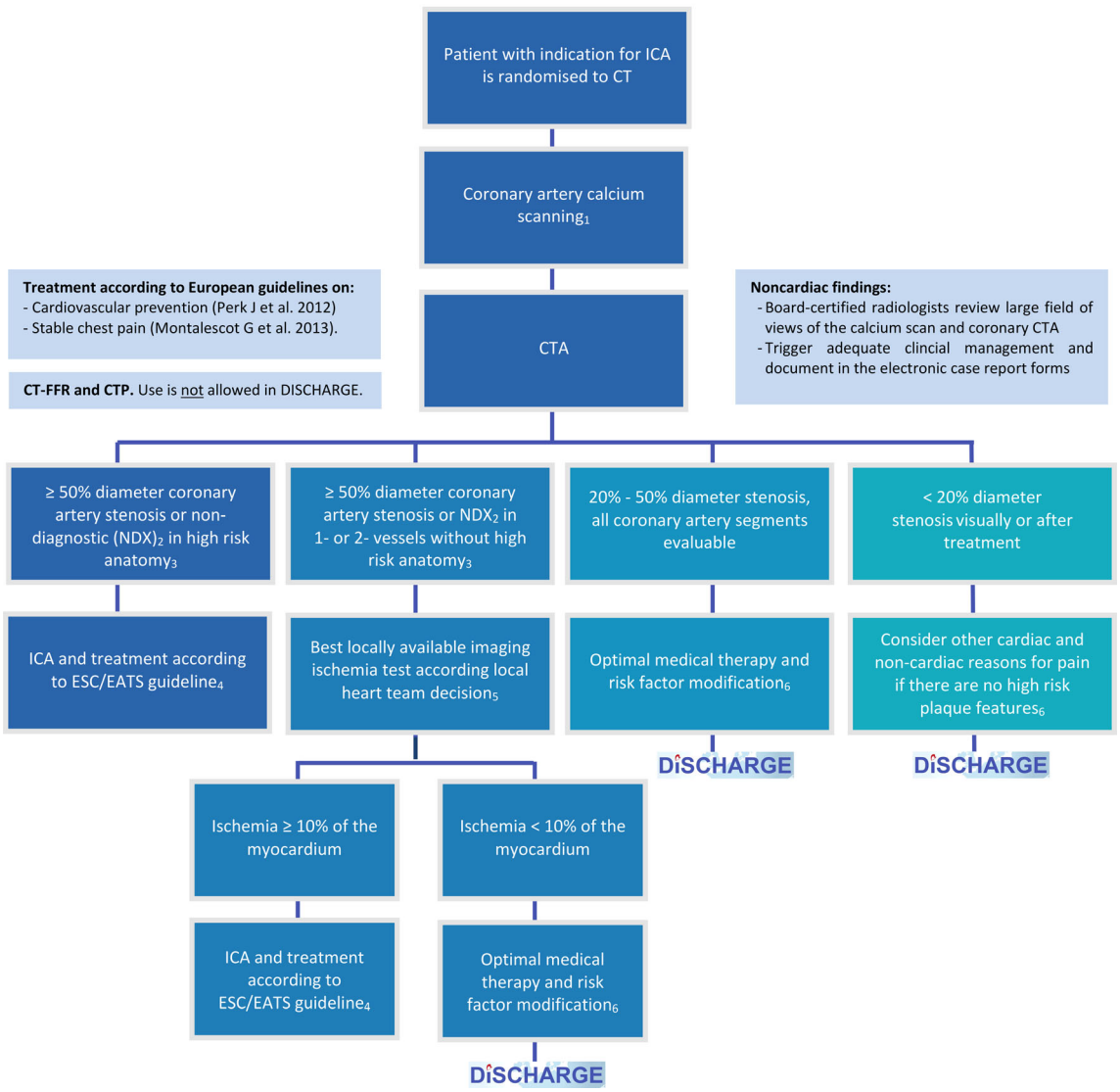

Fig. 5 CT-based management of patients in DISCHARGE:1. The coronary artery anatomic information from calcium scanning can be used to reduce the z-axis coverage of subsequent CT angiography (CTA) by trimming the start and end according to individual patient anatomy to reduce exposure (Leschka S et al., 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 workflow. Even in patients with high calcium scores, CTA will always be done 2. NDX (nondiagnostic segment) defined as presence of a relevant artefact in a vessel with a reference diameter of ≥2 mm (that could hide ≥50 % stenosis) 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 ischaemia test (Shaw LJ et al., Circulation 2008), if not already done, to make a well-informed decision about whether or not ischaemia ≥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 remodelling index ≥1.1 (calculated as the vessel cross-sectional area at the site of maximum stenosis divided by the average of proximal and distal reference segment 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 (noncalcified plaque with a central area of low CT attenuation that is apparently in contact with the lumen; and ring-like higher-attenuation plaque tissue surrounding this central area, Maurovich-Horvat P, et al. Nat Rev 2014

the limitations of current CT technology, which are heavy calcification posing issues in patients with haemodialysis and sinus rhythm providing the best basis for diagnostic image quality. This is important because nondiagnostic results are rather common in such situations and would be considered to reflect 'positive' findings. Nevertheless, we will not exclude patients with contraindications to beta-blockade or high heart rates, thereby making the study more representative and generalizable. The exclusion criteria reflect good clinical practice because we will avoid radiation exposure in pregnant women. An important advantage of the DISCHARGE trial is that we will not exclude patients above certain body mass index levels or body weights in order to be as pragmatic as possible. It is because of this background that the radiation exposure of DISCHARGE will not be very low but has to be tailored to each individual patient with the aim to have as few nondiagnostic CT examinations as possible [44] since these will lead to the need to perform additional ICA. Another practical advantage of the trial is that CT will not be withheld in patients with increased Agatston scores estimated from non-contrast CT performed before CT. Therefore, and because of the limited exclusion criteria, the results will be representative for most patients with low-to-intermediate probability of suspected CAD.

In summary, the multicentre European DISCHARGE trial is designed to pragmatically assess the comparative effectiveness of CT and ICA in patients with suspected CAD and a clinical indication for ICA based on low-to-intermediate probability of disease.

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