Protocol

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

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

DISCHARGE Study Documents

CLINICAL STUDY PROTOCOL

Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies

The "DISCHARGE" Study

A pragmatic randomised controlled trial (PRCT) evaluating the superiority of CT over ICA concerning effectiveness in stable chest pain patients with intermediate pretest probability of coronary artery disease

Protocol Version 1.6, dated 01-Apr-2016

Charité – Universitätsmedizin Berlin

Confidential

Table of Contents

Abbreviations

AHA	American Heart Association
CABG	coronary artery bypass graft
CACS	coronary artery calcium scan
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society Angina Grading Scale
CEA	cost-effectiveness analysis
CEC	clinical events committee
CNS	central nervous system
CRF	case report form
CoMe-CCT	Collaborative Meta-analysis of cardiac CT
CT	computed tomography
CTA	CT angiography
DALY	disability adjusted life years
DISCHARGE	Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies
DSMB	data safety monitoring board
EAB	external advisory board
EBM	evidence-based medicine
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic data capture system
EU	European Union
FFR	fractional flow reserve
GCP	good clinical practice
HF	heart failure
HTA	health technology assessment
ICA	invasive coronary angiography
ICH	intracerebral hemorrhage
IPD	individual patient data
IRB	internal review board

LBBB	left bundle branch block
LVH	left ventricular hypertrophy
MACE	Major adverse cardiovascular events
MI	myocardial infarction
MIP	maximum intensity projections
MPR	multi planar reconstructions
mSv	millisievert
OMT	optimal medical therapy
PRCT	Pragmatic Randomised Controlled Trial
SAE	serious adverse event
SAH	subarachnoidal haemorrhage
SC	steering committee
SCCT	Society of Cardiovascular Computed Tomography
SOP	Standard Operating Procedure
SPC	statistical process control
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TTO	time trade-off
WHO	World Health Organisation

1. Project Summary

Coronary artery disease (CAD) is the leading cause of death in high-income countries. Invasive coronary angiography (ICA) is the reference standard for the diagnosis of CAD and allows immediate therapy. However, only 40% of patients undergoing ICA actually have obstructive CAD and ICA has relatively rare but considerable risks. Coronary computed tomography (CT) is the most accurate diagnostic test for CAD currently available, excellent for the exclusion of disease with high certainty. CT may become the most effective strategy to reduce the ca. 2 million annual negative ICAs in Europe by enabling early and safe discharge of the majority of patients with an intermediate risk of CAD.

To evaluate this, the DISCHARGE project that will be implemented by a multinational European consortium has been established. The core of the project is the DISCHARGE trial, a pragmatic randomised controlled trial (PRCT). The primary hypothesis is that CT is superior to ICA for major adverse cardiovascular events (cardiovascular death, fatal myocardial infarction or stroke) after a maximum follow-up of 4 years in a selected broad population of stable chest pain patients with intermediate pretest probability (10-60%) of CAD. This will be assessed using a pragmatic randomised controlled design in order to generate practical and usable outcomes for clinical decision-making according to comparative effectiveness research methodology. The trial will include 25 clinical sites from 16 European countries which will recruit more than 3500 patients ensuring broad geographical representation.

2. General Information

2.1 Title

Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies (DISCHARGE)

2.2 Trial Registration

Data category	Information
Primary registry and trial identifying number	https://clinicaltrials.gov/ NCT02400229
Date of registration in primary registry	15.01.2015
Secondary identifying numbers	EA1/294/13
Source(s) of monetary or material support	European Commission, 7th Framework Programme
Primary sponsor	Charité – Universitätsmedizin Berlin Charitéplatz 1, 10117 Berlin, Germany
Contact for patient, public, and scientific queries	Study office at Charité: Charité – Universitätsmedizin Berlin Campus Mitte Institute of Radiology Charitéplatz 1, 10117 Berlin Email: herzschmerzen@charite.de Phone: +49-30-450527226
Public title	Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies (DISCHARGE)
Scientific title	A pragmatic, randomised controlled trial evaluating the possible superiority of computed tomography (CT) over invasive coronary angiography (ICA) concerning effectiveness in stable chest pain patients with intermediate pretest probability of coronary artery disease
Countries of recruitment	Austria, Czech Republic, Denmark, Germany, Finland, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Spain, United Kingdom
Health condition(s) or problem(s) studied	Suspected coronary artery disease (CAD), intermediate risk of CAD and stable chest pain Diagnosis, management and safety

Intervention(s)	Experimental intervention: CT-guided management Comparison intervention: ICA guided management
Key inclusion and exclusion criteria	Due to the pragmatic approach[1] of the DISCHARGE trial, only minimal inclusion and exclusion criteria are used for study population identification. *Inclusion criteria:* Patients with suspected coronary artery disease with stable chest pain and intermediate pretest probability (10-60%) of CAD clinically referred for invasive coronary angiography. "Stable chest pain" defined as **not**: - being acute (= first appearance within the last 48 hours) or - instable (= a) first appearance with Canadian Cardiovascular Society Angina Grading Scale (CCS) Class III or IV; b) progredient with at least 1 CCS Class to at least CCS Class III or, now at rest for at least 20 min) angina pectoris Patients at least 30 years of age Written informed consent *Exclusion criteria:* Patients who were or are on hemodialysis, no sinus rhythm, pregnancy, any medical condition that leads to the concern that participation is not in the best interest of health (e.g., extensive comorbidities), participation in other interventional/randomised study
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: single blinded (outcome assessor) Primary purpose: comparative effectiveness evaluation Phase: N/A since pragmatic and not a drug/medical device study
Date of first enrolment	October 2015
Target sample size	3546

Recruitment status	Recruitment will start in October 2015
Primary outcome(s)	MACE (MACE = major adverse cardiovascular event; defined as cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction) after a maximum follow-up of 4 years
Key secondary outcomes	Cost-effectiveness, radiation exposure, cross-over to CT or ICA, gender differences, and health-related quality of life

2.3 Protocol Version

Issue Date: 4 May 2016

Protocol Number: 1.6 Approved by Charité Ethics Committee on 28 April 2016

Revision Chronology:

05 Aug 2013	Version 1.0 For ethical approval. Format from proposal.
…28 May 2014	Draft Version 1.1 Format according to SPIRIT/WHO
…10 October 2014	Draft Version 1.2. Overall revision and addition of major clinical aspects
…01 May 2015	Draft Version 1.3. Incorporation of recommendations from ECRIN, update participating clinical sites and outreach activities, complete SPIRIT and WHO check list items. Include Measurement Section and shift text from Safety section. Shorten Safety Section accordingly.
01 Sept 2015	Draft Version 1.4. Statistical sections with more details to show that the exploratory analysis does not produce bias. Secondary/Other outcomes list added.
01 Oct 2015	Draft Version 1.5. Draft Version 1.4 was slightly revised for consistency and clear phrasing.
01 Apr 2016	Version 1.6. Slight revision of Draft version 1.5 for further clarification, e.g. consistent phrasing Approved by all authors and by the Charité Ethics Committee. This version requires no change of the patient informed consent (dated 9 October 2014) approved by Charité Ethics Committee.

2.4 Protocol Contributors

Marc Dewey[*MD, PhD], Adriane Napp[MSc], Robert Haase[MD], Michael Laule[MD], Georg M Schuetz[MD], Rita Pilger[MSc], Corinna Meier-Windhorst[VM], The-Hoang Do[MSc] , Felix Frömel, Christoph Katzer[MEd, MA], Nina Rieckmann[PhD], Jaqueline Müller-Nordhorn[MD, DPH], Paolo Ibes, Mario Walther[DSc], Peter Schlattmann[MD, PhD, MSc]

The author's affiliations are stated in section 2.6.2 and 2.6.3.
Author's Contributions:

MD, ML and PS conceived the study. MD is the coordinator. PS provided statistical expertise in clinical trial design. AN, RH, GS, and MW developed the study protocol. AN is also the project manager. PS is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript

2.5 Funding

The European Commission is funding the project within the 7th EU Framework Programme, grant No. 603266.

2.6 Roles and Responsibilities

2.6.1 Coordinating Centre/Sponsor

Trial Sponsor: Charité – Universitätsklinikum Berlin
Sponsor's Reference:
Contact name: Marc Dewey, Heisenberg Professor
Address: Charité – Universitätsmedizin Berlin
Humboldt Universität und Freie Universität zu Berlin
Institut für Radiologie
Charitéplatz 1
10117 Berlin
Germany
Telephone: +49 30 450 527353
Fax: +49 30 450 527996
Email: marc.dewey@charite.de

2.6.2 Sponsor and Funder

Sponsor: Charité – Universitätsmedizin
Funder: European Commission

Name	Title/Designation	Address and Contact Numbers
Marc Dewey, MD, PhD	Coordinator and Coordinating Investigator Radiology	Charité – Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin Germany Phone: +49-30-450627226 Fax: +49 30 450 7527920 Email: dewey@charite.de
Michael Laule, MD, PhD	Coordinating Principal Investigator, Cardiology	Charité – Universitätsmedizin Berlin Campus Mitte Medizinische Klinik m.S. Kardiologie und Angiologie Herzkatheterbereich Raum: 2721 046 3.Etage Charitéplatz 1 10117 Berlin
Robert Haase and Sarah Feger	Overall Coordinating Principal Investigators for CT	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie und Kinderradiologie Charitéplatz 1 10117 Berlin
Georg Schütz, MD	Investigator CT	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin
Matthias Rief, MD	Investigator CT	Charité – Universitätsmedizin Berlin

		Campus Mitte Institut für Radiologie Luisenstr. 6 – 8 Charitéplatz 1 10117 Berlin
Elke Zimmermann, MD	Investigator CT	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Luisenstr. 6 – 8 Charitéplatz 1 10117 Berlin
Paolo Ibes	Medical Student	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Luisenstr. 6 – 8 Charitéplatz 1 10117 Berlin
Adriane Napp	Project Manager and Work Package co-leader Dissemination, Certification of Clinical Sites	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin
European Commission		European Commission B-1049 Brussels Belgium

2.6.3 DISCHARGE Centres

Medical Departments

Name	Title/*Designation*	Address and Contact Numbers
1.1 Charité - Universitaetsmedizin Berlin		
Marc Dewey, MD, PhD Michael Laule, MD, PhD	Local Principal Investigators	Street: Charitéplatz 1 Town: Berlin Postal Code: 10117 Country: Germany Phone: +49 30 450 527996 Fax: +49 30 450 513072 Email: dewey@charite.de michael.laule@charite.de
2. Medizinische Universitaet Innsbruck (MUI)		
Gudrun Feuchtner, MD Guy Friedrich, MD	Local Principal Investigators	Street: Anichstr. 35 Town: Innsbruck Postal Code: 6020 Country: Austria Phone: +4351250481898 Fax: Email: gudrun.feuchtner@i-med.ac.at Email2: guy.friedrich@uki.at

3. Fakultni Nemocnice v Motole (FN Motol)		
Josef Veselka, MD, PhD Vojtěch Suchánek, MD	Local Principal Investigators	Street: Vuvalu 84 Town: Praha 5 Postal Code: 150 06 Country Czech Republic Phone: +42608921566 Fax: Email: veselka.josef@seznam.cz Email2: vojtech.suchanek@fnmotol.cz
4. Region Hovedstaden (REGIONH)		
Klaus F. Kofoed, MD, PHD Thomas Engstroem, MD, PhD	Local Principal Investigators	Street: 9 Blegdamsvej 9 Town: Copenhagen Postal Code: 2100 Country: Denmark Phone: +45 26807439 Fax: Email: klaus.kofoed@regionh.dk Email: Thomas.Engstroem@regionh.dk
5. Kliniken des Landkreises Goppingen GGmbH (KaE)		
Stephen Schröder, MD Thomas Zelesny, MD	Local Principal Investigators	Street: Eichertstrasse 3 Town: Goppingen Postal Code: 73035 Country: Germany Phone: +49 7161 642671 Fax: Email: Stephen.Schroeder@af- k.de Email2: Thomas.Zelesny@af-k.de
6. Universitaet Leipzig – Herzzentrum (ULEI)		
Matthias Gutberlet, MD, PhD Lukas Lehmkuhl, MD, PhD	Local Principal Investigators	Street: Strümpellstrasse 39 Town: Leipzig Postal Code 04289 Country: Germany Phone: +49 341 865 1702 Fax: Email: matthias.gutberlet@helios-kliniken.de Email2: Lukas.Lehmkuhl@helios-kliniken.de
7. Semmelweis Egyetem (SE)		
Béla Merkely, MD, PhD Pál Maurovich-Horvat, MD, PhD	Local Principal Investigators	Street: Varosmajor u 68 Town: Budapest Postal Code: 1122 Country: Hungary Phone: (+) 36-203879193 Fax: +3614586842 Email: merkely.bela@gmail.com Email2: maurovich.horvat@gmail.com
8. South Eastern Health and Social Care Trust (SET)		
Patrick Donnelly, MD Peter Ball,	Local Principal Investigators	Street: Upper Newtownards Road Ulster Town: Belfast Postal Code: BT16 1RH Country: United Kingdom

MD		Phone: +44 2890484511 Fax: Email: patrick.donnelly@setrust.hscni.net Email2: peter.ball@setrust.hscni.net
9. University College Dublin, National University of Ireland (NUID UCD)		
Jonathan D. Dodd, MD Martin Quinn, MD, PhD	Local Principal Investigators	Street: Belfield Campus Town: Dublin Postal Code 4 Country Ireland Phone: +353 87 2987313 Fax: Email: j.dodd@st-vincents.ie Email2: quinnmartin2001@yahoo.com
10. Università degli Studi di Cagliari (UNICA)		
Luca Saba, MD Maurizio Porcu, MD	Local Principal Investigators	Street: AOU di Cagliari - Polo di Monserrato SS 554 Town: Monserrato (CA) Postal Code: 09042 Country: Italy Phone: +393206206091 Fax: Email: lucasabamd@gmail.com Email2: porcu.maurizio@gmail.com
11. Università degli Studi di Roma la Sapienza (UNIROMA)		
Marco Francone, MD, PhD Massiomo Mancone, MD	Local Principal Investigators	Street: Viale Regina Elena 324 Town: Roma Postal Code: 00161 Country: Italy Phone: +393357550688 Fax: Email: marco.francone@uniroma1.it Email2: massimo.mancone@uniroma1.itrino.sardella@uniroma1.it
12. Paula Stradiņa Klīniskā universitātes slimnīca (PSKUS)		
Iveta Mintale, MD Ligita Zvaigzne, MD, PhD	Local Principal Investigators	Street: Pilsoņu street 13 Town: Riga Postal Code: LV 1002 Country: Latvia Phone: +37167069333 Phone 2: +37129293376 Fax: Email: Iveta.Mintale@stradini.lv Email2: ligita.zvaigzne@inbox.lv
13. Lietuvos Sveikatos Mokslu Universitetas (LSMU)		
Gintare Sakalyte, MD, PhD Antanas Jankauskas, MD, PhD	Local Principal Investigators	Street: Eivelniu 2 Town: Kaunas Postal Code: 50009 Country: Lithuania Phone: +37069806044 Fax:

		Email: gsakalyte@yahoo.com Email2: jankauskas.antanas@gmail.com
14. Wojevódzki Szpital Specjalistyczny we Wrocławiu (WSS)		
Tomasz Haran, MD Malgorzata Ilnicka-Suckiel, MD	Local Principal Investigators	Street: Ul. Henryka Michala Kamienskiego Town: Wroclaw Postal Code: 51 124 Country: Poland Phone: +48602229211 Fax: Email: haran@interia.pl Email2: malgorzata.ilnicka@gmail.com
15. Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E)		
Nuno Bettencourt, MD, PhD Vasco Gama, MD, PhD	Local Principal Investigators	Street: Rua Conceicao Fernandes Town: Vila Nova De Gaia Postal Code: 4434 502 Country: Portugal Phone: +351934258281 Fax: Email: bettencourt.n@gmail.com Email2: vasco@chvng.min-saude.pt
16. S.C. Cardio Med S.R.L. (CAM)		
Theodora Benedek, MD, PhD Imre Benedek, MD, PhD	Local Principal Investigators	Street: 22 decembrie 1989 Town: Targu-Mures Postal Code: 540156 Country: Romania Phone: +40722560549 Fax: Email: hintea_teodora@yahoo.com Email2: imrebenedek@yahoo.com
17. Institut za kardiovaskularne bolesti Vojvodine (IKVBV)		
Nada Čemerlić Ađić, MD, PhD Oto Ađić, MD, PhD	Local Principal Investigators	Street: Put dr Goldmana 4 Town: Sremska Kamenica Postal Code: 21204 Country: Serbia Phone: +38163433982 Fax: Email: otto@sezampro.rs Email2: ncemerlica@gmail.com
18. Institut Català de la Salut (ICS-HUVH)		
José F. Rodríguez-Palomares, MD Bruno Garcia del Blanco, MD	Local Principal Investigators	Street: Passeig de Vall d'Hebron 119 Town: Barcelona Postal Code: 08035 Country: Spain Phone: +34661857792 Fax: Email: jfrodriguezpalomares@gmail.com Email2: brunogb51@gmail.com
19. University of Glasgow (Glasgow)		
Christian Delles, MD	Local Principal Investigators	Street: University Place 126 Town: Glasgow

Colin Berry, MD, PhD		Postal Code: G12 8TA Country: United Kingdom Phone: +441413302749 Fax: Email: christian.delles@glasgow.ac.uk Email2: Colin.Berry@glasgow.ac.uk
20. Aintree University Hospital (AUHT)		
Gershan K. Davis, MD Erika Thwaite, MD	Local Principal Investigators	Street: Longmoor Lane Town: Liverpool Postal Code: L9 7AL Country: United Kingdom Phone: +44 151 529 2974 Fax: +44 151 529 2724 Email: gershan@hotmail.com Email2: ERICA.THWAITE@aintree.nhs.uk
21. Turku University Hospital / Turku PET Centre		
Juhani Knuuti, MD, PhD, Mikko Pietilä, MD, PhD	Local Principal Investigators	Street: Kiinamyllynkatu 4-8 Town: Turku Postal Code: FI 20520 Country: Finland Phone: (+) 358 23132842 Email: juhani.knuuti@utu.fi Email2: Mikko.Pietila@tyks.fi
22. The Institute of Cardiology in Warsaw (IKARD)		
Cezary Kępka MD, PhD Mariusz Kruk, MD	Local Principal Investigators	Street: Ul. Alpejska 42 Town: Warsaw Postal Code: 04-628 Country: Poland Phone: (+) 48 725993883 Email: ckepka@ikard.pl Email2: mkruk@ikard.pl
23. University of Medicine and Pharmacy Targu-Mures (UMF)		
Theodora Benedek, MD, PhD Imre Benedek, MD, PhD	Local Principal Investigator	Street: 38 Gheorghe Marinescu Street Town: Târgu Mureș Postal Code: 540139 Country: Romania Phone: (+) 40722560549 Phone2: (+) 40265217333 Email: hintea_teodora@yahoo.com Email2: imrebenedek@yahoo.com
24. Clinical Hospital Center Zemun (CHCZ), Faculty of Medicine University of Belgrade (MFUB)		
Radosav Vidakovic, MD, PhD Aleksandar N.	Local Principal Investigators	Street: Vukova 9 Town: Belgrade-Zemun Postal Code: 11080 Country: Serbia Phone: +381 11 3772761

Neskovic, MD, PhD		Phone2: +381 11 3772761 Email: vidra71@yahoo.com Email2: neskovic@hotmail.com
25. OSAKIDETZA Bilbao-Basurto (OSI Bilbao-Basurto)		
Ignacio Díez González, MD Abel Andrés Morist, MD	Local Principal Investigators	Street: Avenida Montevideo, 18 Town: Bilbao Postal Code: 48013 Country: Spain Phone: (+)34652760568 Phone2: Email: IGNACIO.DIEZGONZALEZ@osakidetza.net Email2:

Other Scientific Departments in Work Packages

Name	Title/Designation	Address and Contac Numbers
1.2 KKS Charité		
Olaf Bender Dr. rer. medic Rita Pilger, MSc and Corinna Meier-Windhorst, VM The-Hoang Do Felix Frömel	WP5 Good Clinical Practice and Safety Surveillance WP4 Clinical Data Management	Charité – Universtitätsmedizin KKS Charité Town: Berlin Postal Code: 13353 Country: Germany Street: Augustenburgerplatz 1 Phone: +49 30 450 553016 Email: olaf.bender@charite.de
2. Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum (LUMC)		
Jacob Geleijns, PhD	WP2 EU CT Quality Criteria and Radiation Exposure	Street: Albinusdreef 2 Town: Leiden Postal Code: 2333 ZA Country: Netherlands Phone: +31715262049 Fax: E-Mail: k.geleijns@lumc.nl
3. Institut National De La Sante Et De La Recherche Medicale (INSERM)		
Christine Kubiak, PhD	WP5 Good Clinical Practice and Safety Surveillance	Street: Rue de Tolbiac 101 Town: Paris Postal Code: 75654 Country: Phone: +33144236278 Fax: E-Mail: christine.kubiak@ecrin.org
4. Fundacion Vasca De Innovacion e Investigacion Sanitarias (Osteba-BIOEF)		

Iñaki Gutiérrez-Ibarluzea, MSc. MD Bioethics, MD Epidemiology, PhD Gaizka Benguria-Arrate, M.Sc.	WP 8 Systematic Review of Evidence	Street: Donostia-San Sebastian 1 Town: Vitoria-Gasteiz Postal Code: 01010 Country: Spain Phone: +34945019250 Fax: Email: osteba7-san@ej-gv.es
5. University of Copenhagen, Center for Health Economics and Policy (CHEP)		
Karsten Vrangbæk, MA, PhD Hans Keiding, MSc, PhD (in collaboration with 1. Charité: Marc Dewey and 7. Universitätsklinikum Jena: Peter Schlattmann)	WP9 Cost-effectiveness	Street: Øster Farimagsgade 5 Town: Copenhagen K Postal Code: 1353 Country: Denmark Phone: 0045 29410069 (mobile) Fax: Email: KV@ifs.ku.dk Email2: Hans.Keiding@econ.ku.dk
1.3 Charité, Berlin Institute of Public Health (CHARITE)		
Jacqueline Müller-Nordhorn, MD, DPH Nina Riekmann, PhD	WP10 Quality of Life	Street: Charitéplatz 1 Town: Berlin Postal Code: 10117 Country: Germany Phone: +49 30 450 570872 Fax: E-Mail: jacqueline.mueller-nordhorn@charite.de E-Mail2: nina.rieckmann@charite.de
7. Universitätsklinikum Jena (UKJ)		
Peter Schlattmann, MD, PhD Mario Walther, DSc (leaves UKJ)	WP11 Statistical Analysis	Street: Bachstraße 18 Town: Jena Postal Code: 07743 Country: Germany Phone: +49 3641 934130 Fax: E-Mail: peter.schlattmann@mti.uni-jena.de E-Mail2:

Outreach to Stakeholders including Patient Interest Groups

Participant	Name of Patient Interest Group/ Heart Foundation	Name of Contact Person
1. CHARITE	German Heart Foundation at Berlin-Weißensee	Chair: Mrs. Martina Seiffert
2. MUI	Currently not	Currently not
4. FN Motol	Czech Society for Cardiology	In progress
5. REGIONH	Danish Heart Association	Chair: Henrik Steen Hansen, Odense University Hospital
	Danish Heart Foundation	Chair: Henrik Steen Hansen, Odensen University Hospital
6. ALB	Local “Herzsportgruppe”, Cardiac Training Course for pts with cardiovascular diesease. In cooperation with the established Handball team “Frisch Auf Göppingen”	Dr. C. Hofgärtner, Klinik am Eichert, Göppingen
	Local patient interest group	Peter Drescher in Holzgerlingen
	Membership of the “German Heart Foundation”	Prof. Schröder, Klinik am Eichert, Göppingen
7. ULEI	In progress	In progress
8. SE	Patients' Club	Dr. Gyorgy Barczi
	The SzivSN Foundation	Zsuzsanna Bernáth-Lukács,
	Arrhythmia Foundation	Dr. Orsolya Kiss
	Hungarian National Heart Foundation	Dr. Bela Merkely
9. SET	In progress	In progress
10. SVUH	Downe Cardiac Support Group	Seamus McGoran
	National Institute of Health Research, Patient and Public Involvement Group	Susannah Wood
	Northern Ireland Chest Heart and Stroke	Andrew Dougal
	British Heart Foundation	Majory Burns
11. UNICA	Currently not	Currently not
12. UNIROMA	In progress	In progress
13. PSCUH	“Parsirdi.lv”(Translation: “Aboutheart.lv”) – Society of patients with cardiovascular disease	Inese Maurina
14. LSMU	Currently not	Currently not

15. WSS	Polish Cardiac Society.	
	The Lower Silesian Heart Diseases Centre MEDINET,	Prof. Marian Zembala
	The Małopolska Centre of Biotechnology (MCB) (a joint project of the Jagiellonian University and the University of Agriculture)	Dr. Ewa Stępień
	Silesian Center for Heart Diseases, Zabrze;	Prof. Marian Zembala
	American Heart of Poland S.A.,	Dr. Jarosław Hanaś
16. CHVNG/E	In progress	In progress
17. CAM	Association of Patients with Cardiovascular Diseases	Vajda Stefan
	Asociatia cardiacilor operati pe cord din Romania	Casvean Teodor
	Debrecen Heart Association (Debreceni Szív Egyesület -Hungary)	Dr. Fesus Laszlo
	Association for a Healthy Heart ("Egészséges Szívért" Közhasznú Egyesület -Hungary)	Zlati István
	Association for rehabilitation of cardiovascular patients (Szív és Érrendszeri Betegek Rehabilitációs Egyesülete - Hungary)	Bagdi Sándor
	Transylvanian Association of Transvascular Therapy and Transplantation	Buzas-Colcer Gina
	Romanian National Heart Foundation	Prof. Dan Gaita
	Hungarian National Heart Foundation	Prof. Dr. Nagy Andras
18. IKVBV	Disease Prevention Programme	Provincial Government
	Health life style for healthy heart Progamme	Provincial Government
19. ICS-HUVH	Collaboration Outpatient Centers	e.g., Bački Petrovac, Ruma, Indjija, Šid, Novi Bečej, Bačka Topola, Sremska Mitrovica

	APACOR: Asociación de pacientes coronarios	Mariano Hernanz de las Heras
	Associació Gironina de Prevenció i Ajuda a les Malalties del Cor (GICOR)	Dr. Margarita Gou
	Fundación Española del Corazón	Dr. Leandro Plaza Celemín
	European Heart Network	Inés Galindo
22. University of Glasgow	Scottish Cardiac Society	Dr I Findlay, President
	British Heart Foundation	BHF Chairs, Prof. Rhian Touyz and Prof. Andy Baker
	British Cardiac Imaging Society	Prof. Colin Berry, Member Elect
	British Hypertension Society	Dr. C Delles, Executive Committee member
	Society of Cardiac MRI	Dr. N Tzemos, Member Elect
23. AUHT	Aintree Hospital Cardiac Rehabilitation Interest Group	Mary Torpey Cardiac Rehab Nurse
	British Heart Foundation	Customer Service CentreBHF
	European Heart Network	European Heart Network AISBL
	British Heart Foundation	Customer Service Centre
	British Heart Foundation	Customer Service Centre
29. TURKU	Finnish Heart Association	Professor Matti Uusitupa
	Finnish Cardiac Society	Chairman Mikko Pietilä
30. IKARD	Polskie Towarzystwo Kardiologiczne	Warszawa, Stawki 1/3, secretariat@ptkardio.pl
	Rzecznik Praw Pacjenta	Instytut Kardiologii, Warszawa, Alpeksa 42, tel: +48223434100
	Fundacja Instytutu Kardiologii	Warszawa, Alpejska 42, Ms Blanka Wiśniewska, b.wisniewska@ikard.pl
31. UMF	Romanian National Heart Foundation	Prof. Dan Gaita
	Romanian Society of Cardiology	Dr. Gabriel Tatu Chitoiu
32. MFUB	Serbian Cardiac Care Units Association	Prof. Biljana Putnikovic (putnikovicb@live.co.uk; kjsrbije@hotmail.com)
	Echocardiographic Society of Serbia	Prof. Aleksandar N. Neskovic (neskovic@hotmail.com)
	Cardiology Society of Serbia	kontakt@uksrb.org
33. OSAKIDETZA	Fundación Española del Corazón	Dr. Leandro Plaza Celemín

3. Rationale and Background Information

In order to ensure good reporting quality, this study protocol was primarily drafted according to the WHO (Word Health Organization) recommended format for a research protocol (http://www.who.int/rpc/research_ethics/format_rp/en/). In addition, we made sure that also all recommended items of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement[2] were included.

3.1 Need for a Trial

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 until 2030.[3]

Invasive coronary angiography (ICA) is the reference standard for the diagnosis of CAD and allows immediate intervention. However, only 38-40% of patients undergoing ICA in Europe[4] and the USA[5] actually have obstructive CAD. ICA entails relatively rare but considerable risks for patients such as death, myocardial infarction, or stroke.[6; 7] An effective non-invasive test to rule out CAD would be pivotal to reduce the ca. 2 million annual ICAs in Europe that yield negative results.[4] Coronary computed tomography (CT) angiography is the most accurate non-invasive diagnostic imaging strategy for CAD[8; 9] and promises the greatest societal impact with high cost-effectiveness.[10; 11] With its high sensitivity[8; 9] it is the best non-invasive option to exclude CAD in patients with intermediate risk (pretest probability) of CAD,[12] e.g., patients with equivocal stress test results.[13] However, its costs are not reimbursed by state health insurance, except for the restricted patient population with a pretest probability of 10-29% and a calcium score of 1-400 in the UK.[14] CT applied as the first-line imaging modality to determine further workup may result in early and safe discharge of the majority of patients with intermediate risk of CAD and stable chest pain.

3.2 Relevance of the DISCHARGE Trial

ICA has an established role derived from the long history of its use and because it offers the option of performing interventional therapeutic procedures during the same session; therefore it is still considered the diagnostic gold standard in confirming or ruling out stenosis of the coronary arteries.[15; 16] Nevertheless, catheterisation of the heart is an invasive procedure with considerable mental and physical stress for the patient. What must also be mentioned here is the duration of hospitalisation associated with a catheter-based coronary artery examination and the ensuing health care costs.[17] For these reasons, establishing a reliable noninvasive technique for visualising the coronary arteries while at the same time reducing complication rates and cardiovascular events is of great importance. CT has emerged as the most promising candidate for this purpose. It has already been shown that CT is less expensive[11] than ICA and has fewer complications.[18] In addition, CT in general is already widely spread and used[19] and therefore easily available in urban and rural areas alike. It can be easily performed and evaluated and does not need high

physician input.[20] However, while the diagnostic accuracy (efficacy) of CT for assessing CAD has been investigated comprehensively in original studies[21-26] as well as meta-analyses,[8; 9] there is only little evidence for its actual clinical benefit (effectiveness) in the large population of patients with an intermediate pretest probability of disease, who are most likely to benefit from the examination.[12]

The current European Guidelines on the Management of Stable Angina Pectoris recommend a stress test, after initial clinical evaluation, for risk stratification prior to ICA.[27] However, stress tests do not perform at published diagnostic accuracy rates, as proven by the low proportion of obstructive coronary heart disease in patients undergoing elective catheter-based angiography in the routine clinical setting.[5] This is also due to the high rate of stress tests with nondiagnostic results leading to an indication for ICA. CT has been shown to be superior to stress testing for risk stratification,[28-32] and negative CT was found to predict a 5- to 7-year disease-free period for patients.[33; 34]

There are three major trials RESCUE, PROMISE, and SCOT-HEART which can be compared to some extent to the DISCHARGE PRCT: RESCUE and PROMISE, are federally funded randomised controlled trials in the United States and assess the impact of cardiac CT in comparison to functional imaging strategies in patients with stable chest pain.[35; 36]
By mandating the post testing treatment options, RESCUE is using a more restricted trial design and has to be considered an explanatory RCT. As planned with the DISCHARGE PRCT, PROMISE uses a pragmatic approach in its performance of the randomised controlled trial reflecting usual care.[35] This leads to great flexibility in the realisation of the performance which can be considered to be the main reason why patient recruitment has been very good in PROMISE: all of the 10,000 planned patients were already enrolled within 3 years, the study is finalised and the results are published[36]. Nonetheless, although RESCUE will bring and PROMISE has brought about interesting aspects concerning the diagnostic imaging and treatment options in the clinical management of patients with stable angina, they do only compare cardiac CT to standard functional imaging modalities, but not the gold standard for anatomical evaluation, ICA.
The SCOT-HEART trial recently indicated that cardiac CT may reduce myocardial infarction on follow-up if used in patients with **recent onset stable chest pain or discomfort.**[37]

If the planned trial shows CT to be superior in terms of a significant reduction of events, the findings may potentially lead to changes in current guidelines.[27] This may involve that CT coronary angiography becomes a procedure that could be more established and in this way be made available to a large number of patients with stable chest pain and an intermediate pretest probability of CAD. Finally, this means that CT coronary angiography might replace a relevant proportion of the total of approx. 1 million invasive coronary examinations currently performed in Germany each year or of the approx. 3.5 million in Europe,[4] thereby reducing the number of invasive diagnostic procedures.

3.3 Economic Considerations and Health-related Quality of Life

Coronary artery disease (CAD) is the main cause of death in high-income countries.[38] The World Health Organisation (WHO) estimates there will be about 20 million deaths from cardiovascular reasons in 2015, accounting for 30 percent of all deaths worldwide.[39] The European Parliament initiated the compilation of the 2012 European Cardiovascular Disease Statistics[40] based mostly on unpublished results of the Health Economics Research Centre, University of Oxford. According to this statistics, costs in the EU due to cardiovascular diseases are estimated to almost €196 billion a year (54% direct healthcare costs, 24% productivity losses and 22% informal care of ill people). In 2009, the burden of the EU healthcare system due to cardiovascular diseases was over €106 billion, which represents costs per capita €212, i.e. 9% of EU total healthcare expenditures. Next to direct healthcare system expenditures, cardiovascular diseases represent a burden also due to productivity losses (estimated to be €46 billion in 2009) and informal care (€44 billion in 2009).[40]

Authors of the 2012 European Cardiovascular Disease Statistics[40] focused on CAD (International Classification of Diseases, Chapter IX, I20-I25, 10th Revision). According to their results, coronary heart disease causes 21.0% of all deaths in Europe (14.1% in the EU), and 14.1% of all deaths under the age of 65 in Europe (9.7% in the EU). These numbers are not equally distributed across Europe; **Figure 1** and **Figure 2** from[40] show the distribution of death rates under 65 in men and women in Europe. Moreover, the development in time differs in individual countries, as **Figure 3** and **Figure 4** from[40] indicate. (The figures are placed at the end of this chapter.)

Number of deaths caused by coronary heart disease in Europe reaches 1.8 million per year.[40] In addition to that, CAD and the necessary medical treatments lower the patients' health related quality of life (HRQoL). Both physical and mental HRQoL is impaired in patients with CAD, in particular in older patients and women. Related to HRQoL is the concept of quality adjusted life years (QALYs).[41; 42] It is based on the idea that a year in impaired health has a lower value than one in perfect health. QALYs are usually based on utilities which are determined by a standard gamble or time trade off and can take values between 0 (=immediate death) to 1 (=perfect health).[43] Given the estimation of an expert panel[44] QALYs of patients with symptoms, consistent to those of a coronary ischemia is lowered to an equivalent of 0.85 QALY. If a patient faces complications, the value will be even lower.[44; 45] The resulting impact is huge; hence economic considerations are of great importance, as a small change in expenditures per patient can mean a great amount in the healthcare system budget.

As concerns cost-effectiveness comparison of coronary CTA with other imaging modalities used in coronary artery disease, early modelling results have been promising, although they require further research to be confirmed in large clinical trials. Among the first results, Dewey and Hamm[11] and Genders et al.[41] modelled cost-effectiveness in comparison with both new modalities and the most commonly used traditional diagnostic modalities. Dewey and Hamm concluded that up to a pretest probability for coronary artery disease of 50%, CT coronary angiography was the most cost-effective procedure. A major reason for CTA being cost-effective

compared to CCA is the lower rate of adverse events that indicate further treatment and thereby cause additional direct costs. Genders et al. concluded that the optimal diagnostic work-up depends on the optimisation criterion, prior probability of CAD, and the diagnostic performance of CT coronary angiography; CT coronary angiography was considered cost-effective when the prior probability was lower than 44% and 37% in men and women respectively. The systematic review by Mowatt et al.[45] indicates that CTA might be a cost-effective technology. Quite recently, Hetterich et al.[46] called for more cost-effectiveness research in CTA, especially in European environment. Prazeres et al.[47] and Miller et al.[48] support CTA's cost-effective superiority, however, in US and Brasilian environment. The DISCHARGE study is designed to provide much more reliable evidence.

Although the core of the DISCHARGE project is dedicated to the research of clinical effectiveness, cost-effectiveness research will accompany it with the aim to determine whether CT is not only a clinically effective, but also cost-effective alternative, as former results have indicated.[11; 41; 45; 47-50] Investigating cost-effectiveness has been recently recommended also by the group formulating the future directions for cardiovascular disease comparative effectiveness research.[51] The calculation of costs connected with CAD diagnostics is important due to the large number of patients undergoing CAD testing every year; hence, even a small gain in incremental cost-effectiveness ratio (ICER) may have significant impact on health budgets.

3.4 Implication for the Design of the DISCHARGE Trial

According to comparative effectiveness research, a pragmatic study design is considered to be the most sensible design to assess whether a specific treatment procedure should be used on a large scale based on an evaluation of its effectiveness.[1; 52; 53] Only the proposed study design (pragmatic randomised controlled trial – PRCT) allows direct comparison under the conditions of an intention-to-treat analysis, which assesses the practical benefit (effectiveness) of CT versus ICA in a setting that is similar to clinical routine. On doing so, the DISCHARGE trial has been designed in accordance with a recent proposal of an NHLBI Workshop.[51]

In Europe, we can revert to the experience gained with a similar single-centre pilot study in 340 patients at Charité (CAD-Man, NCT00844220).[54] Based on the results of the CAD-Man trial, it is expected that approx. 80-90% of patients do not have obstructive CAD and can be discharged immediately. To ensure representativeness, the DISCHARGE trial will be conducted at 25 clinical sites in 16 European countries.

Differences in death rates from coronary heart disease in men and women under 65 across Europe, last available data 2009[40]

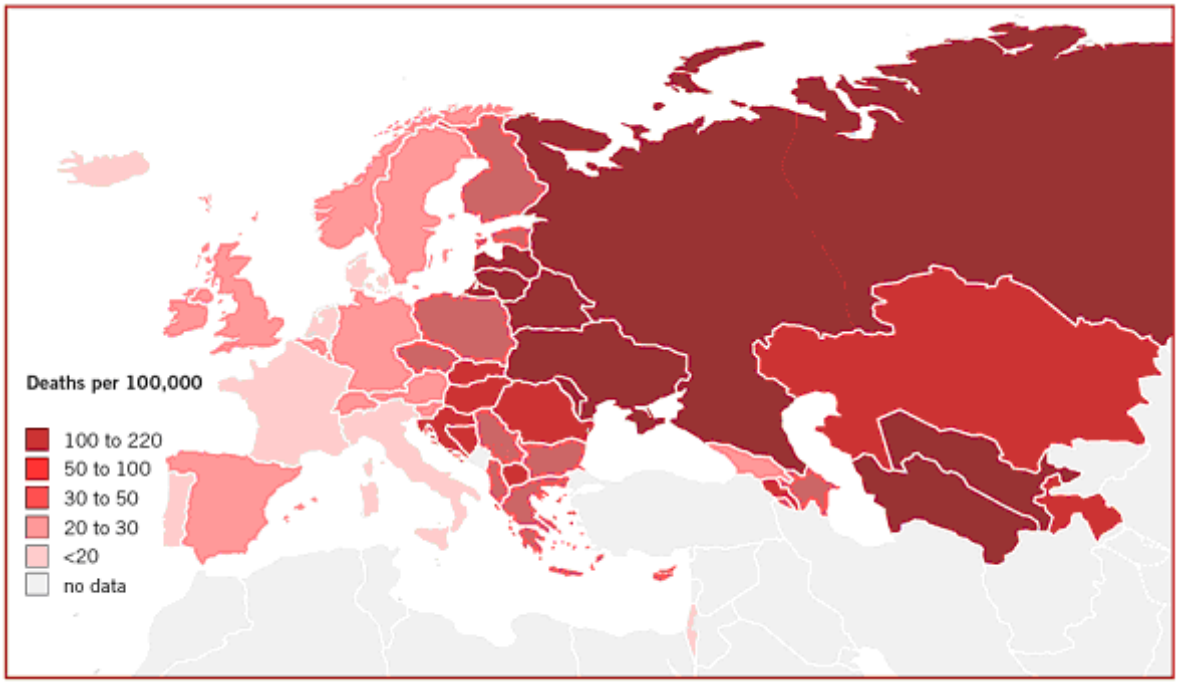

Figure 1. Age-standardised death rates from CHD, men aged under 65, latest available year, Europe

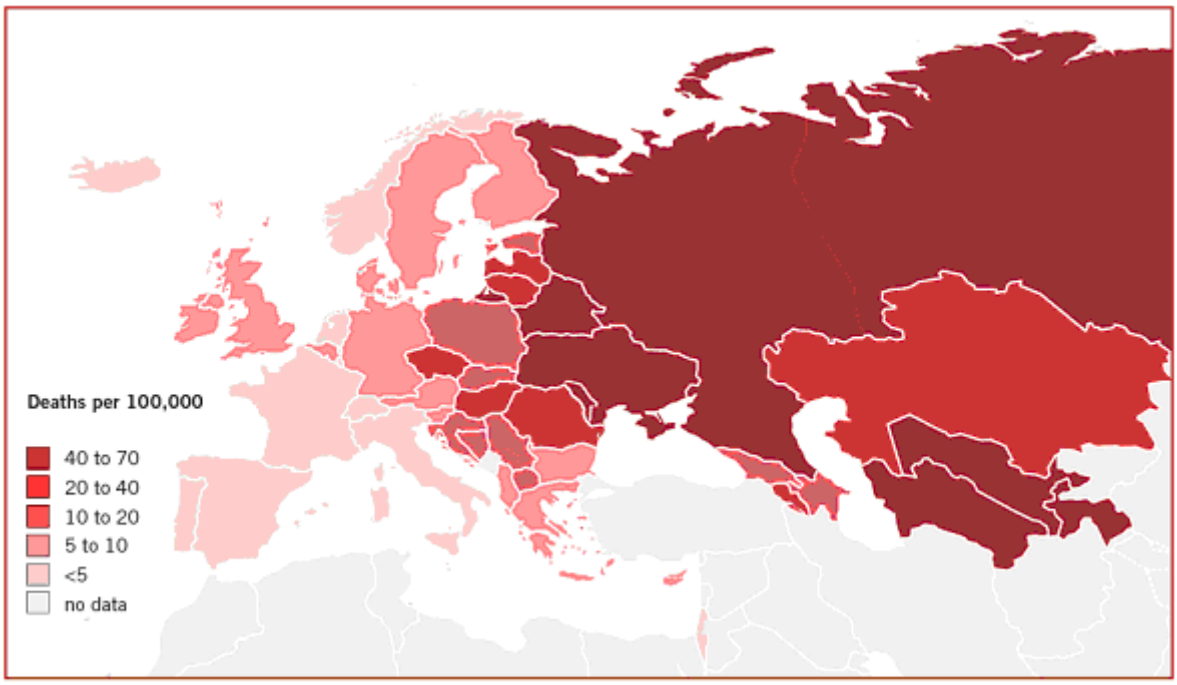

Figure 2. Age standardised death rates from CHD, women aged under 65, latest available year, Europe

Development of death rates from coronary heart disease in men and women under 65 across Europe, last available data 2009[40]

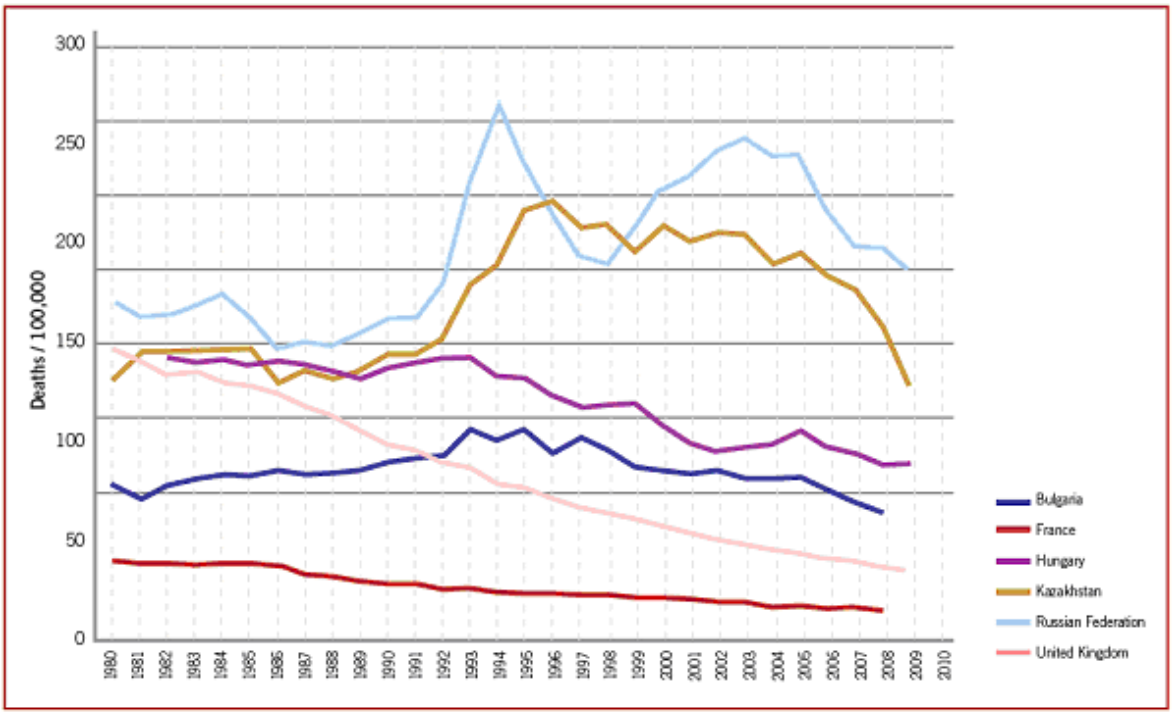

Figure 3. Death rates from CHD, men aged under 65, 1980 to 2010, selected countries

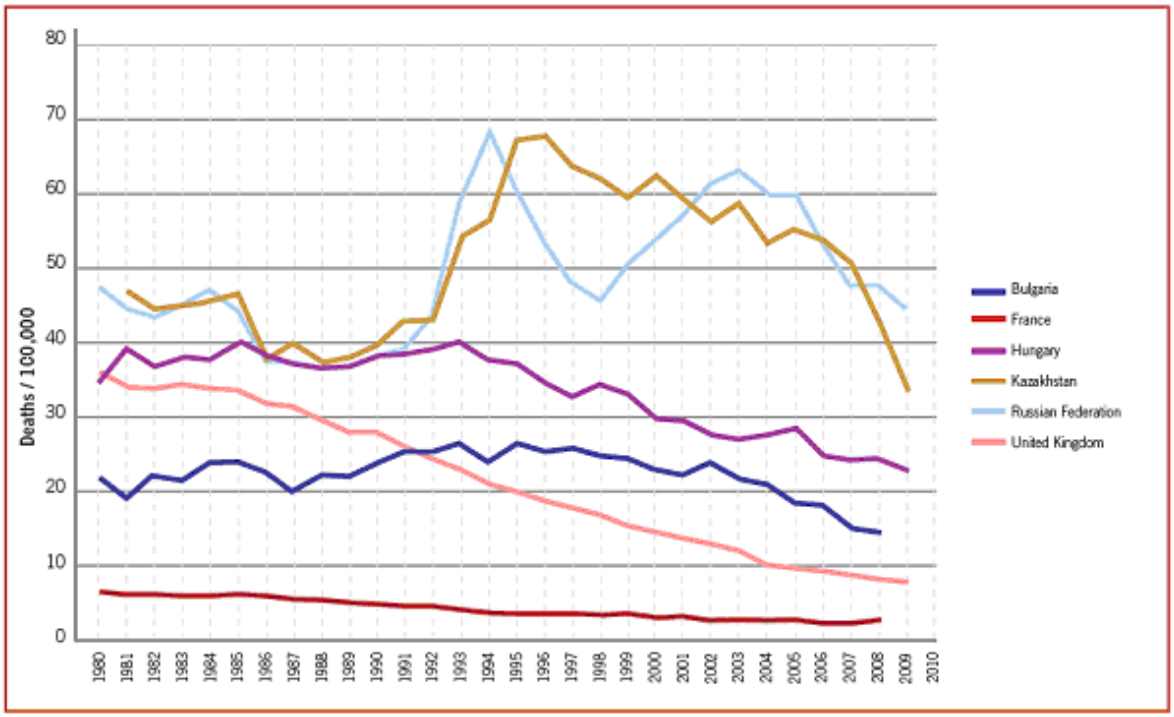

Figure 4. Death rates from CHD, women, aged under 65, 1980 to 2010, selected country

4. Study Goals and Objectives

4.1 Research Hypothesis

The primary hypothesis of this trial is to evaluate the superiority of computed tomography (CT) over invasive coronary angiography (ICA, = conventional coronary angiography or catheter-based coronary angiography) concerning safety in patients with stable chest pain and intermediate pretest probability (10-60%) of coronary artery disease (CAD).

4.2 Study Objectives

A detailed list including the measures is provided in section 6.5.3 “Other Outcome Measures” and published under: https://clinicaltrials.gov/ct2/show/NCT02400229

4.2.1 Primary Objective

The primary objective (or primary outcome measure) for evaluating the superiority of CT over ICA is the occurrence of MACE (MACE = major adverse cardiovascular events; defined as at least one of the following: cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; see Section 6.5.1 "Primary Outcome Measure MACE" for in-detail definition of MACE as well as the electronic case report form (eCRF) after a maximum follow-up of 4 years after CT or ICA in stable chest pain patients with intermediate pretest probability (10-60%) of CAD. A detailed description for evaluating the primary objective is provided in the statistical analysis plan (SAP)as a separate document of the Standard Operating Procedure (SOP) Manual.

4.2.2 Secondary Objectives

Secondary objectives include:

- MACE in Subgroups
- Radiation exposure
- Minor Cardiovascular Events (MICE): They include coronary revascularisation (at least 1 months 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 ischemic attack, and congestive heart failure.
- 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
- Influence of Computed Tomography Angiography and Invasive Coronary Angiography on Angina Pectoris
- Comparison of Incidental Findings in Computed Tomography Angiography and Invasive Coronary Angiography Group and Potential Benefits and Harms of Findings)

- Patient Acceptance/Preference in the Computed Tomography Angiography and Invasive Coronary Angiography Group
- Radiation Exposure in the Computed Tomography Angiography and Invasive Coronary Angiography Group
- Cost-effectiveness Analysis in the Computed Tomography Angiography and Invasive Coronary Angiography Group
- Social-economic Status, Health-related Quality of Life and Lifestyle in the Computed Tomography Angiography and Invasive Coronary Angiography Group
- Gender Analysis in the Computed Tomography Angiography and Invasive Coronary Angiography Group

Procedural complications will be further classified into major and minor. Major procedural complications include death, nonfatal stroke, nonfatal myocardial infarction and other complications requiring a hospital stay of at least 24 hours. Procedural complications that do not fulfil these criteria are classified as minor.

List of Procedural complications:

Major procedural complications

- Death
- Nonfatal myocardial infarction
- Nonfatal stroke
- Further complications prolonging hospitalization by at least 24 hrs

Minor procedural complications

- Hematoma at the puncture site
- Secondary bleeding at the puncture site
- Bradycardia
- Angina without infarction
- Allergoid contrast agent reaction
- Stent migration?
- Hypotension requiring treatment
- Headache
- Hyperthyreodism
- Skin tissue and nerve injuries
- Extravasate
- Cardiac arrhythmia
- Contrast-induced nephropathy (CIN)
- Infections
- Femoral arterial occlusion (or arterial access vessel) or dissection
- New requirement for dialysis
- DVT/pulmonary embolism
- Closure or injury of vessels
- Injury of the heart (e.g. valve or myocardium)
- Cardiac tamponade

- Perforation
- Retroperitoneal bleeding
- Gastrointestinal bleeding
- Genital-urinary bleeding
- Other major bleeding
- Red blood cell (RBC)/Whole blood transfusion
- Twisting or rupture of the catheter parts
- Other equipment mishaps (e.g. retained foreign body guidewire fracture)
- Development of arterio-venous fistula(s)
- Development of pseudo aneurysm at puncture site
- Dissection
- Permanent edema (e.g. due to lymphatic congestion at puncture site)
- Embolisation of central or peripheral vessels due to thromboembolism
- Acute closure of coronary vessels
- Stent infection
- Heart failure
- Cardiogenic shock
- Wrong patient or wrong procedure
- Other

Detailed descriptions for evaluating the secondary objectives are provided in the statistical analysis plan and the cost effectiveness analysis plan.

4.2.3 Other Objectives from Pre-Planned Analyses

- Evaluation of Differences in Europe
- Computed Tomography Angiography and Invasive Coronary Angiography Image-based Secondary Outcomes
- Computed Tomography Image-based Secondary Outcomes: Image Quality
- Computed Tomography Image–based Outcomes: Heart Rate and Dose
- Computed Tomography image-based Secondary Outcomes: Plaques
- Invasive Coronary Angiography Secondary Outcomes
- Planned Cross-over in accordance with management recommendations
- Imaging Ischemia tests
- Comparison of Pre-test Probability Calculators
- Predictive Value of DISCHARGE Calculator
- Development of Novel Pre-test Probability Calculator

5. Study Design

This study is a European multicentre prospective pragmatic randomised controlled trial (PRCT) in patients with suspected CAD conducted at 25 clinical centres. The pragmatic approach of the study addresses practical questions about the risks, benefits, and costs of an intervention as they occur in everyday clinical practice.[52]

CT directed clinical management will constitute the intervention group and ICA directed clinical management will be the control group. Thus, a 2-group randomised approach is utilised. ICA will not be withheld from the patients in the intervention group (CT) but will only be carried out depending on the results of CT. Blinding patients towards the groups - CT or ICA - is not possible. A blinded analysis of all outcomes will address whether CT works under the usual conditions and therefore includes all patients. Thus analysis will be performed in the intention-to-treat population.

5.1 Number of Patients

Approximately 3546 men and women age 30 years or older with suspected CAD and scheduled to undergo invasive coronary angiography will be included in this clinical trial and will be analysed according to the intention-to-treat approach. Patients will be randomised to the intervention (CT) or ICA group.

The study will be conducted at 25 clinical sites (hospitals and heart centres) in 16 European countries (Austria, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Spain, United Kingdom). The results of database searches at each of the 25 clinical sites show that about 50% of the 60950 annual ICAs are performed in patients with suspected CAD comprising 27410 patients. Therefore, it will be feasible to enrol the target number of patients. 20 of these clinical sites are already part of the DISCHARGE consortium and 5 of them are in the inclusion process with the European Commission.

5.2 Eligibility Criteria

Due to the pragmatic approach of this trial,[1] only minimal inclusion and exclusion criteria are used for study population identification.

Inclusion criteria:

- Patients with suspected coronary artery disease with stable chest pain and intermediate pretest probability (10-60%) of CAD referred for invasive coronary angiography.

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

  - being acute
    (= first appearance within the last 48 hours) or
  - instable
    (= (a) first appearance with Canadian Cardiovascular Society Angina Grading Scale (CCS, cf. **Table 1**) 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)
    angina pectoris

- Patients at least 30 years of age
- Written informed consent

Checking for intermediate pretest probability (10-60%) of disease will be the last step

in screening potential patients. It will be performed using a pretest calculator that has been developed at the Charité based on available tools for risk prediction.[55; 56] This calculator uses age, gender, and the patient's clinical presentation of stable chest pain to calculate pretest likelihood 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), a meta-analysis of individual patient data (IPD) of a total of approx. 6,700 cases. This meta-analysis was supported by the German Ministry of Education and Research as part of the joint „clinical study" programme of the ministry and the German Research Foundation (grant number: 01KG1110). At this point in time, the study protocol has been published. [57]

Exclusion criteria:

- Patients who are/were on hemodialysis
- No sinus rhythm
- Pregnancy
- Any medical condition that leads to the concern that participation is not in the best interest of health (e.g., extensive comorbidities)
- Patients who participate in any other randomised/interventional study

Table 1. Classification of angina pectoris according to the Canadian Cardiovascular Society[58]

CCS Class	Description
I	Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina (occurs) with strenuous, rapid or prolonged exertion at work or recreation.
II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
III	Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
IV	Inability to carry on any physical activity without discomfort–anginal symptoms may be present at rest.

5.3 Duration

The expected duration of the study is from October 2015 (start of enrolment) through September 2019 (final follow-up). Patient recruitment and examinations are from October 2015 through September 2017.

For each patient, it is anticipated that the selection period will last less than 1 day.

According to the PRCT design, the number of follow-ups will be minimal in order to avoid interference with usual care. There will be no formal follow-up visits of trial individuals within the DISCHARGE PRCT. Instead, questionnaires (including health status, measures of health-related quality of life, work status, patient preference) will be sent to the patients by mail during the first-year follow-up and several alternative sources (e.g., general practitioners, death registries, and family members) will be utilised for investigating MACE during follow-up. In addition to the final follow-up for MACE, only one exploratory interim analysis will be performed concerning MACE.

6. Methodology

6.1 Interventions

6.1.1 Invasive Coronary Angiography

ICA, as already outlined above, is considered the diagnostic gold standard in confirming or ruling out stenosis of the coronary arteries. All patients participating in the DISCHARGE study will have a referral for ICA based on suspected CAD. The need for this examination was established by the referring physician. However, according to the randomisation schedule, only 50% of the patients enrolled in the study will directly undergo ICA.

In ICA, an X-ray fluoroscopy with administration of contrast medium is performed. For this, a 2 mm flexible plastic tube is threaded to the aortic root of the heart through a punctured artery in the groin or the elbow. When the catheter is advanced to the heart, the coronary arteries and other structures can be depicted by injecting contrast medium through the catheter under fluoroscopy.

In rare cases, the contrast medium can cause mild allergoid reactions (nausea, itching, skin rash, for example). Severe intolerance reactions to the contrast agent (such as impairment of kidney function or allergic shock) are extremely rare as well as other adverse effects. ICA exposes the patient to X-rays. The radiation exposure is about 9-10 mSv, which corresponds to the natural background radiation of 54 to 60 months.

ICA will be performed by cardiologists and cardio-thoracic surgeons.
Detailed information can be found in the electronic case report forms (eCRFs).

6.1.2 Coronary CT Angiography

Two modalities have developed appearing to be suitable to enable noninvasive coronary angiography: CT and magnetic resonance imaging (MRI). Absence of radiation exposure and absence of contrast medium exposure are the two major advantages of MRI. In an earlier study of 130 patients with suspected CAD, 16-row CT and MRI with the standard diagnostic test (ICA) were compared at Charité. CT was found to be significantly superior to MRI in terms of diagnostic accuracy on both the per-patient level and the per-vessel level.[59] The superiority on the patient level

was also confirmed in a large meta-analysis of CT (89 studies) and MRI (20 pooled studies).[8]

Based on these results, it seems desirable to answer the question whether the better results achieved with CT can be translated into a reduction of complications and events compared with the gold standard of catheter-based cardiac angiography. Starting in 1998, multislice CT has been developed as an alternative method to ICA. The aim of this alternative method is to examine the arteries that supply the heart muscle (the coronary arteries) with similar reliability but less invasiveness. Earlier studies show that cardiac CT has an accuracy of 95-97% in detecting narrowing (stenosis) of the coronary arteries. Moreover, CT also allows ruling out stenosis with a high degree of probability (so-called negative predictive value) Therefore, CT allows reliably ruling out suspected stenosis (narrowing) without the need for ICA. In order to ensure adequate diagnostic accuracy, each DISCHARGE clinical site will utilise at least 64-slice CT which is state-of-the-art.[8; 9; 60] The CT examination of the heart takes about 15 to 25 minutes. The actual CT scan takes only about 0.2-8 seconds, depending on the CT scanner used. During this time, it is necessary that patients hold their breath for a short period of time. Before CT, the patient's medical records will be reviewed and blood samples may be taken according to local standards. In addition, an ECG will be obtained, unless a patient has a recent ECG (obtained within 1 month before CT). Caffeine is not allowed for 4 hours before the CT examination (coffee, tea, or chocolate, for example). Patients with a heart rate of more than 50 beats/minute (bpm) will be given metoprolol (a betablocker). Alternatively, in case of beta blocker contraindications, ivabradine or calcium channel blockers can be administered. If, after these medications, the heart rate is still above 55 beats per minute just before the CT scan, additional heart-rate control medication will be available (in order to reach the target heart rate of 60 bpm. Ivabradine cannot be given under a heart rate of 60 bpm.

First, non-contrast coronary artery calcium scan (CACS) will be performed. It will be used to determine start and end position of coronary arteries for the subsequent CTA in order to reduce effective dose. However, no patients will be excluded based on high CACS values in the DISCHARGE trial.

Immediately before the CTA examination, nitroglycerine will be given under the tongue to make the coronary arteries wider, which improves their assessment. As with ICA, the CT examination also involves injection of a contrast agent. The contrast agent is an approved agent for CT examinations and will be injected into a vein in the crook of the elbow. In the DISCHARGE trial, preferably a triphasic injection protocol will be used. Again, in rare cases, the contrast agent can cause mild allergoid reactions (nausea, itching, skin rash, for example). Severe intolerance reactions to the contrast agent (such as impairment of kidney function or allergic shock) are extremely rare as well as other adverse effects.

After the examination, reconstructions for CACS, CTA and noncardiac structures will be made. For reading, workstations that can automatically generate curved multi planar reconstructions (MPRs) will be used and, for interpretation, axial, coronal, sagittal source images, curved MPRs and axial, coronal, and sagittal as well as double-oblique thin-slice maximum intensity projections (MIPs) will be used. For reporting, a modified Society of Cardiovascular Computed Tomography (SCCT) Coronary Segmentation Model with 18 segments based on the American Heart

Association (AHA) 17-segment model will be employed.

The same as ICA, CT is also performed with X-rays. The radiation dose is about 1 to 5 mSv and roughly corresponds to the natural background radiation of 6 to 30 months.
Cardiac CT will be performed by board certified radiologists with at least SCCT level II (or equivalent) qualification. Also cardiac CT lab leadership (SCCT level III or similar, such as Q3 Zertifikat der Deutschen Röntgengesellschaft) needs to be shown by all clinical sites.

In order to ensure minimal standards for the performance of CT, a general 10-step guide specifying the most important aspects – patient preparation, examination, reconstruction, reading, reporting - was developed. Based on this guide, vendor- and scanner-specific scan protocols for the participating clinical sites were worked out. (10-Step Guide to Performing Cardiac CT; vendor- and scanner-specific scan protocols: Toshiba, Siemens, GE, and Philips). Further detailed information can be found in the SOP Manual and CTA-related eCRFs.

6.2 Randomisation

Eligible patients will be randomised to receive either CT or ICA (Sop Manual). Allocation will be concealed and equal allocation to the two trial arms will be ensured by block randomisation. In addition, patients will be stratified according to clinical site, and gender in order to minimise covariate imbalance. The randomisation to the intervention (CT) and control group (ICA) will be performed online by using the randomisation tool of the study software secuTrial®.

An intermediate pretest probability (10%-60%) for CAD will be the final inclusion criterion before randomisation. If the patients do not fulfill this, they will undergo ICA as initially planned and the results of this examination will be recorded. No follow-up will be conducted in these patients. In general, an ongoing log for all patients who were screened for the study and reasons for not being enrolled will be maintained (see corresponding eCRFs).

6.3 Withdrawal

All patients who cannot be analysed per protocol, but have signed informed consent are called drop-outs. Patients who withdraw their participation or who are withdrawn by the principal investigator are also drop-outs and are labelled as withdrawals. Reasons for early withdrawal from a study may include but are not limited to:

1. Patient withdraws consent.
2. Further participation is not in the best interest of the patients health
3. Study ends prematurely.

Patients who withdraw after the diagnostic procedure are considered in the intention-to treat (ITT) analysis. Patients with a randomisation deviation (did not receive diagnostic test they were randomised to) are not considered as drop-outs and are considered as well in the intention-to treat analysis. For both of these cases, new patients need to be recruited. Withdrawals before the diagnostic procedure, do not

count in the ITT analysis.

6.4 Treatment Decisions

Except for basic recommendations based on a combination of current guidelines, the decision-making process concerning treatment options as part of the CT- and ICA-guided management of patients will be made by the local heart team at each individual centre (see below Figure 5. Design of the DISCHARGE pragmatic randomised controlled trial, and SOP Manual), thus reflecting the pragmatic routine practice approach of the DISCHARGE trial.

In the ICA arm of DISCHARGE, the local heart team makes the treatment decisions according to the ESC/EACTS guideline.[61]
In the CT arm of the trial, only patients with high-risk anatomy (left main stenosis or equivalent, proximal LAD [left anterior descending] stenosis, or 3-vessel disease)[61] will be recommended to receive ICA (and fractional flow reserve [FFR], if available) to clarify anatomy and to decide which lesion to revascularise in which way according to the ESC/EACTS guideline.[61] This is recommended because of the imperfect positive predictive value of CT in intermediate risk patients.[12] In patients with 1- or 2-vessel disease in CT, the local heart team will use the best locally available ischemia test (stress echo, SPECT, or stress MRI) before making the decision to perform ICA.[62] In case of <10% ischemic myocardium, only optimal medical therapy (OMT) is recommendend.[63] In case of >10% ischemic myocardium, ICA (and FFR, if available) is recommended before making the final decision for or against revascularisation.[63]
It can be expected that about 80-90% of patients have no obstructive (≥50%) stenosis. These patients will receive guideline-oriented medical therapy and will be immediately discharged.[62; 64; 65]

Also, cardiac and noncardiac secondary findings at CT which can range from being of no consequence to being clinically very relevant and requiring immediate intervention, additional diagnosis, or follow-up (e.g., suspected cancers) will be available to the **local heart team** for treatment decisions[66] in order to ensure that these incidental findings will be used in a beneficial way. Diagnostic and treatment decisions of secondary findings will primarily be made by the local team and depend on the entity of the secondary finding. Incidentally detected lung nodules will be followed up according to Lung CT Screening Reporting and Data System of the American College of Radiology (Lung RADS)[67] modified for DISCHARGE (SOP Manual).

The local heart team will determine **optimal medical therapy** and **risk factor modification** according to European guidelines[13; 68] and usual care. 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 by which cardiac events can be predicted[69; 70] or high-risk plaque features such as low-attenuation noncalcified plaques (≤50 HU[71] [The threshold might change with intraluminal enhancement]), a positive remodeling index ≥1.1[72-74] (calculated as the vessel cross-sectional area at the site of maximal stenosis divided by the average of proximal and distal reference segments' cross-sectional areas) or the presence of a napkin-ring sign[72; 74] (non-calcified plaque with a central area of low CT

attenuation that is apparently in contact with the lumen; and a ring-like higher attenuation plaque tissue surrounding this central area). For details see the **plaque characterisation document** in the SOP Manual. It is recommended to treat patients according to guidelines with clear target values for blood pressure and lipids according to the European guideline on cardiovascular disease prevention[68] and management of stable angina.[13] For risk factor modification in DISCHARGE please check the recommendation "What is CVD prevention" (SOP Manual).

As the DISCHARGE trial concentrates on the assessment of coronary CT angiography in comparison with ICA, it has to be specifically mentioned that **no CT perfusion** or **CT FFR will be allowed** within the trial. The following ischemia tests: are allowed: Echo, MRI, SPECT, PET-CT, and ECG.

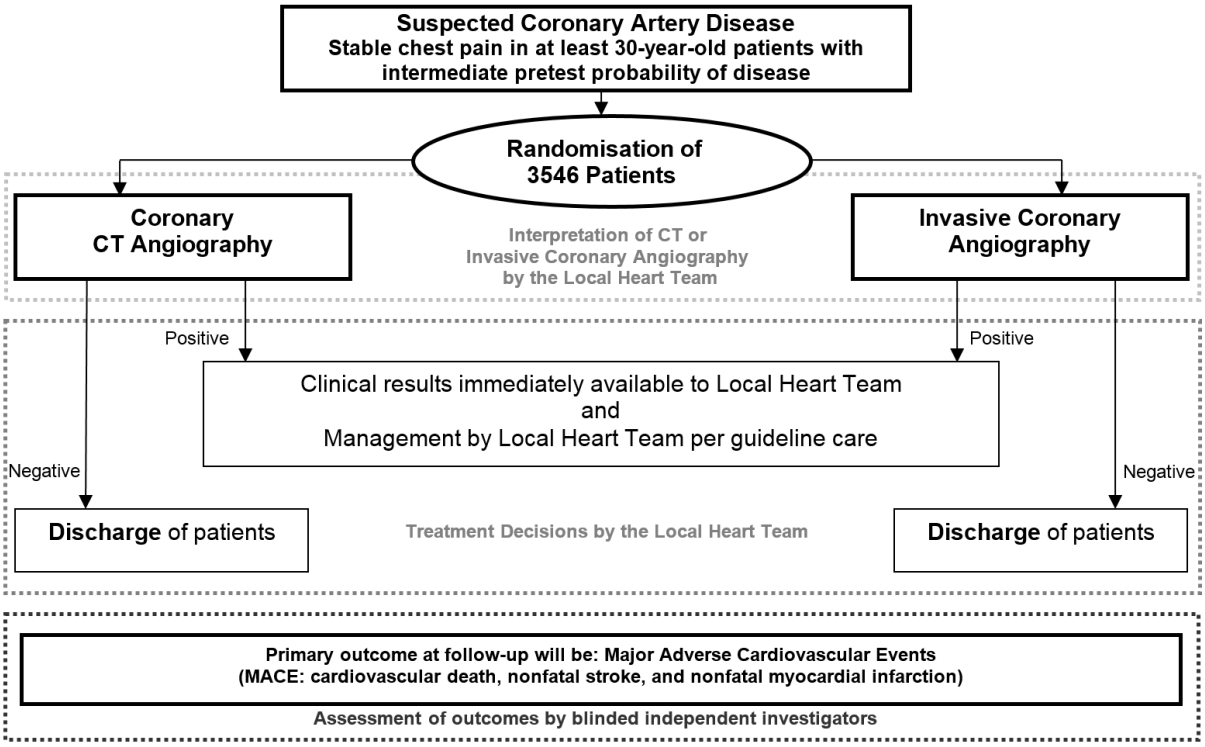

Figure 5. Design of the DISCHARGE pragmatic randomised controlled trial

6.5 Outcome Measures

6.5.1 Primary Outcome Measure MACE

The primary outcome measure is the composite endpoint "major adverse cardiovascular event (MACE)". It is defined as at least one of the following:

- cardiovascular death
- nonfatal myocardial infarction
- nonfatal stroke

Time Frame: 1 minute after CT/ICA diagnosis/procedure and during follow-up
Designated as safety issue: No

In the following sections, definitions for each of the above listed elements of MACE will be provided:

6.5.1.1 Cardiovascular Death

The standardised definitions for cardiovascular and stroke end point events in clinical trials by the Cardiac Safety Research Consortium[75] will be implemented. According to this definition, cardiovascular death includes death resulting from:

a) Acute myocardial infarction
b) Sudden cardiac death
c) Death due to heart failure
d) Death due to stroke
e) Death due to cardiovascular procedures
f) Death due to cardiovascular hemorrhage
g) Death due to other cardiovascular causes

In the following, the main aspects of the referred document are summarised. For detailed information please see the original article.[75]

a) Death due to acute myocardial infarction
Death due to acute MI refers to death by any cardiovascular mechanism after a MI related to the immediate consequences of the MI.
Death resulting from a procedure to treat an MI or to treat a complication resulting from MI should be considered death due acute MI.
Death resulting from an elective coronary procedure to treat myocardial ischemia or death due to an MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as death due to cardiovascular procedure.

b) Sudden cardiac death
Sudden cardiac death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- Death after unsuccessful resuscitation from cardiac arrest
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

c) Death due to heart failure
Death due to heart failure (HF) refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology (see document for details).

d) Death due to stroke
Death due to stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke.

e) Death due to cardiovascular procedures
Death due to cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure.

f) Death due to cardiovascular hemorrhage
Death due to cardiovascular hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g. aortic aneurysm) or hemorrhage causing cardiac tamponade.
g) Death due to other cardiovascular causes
Death due to other cardiovascular causes refers to a cardiovascular death not included in the above categories but with a specific, known cause (e.g. pulmonary embolism or peripheral artery disease).

6.5.1.2 Nonfatal Myocardial Infarction

The actual definition of myocardial infarction (MI) of the ESC/ACCF/AHA/WHF Task Force[76] will be implemented. The **Infobox** in **Table 2** briefly summarises the criteria which, under these conditions, constitute the diagnosis for MI. Events are defined as nonfatal if they are not leading to death of the included patient. All fatal events will be recorded and discussed in section 7.3 Cardiovascular death.

Table 2. Infobox. Criteria for acute myocardial infarction

Setting	Criteria
1	Spontaneous MI and MI secondary to an ischemic imbalance: ▪ Detection of a significant rise and/or fall of cardiac biomarker enzymes *Plus* ▪ symptoms of ischemia *OR* ▪ new or presumed new significant ST-Segment-T wave (ST-T) changes or new left bundle branch block (LBBB) in the ECG *OR* ▪ development of pathological Q waves *OR* ▪ imaging evidence of new loss of viable myocardium or new regional wall motion abnormality *OR* ▪ Identification of an intracoronary thrombus by angiography *or autopsy**
2	*Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block (LBBB), but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased**
3	Percutaneous coronary intervention (PCI) related MI: ▪ significant elevation of cardiac biomarker enzymes in patients with normal baseline value *OR* ▪ rise of biomarker enzyme values >20 % if the baseline values are elevated and are stable or falling. *Plus* ▪ symptoms suggestive of myocardial ischemia *OR* ▪ new ischemic ECG changes *OR* ▪ angiographic findings consistent with a procedural complication *OR* ▪ imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality
4	Stent Thrombosis related MI: ▪ detected by coronary angiography *or autopsy** *Plus* ▪ significant rise and/or fall of cardiac biomarker values
5	Coronary artery bypass graft (CABG) related MI:

	▪ significant elevation of cardiac biomarker values *Plus* ▪ new pathological Q waves or new LBBB *OR* ▪ angiographic documented new graft or new native coronary artery occlusion *OR* ▪ imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

**Myocardial infarction resulting in death will be recorded in section 6.5.1.1 Cardiovascular death*

Please note that only symptomatic events are defined as MACE. Asymptomatic events are defined as incidental findings – if they will be detected at all. The latter will be discussed below (see "Silent myocardial infarction").

Biomarker detection of myocardial injury and ECG detection

For detailed information about biomarker detection of myocardial injury and ECG detection please look at the referred consensus document.[76] The following extracts represent the main aspects:

Biomarker detection

- The preferred biomarker of MI is cardiac troponin I or T (cTn)
- If a cTn assay is not available, the best alternative is creatine kinase MB isoform (CKMB).

ECG detection

ECG changes in patients that suffer myocardial infarction may be inscribed in the PR segment, the QRS complex, the ST-segment or the T wave. The following **Table 3** lists ST-T wave criteria for the diagnosis of acute myocardial ischemia that may lead to MI.

Table 3. ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and LBBB)

Changes	Description
ST elevation	New ST elevation at the J point in two contiguous leads with the cut-point: ▪ ≥0.1 mv ▪ exception: V_2-V_3: o ≥0.2mVin men ≥40 years o ≥0.25mV in men <40 years o ≥0.15mV in women
ST depression and T wave changes	New horizontal or down-sloping ST depression ▪ ≥0,05mV in two contiguous leads *AND/OR* ▪ T-inversion ≥0,1mV in two contiguous leads with prominent R wave or R/S ratio >1

Classification of myocardial infarction

In addition, each nonfatal myocardial infarction will be classified as indicated by the ESC/ACCF/AHA/WHF Task Force (**Table 4**).

Table 4. Universal classification of myocardial infarction

Type	Description
1	**Spontaneous myocardial infarction** Related to atherosclerotic plaque rupture, ulceration, assuring, erosion or dissection with resulting intraluminal thrombus in one or more of the coronary arteries with ensuing myocyte necrosis.
2	**Myocardial infarction secondary to an ischemic imbalance** Myocardial necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand. E.g. coronary endothelial dysfunction, coronary artery spasm, coronary

	embolism etc.
3	***Myocardial infarction resulting in death when biomarker values are unavailable****
4a	**Myocardial infarction related to percutaneous coronary intervention (PCI)**
4b	**Myocardial infarction related to stent thrombosis**
5	**Myocardial infarction related to coronary artery bypass grafting (CABG)**

** Myocardial infarction resulting in death will be recorded in section 6.5.1.1 Cardiovascular death*

Silent myocardial infarction
Silent myocardial infarctions will be treated as incidental findings. When, e.g., a Q wave MI without any symptoms is detected, it will be recorded as an incidental finding and the Clinical Events Committee (CEC) will be informed. Furthermore, temporal aspects of silent myocardial infarctions will be recorded if such data is available. For example, when a patient presents with normal ECG findings at the enrolment stage of the study and a Q wave MI is detected at a later moment within study conduction, the infarction will be recorded as having been occurred during study conduction.

6.5.1.3 Nonfatal Stroke

Unfortunately, no uniform definition of stroke in cooperation with a European medical society exists. Therefore, the definition of stroke by the AHA/ASA[77] was implemented. In the following, the main aspects of the referred document are summarised. For detailed information please see the original article.[77]
Please note that, similar to acute myocardial infarction, only symptomatic events are defined as MACE. Asymptomatic events are defined as incidental findings – if they will be detected at all. The latter will be discussed below (see "Silent CNS infarction").

Definition of ischemic stroke:
An episode of neurological dysfunction caused by focal infarction of the central nervous system (CNS).

Definition of CNS infarction:
CNS infarction is brain, spinal cord or retinal cell death attributable to ischemia, based on

1. Pathological imaging, or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution; or
2. Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.

CNS infarction includes hemorrhagic infarctions, types I and II; see "Hemorrhagic Infarction."

Hemorrhagic infarction
The term "hemorrhagic stroke" is confusing because it could mean hemorrhage after infarction or primary intracerebral hemorrhage (ICH) or subarachnoidal hemorrhage (SAH). The use of this term should be discontinued. A more standardised approach has been used in clinical trials: hemorrhagic infarction and parenchymal hemorrhage. Hemorrhagic infarction is characterised by its lack of mass effect and is divided into

type I and II. Hemorrhagic infarction type I is defined by petechiae of blood along the margins of the infarction, whereas type II has confluent petechiae within the infarction but without a space-occupying effect. These hemorrhagic infarctions typically present with clinical manifestations similar to non-hemorrhagic infarctions and are often treated according to typical ischemic stroke recommendations and there should be considered cerebral infarctions.

In contrast, parenchymal hemorrhage is defined by the presence of mass effect, similar to the ICH definition of a focal collection of blood. Parenchymal hemorrhage type I is a confluent hemorrhage limited to ≤30% of the infracted are with only mild space-occupying effect, and type II is >30% of the infracted are and/or exerts a significant space-occupying effect. These parenchymal hemorrhages may present with signs and symptoms of mass effect and may require reversal of antithrombotic therapy, aggressive antihypertensive therapy, and/or anti-edema therapy, all of which are distinctly atypical for infarctions but are common recommendations for the treatment of ICH. Therefore, parenchymal hemorrhages should be considered ICHs.

Cerebral hemorrhage
Hemorrhages in the CNS will be classified as stroke if they are nontraumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages will not be characterised as stroke. The diagnoses included in cerebral hemorrhage are *intracerebral hemorrhage (ICH), subarachnoidal hemorrhage (SAH)* (both aneurysmal and nonaneurysmal), and *intraventricular hemorrhage*.

Intracerebral hemorrhage (ICH)
Definition of intracerebral hemorrhage:
A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. (Note: Intracerebral hemorrhage includes parenchymal hemorrhages after CNS infarction, types I and II—see “Hemorrhagic Infarction.”)
Definition of stroke caused by intracerebral hemorrhage:
Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Subarachnoidal hemorrhage (SAH)
Spontaneous SAH is defined as a stroke because it is a CNS hemorrhage with a vascular cause that commonly results in permanent injury to the CNS.

Definition of subarachnoid hemorrhage:
Bleeding into the subarachnoid space.
Definition of stroke caused by subarachnoid hemorrhage:
Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space, which is not caused by trauma.

Intraventricular hemorrhage
Intraventricular hemorrhage is considered a subtype of ICH.

Cerebral venous thrombosis
Definition of stroke caused by cerebral venous thrombosis:
Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.

Silent CNS infarction
Silent CNS infarctions will be treated as incidental findings. When, for example, there is imaging evidence of prior cerebral infarction without clinical symptoms, it wil be recorded as an incidental finding and the Clinical Events Committee (CEC) will be informed. Furthermore, temporal aspects of silent CNS infarctions will be recorded if such data is available. E.g., when a patient presents with imaging evidence of no CNS infarction at the enrolment stage of the study and a silent CNS infarction is detected at a later moment within study conduction, the infarction will be recorded as having been occurred during study conduction.

Important note
"At the end of deliberations, the final recommendations for the definition of stroke were not acceptable by the leadership of the European Stroke Organisation and World Stroke Organisation. These organisations declined to participate further in this statement. Their dissent was mainly associated with the inclusion of silent cerebral infarction and silent cerebral hemorrhage within the universal definition of stroke."
According to the consensus of the DISCHARGE Kick-Off-Meeting, these entities will not be defined as MACE in the DISCHARGE trial, anyway. Therefore, the referred document will be implemented.

6.5.1.4 General Considerations

MACE is a composite endpoint. A composite endpoint consists of two or more single events combined in one outcome that should represent an overall clinically relevant and valid measure.[78] Clinical sites will have to pay close attention to the effects not only on the composite endpoint overall, but also on each component of the composite endpoint. As an example, all events will be reported separately in a clear and complete manner which will be assured by the eCRF. More information about composite endpoints can be found in the European Network for Health Technology Assessment Guideline.[78]

6.5.2 Secondary and Other Outcome Measures for Pre-planned Analysis

All details can be found in the SAP, Cost-Effectiveness (CEA) Analysis Plan and on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02400229).

6.6 Pilot Study

The DISCHARGE PRCT is preceded by a pilot study to gain important data for the work packages Cost-effectiveness Analysis (CEA, WP9) and Health-related Quality of Life (QoL, WP10). This pilot study has three main purposes:

1. To collect data for the main CEA of every clinical site using a micro-costing approach (WP9).
2. To test several quality of life instruments as well as a time trade-off question (WP10) to select the best suitable questionnaires for the main PRCT.
3. Too ensure image quality for CT/ICA and test the 10-steps guide for cardiac CT and the scanner specific CT scan protocols.

The pilot study is neither randomised nor controlled. All patients with stable chest discomfort, at least 30 years of age and with suspected coronary artery disease (CAD) and a referral are suitable for inclusion. Each clinical site has to include 30 patients scheduled for routinely performed cardiac computed tomography angiography (CTA) and 30 patients for invasive coronary angiography (ICA). In comparison to the main PRCT there is no restriction in the pretest probability for CAD, which will be assessed retrospectively.

If locally required, the clinical sites obtained ethical approval for the pilot study. All data should be collected anonymously without written informed consent, since this process is contradictory to anonymous collection. Clinical sites with ethics committees that require to employ written informed consent need to anonymise the data. The pilot study participants do not undergo any follow-up. Paper based case report forms (CRF) were designed to collect the data which is then entered in a digital spreadsheet and sent to the coordinating center for remote monitoring as well as hard copies of these documents for further quality control. A pilot study package was distributed to the clinical sites containing all necessary documents as well as a dedicated comprehensive manual to ensure the correct conduct of the pilot study.
Pilot patients complete the quality of life questionnaire that includes several measures of health-related quality of life (EQ-5D-3L, SF-12-v2, Hospital Anxiety and Depression Scale, WHO-5), [79; 80] and a time trade-off question regarding chest pain. The time trade-off method allows for the assessment of differences in perceptions regarding how different health states impact on life quality, in this case chest pain. This method quantifies preferences by “assessing how much time a patient would be willing to give up to be freed from a reduced health state” [81]. The time-trade-off (TTO) utility is defined as the “number of years left to live symptom-free” (number of years left to live minus the number of years traded for symptom-free living) divided by the “number of years to live with symptoms”. Due to the pragmatic nature of DISCHARGE, it was decided that TTO should be administered via a self-administered questionnaire. The TTO question in the pilot study is based upon a study published by Burström and colleagues in 2006.[82]

In addition, a short from of the Rose Angina questionnaire was included to assess “exertional chest pain”.[83] The patients were asked about the time needed to complete all of the above questions.

At the Charité, a subsample of the pilot study participants take part in a cognitive

interviewing substudy, which was also approved by the ethics committee (EA1/209/14)
The purpose of this substudy is to assess patients' understanding, potential problems with and acceptability of the questionnaire items. This is done using cognitive interviewing, a general method to evaluate the transfer of information through questionnaires. While answering the questions the participants are asked to think aloud so the interviewer can follow the process used to come to an answer. In addition verbal probing techniques are used to test the participants comprehension of specific terms.[84]

The pilot study micro-costing CRFs are filled out by the study personnel observing the scheduled examinations and documenting the participants' age, gender, hospital stay, angina classification and examination results. Further data on staff involvement time, complications and consumables are recorded as well.
All data related to costs for consumables and to the clinical site's local health care system, reimbursement structures, acquisition costs and other costs of hospitalisation will be asked in a second general questionnaire which will be completed yearly during the main PRCT.

For assessing image quality, the clinical sites will submit images from 3 CT and 3 ICA patients. The CT patients need to be examined according to the 10-steps guide for cardiac CT and the scanner specific protocol.

6.1 Adverse Events Monitoring for CT/ICA

Safety monitoring of the CT/ICA examination will be performed by collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of study interventions or study conduct. This will include documentation, reporting and monitoring of adverse events possibly related to study-related procedures; such as CT/ICA contrast agent administration, and medications used for the CT (such as beta-blockers and nitroglycerine). Clinical laboratory tests (e.g., creatinine) will be reviewed. Assessment of allergic reactions will be performed.

7. Safety Considerations

The identification and documentation of adverse events is at the core of the DISCHARGE trial. The primary outcome measure of the DISCHARGE-trial will be the composite endpoint consisting of Major Adverse Cardiovascular Events (MACE). Secondary outcomes include adverse events as well.

7.1 Definitions

The definitions are adopted from ICH-GCP to study specific requirements.

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical trial

subject administered a study procedure and which does probably have a causal relationship with study conduct.

An AE could be diseases, signs or symptoms which occur or worsen after the study procedure.

The following events are considered to be AEs:

- Bleeding or bruising at the site of the incision
- Infection at the incision site
- Mild to moderate allergic reaction or a serious life-threatening allergic
- Reaction to the contrast dye
- Heart attack
- Stroke
- Blood vessel damage (requiring further surgery)
- Death
- Thrombosis

Adverse Events are assessed as follows:

- Mild
- Moderate
- Severe
- If criteria for a serious adverse event (SAE) apply

For every event the causality will be analysed:

- Definite
- Probable
- Possible
- Unlikely
- Unrelated

Serious Adverse Event (SAE)

Serious adverse events are AEs according to the following categories.

1. Fatal
2. Is life threatening?
3. Results in persistent or significant disability or incapacity
4. Is a congenital anomaly or birth defect?
5. Requires inpatient hospitalisation or prolongation of existing hospitalisation with the following exceptions:
    a. Preplanned (prior to study), unless hospitalisation is prolonged
    b. Ambulatory treatment units or <24 hour re-hospitalisations
    c. Hospitalisation for elective procedure

- Emergency room visit
- MACE is an SAE
- any medically important event that may not result in death, be life-threatening, or require hospitalisation when based upon the medical judgement of the investigator may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Major Adverse Cardiovascular Event (MACE)

- Nonfatal myocardial infarction
- Nonfatal stroke
- Cardiovascular death

7.2 Treatment of SAEs and AEs

All AEs should be treated appropriately. Such treatment may include changes in study treatment/procedures including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalisation or any other medically required intervention.

7.3 Assessment of SAEs and AEs

As far as possible, each AE should be evaluated to determine:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study procedure
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; hospitalisation; …)
5. whether it constitutes a serious adverse event (SAE)

7.4 Assessment of Seriousness

Seriousness shall be determined according to the definition above.

Furthermore medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

7.5 Assessment of Intensity

Mild: Symptoms are barely noticeable to the patient or does not cause discomfort. The AE does not affect performance or functioning. Prescription medications are not usually needed for relief of symptoms.

Moderate: Symptoms are of sufficient severity to make the patient uncomfortable. The AE may effect performance of daily activities. Treatment of symptoms may be needed

Severe: Symptoms are of sufficient severity to make the patient uncomfortable. The AE may affect performance of daily activities. Treatment of symptoms may be needed.

7.6 Assessment of Causality

The safety profile and known side effects and expected adverse events related to contrast media have been well described in the literature. Known and anticipated events include, but are not limited to, allergic reaction (mild or severe), anaphylaxis, pruritus, rash, renal impairment, renal failure, contrast-induced nephropathy, vasovagal reaction. Known risks of intravenous line placement include bleeding, infection, tissue or nerve injury, and vasovagal reaction. Known risks related to beta-blocker medication include, but are not limited to, hypotension, bradyarrhythmia, allergic reaction, bronchospasm, and precipitation of reactive airway disease, heart block. Known risks of nitroglycerine use include headache, reduction in blood pressure, hypotension.

Every AE will be assessed regarding the causal relationship to

- underlying disease
- interventional procedure
- other

To assess causality between the study procedure/conduct and the Adverse Event the following definitions apply:

- Definite:
  An Adverse Event that follows a reasonable temporal sequence from the study procedure.
- Probable:
  An Adverse Event that follows a reasonable temporal sequence from the study procedure and for which involvement of other factors such as underlying diseases, complications, concomitant medications and concurrent treatments mayaiso be responsible.
- Possible:
  An Adverse Event that follows a reasonable temporal sequence from the study procedure for which possible involvement of the study procedure may be argued; although factors other than the procedure may be the causative factor including underlying diseases, complications, concomitant drugs and concurrent treatments.
- Unlikely:
  An Adverse Event that does not follow a reasonable temporal sequence from the study procedure or that can be reasonable explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.
- Unrelated:
  An Adverse Event that does not follow a reasonable temporal sequence from the study procedure or that can be reasonable explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments

7.7 Documentation of AEs and SAEs

All SAEs and all AEs need to be documented in the patient's medical chart and in the respective forms of the CRF. The documentation needs to include the type of event, start, duration, severity and causality.
SAEs need to be documented additionally on a separate SAE form.
The Sponsor will carefully document all AEs reported by the Investigator.

7.8 Reporting of SAEs

The Investigator will report any SAE within 24 hours after becoming aware to the KKS Charité via fax:
Central pharmacovigilance KKS Charité
Phone: +49 30 450 553872
Fax: + 49 30 450 7553856
Email: *pharmacovigilance-kks@charite.de*

If required by single national regulation fatal and life-threatening events will be reported by the national investigator to the concerned Ethics Committee (EC) (see approval/favourable opinion of local EC).

7.9 Follow-up of Adverse Events

Once an AE is detected, it should be followed until its resolution or stabilisation, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study, the interventions required to treat it and the outcome.
Follow-up information will be sent to the same address to which the original SAE Report Form is sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.
For a follow-up report, the investigator may be required to collect further information for a detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents.

7.10 Monitoring of Safety Risks

For the monitoring of safety risks and potential harms for the study participants caused by study procedure or study design the sponsor and a Data Safety Monitoring Board (DSMB) will carefully review all (S)AEs (see also section DSMB). In case of any safety issue that might change the risk benefit balance unfavourable the sponsor will take appropriate measures to guarantee the safety of the patients (e.g., adoption of protocol design).

8. Data Management

8.1 Database Set-up

A study specific database will be implemented to store the study data and the appropriate eCRF will be designed and created as well. Therefore a professional software solution - an Electronic Data Capture system (EDC) - will be used for this purpose. This system operates according to the principle of online data capture and is compliant with the code of federal regulations (FDA 21 CFR Part 11) to ensure reliability to the recorded data. It allows the documentation of study data in electronic case report forms (eCRF). The software is specially designed for the data entry according to Good Clinical Practice (GCP). This EDC system offers the major functions: system checks and plausibility, consistency and range checks, Query management tool, Audit Trail to log all activities, which are necessary and helpful for the data entry process.

Due to data safety reasons and to comply with the data privacy protection, the personal data of every patient will be pseudonymised. This ensures the strictly split between the personal data and patient-related dataset (study data). The EDC system automatically generates a pseudonym for every new patient. The pseudonym will be a combination of six alphanumeric characters. All study data of the patient will be linked with this pseudonym. Personal data of the patient will not be saved in the study database at any time.

The participating study centres will enter the data by using the electronic case report forms (eCRF). The eCRF is reachable via the internet at any time. The system uses a secured data connection (with Secure-Sockets-Layer protocol, SSL) to transfer the data from the study centres to the central database.

8.2 Data Management During Study

After the database is created and the eCRF is released the data entry process can be performed by the study centres. The Coordinating Centre of Clinical Studies at Charité (KKS Charité) will ensure the availability of the database and the continuous access to the eCRF.

Furthermore the technical support will be provided for the study centres during the study duration (administration of logins, roles and rights). In addition the database and the eCRF will be adapted due to changes in the study design, if necessary. Due to data availability and data security the study database will be hosted in a secured data centre of the Charité and will be backed up periodically.

In case of scheduled, unscheduled analyses or other needed reports the data will be exported from the database. In a further process these data will be checked, prepared and delivered for these purposes.

8.3 Data Export for Final Statistical Analysis

At the end of the study the entire database will be exported. The final data management process contains plausibility, consistency and range checks of the data. The missing data will be identified as well. If there are any queries, Data Clarification Forms will be generated and will be sent to the respective study centres for clarification. The related data correction will be performed either direct in the eCRF by the study centres or with programmed scripts by the data management team.

After all data management processes are completed, the cleaned data will be available for the statistical analysis. The final data can be delivered in a defined data format like SAS data file (*.sas7bdat), SPSS data file (*.sav), CSV file (*.csv), etc., including a data management report as well.

9. Statistical Analysis

9.1 Justification of Sample Size

This study is designed to show superiority with respect to MACE of CT versus ICA. For sample size calculation a power of at least 80% and a 0.05 two-sided level of significance is assumed.

The primary endpoint is the MACE incidence after a maximum follow-up of 4 years after CT or ICA. For this time to event data an exponential survival distribution is assumed with corresponding exponential parameter λ in each of the two groups. For the CT group we expect an exponential parameter of λ_1=0.00803 (corresponding to a one year MACE incidence of 0.8%, based on Noto TJ et al.,[6] Boden WE et al.,[64] Hulten EA et al.,[85] Serruys PW et al.[86]) and for the ICA group an exponential parameter of λ_2=0.0141 (corresponding to a one-year MACE incidence of 1.4%, based on Noto TJ et al.,[6] Boden WE et al.,[64] Serruys PW et al.,[86] Lichtlen PR et al.,[87] and Papanicolaou MN et al.[88]) yielding a constant hazard ratio of 0.5695. When the sample size in each group is 1773, with a total number of major adverse cardiovascular events required, of 99, an exponential maximum likelihood test of equality of survival curves will have desired power of 80% to detect the difference between the exponential parameter of the CT group and ICA group. Thus in total 3546 patients have to be allocated.

Furthermore, this sample size calculation assumes an accrual period of 2 years, a maximum follow-up time of 4 years, and a common exponential drop-out rate of 0.0513 (5% per year).

Sample size calculation for the pragmatic DISCHARGE trial was performed using nQuery 7.0.

9.2 Data Analysis

The primary endpoint, MACE incidence, will be evaluated in the intention-to-treat population using a Cox proportional hazards model to assess the effect of the investigation group adjusted for gender due to stratified randomisation. To check for robustness, additional analyses with other covariates (e.g. age, education) will be conducted. As a sensitivity analysis a cox proportional hazards model with random effects[89; 90] (frailty model) will be applied. This model is used in order to take variability between study centres and unobserved heterogeneity into account. This unobserved heterogeneity might be for example the result of different therapeutic adherence within each centre.

The **secondary endpoints** will be evaluated by parametric or non-parametric tests according to scaling. Appropriate parameters of effect size (e.g. odds ratios, relative risks, mean values) with confidence intervals will be calculated. Subgroups (gender, age groups, clinical sites) will be analysed exploratively.

Missing values for confounding variables are likely to occur. Thus, multiple imputation methods will be used in order to deal with missing values. Also a sensitivity analysis will be performed to compare results based on the multiple imputations with the complete case setting.

One exploratory analysis will be performed after the occurrence of 50 MACE. Here, a group sequential design with O'Brien-Fleming spending function for time-to-event outcome with a sample size of 3546 was used for planning.[91-93] At this point, also QoL and Cost-Effectiveness will be analysed. The exploratory analysis includes estimation of the survival function (Kaplan-Meier curve) and testing the hypothesis for differences in the hazards between the intervention and the control group applying Cox proportional hazards model. One sided level of significance for the exploratory analysis is set at 0.0026. In case of a significant result the decision concerning continuation of the DISCHARGE trial is in the responsibility of the Steering Committee based on the recommendation of the DSMB (data safety monitoring board).

Further detailed description of statistical analysis and missing values is also provided in the SAP.

To avoid missing values, the clinical database has been programmed accordingly. Also, a timely data entry is required and gets monitored.

9.3 Statistical Process Control

Statistical process control (SPC) is a powerful tool for quality measurement of phenomena over time (dynamic process) and the improvement of processes. SPC applied to measurement data can be used to highlight areas that would benefit from further investigation. These techniques enable the investigator to identify variation within the process. The implementation of SPC usually requires the production of control charts which depends on the type of data to be plotted. For continuous data the *x*-chart will be used, whereas for discrete data the *p*-chart is more appropriate. Both control charts include a plot of the data over time with three additional lines

- the centre line (usually based on the mean)
- and an upper and lower control limit (typically set at ±3 standard deviations from the mean, respectively).[94]

Optionally warning limits (typically set at ±2 standard deviations from the mean)[94] can be included in a control chart. Thus a control chart enables the monitoring of the process level and identification of the type of variation in the process over time with additional rules associated with the control (and warning) limits. SPCs will be implemented for each clinical site.

10. Quality Assurance

10.1 Methods Against Bias

The risk of bias will be minimised in several ways. Essentially, the patient population under investigation is eligible for randomisation to both arms and at all clinical sites both CT and ICA are firmly established. Blinding patients towards 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, to minimise covariate imbalance patients will be stratified according to gender in each clinical site.[95] This central assignment will be implemented online and will be easily accessible by the clinical sites when evaluating eligible patients for randomisation. According to the PRCT design, only low-intensity feedback concerning guideline adherence will be given to the sites and adherence is measured unobtrusively.[1] The blinded analysis of all outcomes will address whether CT works under the usual conditions and therefore includes all patients (intention-to-treat).

10.2 Clinical Monitoring and QA

Monitoring activities will be conducted in accordance with Good Clinical Practices (GCP) as far as applicable for the pragmatic study and the monitoring plan. This is a pragmatic study and thus has monitoring strategies outlined specific to this study design. In general, a risk-based approach will be taken by defining the intensity of monitoring required and implement a system for central monitoring and central review of monitoring reports. On-site monitoring will be replaced by monitoring activities that can be done as well or better remotely (e.g., consistency, completeness and plausibility checks of data, unusual distribution of data within and between sites) by using the EDC system SecuTrial ® (central monitoring). All tests/procedures outlined in the protocol are to be completed at the discretion of the treating physician as part of routine clinical practice.

The monitoring plan defines the minimum requirements for monitoring activities of this study.

Monitoring activities include on-site visits, remote monitoring or telephone contacts. On-site monitoring visits will be documented in Monitoring Visit Reports and should be recorded at the site on a Monitoring Visit Log.

Contact reports can be used to document significant communications with site staff between monitoring visits.

The investigators allow the monitor to have access to all of the study materials needed for source data verification and proper review of the study progress. At all times, the sponsor/investigators/monitors will maintain the confidentiality of the study documents. Furthermore, problems with inconsistent and incomplete data will be discussed. By signing the declaration of informed consent the participants allow access to their documents. With the signature in the protocol, the investigators confirm that auditors and health authority inspectors may have access to the study documentation and accordant medical records. Auditors and inspectors are bound by professional confidentiality and may not pass on any personal information that comes to their knowledge. In the course of audits or inspections, data in the CRF will be compared with the data for medical records. All the documentation held by the investigators within the scope of the clinical trial as well as the drug logs of the study medications will be verified.

10.3 Standard operating procedures (SOPs)

The Standard Operating Procedure (SOPs) manual includes the patient inclusion flow chart, CT-based management, ESC/ EACTS guidelines for revascularisation, CT-based management for lung findings, plaque characterisation document, CVD prevention, cardiac CT readers qualification, and data entry instructions for the eCRF. Also, a general 10-step guide for cardiac CT was developed in order to ensure minimal standards for the performance. Based on this guide, vendor- and scanner-specific scan protocols for the participating clinical sites were worked out (Toshiba, Siemens, Philips, and GE).

10.4 Laboratory Test Results

Laboratory tests are not mandatory. Still, clinically relevant values should be documented and provided in case tests have been carried out. These are, for example, creatinine, glucose, thyroid-stimulating hormone, and myocardial biomarkers.

All laboratory values must be reviewed and appraised by the investigator or research personnel for clinical significance. For any abnormal laboratory value considered to be new since baseline and clinically significant, details must be provided on the Laboratory Adverse Event case report form. This will include whether the event is considered serious, the relationship to the CT/ICA contrast agent or other agents, the action taken, and patient outcome. Significant abnormal values occurring during the study are to be followed until repeatedly measured values return to normal, stabilise, or are no longer considered clinically significant.

10.5 Clinical Events Committee (CEC)

All events will be adjudicated by an independent **clinical events committee (CEC)** which is composed as follows:

Name	Title/Designation	Address and Contact Numbers
Hans-Jürgen Scholze	General Internist	juergen.scholze@yahoo.de
Fabian Knebel	Cardiologist	fabian.knebel@charite.de
Simon Dushe	Cardiac Surgeon	simon.dushe@charite.de
Klemens Ruprecht	Neurologist	klemens.ruprecht@charite.de

The data about the adverse events that belong to the primary endpoint (MACE) will be given to the **CEC** timely after occurrence. All reviews will be blinded. Each **CEC** member reviews the case in a first step on his/her own for a subsequent possible discussion (written, phone, or/and in-person) to seek consensus.

Special eCRFs for MACE and (S)AEs were developed to collect detailed information. A first decision, if the event can be adjudicated to CT/ICA is made by the principal investigators at the clinical site. The role of the **CEC** is thus to confirm or reject the decisions of the principal investigators objectively.

As a basis for decisions the **CEC** members will receive a report that includes the following:

1. Summary of all (S)AEs that could be a MACE.
2. Details from the MACE eCRF
3. Details to enable adjudication and list for decisions if (S)AE, MACE can be adjudicated to ICA/CT as already pre-decided by the principal investigator.

10.6 Data Safety and Monitoring Board (DSMB)

During the course of the “DISCHARGE Trial”, the coordinating centre will carry out periodic data analyses and present data reports to the Data and Safety Monitoring Board **(DSMB)**, [96] who does not participate in the trial. The **DSMB** will semi-annually review the safety data and can give advice to the about necessary changes in the trial conduct to the Coordinator and the steering committee (**SC)**. The review can be unblinded if appropriate and the unblinding can be performed with the clinical database management system.

During the first three months and then semi-annually during subsequent months the **DSMB** will review reports on study performance including recruitment, protocol violations, complications of the CT technology and invasive angiography, the occurrence of patient drop-out and patient lost-to-follow-up, and adverse events associated with the CTA/ICA examination. Examples of the types of tables found in the DSMB report are shown below. During the last year of the trial the **DSMB** will mainly review the trial progress with regard to follow-up and occurrence of cardiovascular events. The **DSMB** will also make the final (blinded) decision about the classification of cardiovascular events and/or complications in case of disagreements or vagueness. Each **DSMB** member reviews the cases in a first step on his/her own for a subsequent possible discussion (written, phone, or/and in-person) to seek consensus. Extraordinary meetings with 7 day written notice may

take place and a meeting after the study when the data from all patients is available.

The following is an outline of the **DSMB** report that will be generated for the conferences:

1. Summary of Main Findings
2. Recent Issues
3. Recruitment Status
4. CRF Status
5. Safety (Serious Adverse Events, Adverse Events following CTA/ICA)
6. Follow-up Results

The DSMB is composed of the following four members:

Name	Title/Designation	Address and Contact Numbers
Universitätsklinikum des Saarlandes		
Danilo Fliser, MD, Prof.	Nephrologist	Street: Kirrberger Straße 100 Town: Homburg/Saar Postal: Code: 66424 Country: Germany Phone: +49 6841 16 23526 Fax: +49 6841 16 23540 E-Mail: Danilo.Fliser@Uniklinikum-Saarland.de
Radiologische Allianz GbR		
Jörn Sandstede, MD, Prof.	Radiologist	Street: Schäferkampsallee 5-7 Town: Hamburg Postal Code: 20357 Country: Germany Phone: +49 40 32 55 52 100 Fax: +49 40 32 55 52 222 E-Mail: joern.sandstede@radiologische-allianz.de
Cardioangiologisches Centrum Bethanien		
Axel Schmermund, MD, Prof.	Cardiologist	Street: Im Prüfling 23 Town: Frankfurt am Main Postal Code: 60389 Country: Germany Phone: +49 69 9450 28 0 Fax: +4 69 4616139 E-Mail: a.schmermund@ccb.de
Georg-August-Universität Göttingen		
Tim Friede, PhD, Prof.	Statistician	Street: Humboldtallee 32 Town: Göttingen Postal Code: 37073 Country: Germany

		Phone: +49 551-39-4991 Fax: +49 551-39-4995 E-Mail: tim.friede@med.uni-goettingen.de

10.7 Steering Committee

The entire project will be overseen by the SC which has delegated authority from all consortium members. It will consist of the work package (WP) leaders and five designated regional representatives of the clinical sites and the coordinator (Marc Dewey).

10.8 External Advisory Board (EAB)

For qualitative assessment, continuous guidance, and additional input throughout the project, several external experts have reviewed this application and will form the **external advisory board (EAB)**.

Name	Title/Designation	Address and Contact Numbers
Dartmouth Institute		
Harold Sox, MD, Prof. (Chair)	Chair of the Institute of Medicine's (www.iom.edu) Committee on Comparative Effectiveness Research Priorities, former Editor-in-chief of the Annals of Internal Medicine	Street: Town: Hannover Postal Code: NH 03755 Country: United States of America Phone: +1 603 653 0897 Fax: E-Mail: hsox@comcast.net
Universitätsklinik Heidelberg, Radiologische Klinik, Diagnostische und Interventionelle Radiologie		
Kauzor	Professor for Diagnostic Radiology at the University of Heidelberg, Medical Director for Diagnostic and Interventional Radiology at the University Hospital of Heidelberg	Street: Im Neuenheimer Feld 110 Town: Heidelberg Postal Code: 69120 Country: Germany Phone: +1 603 653 0897 Fax: E-Mail: hans-ulrich.kauczor@med.uni-heidelberg.de
Institute for Quality and Efficiency in Health Care		
Stefan Sauerland, MD	Head of the department of non-drug interventions of	Street: Im Mediapark 8 (Kölnturm) Town: Köln Postal Code: 50670

	the Institute for Quality and Efficiency in Health Care (IQWiG), Comparative Effectiveness and Cost-Effectiveness Expert	Country: Germany Phone: +49 221 356850 Fax: +49 221 356851 E-Mail: stefan.sauerland@iqwig.de
Leiden University Medical Centre, Department Cardiothoracic Surgery		
Robert JM Klautz, MD, Prof.	Chief of Department of Cardiothoracic Surgery Cardiac Surgery Expert	Street: Albinusdreef 2 Town: Leiden Postal Code: 2333 ZA Country: Netherlands Phone: +31 71 526 4022 Fax: +31 71 526 6965 E-Mail: r.j.m.klautz@lumc.nl
UT Southwestern Medical Center		
Steve Marso, MD, Prof.	Director of Interventional Cardiology, member of the CathPCI registry (www.ncdr.com), Intervention Expert	Street: 5939 Harry Hines Blvd Town: Dallas Postal Code: TX 9047 Country: United States of America Phone: +1 214 645-7500 Fax: +1 214 645 7501 E-Mail: Steven.Marso@utsouthwestern.edu
Cleveland Clinic, Cleveland, Ohio		
Paul Schoenhagen, MD, Prof.	Editor-in-chief of Cardiovascular Diagnosis and Therapy, Department of Diagnostic Radiology and Department of Cardiovascular Medicine, CT Expert	Street: Euclid Avenue Town: Cleveland Postal Code: 9500 Country: United States of America Phone: +1 216 445 7579 Fax: +1 216 636 0822 E-Mail: schoenp1@gmail.com
Carlos Aguiar, MD, Prof.	Vice-President of the Portuguese Society of Cardiology UEMS, Echo expert	Street: Town: Postal Code: Country: Phone: Fax: E-Mail: ctaguiar@sapo.pt
Klinik für Nuklearmedizin Medizinische Hochschule Hannover		
Frank Bengel, MD, Prof.	Director of the Department of	Street: Carl-Neuberg-Str. 1 Town: Hannover

	Nuclear Medicine, Nuclear medicine expert	Postal Code: 30625 Country: Germany Phone: +49 511 532 2577 Fax: +49 511 532 3761 E-Mail: Bengel.Frank@mh-hannover.de
University of Bristol		
Andreas Baumbach, MD, Prof.	Cardiologist	Street: Tyndall Avenue Town: Bristol Postal Code: BS8 1TH Country:United Kingdom Phone: +44 117 342 6573 Fax: E-Mail: Andreas.Baumbach@ubht.nhs.uk
School of Health and Caring Sciences, Linnaeus University		
Joep Perk, MD, Prof.	Chair of the ESC guideline on cardiovascular disease prevention;[68]	Street: Town: Kalmar Postal Code: 391 82 Country: Sweden Phone: +46 772 28 80 00 Fax: +46 480 44 60 32 E-Mail: joep.perk@lnu.se
OLV Ziekenhuis Aalst		
William Wijns, MD, Prof.	Author/Task Force Member of the ESC/EACTS guideline on cardiovascular revascularisation, former ESC chairperson.[61; 97]	Street: Moorselbaan 164 Town: Aalst Postal Code: 9300 Country: Belgium Phone: +32 53 72.44.39 Fax: +32 53 72 45 87 E-Mail: william.wijns@olvz-aalst.be
University of Glasgow, Institute of Health & Wellbeing		
Andrew Briggs, MSc, PhD, Prof.	Health Economics, Cost-Effectiveness Expert	Street: 1 Lilybank Gardens Town: Glasgow Postal Code: G12 8RZ Country: United Kingdom Phone: +44 1413305017 Fax: E-Mail: Andrew.Briggs@glasgow.ac.uk
University of Michigan at Ann Arbor, Radiology		
Ella A Kazerooni, MD, Prof.	Thoracic Radiology, Cardiovascular Radiology, Radiology	Street: 1500 E Medical Center Dr SPC 5868 Town: Ann Arbor Postal: MI 48109 Country: United States of America Phone: (+) 001-

		734-936-4366 Fax: E-Mail: ellakaz@med.umich.edu
University of Bristol, School of Social and Community Medicine		
William Hollingworth, MSc, PhD, Prof.	Health Economics, Cost-Effectiveness Expert	Street: 39 Whatley Road Town: Bristol Postal Code: BS8 2PS Country: United Kingdom Phone: +44 117 9287355 Fax: E-Mail: William.Hollingworth@bristol.ac.uk
Patient Interest Group, Berlin		
Martina Seifert	Patient Interest Group	Weissensee, Berlin

11. Expected Outcomes of the Study

The anticipated impact of the DISCHARGE project will be multiple and will generate beneficial and usable outcomes in a European context on several levels. We predict that the DISCHARGE PRCT, the core of the project, may prove that CT, as the most promising currently available noninvasive imaging modality, utilised as the primary diagnostic strategy in stable chest pain and intermediate pretest probability of CAD is superior to ICA concerning MACE. We further predict that it will lead to better health-related quality of life and increased cost-effectiveness. Special consideration will be given to including and analysing gender aspects and putting emphasis on gender balance throughout the project as it has been shown that the evaluation of chest pain in women is less straightforward than in men because of gender differences in presentation and disease manifestation.[98] It will ensure European regulatory and quality standards concerning the interpretation of CT radiation exposure, good clinical practice, the quality of the data, and clinical treatment guidelines. The results of the DISCHARGE project will provide systematic evidence by applying a pragmatic study design, best reflecting the demand of comparative effectiveness research for routine clinical practice evaluation[99] and including evidence-based medicine (EBM) as well as health technology assessment (HTA) methodology by performing systematic review of evidence and cost-effectiveness analysis. Generalisability of results will be guaranteed by forming a consortium including 30 partners from 18 different European countries. By its collaborative approach of cardiologists, radiologists, and experts in comparative effectiveness research, the DISCHARGE project will enhance communication between these disciplines and facilitate transfer of knowledge. The results of DISCHARGE will have a major impact on influencing standards and guidelines of diagnostic pathways and will also provide information for coverage decisions in Europe concerning the utilisation of CT in the broad population of patients with stable chest pain symptoms and intermediate pretest probability of CAD.

Primarily, stable chest pain patients with intermediate pretest probability of CAD will benefit as the results will enable **early and safe discharge** of the majority using CT

as the initial modality for evaluation. In doing so, unnecessary invasive procedures and hard adverse events will be reduced. Second, health care providers such as physicians and hospitals will be informed about the results of DISCHARGE and will benefit from guideline modifications and information on coverage decisions alike. They will be able to provide more effective imaging strategies utilising CT and will be able to spare scarce resources by implementing a more cost-effective diagnostic workup algorithm. Third, in case of an advantage of CT, the responsible European and national authorities and decision-makers will consider including coronary CT angiography among the reimbursed medical procedures. Thus, the trial results will also have important economic and societal consequences that will be disseminated on the European level to increase its impact.

In summary, the DISCHARGE project will inform patients, health care providers, and decision-makers alike about the effectiveness and cost-effectiveness of CT as the primary diagnostic imaging modality when evaluating stable chest pain symptoms suggesting an intermediate risk of coronary artery disease.

The main impact of the PRCT itself will be to prove that CT, as the most promising currently available noninvasive imaging modality, utilised as the primary diagnostic strategy in the selected broad population of stable chest pain patients with an intermediate pretest probability of CAD is superior to ICA concerning the primary endpoint MACE. The trial will be executed according to a pragmatic design approach thus exploring the effectiveness of CT in comparison to the gold standard ICA in a routine practice and usual care setting and thus leading to clinically meaningful outcomes. The performance of the trial will enhance a close collaboration between the disciplines of radiology and cardiology and will give the great opportunity of laying the foundation to inform patients, health care providers, and decision-makers alike about the most promising new cardiovascular imaging technology by applying a unique multi-national European network cooperation.

In addition to the main impact, an elaborate list of secondary outcomes has been developed to enable a maximum output of the project.

12. Dissemination of Results and Publication Policy

The exploitation and dissemination of results will be planned and procedures and implementation of publications, presentations, and stakeholder information will be addressed in an extra work package.

The dissemination committee **(DC)** initiates, coordinates, and oversee all efforts for dissemination of the results. Dissemination policies and a publication plan will be written. In this way, the efficient and consistent exploitation of the project is ensured. International distribution of findings and raising awareness on outcomes to the health care workforce will be achieved by publication of the results in relevant, high-priority medical journals, presentations at congresses and meetings, and by enforcing collaboration with the professional societies. For the dissemination among policy makers and HTA bodies, the diffusion system of OSTEBA as member of HTA networks including EUnetHTA and INAHTA will be utilised. Patients and the general public will be informed as well to outreach beyond the scientific community.

Raw anonymised data sets can be made available to the scientific community upon request, through the Coordinator to the DISCHARGE DC In cases where the respective results have been published and due time has elapsed, the DC will, in general, support this availability to the scientific community. Single decisions will be made case by case by taking the specifics into consideration.

The 13 members of the **DC** are radiologists, cardiologists and work package leaders and two chairs from radiology and cardiology. The members are not part of the **SC**. The **DC** is the main decision making body for dissemination and the **SC** is only contacted for advice and/or decisions when more serious issues arise.

Name	Title/Designation	Address and Contact Numbers
P02 Medizinische Universität Innsbruck (MUI)		
Guy Friedrich, MD, Prof. (Chair)		Street: Anichstr. 35 Town: Innsbruck Postal Code: 6020 Country: Austria Phone: +4351250481898 Fax: E-Mail: guy.friedrich@tirol-kliniken.at
P10 University College Dublin, National University of Ireland (NUID UCD)		
Jonathan Dodd, MD, Prof. (Co-Chair)		Street: Belfield Campus Town: Dublin Postal Code 4 Country Ireland Phone: +353 87 2987313 Fax: E-Mail: j.dodd@st-vincents.ie

P18 Institut za kardiovaskularne bolesti Vojvodine (IKVBV)		
Nada Čemerlić Adjić, MD, Prof.		Street: Put dr Goldmana 4 Town: Sremska Kamenica Postal Code: 21204 Country: Serbia Phone: +38163433982 Fax: E-Mail: ncemerlica@gmail.com
P23 Aintree University Hospital (AUHT)		
Gershan Davis. MD, Dr.		Street: Longmoor Lane Town: Liverpool Postal Code: L9 7AL Country: United Kingdom Phone: +44 151 529 2974 Fax: +44 151 529 2724 E-Mail: gershan@hotmail.com
P16. Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E)		
Nuno Bettencourt, MD, Prof.		Street: Rua Conceicao Fernandes Town: Vila Nova De Gaia Postal Code: 4434 502 Country: Portugal Phone: +351934258281 Fax: E-Mail: bettencourt.n@gmail.com
P19 Institut Català de la Salut (ICS-HUVH)		
José Rodriguez Palomares, MD, Dr.	Cardiologist	Street: Passeig de Vall d'Hebron 119 Town: Barcelona Postal Code: 08035 Country: Spain Phone: +34934894013 Fax: E-Mail: jfrodriguezpalomares@gmail.com
P06 Kliniken des Landkreises Goppingen GGmbH (KaE)		
Stephen Schröder, MD, Prof.	Chair of the Department of Cardiology	Street: Eichertstrasse 3 Town: Goppingen Postal Code: 73035 Country: Germany Phone: +49 7161 642671 Fax: E-Mail: Stephen.Schroeder@af- k.de

P02 Medizinische Universitaet Innsbruck (MUI)		
Gudrun Feuchtner, MD, Prof.	Radiologist	Street: Anichstr. 35 Town: Innsbruck Postal Code: 6020 Country: Austria Phone: +4351250481898 Fax: Email: gudrun.feuchtner@i-med.ac.at
P14 LIETUVOS SVEIKATOS MOKSLU UNIVERSITETAS (LSMU)		
Antanas Jankauskas. MD, Dr.	Radiologist	Street: Eiveniu str. 2 Town: Kaunas Postal code: 50009 Country: Lithuania Phone: + 37065745548 Fax: E-Mail: jankauskas.antanas@gmail.com
P11 Università degli Studi di Cagliari (UNICA)		
Luca Saba, MD, Prof.	Radiologist	Street: AOU di Cagliari - Polo di Monserrato SS 554 Town: Monserrato (CA) Postal Code: 09042 Country: Italy Phone: +393206202091 Fax: E-Mail: lucasabamd@gmail.com
P01 Charité, Berlin School of Public Health (CHARITE)		
Jacqueline Müller-Nordhorn, MD, DPH, Prof.	Spokesperson of the Institute of Public Health, Head of Public Health/Epidemiology, Study Course Chief	Street: Charitéplatz 1 Town: Berlin Postal Code: 10117 Country: Germany Phone: +49 30 450 570872 Fax E-Mail: jacqueline.mueller-nordhorn@charite.de
P27 Fundacion Vasca De Innovacion e Investigacion Sanitarias (Osteba-BIOEF)		
Iñaki Gutiérrez-Ibarluzea, MSc, Dr.	Knowledge Manager and Coordinator of the early awareness and alert system of Osteba, the Basque Office for HTA, Basque Government	Street: Donostia-San Sebastian 1 Town: Vitoria-Gasteiz Postal Code: 01010 Country: Spain Phone: +34945019250 Fax:

		E-Mail: osteba7-san@ej-gv.es
P28 Universitätsklinikum Jena (UKJ)		
Peter Schlattmann, MD, PhD, Prof. (Affiliated)	Statistician	Street: Bachstraße 18 Town: Jena Postal Code: 07743 Country: Germany Phone: +49 3641 934130 Fax: E-Mail: peter.schlattmann@mti.uni-jena.de
P01 Charité – Universitaetsmedizin Berlin (CHARITE)		
Marc Dewey, MD, PhD, Prof. (Coordinator)	Coordinator	Charité – Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin Germany Phone: +49-30-450627226 Fax: +49 30 450 7527920 Email: dewey@charite.de

13. Duration of the Project

The first-patient in will be in the first month of the PRCT and the last-patient out will be at the end of month 48 of the PRCT (overall duration: 4 years). Patients will be recruited over a period of 2 years.

Timeline
Recruitment (month 1-24):
The recruitment of eligible patients will be done by medical doctorate candidates and study nurses. Patients will be checked for intermediate pretest probability of disease and will be centrally randomised and stratified (according to site and gender) at each site to either CT angiography or ICA. Recruited patients will fill out the questionnaires after informed consent but *prior* to randomisation.

CT and ICA and patient preference (month 1-24)
The patients will undergo regular CT angiography and ICA and will fill out a patient preference questionnaire[100] afterwards.

Meetings of data safety monitoring board and clinical events committee (month 1-48):
The DSMB will review safety data semi-annually and the clinical events committee will review the possible occurrence of MACE. They will discuss the results internally and will then report directly to the coordinator through the project management office.

Low intensity feedback (month 3-24):
According to the pragmatic design, only low-intensity feedback concerning guideline adherence will be given to the sites by the project management.

First year follow-up (month 13-36):
Due to the pragmatic design, no in-person visits during the first-year follow-up from the patients are planned to avoid interference with the trial. Patients will be sent questionnaires with sections for their medical status (including a possible change in medication), Cost-Effectiveness, and Quality of Life.

Final follow-up (month 37-48):
Due to the pragmatic design, no in-person visits from the patients are mandatory. The patients will be sent patient preference questionnaires and the questionnaire from the first year follow-up. In order to avoid loss to follow-up, several information sources will be used (general practitioners, death registries, and family members) concerning the primary outcome measure of MACE. In addition, they will be given the opportunity to consult the principal investigator in person. For this possible visit, funding has been set aside for patients with low income

14. Problems Anticipated

The PRCT follows usual hospital care and entails the regular risks of cardiac CT and invasive coronary angiography. These risks will be addressed during the informed consent procedure. Thus there are no additional risks as a result of participating in

the study. As for the exposure to radiation, an own work package (WP3) has been defined and the trial will be submitted to the German Federal Office for Radiation Protection for approval.
The main risk of the trial and thus the entire DISCHARGE project is the recruitment rate at the clinical sites to reach a total of 3546 patients. The clinical site partners were chosen very carefully, each one of them being carefully checked for their track record in delivering on clinical trials. They are generally tertiary referral centres and crucial for regional delivery of health care and are not at risk of being restructured or closed down.

The 25 clinical sites in the DISCHARGE consortium performing the trial have a high recruitment potential. Altogether 121900 patients are expected to be referred to them for ICA within the duration of the two year recruitment phase. Out of these patients, approximately 54820 (45%) are estimated to have suspected CAD. Each one of the 25 single sites has a sufficient number of referred patients for ICA. Altogether **only 6.5%** of these patients with suspected CAD need to be recruited. In the case that one clinical site fails to recruit the expected number of patients, any one of the others has the capacity to take over. This may occur due to a late ethical approval and/or a general low recruitment rate. While shifting the number of patients to another clinical site, an appropriate transfer of the salaries and person-months will be taken into account.
Another risk may be the loss of patients during the follow-up phase. To minimise this risk, measures are foreseen (e.g., involvement of family members). Also, in the case patients would like to come in person to the hospital for the final follow-up and cannot afford travelling, after, for example moving to another city, funding has been set aside.

15. Project Management

The project is led by the coordinator Marc Dewey (Heisenberg Prof., consultant radiologist, vice-chair of the radiology department) and the project manager, Adriane Napp (Master of Science in Clinical Trial Management and licensed Clinical Monitor and Database Manager) is an expert in clinical trials. She will thus place an emphasis on overseeing the progress of the Pragmatic Randomised Controlled Trial. She will be strongly supported by the partner INSERM/ ECRIN-ERIC and by Charité-KKS which is a member of the international KKS network and therefore the German partner of ECRIN-ERIC. These institutions will also lead **WP4** “Good Clinical Practice and Surveillance System” and **WP5** “Clinical Data Management” within the DISCHARGE project set-up.

ECRIN-ERIC provides a sustainable, not-for-profit infrastructure with clinical trial units and academic coordinating centres and can support multinational clinical research projects in Europe.

ECRIN–ERIC, led by Christine Kubiak, will be responsible for the on-site monitoring of the clinical trial and safety surveillance and to ensure that the trial is performed efficiently with highest quality and according to GCP and national and international standards. Specifically, this will include the review of ethical and applicable authority approval and respective notifications, site monitoring, safety reporting, and quality

assurance.

The defined services will be performed by ECRIN-ERIC's scientific partners in all non-German DISCHARGE countries. The German clinical sites will be monitored by KKS-Charité under the lead of Corinna Meier-Windhorst.

16. Ethics

The Pragmatic Randomised Controlled Trial (PRCT) will be submitted to all responsible ethics committees and the German Federal Office for Radiation Protection for approval. The patients have been referred to cardiac CT and ICA. In many countries, ICA is the gold standard for patients with stable chest pain and intermediate risk of coronary artery disease. Yet, in countries with less income per capita, cardiac CT is the preferred choice for health care providers (insurances) and has shown to be a very good and gentler alternative. The investigators from the clinical sites have altogether performed over 50 studies with ethical approval from their internal review board (IRB) about cardiac CT and are thus highly experienced.

The study and the pilot study have already been approved by the ethics committee at Charité (No. EA1/294/13 for PRCT and pilot study; No. EA1/209/14 for cognitive interviews).

Important protocol amendments will be communicated to all partners with the request to seek local IRB approval. A scan of the first IRB approval and amendment needs to be provided to Charité by each clinical site for compliance control.

Informed consent will be sought by the investigators from cardiology and radiology for the PRCT. The pilot study only foresees informed consent if requested by the local IRB (see section 6.6 Pilot Study). The researchers from the Institute of Public Health (e.g. physicians, psychologists) will obtain informed consent for the cognitive interviews.

Patient informed consent also includes confidentiality/data protection.

16.1 Ethical Approval PRCT and Pilot Study - Charité

Initial Approval at Charité:

CHARITÉ

Charité | 10117 Berlin

Herrn
Prof. Dr. med. Marc Dewey
Institut für Radiologie

CCM

Ethikkommission
Ethikausschuss 1 am Campus Charité - Mitte

Vorsitzender: Prof. Dr. R. Lobbrecht

Geschäftsführung: Dr. med. Katja Grosshennig
ethikkommission@charite.de

Kommunikationsadresse: Charitéplatz 1, 10117 Berlin
Tel.: 0049/450-517222
Fax: 0049/450-517952

http://ethikkommission.charite.de

Datum: 24.10.2013

Diagnostische Bildgebungsstrategien bei Patienten mit stabilem Brustschmerz und mittlerem Risiko einer koronaren Herzerkrankung: Vergleichende Nutzenbewertung existierender Technologien (DISCHARGE)
Antragsnummer: EA1/294/13

Sehr geehrter Herr Professor Dewey,

die von Ihnen eingereichte o.g. Studie wurde durch den Ethikausschuss 1 der Ethikkommission auf der Sitzung am 17.10.2013 beraten.

Die Ethikkommission stimmt dem o.g. Vorhaben zu.

Als Hinweis wird mitgeteilt, dass es nur 1 einzigen primären Endpunkt geben kann, nicht mehrere (Ethikantrag, Punkt 4, Seite 2, Zeile 2).

Es ist zu prüfen, ob eine Strahlen-Haftpflicht-Versicherung gemäß § 24 Abs.1 Nr.10 StrlSchV bzw. § 28 b Abs. 2 Nr. 5 RöV abgeschlossen werden muss, da die Studie nicht ausschließlich an der Charité durchgeführt wird.

Die Ethikkommission bestätigt zur Vorlage beim BfS, dass für das beantragte Vorhaben ein zwingendes Bedürfnis im Sinne des § 28b Absatz 1 Nummer 1 RöV (bzw. § 24 Absatz 1 Nummer 1 StrlSchV) besteht.

Folgende Unterlagen wurden zur Begutachtung eingereicht:

- Ethikantrag, 02.10.13
- Patienteninformation, Version vom 30.09.13
- Einwilligungserklärung, Versionsdatum fehlt
- Zustimmung des Direktors, 25.09.13
- Studienprotokoll, Version 1.0 vom 05.08.13
- Fragebögen

First amendment of ethical approval at Charité:

CHARITÉ

Charité | 10117 Berlin

Ethikkommission
Ethikausschuss 1 am Campus Charité - Mitte

Vorsitzender: Prof. Dr. R. Uebelhack

Geschäftsführung: Dr. med. Katja Orzechowski
ethikkommission@charite.de

Korrespondenzadresse: Charitéplatz 1, 10117 Berlin
Tel: [illegible]
Fax: [illegible]

http://ethikkommission.charite.de

Herrn
Prof. Dr. med. Marc Dewey
Institut für Radiologie

CCM

Datum: 23.10.2014

Diagnostische Bildgebungstrategien bei Patienten mit stabilem Brustschmerz und mittlerem Risiko einer koronaren Herzerkrankung: Vergleichende Nutzenbewertung existierender Technologien (DISCHARGE)
Antragsnummer: EA1/294/13
Vorgang vom 15.10.2014, Eingang am 20.10.2014, per E-Mail am 20.10.2014

Sehr geehrter Herr Professor Dewey,

hiermit bestätigen wir Ihnen den Eingang Ihres Schreibens vom 15.10.2014 mit folgenden Anlagen:

- Ethikantrag, Version vom 16.10.2014
- Patienteninformation, Version vom 09.10.2014
- Einwilligungserklärung, Version vom 09.10.2014

Wir danken für die Kenntnisgabe. Die Ethikkommission erhebt keine Einwände gegenüber den Änderungen.

Mit freundlichen Grüßen

Prof. Dr. med. R. Uebelhack
Vorsitzender

CHARITÉ – UNIVERSITÄTSMEDIZIN BERLIN
Schumannstr. 20/21 | 10098 Berlin Telefon +49 30 450-0 www.charite.de
Bankname | BLZ Bankleitzahl Konto Kontonummer

Ethical approval for cognitive Interviews at Charité:

CHARITÉ

Charité | 10117 Berlin

Ethikkommission
Ethikausschuss 1 am Campus Charité - Mitte

Vorsitzender: Prof. Dr. R. Uebelhack

Geschäftsführung: Dr. med. Katja Grasshoff
ethikkommission@charite.de

Kommunikationsadresse: Charitéplatz 1, 10117 Berlin
Tel.: 030/450-615233
Fax: 030/450-[illegible]

http://ethikkommission.charite.de

Herrn
Prof. Marc Dewey
Institut für Radiologie

CCM

Datum: 29.07.2014

Pilotstudie „Quality of Life"
Antragsnummer: EA1/209/14

Sehr geehrter Herr Professor Dewey,

die vor Ihnen eingereichte o.g. Studie wurde durch den Ethikausschuss 1 der Ethikkommission auf der Sitzung am 24.07.2014 beraten.

Die Ethikkommission stimmt dem o.g. Vorhaben zu.

Folgende Unterlagen wurden zur Begutachtung eingereicht:

- Ethikantrag, 02.07.14
- Patienteninformation, 02.06.14
- Einwilligungserklärung, 02.06.14
- QoL-Pilot-Fragebogen_Patient, 17.06.14
- QoL-Pilot-Fragebogen_Personal, 17.06.14

Die Ethikkommission weist darauf hin, dass die ethische und rechtliche Verantwortung für die Durchführung des Forschungsprojektes -vom Beratungsergebnis der Ethikkommission unabhängig- beim Leiter des Forschungsvorhabens und seinen Mitarbeitern verbleibt.

Mit freundlichen Grüßen

Prof. Dr. med. R. Uebelhack
Vorsitzender

17. Conflicts of Interest

Conflicts of Interest are listed in the full version of the study protocol (www.dischargetrial.eu)

18. Curriculum Vitae

Curriculum vitae are incorporated in the full version of the study protocol (www.dischargetrial.eu)

19. References

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Appendix

Below are the English Versions of the informed consent forms. They will be translated into local languages by the clinical sites and checked for correctness by Charité's project management office. Final versions that also considered the local requirements of the IRB are also collected and checked at Charité to ensure compliance with GCP considering the consistency of informed consent forms in multi-centre trials.

1. Patient Informed Consent Form - PRCT

Patient Information - Version 09.10.2014

Title of the study: "Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies (DISCHARGE)"

Dear Patient:

You are invited to participate in our pragmatic clinical DISCHARGE study. This is a European multicentre research study organised by the sponsor Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. Professor Dewey from the Department of Radiology is the coordinator of this study. Three other radiologists of our department are involved in the study: Dr. med. Elke Zimmermann, Dr. med. Matthias Rief and Dr. med. Georg Schütz. The study is conducted in cooperation with the Department of Cardiology (Investigators: PD Dr. med. Michael Laule and Dr. med. Henryk Dreger).

1. What is the aim of the study?

You have been referred for an invasive coronary angiography (ICA, catheter examination). You have a suspected coronary artery disease with stable chest pain and a clinical indication for ICA. This makes you a possible candidate for the DISCHARGE study. The study investigates whether CT is better than a catheter examination of the heart. In order to participate, the probability that you have coronary artery disease (CAD; defined as at least 50% narrowing of the coronary arteries) has to be 10% to 60% - what we refer to as an intermediate pretest probability of CAD. This intermediate pretest probability of CAD will be tested as the last step of the inclusion process for the study. If you have an intermediate pretest probability of 10% to 60% for CAD, you can participate in the study and undergo either ICA or a CT computed tomography (CT) scan of the heart. Which of the two diagnostic tests (ICA or CT) you will undergo will be decided by a random distribution with a 50:50 chance of being assigned (randomised) to CT or ICA. The chance of assignment (randomisation) to either test cannot be influenced in any way by you or the study personnel. Based on the diagnosis made by these tests, further treatment decisions will be made by the local heart team. If you do not have an intermediate pretest probability of 10% to 60% for CAD, you cannot participate in the study and you will **not** be assigned by chance (randomised) to one of the two tests (ICA or CT). Instead you will undergo ICA as planned. The results will be provided to the study sponsor and your personal data will be recorded.

The study is a so-called pragmatic randomised study. This means that the medical care given to patients who participate in the study reflects the normal clinical situation as much as possible. This

is the aim in order to obtain realistic and practical results. It is planned to include a total of 3546 patients into the study at 23 hospitals all over Europe. The Charité will randomise between 128 and 320 patients for the study.

2. Benefits and risks of participating in the study

Because of the low to intermediate pretest probability of CAD (10-60%), as explained above, it can be expected that about **80-90%** of the randomised patients will not have CAD. Following the examination by CT or ICA, patients can be discharged from the hospital unless there are other medical reasons for staying. In the patients who will be examined by CT, the presence of CAD can be ruled out without an invasive examination. This is an advantage for the patients in the CT group. **Some patients** in the CT group may encounter additional advantages. Other diseases such as a pulmonary embolism (blood clot in a lung artery), a hiatal hernia of the esophagus (displacement of a part of the stomach from the abdomen into the chest cavity) or an aortic dissection (tear of the inner layer of the wall of the main artery from the heart) can cause chest pain. These and other diseases of the chest can be reliably detected by CT. The resulting potential advantage is that patients in whom such diseases are detected earlier by CT may benefit from earlier treatment. In most cases, narrowing of the coronary arteries is caused by so-called coronary plaques (deposits in the walls of blood vessels). Such plaques are also identified by CT, and their composition can be assessed. Certain types of such plaques have been shown to bear a higher risk of rupture (plaques that contain a large amount of fat or a lot of calcium, for example). If such a situation is found, this will lead to a recommendation to change medical treatment and/or risk factor modification. Finally, patients may benefit from the fact that the CT findings allow better planning of treatment in those patients who should be treated by reopening of narrowed coronary arteries (with a catheter or surgery). If CT will be shown to be superior, the expected **benefit for future patients** arises, in that a large number of the examinations in patients with stable chest pain and an intermediate probability of CAD may be performed by CT instead of ICA in Germany and in Europe. This is an important advantage given that around 2 million ICAs are considered to be avoidable in Europe each year. In accordance with the pragmatic approach of the DISCHARGE study, participants only have the usual risks of CT or ICA. If one of the usual risks occurs, physicians are available at Charité who can immediately take measures to take care of any undesired effects. It must be noted that CT is expected to identify narrowing of coronary arteries in about 10-20% of the patients. In these patients, additional tests to measure heart perfusion may become necessary as well as a subsequent intervention, percutaneous coronary intervention (PCI) or surgery, for treatment of one or several stenoses. These patients will have a higher radiation exposure and will be given additional contrast medium. This also means that it may take longer in these situations to complete treatment. It may occur that in very seldom cases not all findings can be diagnosed in the CT group that may have been found in the ICA group. It is to be noted though, that in general more information comes from CT.

3. What are the requirements for study participation?

To participate in the study, patients suspected of having CAD must have been referred for ICA. They must be at least 30 years old and give written informed consent. Other criteria include stable chest pain and an intermediate probability of coronary artery disease (10-60%). Women can participate if they are not pregnant. **Patients cannot participate** if their heart beat is irregular or if they undergo haemodialysis.

To decide whether a patient is suitable for study participation and to ensure optimal care, the investigators will review patients' medical records before and during the study in order to document data that are relevant for the study.

4. How will the study be conducted?

4.1. Preparation

After the investigator has determined that a patient is suitable and after written informed consent has been given, the patient will be checked for presence of 10 – 60% pretest probability for CAD. For this reason the physician will obtain relevant data including personal details, important aspects of the medical history and information about risk factors (elevated fat levels, overweight, smoking etc.) and current medications. . While waiting for their test and before they are informed about the presence of a 10 – 60% pretest probability for CAD, the patients complete questionnaires (on quality of life, for example). If the patient has an intermediate pretest probability of 10% to 60% for CAD he can participate in the study and he will be assigned (randomised) with a 50:50 chance to CT or ICA. Before and after the diagnostic test is conducted the patient will be handed a questionnaire on satisfaction to be completed. If the Patient does not have an intermediate pretest probability of 10% to 60% for CAD, he cannot participate in the study and he will **not** be assigned (randomised) with a 50:50 chance to CT or ICA. Instead he will undergo ICA as planned, the results of which will be provided to the study sponsor and his personal data will be recorded.

4.2.1. Invasive coronary angiography (ICA)

All patients participating in the DISCHARGE study have a referral for ICA (the current standard) based on suspected CAD. The need for this examination was established by our referring physician. However, according to the randomisation schedule, only 50% of the patients enrolled in the study will undergo ICA. In ICA, an X-ray fluoroscopy with administration of contrast medium is performed. In rare cases, the contrast medium can cause mild allergoid reactions (nausea, itching, skin rash, for example). Severe intolerance reactions to the contrast agent (such as impairment of kidney function or allergic shock) are extremely rare as well as other adverse effects. If such a reaction occurs, immediate treatment is available in the hospital. ICA exposes the patient to X-rays. The radiation exposure is about 9-10 mSv, which corresponds to the natural background radiation of 54 to 60 months. This radiation exposure is clinically indicated because your referring

physician decided that ICA is necessary. This radiation exposure is not due to participation in our study.

4.2.2. Computed Tomography (CT)

Starting in 1998, multislice CT has been developed as an alternative method to ICA. The aim of this alternative method is to examine the arteries that supply the heart muscle (the coronary arteries) with similar reliability but less invasiveness. Earlier studies show that cardiac CT has an accuracy of 95-97% in detecting narrowing (stenosis) of the coronary arteries. Moreover, CT also allows ruling out stenosis with a high degree of probability (so-called negative predictive value of 95%). Therefore, CT allows reliably ruling out suspected stenosis (narrowing) without the need for ICA.

The CT examination of the heart takes about 15 to 25 minutes. The actual CT scan takes only about 0.2-8 seconds, depending on the CT scanner used. During this time, it is necessary that patients hold their breath for a short period of time. Before CT, the patient's medical records will be reviewed and blood samples may be taken according to local standards. In addition, an ECG will be obtained, unless a patient has a recent ECG (obtained within 1 month before CT). Caffeine is not allowed for 4 hours before the CT examination (coffee, tea, or chocolate, for example). Patients with a heart rate of more than 50 beats/minute will be given a betablocker. If betablockers cannot be used due to a contraindication, ivabradine will be given. However, ivabradine will not be used if the heart rate is under 60 beats per minute. If, after these medications, the heart rate is still above 55 beats just before the CT scan, additional betablocker could possibly be given by intravenous injection. Immediately before the examination, nitroglycerin will be given under the tongue to make the coronary arteries wider, which improves their assessment. As with ICA, the CT examination also involves injection of a contrast agent. The contrast agent is an approved agent for CT examinations and will be injected into a vein in the crook of the elbow. Again, in rare cases, the contrast agent can cause mild allergoid reactions (nausea, itching, skin rash, for example. Severe intolerance reactions to the contrast agent (such as impairment of kidney function or allergic shock) are extremely rare as well as other adverse effects. If such a reaction does occur, immediate treatment is available in the hospital. CT is also performed with X-rays. The radiation dose is about 1 to 5 mSv and roughly corresponds to the natural background radiation of 6 to 30 months.

4.3. Treatment strategy

The findings of CT or ICA will immediately be made available to the **local heart team** for analysis. The local heart team includes cardiologists, cardiac surgeons and radiologists. Patients will be discharged immediately if the findings are negative (that is if the examination does not reveal significant (≥ 50%) diameter stenosis of the coronary arteries), unless other medical reasons require further hospitalisation. Risk factor modification and optimal medical therapy may be initiated for the patients based on current European guidelines. If the results are positive (CAD ≥ 50% diameter stenosis is demonstrated) further treatment is based on study recommendations, the

hospital's standard procedure, and European guidelines:

a) In the ICA group, the local heart team will decide on further diagnostic and therapeutic measures following the current guidelines of the European Society of Cardiology (ESC) and the European Society of Cardiothoracic Surgery (EACTS) for reopening narrowed coronary arteries.

b) If a patient assigned to the **CT group** of the study, turns out to have high-risk disease (defined as stenosis of the left main coronary artery, stenosis of the proximal LAD, or 3-vessel disease), according to ESC/EACTS guidelines, it is recommended that he or she should have an ICA after CT to confirm that a revascularisation procedure is necessary. In patients in whom the CT scan reveals narrowing of only one or two coronary arteries, the local heart team will perform the best imaging ischemia test available at the hospital (e.g., stress echocardiography, scintigraphy or magnetic resonance imaging) before deciding about whether ICA should be performed. If patients with these CT findings already had a positive ischemia test (>10% of myocardium) before being enrolled in the study, it is recommended to directly proceed to ICA after the CT scan. Incidental CT findings will also be taken into account when the local heart team decides about the patient's further care. The local heart team will decide about measures to modify risk factors in accordance with European guidelines and the usual standard of care. Specifically, cardiac events can be predicted when a patient has noncalcified high risk plaques or has a coronary calcium score according to Agatston (indicator for the calcium burden in blood vessels) of at least 400. In the patients examined by CT, the local heart team will take these high-risk plaque features into account in making their decision concerning guideline-based risk factor modification. It is expected that about 80-90% of the patients in the CT group will not have obstructive stenosis (≥ 50%), i.e., no coronary artery disease. These patients receive guideline-oriented medical therapy and will normally be discharged on the same day.

4.4. Follow-up

It is planned to conduct two follow-up surveys of the patients who participate in the study: the first follow-up survey is planned to be conducted after one year, the second between two and four years after enrollment in the study. The follow-up will be conducted in the form of a questionnaire survey. The questionnaires (covering topics such as quality of life and patient satisfaction, for example) will be mailed to the patients by the Charité (Dept. of Radiology). Completing and returning the questionnaires is very important for the success of our study. Therefore, all patients are asked to carefully complete the questionnaires and provide correct information. Please kindly inform the study centre about any change of address, email address, or phone number, so we can contact you. In addition, your referring physician will be informed about your participation in this study. In order to obtain missing information (e.g., in case of a change of address), we ask you to authorise/ release from medical confidentiality obligation the following persons/third parties in order to provide data that are relevant for the study: your first-degree relatives, your general practitioner/cardiologist, your health insurer and any involved authorities (e.g., population

registries, public health agencies, statistical authorities) and the respective affiliated physicians of these authorities. Your rights to confidentiality of your data will be protected any time. You can always contact us directly by telephone should you have questions concerning your treatment or the questionnaires. Should you note a change in your well-being or symptoms, contact your local medical services and inform us as well. The questionnaires used in the follow-up survey correspond to the questionnaires you are asked to complete immediately after having consented to participation in the study. In this way, we hope to minimise your efforts and the time required for completing the questionnaires. For your convenience, we will enclose self-addressed, stamped envelopes for returning the completed questionnaires to the Charité. Your data will be collected and stored at the xx and transmitted to the coordinating centre at Charité, Berlin, Germany (see next section).

5. What will happen to my data?

Information on data protection

The study will be conducted in accordance with current data protection laws. Any personal data relating to you that we collect and send to the central study database at Charité - Universitätsmedizin Berlin and AGMednet are pseudonymised. This means that the persons handling the data cannot trace them back to individual participants.

With your signature on the informed consent form, you agree to the storage and processing of person-related data for the purpose of the above-named study by the investigator and his or her co-workers.

Person-related data include your name, data of birth, sex, ethnicity, data on your physical and mental health, and other personal data that are collected during the study or at follow-up with, for example, questionnaires.

The investigator will use your person-related data for administration and conduct of the study as well as for research and statistical analysis.

The original informed consent form with your nonpseudonymised personal data will be filed at the investigator's study centre.

Data collected by the local investigator at the study centre during the study will be transmitted in pseudonymised form to the coordinator, Prof. Dr. med. Marc Dewey - Charité - Universitätsmedizin Berlin, Campus Mitte, Dept. of Radiology and Neuroradiology, Charitéplatz 1, 10117 Berlin, Germany.

Study-related data (questionnaires, patient forms, medical documentation) will be stored for processing, analysis and scientific investigation in the local study centre (Charité, Berlin, Humboldt-Universität, Charitéplatz 1, 10117 Berlin, Germany, phone: ++49 (0)30 450-627264). The local principal investigator is responsible for data collection, processing, and transmission. The image data will be stored on behalf of Charité at AGMednet, Inc.,2 Atlantic Avenue, Boston, Massachusetts 02110, phone: 855-246-3363.

In the study centre, data will be processed in pseudonymised form. To this end, the investigator assigns a code to the datasets (pseudonymisation of the data). This code is used when your data are transmitted to the central database. The key to the code that allows tracing the data back to you is only available to the local principal investigator and other staff authorised by him. All documents that allow identification of your person will be handled with strict confidence.

All person-related data that are kept by the investigator can be reviewed by the coordinator Prof. Dr. med. Marc Dewey and/or his or her representatives and specific study personnel (e.g., monitors, auditors), who will not be able to them trace back to the individual participant and will be

bound to confidentiality. These reviews may become necessary to ensure that the study is conducted properly and/or to ensure the quality of the study-related data.

You have been informed that the data/details concerning your health that we collect for the study and which are documented on questionnaires and on electronic media can be transmitted pseudonymised to the following parties:

a) the responsible monitoring authority (in the present study: German Federal Office for Radiation Protection, Salzgitter) for the purpose of checking whether the study is conducted properly and for assessing study results and adverse events;

b) the sponsor = coordinating study centre (Charité, Berlin, Humboldt-Universität, Charitéplatz 1, 10117 Berlin, Germany; phone ++49 (0)30 450 527353) for scientific analysis and for conducting the follow-up survey; on behalf of Charité at AGMednet, Inc.,2 Atlantic Avenue, Boston, Massachusetts 02110, phone: 855-246-3363

You are free to withdraw your consent to the processing of your data at any time during the study. In this case, no new data will be collected and your stored personal data and the corresponding key will be deleted or destroyed unless there are legal regulations that require storage for certain periods.

You have the right to know which personal data are stored. You can request correction of your person-related data in case of inaccuracies. If you wish to make a request, please contact your investigator, who will then immediately provide the information you wish to have.

After the end of the study, your data must be kept on file for another 10 years (according to the German regulation for procedures involving the use of X-rays). After this 10-year period, your person-related data will be deleted unless there are other legal or contractual regulations that require us to store the data for even longer periods.

Please note that the results of the study may be published in medical journals; in this case your identity will be hidden and it will not be possible to trace any published results back to you.

6. Will there be costs for me when I participate in the study?

No costs will arise and you will receive no payment.

7. Who can decide about removing me from the study?

There are some circumstances that may result in excluding you from the further study. This decision is made by the investigator, and you have no influence on the decision. Reasons for excluding you may be that further participation is not in the best interest of your health or that the study ends prematurely.

8. Will I be insured during the study?

Participants in the DISCHARGE Study, who will be randomised into the cardiac CT or ICA group, will be insured by ECCLESIA. A maximum coverage of 500,000 Euro is put in place. Fault-based damage (caused by the clinic staff) will be covered through the business liability insurance of the respective clinic for the entire duration of the study. The patient is responsible to notify the clinical site about possible radiation-induced damage. Coverage (e.g., for lost wages or pain) as a result of damage to persons will only be paid if it is covered by ECCLESIA.

9. What else do I need to know?

Please note that the results of the study may be published in a medical journey. This will be done without revealing your identity. You need not participate in this study to receive standard medical care. If you do not participate in the study, you will undergo ICA.

During your participation in the study, please follow the physicians' instructions and immediately report to them any change in your health.
Participation in this study is entirely voluntary. Please read and sign the attached Informed Consent form. You can withdraw consent at any time without giving a reason. If you do not wish to participate, this has no consequences for your further treatment or for the relationship to your doctor. You will continue to receive the best medical care. We expect the study to improve future diagnostic management and treatment of coronary artery disease.

10. Who will answer my questions?

Do you have any questions? We are always available to answer any questions you may have concerning this written information and the examinations. The following questions have been discussed:

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At the Department of Radiology (Charitéplatz 1, 10117 Berlin), your investigator, **Prof. Dr. med. M. Dewey** (phone: **030 450-627 353),** or the study centre (phone: **030 450-627 264**) will be available to answer your questions.

If you do not have further questions, please sign the attached Informed Consent form and enter the date of your consent. You will be handed a copy of this patient information and of the signed Informed Consent form. We thank you for taking the time to consider participation in this study.

I confirm that I have read and understood this patient information. A copy has been handed to me.

_____ _____

Berlin (date) (Patient's signature)

Informed Consent Version 09.10.2014

Title of the study: " Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies (DISCHARGE)"

Please read this Informed Consent form carefully. Do not hesitate to ask us if anything is unclear or if you wish to have further information.

Hereby I,
First name:
Last name:
Date of birth:

confirm that Mr./Ms./Mrs./Dr./Prof. has informed me, both orally and in writing, about the nature, significance, scope and risks of the scientific investigation in the DISCHARGE study conducted by the Department of Radiology at Charité. I had sufficient time to ask questions and seek clarification from the investigator.

I understand that my participation in the study is entirely voluntary and that I may discontinue my participation at any time without giving a reason. This will not in any way affect my further treatment.

I am aware that if I do not fulfill the final inclusion criterion of an intermediate pretest probability (10% - 60%) for CAD I cannot participate in the study and I **will undergo ICA** as planned. I agree that the results as well as my personal data will be recorded and analysed. I am aware that no follow-up will be conducted if I cannot participate in the study.

If I fulfill the final inclusion criterion of an intermediate pretest probability (10% - 60%) for CAD I want to participate in the study for the comparison of computed tomography (CT) and ICA. I am aware that I will be assigned by chance to one of the two diagnostic tests and their subsequent patient management strategies. The chances are 50:50 that I will receive a CT examination or ICA.I authorise my treating and referring physicians (family doctor, cardiologist) to provide the clinical study centre (Charité, Berlin) with information regarding my exact diagnosis and the further development of my medical status during the follow-up period of the study. I also agree that they pass on copies of relevant medical records. I authorise/ release from medical confidentiality obligation my first-degree relatives, my treating family physician/cardiologist, my health insurer and all relevant authorities (e.g., population registries, health authorities, statistical authorities), including affiliated physicians of these authorities to provide the local investigator of the Charité with confidential data that are relevant for the study. I also authorise the clinical study center to inform the above mentioned parties about my participation in the study.

Specifically, I have read and understood the written patient information (dated October 9, 2014) and I have been handed a copy of the information and of this informed consent. I

agree to the use of X-rays in my examinations. I explicitly confirm that I consent that the responsible German authority (the German Federal Office for Radiation Protection) will be notified about my participation in this study and the resulting radiation exposure. With regard to my study participation and the resulting radiation exposure, this authority can review my personal data. My consent to reporting the received radiation exposure is irrevocable. This does not apply to medical data. I am aware that a copy of this Informed Consent form will be kept in the files. This will be done in strict compliance with legal regulations concerning the protection of data and I explicitly agree to this procedure.

Informed consent concerning data handling

1) I am aware that all data concerning me will be stored in computerised and pseudonymised form during the course of the study. This will be done by the local study centre (Charité, Department of Radiology, Charitéplatz 1, 10117 Berlin, Germany) with strict adherence to data protection regulations. My personal data (name and address, for instance) will be strictly separated from my other data. Only the local investigator has access to my personal data.

2) All analyses performed that involve my data will be done using the data in pseudonymised form (this means that the data cannot be traced back to me). I have been informed that my study-related data will be handled in accordance with the regulations for the confidentiality of data and data protection laws.

3) I confirm that I agree to the documentation of my study-related data/details concerning my health and to the storage of these data in electronic form. These data can be transmitted in pseudonymised form to the following persons and other third parties:

a) the sponsor = coordinating study centre (Charité, Berlin, Humboldt-Universität, Charitéplatz 1, 10117 Berlin, Germany; phone ++49 (0)30 450 527353) for scientific analysis and for conducting the follow-up survey; on behalf of Charité at AGMednet, Inc.,2 Atlantic Avenue, Boston, Massachusetts 02110, phone: 855-246-3363

b) the state monitoring authorities (Landesamt für Arbeitsschutz, Gesundheitsschutz und Technische Sicherheit), the highest federal authority (Bundesamt für Strahlenschutz) and the ethics committee, if they request these data for verification of study results and adverse events.

4) All person-related data that are kept by the local investigator can be reviewed by the coordinator Prof. Dr. med. Marc Dewey and/or his or her representatives and specific study personnel (e.g., monitors, auditors), who will not be able to them trace back to the individual participant and will be bound to confidentiality. These reviews may become necessary to ensure that the study is conducted properly and/or to ensure the quality of the study-related data. For this purpose, I authorise the investigator to disclose the required information.

5) You have the right to know which personal data are stored. You can request correction of your person-related data in case of inaccuracies. If you wish to make a request, please contact your investigator, who will then immediately provide the information you wish to have.

6) You are free to withdraw your consent to the processing of your data at any time during the study. In this case, no new data will be collected and your stored personal data and the corresponding key will be deleted or destroyed unless there are legal regulations that require storage for certain periods.

7) After the end of the study, your data must be kept on file for another 10 years (according to the German regulation for procedures involving the use of X-rays). After this 10-year period, your person-related data will be deleted unless there are other legal or contractual regulations that require us to store the data for even longer periods.

I consent to undergoing the examination in the setting of the above-referenced study.

_____ _____

Berlin (date) (Patient's signature)

I confirm that I have explained the nature, significance, scope and risks of this study. Both written and oral information has been provided. The patient has been handed a copy of the written information and of this informed consent form.

Berlin (date)	(Investigator's signature)

2. Patient Information Pilot Study

Participant Information

Purpose of the study
You are being asked to participate in a research study. The purpose of the study is to assess the quality of life in patients with stable angina/chest pain. Quality of life is about how you perceive your health, your ability of pursuing everyday activities and your well-being. In this study we compare different questionnaires of quality of life in 18 European countries. We want to know how long it takes participants to complete these questionnaires and whether there are differences between countries. The study is funded by the European Union.

Description of the research
You will receive a short questionnaire about how you perceive your health. Additionally the study personnel will ask you some questions about your symptoms and medical status. The diagnostic procedure and its result will be documented. Independently we may document the estimated costs of your hospitalisation.

Potential risks and discomfort
You may feel some anxiety and stress while answering questions during the study.

Voluntary participation
Participation in this study is voluntary. If you decide not to participate, this will not affect your ability to receive medical care at the hospital or to receive any benefits to which you are otherwise entitled. You may discontinue participation during the study at any time without penalty or loss of benefits to which you are otherwise entitled.

Contact person
If you have any questions, please contact:

Contact address: to be completed
Thank you for your participation.
Write signature page if necessary

3. Patient Informed Consent – Cognitive Interviews

This form is only available in German, since it the study is only being performed at Charité.
Other clinical centers can conduct the study upon request and would need to translate the informed consent form into local language.

Studientitel: Pilotstudie - Quality of Life

Sehr geehrte Patientin, sehr geehrter Patient,

hiermit bieten wir Ihnen die Teilnahme an einer wissenschaftlichen Studie an! Sollten Sie sich entschließen an der Studie teilzunehmen, helfen Sie uns die Erfassung der gesundheitsbezogenen Lebensqualität von Patienten mit Brustschmerz zu verbessern. Diese Studie wird von der Charité in Berlin koordiniert. Sponsor ist das Institut für Radiologie der Charité - Universitätsmedizin Berlin.

Ziel der Studie

Gegenstand der Studie ist die Erfassung der gesundheitsbezogenen Lebensqualität bei Patienten mit Brustschmerz. Lebensqualität beinhaltet verschiedene Aspekte: Es geht darum wie Sie Ihre Gesundheit einschätzen, wie gut Sie Ihren üblichen Tätigkeiten im Alltag nachgehen können und wie ihr psychisches Wohlbefinden ist. Wir vergleichen in dieser Studie Fragebögen zur Lebensqualität, in 18 europäischen Ländern. Insgesamt werden in 23 klinischen Zentren jeweils 60 Patienten den Fragebogen ausfüllen und zu diesem befragt. Ziel der Studie ist es herauszufinden, wie lange das Ausfüllen dieser Fragebögen dauert und inwieweit dieser verbessert werden kann, damit der Fragebogen in einer validierten Form in einer späteren Studie genutzt werden kann.

Ablauf der Studie

Sie erhalten einen Fragebogen zum Ausfüllen. Während Sie den Fragebogen ausfüllen, werden Sie von dem Studienmitarbeiter gebeten Ihre Meinung und Ihre Probleme bei den einzelnen Fragen zu formulieren. Im Anschluss wird Ihnen der Studienmitarbeiter einige Fragen zur Einschätzung Ihres Brustschmerzes stellen. Die Gespräche werden dabei mit einem digitalen Aufnahmegerät aufgenommen. Nach dem Interview wird der Studienmitarbeiter bei ihrem behandelnden Arzt dokumentieren welche diagnostische Prozedur Sie im Rahmen Ihrer klinischen Versorgung erhalten werden oder bereits erhalten haben (entweder eine Computertomographie oder Koronarangiografie) sowie den klinischen

Schweregrad ihres Brustschmerzes. Hier bitten wir sie die Beteiligten von der ärztlichen Schweigepflicht zu befreien. Die Fragebögen und Tonaufzeichnungen der Interviews werden im Nachgang ausgewertet um den Fragebogen für eine spätere Studie zu verbessern.

Dauer der Teilnahme

Das Ausfüllen des Fragebogens und das Interview mit dem/der Studienmitarbeiter/in dauern ca. eine Stunde.

Mögliche Risiken

Risiken durch das Ausfüllen der Fragebogen oder die Teilnahme an dem Interview sind nicht bekannt.

Datenschutz

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Versicherung

Für diese Studie wurde keine spezielle Versicherung für die Patienten abgeschlossen. Die an der Studie beteiligten Mitarbeiter der Charité (Studienärzte und -ärztinnen, Studienschwestern und –pfleger etc.) sind durch die Betriebshaftpflichtversicherung der Charité gegen Haftpflichtansprüche, welche aus ihrem schuldhaften Verhalten resultieren könnten, versichert.

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Für die Teilnahme an der Studie ist keine Aufwandsentschädigung vorgesehen. Durch Ihre Teilnahme an der Studie entstehen Ihnen keine Kosten.

An wen kann ich mich wenden, wenn ich weitere Fragen habe?

Sie haben jederzeit das Recht, Fragen über alle Angelegenheiten, die die Studie betreffen, zu stellen. Wenden Sie sich bitte an die Studienzentrale des Instituts für Radiologie (Telefon: **030 450-627 264**).

_____ _____

Berlin (Datum) (Unterschrift des Studienleiters)

CLINICAL STUDY PROTOCOL

Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies

The "DISCHARGE" Study

A pragmatic randomised controlled trial (PRCT) evaluating the superiority of CT over ICA concerning effectiveness in stable chest pain patients with intermediate pretest probability of coronary artery disease

Protocol Version 1.8, dated 09-Nov-2020

Charité – Universitätsmedizin Berlin

Confidential

Table of Contents

Abbreviations

AHA	American Heart Association
CABG	coronary artery bypass graft
CACS	coronary artery calcium scan
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society Angina Grading Scale
CEA	cost-effectiveness analysis
CEC	clinical events committee
CNS	central nervous system
CRF	case report form
CoMe-CCT	Collaborative Meta-analysis of cardiac CT
CT	computed tomography
CTA	CT angiography
DALY	disability adjusted life years
DISCHARGE	Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies
DSMB	data safety monitoring board
EAB	external advisory board
EBM	evidence-based medicine
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic data capture system
EU	European Union
FFR	fractional flow reserve
GCP	good clinical practice
HF	heart failure
HTA	health technology assessment
ICA	invasive coronary angiography
ICH	intracerebral hemorrhage
IPD	individual patient data
IRB	internal review board

LBBB	left bundle branch block
LVH	left ventricular hypertrophy
MACE	Major adverse cardiovascular events
MI	myocardial infarction
MIP	maximum intensity projections
MPR	multi planar reconstructions
mSv	millisievert
OMT	optimal medical therapy
PRCT	Pragmatic Randomised Controlled Trial
SAE	serious adverse event
SAH	subarachnoidal haemorrhage
SC	steering committee
SCCT	Society of Cardiovascular Computed Tomography
SOP	Standard Operating Procedure
SPC	statistical process control
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TTO	time trade-off
WHO	World Health Organisation

1. Project Summary

Coronary artery disease (CAD) is the leading cause of death in high-income countries. Invasive coronary angiography (ICA) is the reference standard for the diagnosis of CAD and allows immediate therapy. However, only 40% of patients undergoing ICA actually have obstructive CAD and ICA has relatively rare but considerable risks. Coronary computed tomography (CT) is the most accurate diagnostic test for CAD currently available, excellent for the exclusion of disease with high certainty. CT may become the most effective strategy to reduce the ca. 2 million annual negative ICAs in Europe by enabling early and safe discharge of the majority of patients with an intermediate risk of CAD.

To evaluate this, the DISCHARGE project that will be implemented by a multinational European consortium has been established. The core of the project is the DISCHARGE trial, a pragmatic randomised controlled trial (PRCT). The primary hypothesis is that CT is superior to ICA for major adverse cardiovascular events (cardiovascular death, fatal myocardial infarction or stroke) after a maximum follow-up of 4 years in a selected broad population of stable chest pain patients with intermediate pretest probability (10-60%) of CAD. This will be assessed using a pragmatic randomised controlled design in order to generate practical and usable outcomes for clinical decision-making according to comparative effectiveness research methodology. The trial will include 26 clinical sites from 16 European countries which will recruit more than 3500 patients ensuring broad geographical representation.

2. General Information

2.1 Title

Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies (DISCHARGE)

2.2 Trial Registration

Data category	Information
Primary registry and trial identifying number	https://clinicaltrials.gov/ NCT02400229
Date of registration in primary registry	15.01.2015
Secondary identifying numbers	EA1/294/13
Source(s) of monetary or material support	European Commission, 7th Framework Programme
Primary sponsor	Charité – Universitätsmedizin Berlin Charitéplatz 1, 10117 Berlin, Germany
Contact for patient, public, and scientific queries	Study office at Charité: Charité – Universitätsmedizin Berlin Campus Mitte Institute of Radiology Charitéplatz 1, 10117 Berlin Email: herzschmerzen@charite.de Phone: +49-30-450527226
Public title	Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies (DISCHARGE)
Scientific title	A pragmatic, randomised controlled trial evaluating the possible superiority of computed tomography (CT) over invasive coronary angiography (ICA) concerning effectiveness in stable chest pain patients with intermediate pretest probability of coronary artery disease
Countries of recruitment	Austria, Czech Republic, Denmark, Germany, Finland, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Spain, United Kingdom
Health condition(s) or problem(s) studied	Suspected coronary artery disease (CAD), intermediate risk of CAD and stable chest pain Diagnosis, management and safety

Intervention(s)	Experimental intervention: CT-guided management Comparison intervention: ICA guided management
Key inclusion and exclusion criteria	Due to the pragmatic approach[1] of the DISCHARGE trial, only minimal inclusion and exclusion criteria are used for study population identification. *Inclusion criteria:* Patients with suspected coronary artery disease with stable chest pain and intermediate pretest probability (10-60%) of CAD clinically referred for invasive coronary angiography. "Stable chest pain" defined as **not**: - being acute (= first appearance within the last 48 hours) or - instable (= a) first appearance with Canadian Cardiovascular Society Angina Grading Scale (CCS) Class III or IV; b) progredient with at least 1 CCS Class to at least CCS Class III or, now at rest for at least 20 min) angina pectoris Patients at least 30 years of age Written informed consent *Exclusion criteria:* Patients who were or are on hemodialysis, no sinus rhythm, pregnancy, any medical condition that leads to the concern that participation is not in the best interest of health (e.g., extensive comorbidities), participation in other interventional/randomised study
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: single blinded (outcome assessor) Primary purpose: comparative effectiveness evaluation Phase: N/A since pragmatic and not a drug/medical device study
Date of first enrolment	October 2015
Target sample size	3546

Recruitment status	Recruitment will start in October 2015
Primary outcome(s)	MACE (MACE = major adverse cardiovascular event; defined as cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction) after a maximum follow-up of 4 years
Key secondary outcomes	MICE (MICE=minor adverse cardiac event), procedural complications, health-related quality of life, Cost-effectiveness, radiation exposure, other secondary outcomes. All include gender aspects.

2.3 Protocol Version

Issue Date: 09. November 2020

Protocol Number: 1.8 Approved by Charité Ethics Committee on 17. November 2020

Revision Chronology:

05 Aug 2013	Version 1.0 For ethical approval. Format from proposal.
…28 May 2014	Draft Version 1.1 Format according to SPIRIT/WHO
…10 October 2014	Draft Version 1.2. Overall revision and addition of major clinical aspects
…01 May 2015	Draft Version 1.3. Incorporation of recommendations from ECRIN, update participating clinical sites and outreach activities, complete SPIRIT and WHO check list items. Include Measurement Section and shift text from Safety section. Shorten Safety Section accordingly.
01 Sept 2015	Draft Version 1.4. Statistical sections with more details to show that the exploratory analysis does not produce bias. Secondary/Other outcomes list added.
01 Oct 2015	Draft Version 1.5. Draft Version 1.4 was slightly revised for consistency and clear phrasing.
01 Apr 2016	Version 1.6. Slight revision of Draft version 1.5 for further clarification, e.g. consistent phrasing Approved by all authors and by the Charité Ethics Committee. This version requires no change of the patient informed consent (dated 9 October 2014) approved by Charité Ethics Committee.
15 Jan 2019	Version 1.7 Adjustments were performed in section 4.2.2 on procedural complications which will be specified according to the NCDR®CathPCI Registry®v4.4 Coder´s Data Dictionary. The timeframe for Major Adverse Cardiovascular Event (MACE) was re-defined from “1 minute after CT/ICA diagnosis/ procedure” to “1 minute after randomisation to CT/ICA diagnostic procedure”. The same timeframe was added as definition to Minor Adverse cardiovascular Events (MICE). Project management changed from Adriane Napp to Maria Bosserdt and Melanie Estrella on 1.2.2018 is recorded as well as other personnel changes.
09 Nov 2020	Version 1.8 Adjustments were performed in section 2.6.3. regarding addition of team members, Peter Martus and Konrad Neumann as well as clarification of the first analysis time point in section 6.5.2.

2.4 Protocol Contributors

Marc Dewey[*MD, PhD], Adriane Napp[MSc], Robert Haase[MD], Michael Laule[MD], Georg M Schuetz[MD], Rita Pilger[MSc], Corinna Meier-Windhorst[VM], The-Hoang Do[MSc] , Felix Frömel, Christoph Katzer[MEd, MA], Nina Rieckmann[PhD], Jacqueline Müller-Nordhorn[MD, DPH], Paolo Ibes, Mario Walther[DSc], Peter Schlattmann[MD, PhD, MSc]

The author's affiliations are stated in section 2.6.2 and 2.6.3.
Author's Contributions:

MD, ML and PS conceived the study. MD is the coordinator. PS provided statistical expertise in clinical trial design. AN, RH, GS, and MW developed the study protocol. AN is also the project manager. Maria Bosserdt (MB) and Melanie Estrella (ME) replaced Adriane Napp as project manager from 1.2.2018. PS is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript

2.5 Funding

The European Commission is funding the project within the 7th EU Framework Programme, grant No. 603266.

2.6 Roles and Responsibilities

2.6.1 Coordinating Centre/Sponsor

Trial Sponsor: Charité – Universitätsklinikum Berlin
Sponsor's Reference:
Contact name: Marc Dewey, Heisenberg Professor
Address: Charité – Universitätsmedizin Berlin
Humboldt Universität und Freie Universität zu Berlin
Institut für Radiologie
Charitéplatz 1
10117 Berlin
Germany
Telephone: +49 30 450 527353
Fax: +49 30 450 527996
Email: marc.dewey@charite.de

2.6.2 Sponsor and Funder

Sponsor: Charité – Universitätsmedizin
Funder: European Commission

Name	Title/Designation	Address and Contact Numbers
Marc Dewey, MD, PhD	Coordinator and Coordinating Investigator Radiology	Charité – Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin Germany Phone: +49-30-450627226 Fax: +49 30 450 7527920 Email: dewey@charite.de
Henryk Dreger, MD, PD	Overall Coordinating Principal Investigator for ICA	Charité - Universitätsmedizin Berlin Medizinische Klinik m.S. Kardiologie und Angiologie Campus Charité Mitte Charitéplatz 1 10117 Berlin
Michael Laule, MD, PhD	Principal Investigator, Cardiology	Charité – Universitätsmedizin Berlin Campus Mitte Medizinische Klinik m.S. Kardiologie und Angiologie Herzkatheterbereich Raum: 2721 046 3.Etage Charitéplatz 1 10117 Berlin
Matthias Rief, MD	Overall Coordinating Principal Investigator for CT	Charité – Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Luisenstr. 6 – 8 Charitéplatz 1 10117 Berlin

Elke Zimmermann, MD, PD	Principal Investigators for CT	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Luisenstr. 6 – 8 Charitéplatz 1 10117 Berlin
Adriane Napp	Project Manager and Work Package co-leader Dissemination, Certification of Clinical Sites until 31.1.2018	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin
Maria Bosserdt	Project Manager from 1.2.2018	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin
Melanie Estrella	Project Manager from 1.2.2018	Charité - Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin
European Commission		European Commission B-1049 Brussels Belgium

2.6.3 DISCHARGE Centres

Medical Departments

Name	Title/*Designation*	Address and Contact Numbers
1.1 Charité - Universitaetsmedizin Berlin		
Michael Laule, MD, PhD, Elke Zimmermann, MD, PD	Local Principal Investigators	Street: Charitéplatz 1 Town: Berlin Postal Code: 10117 Country: Germany Phone: +49 30 450 527996 Fax: +49 30 450 513072 Email: michael.laule@charite.de elke.zimmermann@charite.de
2. Medizinische Universitaet Innsbruck (MUI)		
Gudrun Feuchtner, MD Guy Friedrich, MD	Local Principal Investigators	Street: Anichstr. 35 Town: Innsbruck Postal Code: 6020 Country: Austria Phone: +4351250481898 Fax: Email: gudrun.feuchtner@i-med.ac.at Email2: guy.friedrich@uki.at

3. Fakultni Nemocnice v Motole (FN Motol)		
Josef Veselka, MD, PhD Vojtěch Suchánek, MD	Local Principal Investigators	Street: Vuvalu 84 Town: Praha 5 Postal Code: 150 06 Country Czech Republic Phone: +42608921566 Fax: Email: veselka.josef@seznam.cz Email2: vojtech.suchanek@fnmotol.cz
4. Region Hovedstaden (REGIONH)		
Klaus F. Kofoed, MD, PHD Thomas Engstroem, MD, PhD	Local Principal Investigators	Street: 9 Blegdamsvej 9 Town: Copenhagen Postal Code: 2100 Country: Denmark Phone: +45 26807439 Fax: Email: klaus.kofoed@regionh.dk Email: Thomas.Engstroem@regionh.dk
5. Kliniken des Landkreises Goppingen GGmbH (KaE)		
Stephen Schröder, MD Thomas Zelesny, MD	Local Principal Investigators	Street: Eichertstrasse 3 Town: Goppingen Postal Code: 73035 Country: Germany Phone: +49 7161 642671 Fax: Email: Stephen.Schroeder@af- k.de Email2: Thomas.Zelesny@af-k.de
6. Universitaet Leipzig – Herzzentrum (ULEI)		
Matthias Gutberlet, MD, PhD Lukas Lehmkuhl, MD, PhD	Local Principal Investigators	Street: Strümpellstrasse 39 Town: Leipzig Postal Code 04289 Country: Germany Phone: +49 341 865 1702 Fax: Email: matthias.gutberlet@helios-kliniken.de Email2: Lukas.Lehmkuhl@helios-kliniken.de
7. Semmelweis Egyetem (SE)		
Béla Merkely, MD, PhD Pál Maurovich-Horvat, MD, PhD	Local Principal Investigators	Street: Varosmajor u 68 Town: Budapest Postal Code: 1122 Country: Hungary Phone: (+) 36-203879193 Fax: +3614586842 Email: merkely.bela@gmail.com Email2: maurovich.horvat@gmail.com
8. South Eastern Health and Social Care Trust (SET)		
Patrick Donnelly, MD Peter Ball,	Local Principal Investigators	Street: Upper Newtownards Road Ulster Town: Belfast Postal Code: BT16 1RH Country: United Kingdom

MD		Phone: +44 2890484511 Fax: Email: patrick.donnelly@setrust.hscni.net Email2: peter.ball@setrust.hscni.net
9. University College Dublin, National University of Ireland (NUID UCD)		
Jonathan D. Dodd, MD Martin Quinn, MD, PhD	Local Principal Investigators	Street: Belfield Campus Town: Dublin Postal Code 4 Country Ireland Phone: +353 87 2987313 Fax: Email: j.dodd@st-vincents.ie Email2: quinnmartin2001@yahoo.com
10. Università degli Studi di Cagliari (UNICA)		
Luca Saba, MD Maurizio Porcu, MD	Local Principal Investigators	Street: AOU di Cagliari - Polo di Monserrato SS 554 Town: Monserrato (CA) Postal Code: 09042 Country: Italy Phone: +393206206091 Fax: Email: lucasabamd@gmail.com Email2: porcu.maurizio@gmail.com
11. Università degli Studi di Roma la Sapienza (UNIROMA)		
Marco Francone, MD, PhD Massiomo Mancone, MD	Local Principal Investigators	Street: Viale Regina Elena 324 Town: Roma Postal Code: 00161 Country: Italy Phone: +393357550688 Fax: Email: marco.francone@uniroma1.it Email2: massimo.mancone@uniroma1.itrino.sardella@uniroma1.it
12. Paula Stradiņa Klīniskā universitātes slimnīca (PSKUS)		
Iveta Mintale, MD Ligita Zvaigzne, MD, PhD	Local Principal Investigators	Street: Pilsoņu street 13 Town: Riga Postal Code: LV 1002 Country: Latvia Phone: +37167069333 Phone 2: +37129293376 Fax: Email: Iveta.Mintale@stradini.lv Email2: ligita.zvaigzne@inbox.lv
13. Lietuvos Sveikatos Mokslu Universitetas (LSMU)		
Gintare Sakalyte, MD, PhD Antanas Jankauskas, MD, PhD	Local Principal Investigators	Street: Eivelniu 2 Town: Kaunas Postal Code: 50009 Country: Lithuania Phone: +37069806044 Fax:

		Email: gsakalyte@yahoo.com Email2: jankauskas.antanas@gmail.com
14. Wojevódzki Szpital Specjalistyczny we Wrocławiu (WSS)		
Tomasz Haran, MD Malgorzata Ilnicka-Suckiel, MD	Local Principal Investigators	Street: Ul. Henryka Michala Kamienskiego Town: Wroclaw Postal Code: 51 124 Country: Poland Phone: +48602229211 Fax: Email: haran@interia.pl Email2: malgorzata.ilnicka@gmail.com
15. Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E)		
Rita Faria, MD, Vasco Gama, MD, PhD	Local Principal Investigators	Street: Rua Conceicao Fernandes Town: Vila Nova De Gaia Postal Code: 4434 502 Country: Portugal Phone: +351934258281 Fax: Email: rita.d.faria@gmail.com Email2: vasco@chvng.min-saude.pt
16. S.C. Cardio Med S.R.L. (CAM)		
Theodora Benedek, MD, PhD Imre Benedek, MD, PhD	Local Principal Investigators	Street: 22 decembrie 1989 Town: Targu-Mures Postal Code: 540156 Country: Romania Phone: +40722560549 Fax: Email: hintea_teodora@yahoo.com Email2: imrebenedek@yahoo.com
17. Institut za kardiovaskularne bolesti Vojvodine (IKVBV)		
Nada Čemerlić Ađić, MD, PhD Oto Ađić, MD, PhD	Local Principal Investigators	Street: Put dr Goldmana 4 Town: Sremska Kamenica Postal Code: 21204 Country: Serbia Phone: +38163433982 Fax: Email: otto@sezampro.rs Email2: ncemerlica@gmail.com
18. Institut Català de la Salut (ICS-HUVH)		
José F. Rodríguez-Palomares, MD Bruno Garcia del Blanco, MD	Local Principal Investigators	Street: Passeig de Vall d'Hebron 119 Town: Barcelona Postal Code: 08035 Country: Spain Phone: +34661857792 Fax: Email: jfrodriguezpalomares@gmail.com Email2: brunogb51@gmail.com
19. University of Glasgow (Glasgow)		
Christian Delles, MD	Local Principal Investigators	Street: University Place 126 Town: Glasgow

Colin Berry, MD, PhD		Postal Code: G12 8TA Country: United Kingdom Phone: +441413302749 Fax: Email: christian.delles@glasgow.ac.uk Email2: Colin.Berry@glasgow.ac.uk
20. Aintree University Hospital (AUHT)		
Gershan K. Davis, MD Erika Thwaite, MD	Local Principal Investigators	Street: Longmoor Lane Town: Liverpool Postal Code: L9 7AL Country: United Kingdom Phone: +44 151 529 2974 Fax: +44 151 529 2724 Email: gershan@hotmail.com Email2: ERICA.THWAITE@aintree.nhs.uk
21. Turku University Hospital / Turku PET Centre		
Juhani Knuuti, MD, PhD, Mikko Pietilä, MD, PhD	Local Principal Investigators	Street: Kiinamyllynkatu 4-8 Town: Turku Postal Code: FI 20520 Country: Finland Phone: (+) 358 23132842 Email: juhani.knuuti@utu.fi Email2: Mikko.Pietila@tyks.fi
22. The Institute of Cardiology in Warsaw (IKARD)		
Cezary Kępka MD, PhD Mariusz Kruk, MD	Local Principal Investigators	Street: Ul. Alpejska 42 Town: Warsaw Postal Code: 04-628 Country: Poland Phone: (+) 48 725993883 Email: ckepka@ikard.pl Email2: mkruk@ikard.pl
23. University of Medicine and Pharmacy Targu-Mures (UMF)		
Theodora Benedek, MD, PhD Imre Benedek, MD, PhD	Local Principal Investigator	Street: 38 Gheorghe Marinescu Street Town: Târgu Mureș Postal Code: 540139 Country: Romania Phone: (+) 40722560549 Phone2: (+) 40265217333 Email: hintea_teodora@yahoo.com Email2: imrebenedek@yahoo.com
24. Clinical Hospital Center Zemun (CHCZ), Faculty of Medicine University of Belgrade (MFUB)		
Radosav Vidakovic, MD, PhD Aleksandar N.	Local Principal Investigators	Street: Vukova 9 Town: Belgrade-Zemun Postal Code: 11080 Country: Serbia Phone: +381 11 3772761

Neskovic, MD, PhD		Phone2: +381 11 3772761 Email: vidra71@yahoo.com Email2: neskovic@hotmail.com
25. OSAKIDETZA Bilbao-Basurto (OSI Bilbao-Basurto)		
Ignacio Díez González, MD Abel Andrés Morist, MD	Local Principal Investigators	Street: Avenida Montevideo, 18 Town: Bilbao Postal Code: 48013 Country: Spain Phone: (+)34652760568 Phone2: Email: IGNACIO.DIEZGONZALEZ@osakidetza.net Email2:
26. *Royal Liverpool and Broadgreen University Hospitals NHS Trust* (RLUH)		
Balasz Ruzsics, MD Michael Fisher, MD	Local Principal Investigators	Street: Prescot Street Town: Liverpool Postal Code: L7 8XP Country: United Kingdom Phone: (+) 44 151 706 3577 Phone2: (+) 44 741 148 3489 Email: Balazs.Ruzsics@rlbuht.nhs.uk Email2: Michael.Fisher@rlbuht.nhs.uk

Other Scientific Departments in Work Packages

Name	Title/Designation	Address and Contac Numbers
1.2 KKS Charité		
Olaf Bender Dr. rer. medic Rita Pilger, MSc and Corinna Meier-Windhorst, VM The-Hoang Do Felix Frömel	WP5 Good Clinical Practice and Safety Surveillance WP4 Clinical Data Management	Charité – Universtitätsmedizin KKS Charité Town: Berlin Postal Code: 13353 Country: Germany Street: Augustenburgerplatz 1 Phone: +49 30 450 553016 Email: olaf.bender@charite.de
2. Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum (LUMC)		
Jacob Geleijns, PhD	WP2 EU CT Quality Criteria and Radiation Exposure	Street: Albinusdreef 2 Town: Leiden Postal Code: 2333 ZA Country: Netherlands Phone: +31715262049 Fax: E-Mail: k.geleijns@lumc.nl
3. Institut National De La Sante Et De La Recherche Medicale (INSERM)		
Christine Kubiak, PhD	WP5 Good Clinical Practice and Safety Surveillance	Street: Rue de Tolbiac 101 Town: Paris Postal Code: 75654 Country: Phone: +33144236278 Fax:

		E-Mail: christine.kubiak@ecrin.org
4. Fundacion Vasca De Innovacion e Investigacion Sanitarias (Osteba-BIOEF)		
Iñaki Gutiérrez-Ibarluzea, MSc. MD Bioethics, MD Epidemiology, PhD Gaizka Benguria-Arrate, M.Sc.	WP 8 Systematic Review of Evidence	Street: Donostia-San Sebastian 1 Town: Vitoria-Gasteiz Postal Code: 01010 Country: Spain Phone: +34945019250 Fax: Email: osteba7-san@ej-gv.es
5. University of Copenhagen, Center for Health Economics and Policy (CHEP)		
Karsten Vrangbæk, MA, PhD Hans Keiding, MSc, PhD (in collaboration with 1. Charité: Marc Dewey and 7. Universitätsklinikum Jena: Peter Schlattmann)	WP9 Cost-effectiveness	Street: Øster Farimagsgade 5 Town: Copenhagen K Postal Code: 1353 Country: Denmark Phone: 0045 29410069 (mobile) Fax: Email: KV@ifs.ku.dk Email2: Hans.Keiding@econ.ku.dk
1.3 Charité – Universitätsmedizin Berlin, Institute of Public Health		
Jacqueline Müller-Nordhorn, MD, DPH (WP leader until 05 – 31 2018) Nina Rieckmann, PhD (WP leader since 06 – 01 2018)	WP10 Quality of Life	Street: Seestr. 73 Town: Berlin Postal Code: 13347 Country: Germany Phone: +49 30 450 570824 Fax: E-Mail: nina.rieckmann@charite.de Email2: jacqueline.mueller-nordhorn@charite.de
7. Universitätsklinikum Jena (UKJ)		
Peter Schlattmann, MD, PhD Mario Walther, DSc (leaves UKJ)	WP11 Statistical Analysis (Planning statistican)	Street: Bachstraße 18 Town: Jena Postal Code: 07743 Country: Germany Phone: +49 3641 934130 Fax: E-Mail: peter.schlattmann@mti.uni-jena.de E-Mail2:
8. Universitätklinikum Tübingen		
Peter Martus; Prof. Dr.	Conduct of main statistical analysis	Street: Silcherstraße 5 Town: Tübingen Postal Code: 72076 Country: Germany

		Phone: +49 07071 29-78253 Fax: E-Mail: Peter.Martus@med.uni-tuebingen.de E-Mail2:
1.4 Charité – Universitätsmedizin Berlin, Institute of Biometry and Clinical Epidemiology		
Konrad Neumann, PhD	Conduct of health status statistical analysis	Street: Charitéplatz 1 Town: Berlin Postal Code: 10117 Country: Germany Phone: +49 450 562184 Fax: E-Mail: konrad.neumann@charite.de E-Mail2:

Outreach to Stakeholders including Patient Interest Groups

Participant	Name of Patient Interest Group/ Heart Foundation	Name of Contact Person
1. CHARITE	German Heart Foundation at Berlin-Weißensee	Chair: Mrs. Martina Seiffert
2. MUI	Currently not	Currently not
4. FN Motol	Czech Society for Cardiology	In progress
5. REGIONH	Danish Heart Association	Chair: Henrik Steen Hansen, Odense University Hospital
	Danish Heart Foundation	Chair: Henrik Steen Hansen, Odensen University Hospital
6. ALB	Local “Herzsportgruppe”, Cardiac Training Course for pts with cardiovascular diesease. In cooperation with the established Handball team “Frisch Auf Göppingen”	Dr. C. Hofgärtner, Klinik am Eichert, Göppingen
	Local patient interest group	Peter Drescher in Holzgerlingen
	Membership of the “German Heart Foundation”	Prof. Schröder, Klinik am Eichert, Göppingen
7. ULEI	In progress	In progress
8. SE	Patients' Club	Dr. Gyorgy Barczi
	The SzivSN Foundation	Zsuzsanna Bernáth-Lukács,
	Arrhythmia Foundation	Dr. Orsolya Kiss
	Hungarian National Heart Foundation	Dr. Bela Merkely
9. SET	In progress	In progress
10. SVUH	Downe Cardiac Support Group	Seamus McGoran
	National Institute of Health Research, Patient and Public Involvement Group	Susannah Wood
	Northern Ireland Chest Heart and Stroke	Andrew Dougal
	British Heart Foundation	Majory Burns
11. UNICA	Currently not	Currently not
12. UNIROMA	In progress	In progress
13. PSCUH	“Parsirdi.lv”(Translation: “Aboutheart.lv”) – Society of patients with cardiovascular disease	Inese Maurina
14. LSMU	Currently not	Currently not

15. WSS	Polish Cardiac Society.	
	The Lower Silesian Heart Diseases Centre MEDINET,	Prof. Marian Zembala
	The Małopolska Centre of Biotechnology (MCB) (a joint project of the Jagiellonian University and the University of Agriculture)	Dr. Ewa Stępień
	Silesian Center for Heart Diseases, Zabrze;	Prof. Marian Zembala
	American Heart of Poland S.A.,	Dr. Jarosław Hanaś
16. CHVNG/E	In progress	In progress
17. CAM	Association of Patients with Cardiovascular Diseases	Vajda Stefan
	Asociatia cardiacilor operati pe cord din Romania	Casvean Teodor
	Debrecen Heart Association (Debreceni Szív Egyesület -Hungary)	Dr. Fesus Laszlo
	Association for a Healthy Heart ("Egészséges Szívért" Közhasznú Egyesület -Hungary)	Zlati István
	Association for rehabilitation of cardiovascular patients (Szív és Érrendszeri Betegek Rehabilitációs Egyesülete - Hungary)	Bagdi Sándor
	Transylvanian Association of Transvascular Therapy and Transplantation	Buzas-Colcer Gina
	Romanian National Heart Foundation	Prof. Dan Gaita
	Hungarian National Heart Foundation	Prof. Dr. Nagy Andras
18. IKVBV	Disease Prevention Programme	Provincial Government
	Health life style for healthy heart Progamme	Provincial Government
19. ICS-HUVH	Collaboration Outpatient Centers	e.g., Bački Petrovac, Ruma, Indjija, Šid, Novi Bečej, Bačka Topola, Sremska Mitrovica

	APACOR: Asociación de pacientes coronarios	Mariano Hernanz de las Heras
	Associació Gironina de Prevenció i Ajuda a les Malalties del Cor (GICOR)	Dr. Margarita Gou
	Fundación Española del Corazón	Dr. Leandro Plaza Celemín
	European Heart Network	Inés Galindo
22. University of Glasgow	Scottish Cardiac Society	Dr I Findlay, President
	British Heart Foundation	BHF Chairs, Prof. Rhian Touyz and Prof. Andy Baker
	British Cardiac Imaging Society	Prof. Colin Berry, Member Elect
	British Hypertension Society	Dr. C Delles, Executive Committee member
	Society of Cardiac MRI	Dr. N Tzemos, Member Elect
23. AUHT	Aintree Hospital Cardiac Rehabilitation Interest Group	Mary Torpey Cardiac Rehab Nurse
	British Heart Foundation	Customer Service CentreBHF
	European Heart Network	European Heart Network AISBL
	British Heart Foundation	Customer Service Centre
	British Heart Foundation	Customer Service Centre
	Finnish Heart Association	Professor Matti Uusitupa
29. TURKU	Finnish Cardiac Society	Chairman Mikko Pietilä
30. IKARD	Polskie Towarzystwo Kardiologiczne	Warszawa, Stawki 1/3, secretariat@ptkardio.pl
	Rzecznik Praw Pacjenta	Instytut Kardiologii, Warszawa, Alpeksa 42, tel: +48223434100
	Fundacja Instytutu Kardiologii	Warszawa, Alpejska 42, Ms Blanka Wiśniewska, b.wisniewska@ikard.pl
31. UMF	Romanian National Heart Foundation	Prof. Dan Gaita
	Romanian Society of Cardiology	Dr. Gabriel Tatu Chitoiu
32. MFUB	Serbian Cardiac Care Units Association	Prof. Biljana Putnikovic (putnikovicb@live.co.uk; kjsrbije@hotmail.com)
	Echocardiographic Society of Serbia	Prof. Aleksandar N. Neskovic (neskovic@hotmail.com)
	Cardiology Society of Serbia	kontakt@uksrb.org
33. OSAKIDETZA	Fundación Española del Corazón	Dr. Leandro Plaza Celemín

3. Rationale and Background Information

In order to ensure good reporting quality, this study protocol was primarily drafted according to the WHO (Word Health Organization) recommended format for a research protocol (http://www.who.int/rpc/research_ethics/format_rp/en/). In addition, we made sure that also all recommended items of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement[2] were included.

3.1 Need for a Trial

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 until 2030.[3]

Invasive coronary angiography (ICA) is the reference standard for the diagnosis of CAD and allows immediate intervention. However, only 38-40% of patients undergoing ICA in Europe[4] and the USA[5] actually have obstructive CAD. ICA entails relatively rare but considerable risks for patients such as death, myocardial infarction, or stroke.[6; 7] An effective non-invasive test to rule out CAD would be pivotal to reduce the ca. 2 million annual ICAs in Europe that yield negative results.[4] Coronary computed tomography (CT) angiography is the most accurate non-invasive diagnostic imaging strategy for CAD[8; 9] and promises the greatest societal impact with high cost-effectiveness.[10; 11] With its high sensitivity[8; 9] it is the best non-invasive option to exclude CAD in patients with intermediate risk (pretest probability) of CAD,[12] e.g., patients with equivocal stress test results.[13] However, its costs are not reimbursed by state health insurance, except for the restricted patient population with a pretest probability of 10-29% and a calcium score of 1-400 in the UK.[14] CT applied as the first-line imaging modality to determine further workup may result in early and safe discharge of the majority of patients with intermediate risk of CAD and stable chest pain.

3.2 Relevance of the DISCHARGE Trial

ICA has an established role derived from the long history of its use and because it offers the option of performing interventional therapeutic procedures during the same session; therefore it is still considered the diagnostic gold standard in confirming or ruling out stenosis of the coronary arteries.[15; 16] Nevertheless, catheterisation of the heart is an invasive procedure with considerable mental and physical stress for the patient. What must also be mentioned here is the duration of hospitalisation associated with a catheter-based coronary artery examination and the ensuing health care costs.[17] For these reasons, establishing a reliable noninvasive technique for visualising the coronary arteries while at the same time reducing complication rates and cardiovascular events is of great importance. CT has emerged as the most promising candidate for this purpose. It has already been shown that CT is less expensive[11] than ICA and has fewer complications.[18] In addition, CT in general is already widely spread and used[19] and therefore easily available in urban and rural areas alike. It can be easily performed and evaluated and does not need high

physician input.[20] However, while the diagnostic accuracy (efficacy) of CT for assessing CAD has been investigated comprehensively in original studies[21-26] as well as meta-analyses,[8; 9] there is only little evidence for its actual clinical benefit (effectiveness) in the large population of patients with an intermediate pretest probability of disease, who are most likely to benefit from the examination.[12]

The current European Guidelines on the Management of Stable Angina Pectoris recommend a stress test, after initial clinical evaluation, for risk stratification prior to ICA.[27] However, stress tests do not perform at published diagnostic accuracy rates, as proven by the low proportion of obstructive coronary heart disease in patients undergoing elective catheter-based angiography in the routine clinical setting.[5] This is also due to the high rate of stress tests with nondiagnostic results leading to an indication for ICA. CT has been shown to be superior to stress testing for risk stratification,[28-32] and negative CT was found to predict a 5- to 7-year disease-free period for patients.[33; 34]

There are three major trials RESCUE, PROMISE, and SCOT-HEART which can be compared to some extent to the DISCHARGE PRCT: RESCUE and PROMISE, are federally funded randomised controlled trials in the United States and assess the impact of cardiac CT in comparison to functional imaging strategies in patients with stable chest pain.[35; 36]
By mandating the post testing treatment options, RESCUE is using a more restricted trial design and has to be considered an explanatory RCT. As planned with the DISCHARGE PRCT, PROMISE uses a pragmatic approach in its performance of the randomised controlled trial reflecting usual care.[35] This leads to great flexibility in the realisation of the performance which can be considered to be the main reason why patient recruitment has been very good in PROMISE: all of the 10,000 planned patients were already enrolled within 3 years, the study is finalised and the results are published[36]. Nonetheless, although RESCUE will bring and PROMISE has brought about interesting aspects concerning the diagnostic imaging and treatment options in the clinical management of patients with stable angina, they do only compare cardiac CT to standard functional imaging modalities, but not the gold standard for anatomical evaluation, ICA.
The SCOT-HEART trial recently indicated that cardiac CT may reduce myocardial infarction on follow-up if used in patients with **recent onset stable chest pain or discomfort.**[37]

If the planned trial shows CT to be superior in terms of a significant reduction of events, the findings may potentially lead to changes in current guidelines.[27] This may involve that CT coronary angiography becomes a procedure that could be more established and in this way be made available to a large number of patients with stable chest pain and an intermediate pretest probability of CAD. Finally, this means that CT coronary angiography might replace a relevant proportion of the total of approx. 1 million invasive coronary examinations currently performed in Germany each year or of the approx. 3.5 million in Europe,[4] thereby reducing the number of invasive diagnostic procedures.

3.3 Economic Considerations and Health-related Quality of Life

Coronary artery disease (CAD) is the main cause of death in high-income countries.[38] The World Health Organisation (WHO) estimates there will be about 20 million deaths from cardiovascular reasons in 2015, accounting for 30 percent of all deaths worldwide.[39] The European Parliament initiated the compilation of the 2012 European Cardiovascular Disease Statistics[40] based mostly on unpublished results of the Health Economics Research Centre, University of Oxford. According to this statistics, costs in the EU due to cardiovascular diseases are estimated to almost €196 billion a year (54% direct healthcare costs, 24% productivity losses and 22% informal care of ill people). In 2009, the burden of the EU healthcare system due to cardiovascular diseases was over €106 billion, which represents costs per capita €212, i.e. 9% of EU total healthcare expenditures. Next to direct healthcare system expenditures, cardiovascular diseases represent a burden also due to productivity losses (estimated to be €46 billion in 2009) and informal care (€44 billion in 2009).[40]

Authors of the 2012 European Cardiovascular Disease Statistics[40] focused on CAD (International Classification of Diseases, Chapter IX, I20-I25, 10th Revision). According to their results, coronary heart disease causes 21.0% of all deaths in Europe (14.1% in the EU), and 14.1% of all deaths under the age of 65 in Europe (9.7% in the EU). These numbers are not equally distributed across Europe; **Figure 1** and **Figure 2** from[40] show the distribution of death rates under 65 in men and women in Europe. Moreover, the development in time differs in individual countries, as **Figure 3** and **Figure 4** from[40] indicate. (The figures are placed at the end of this chapter.)

Number of deaths caused by coronary heart disease in Europe reaches 1.8 million per year.[40] In addition to that, CAD and the necessary medical treatments lower the patients' health related quality of life (HRQoL). Both physical and mental HRQoL is impaired in patients with CAD, in particular in older patients and women. Related to HRQoL is the concept of quality adjusted life years (QALYs).[41; 42] It is based on the idea that a year in impaired health has a lower value than one in perfect health. QALYs are usually based on utilities which are determined by a standard gamble or time trade off and can take values between 0 (=immediate death) to 1 (=perfect health).[43] Given the estimation of an expert panel[44] QALYs of patients with symptoms, consistent to those of a coronary ischemia is lowered to an equivalent of 0.85 QALY. If a patient faces complications, the value will be even lower.[44; 45] The resulting impact is huge; hence economic considerations are of great importance, as a small change in expenditures per patient can mean a great amount in the healthcare system budget.

As concerns cost-effectiveness comparison of coronary CTA with other imaging modalities used in coronary artery disease, early modelling results have been promising, although they require further research to be confirmed in large clinical trials. Among the first results, Dewey and Hamm[11] and Genders et al.[41] modelled cost-effectiveness in comparison with both new modalities and the most commonly used traditional diagnostic modalities. Dewey and Hamm concluded that up to a pretest probability for coronary artery disease of 50%, CT coronary angiography was the most cost-effective procedure. A major reason for CTA being cost-effective

compared to CCA is the lower rate of adverse events that indicate further treatment and thereby cause additional direct costs. Genders et al. concluded that the optimal diagnostic work-up depends on the optimisation criterion, prior probability of CAD, and the diagnostic performance of CT coronary angiography; CT coronary angiography was considered cost-effective when the prior probability was lower than 44% and 37% in men and women respectively. The systematic review by Mowatt et al.[45] indicates that CTA might be a cost-effective technology. Quite recently, Hetterich et al.[46] called for more cost-effectiveness research in CTA, especially in European environment. Prazeres et al.[47] and Miller et al.[48] support CTA's cost-effective superiority, however, in US and Brasilian environment. The DISCHARGE study is designed to provide much more reliable evidence.

Although the core of the DISCHARGE project is dedicated to the research of clinical effectiveness, cost-effectiveness research will accompany it with the aim to determine whether CT is not only a clinically effective, but also cost-effective alternative, as former results have indicated.[11; 41; 45; 47-50] Investigating cost-effectiveness has been recently recommended also by the group formulating the future directions for cardiovascular disease comparative effectiveness research.[51] The calculation of costs connected with CAD diagnostics is important due to the large number of patients undergoing CAD testing every year; hence, even a small gain in incremental cost-effectiveness ratio (ICER) may have significant impact on health budgets.

3.4 Implication for the Design of the DISCHARGE Trial

According to comparative effectiveness research, a pragmatic study design is considered to be the most sensible design to assess whether a specific treatment procedure should be used on a large scale based on an evaluation of its effectiveness.[1; 52; 53] Only the proposed study design (pragmatic randomised controlled trial – PRCT) allows direct comparison under the conditions of an intention-to-treat analysis, which assesses the practical benefit (effectiveness) of CT versus ICA in a setting that is similar to clinical routine. On doing so, the DISCHARGE trial has been designed in accordance with a recent proposal of an NHLBI Workshop.[51]

In Europe, we can revert to the experience gained with a similar single-centre pilot study in 340 patients at Charité (CAD-Man, NCT00844220).[54] Based on the results of the CAD-Man trial, it is expected that approx. 80-90% of patients do not have obstructive CAD and can be discharged immediately. To ensure representativeness, the DISCHARGE trial will be conducted at 26 clinical sites in 16 European countries.

Differences in death rates from coronary heart disease in men and women under 65 across Europe, last available data 2009[40]

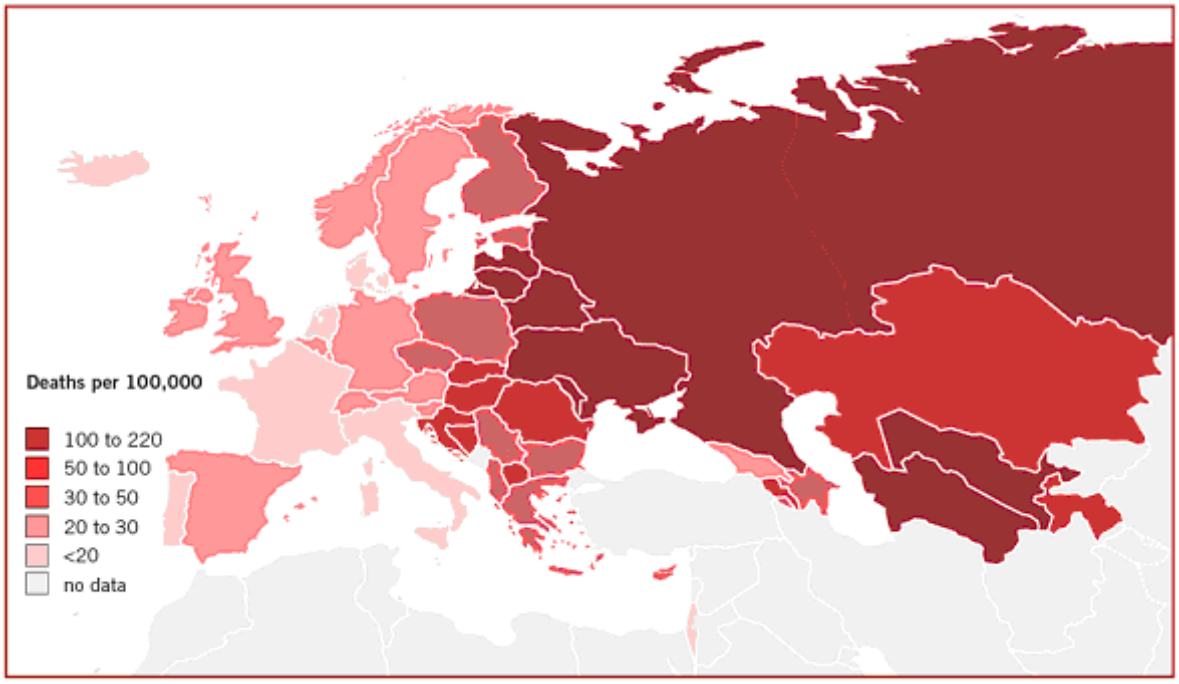


Figure 1. Age-standardised death rates from CHD, men aged under 65, latest available year, Europe

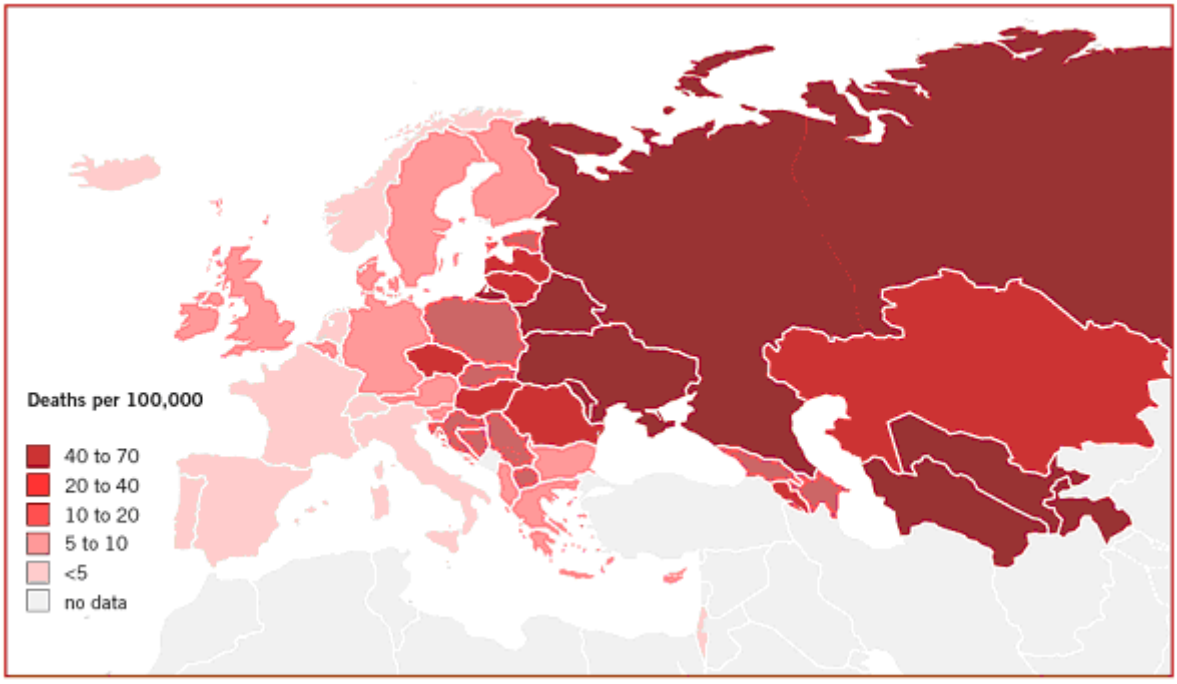


Figure 2. Age standardised death rates from CHD, women aged under 65, latest available year, Europe

Development of death rates from coronary heart disease in men and women under 65 across Europe, last available data 2009[40]

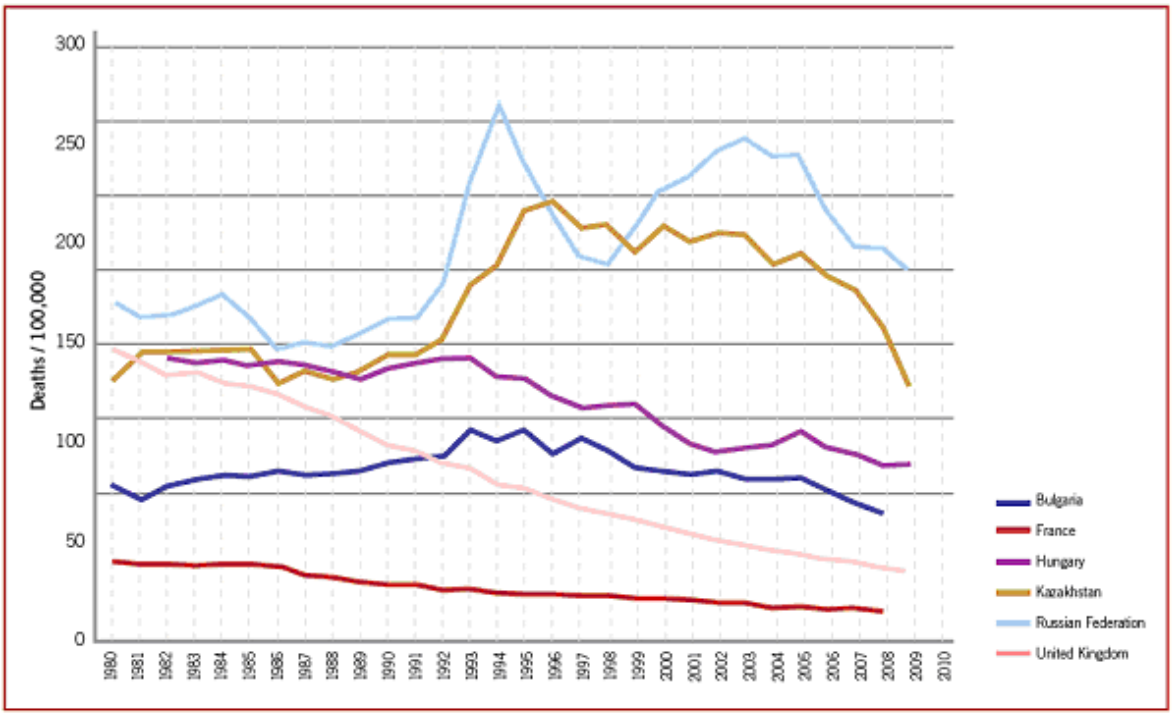


Figure 3. Death rates from CHD, men aged under 65, 1980 to 2010, selected countries

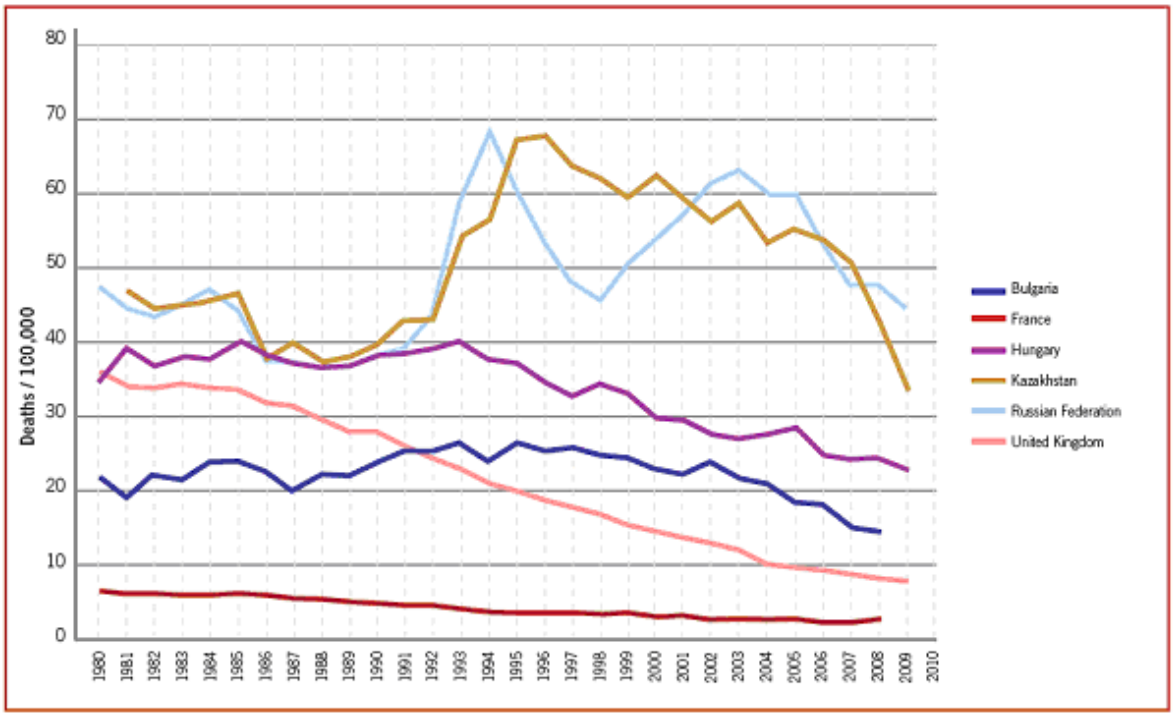


Figure 4. Death rates from CHD, women, aged under 65, 1980 to 2010, selected country

4. Study Goals and Objectives

4.1 Research Hypothesis

The primary hypothesis of this trial is to evaluate the superiority of computed tomography (CT) over invasive coronary angiography (ICA, = conventional coronary angiography or catheter-based coronary angiography) concerning safety in patients with stable chest pain and intermediate pretest probability (10-60%) of coronary artery disease (CAD).

4.2 Study Objectives

A detailed list including the measures is provided in section 6.5.3 “Other Outcome Measures” and published under: https://clinicaltrials.gov/ct2/show/NCT02400229

4.2.1 Primary Objective

The primary objective (or primary outcome measure) for evaluating the superiority of CT over ICA is the occurrence of MACE (MACE = major adverse cardiovascular events; defined as at least one of the following: cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; see Section 6.5.1 "Primary Outcome Measure MACE" for in-detail definition of MACE as well as the electronic case report form (eCRF) after a maximum follow-up of 4 years after CT or ICA in stable chest pain patients with intermediate pretest probability (10-60%) of CAD. A detailed description for evaluating the primary objective is provided in the statistical analysis plan (SAP) as a separate document of the Standard Operating Procedure (SOP) Manual.

4.2.2 Secondary Objectives

Secondary objectives include:

- MACE in Subgroups
- Radiation exposure of the tests
- Minor Cardiovascular Events (MICE): They include coronary revascularisation following new, non-index related ICA, peripheral artery revascularisation, hospitalisation for chest pain/discomfort, emergency department visit for chest pain/discomfort, transient ischemic attack, and congestive heart failure. Time frame for MICE: 1 minute after randomisation to CT/ICA diagnostic procedure and during follow-up.

- 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
- Influence of Computed Tomography Angiography and Invasive Coronary Angiography on Angina Pectoris
- Comparison of Incidental Findings in Computed Tomography Angiography and

Invasive Coronary Angiography Group and Potential Benefits and Harms of Findings)
- Patient Acceptance/Preference in the Computed Tomography Angiography and Invasive Coronary Angiography Group
- Radiation Exposure in the Computed Tomography Angiography and Invasive Coronary Angiography Group
- Cost-effectiveness Analysis in the Computed Tomography Angiography and Invasive Coronary Angiography Group
- Social-economic Status, Health-related Quality of Life and Lifestyle in the Computed Tomography Angiography and Invasive Coronary Angiography Group
- Gender Analysis in the Computed Tomography Angiography and Invasive Coronary Angiography Group

Procedural complications will be further classified into major and minor. Major procedural complications include death, nonfatal stroke, nonfatal myocardial infarction and other complications requiring a prolonged hospital stay of at least 24 hours. Procedural complications that do not fulfil these criteria are classified as minor.

Time frame for procedural complications: Occur during the procedure or within 48 hours post last related procedure; relevant procedures are CTA, ICA, PCI, CABG and ischemia test).

List of Procedural complications:

<u>Major procedural complications</u>

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

<u>Minor procedural complications</u>

- Hematoma at the puncture site
- Secondary bleeding at the puncture site
- Bradycardia
- Angina without infarction
- Allergoid contrast agent reaction
- Stent migration
- Hypotension requiring treatment
- Headache
- Hyperthyreodism

- Skin tissue and nerve injuries
- Extravasate
- Contrast-induced nephropathy (CIN)
- Infections
- Femoral arterial occlusion (or arterial access vessel) or dissection
- New requirement for dialysis
- DVT/pulmonary embolism
- Closure or injury of vessels
- Injury of the heart (e.g. valve or myocardium)
- Perforation
- Gastrointestinal bleeding
- Genital-urinary bleeding
- Other major bleeding
- Red blood cell (RBC)/Whole blood transfusion
- Twisting or rupture of the catheter parts
- Other equipment mishaps (e.g. retained foreign body guidewire fracture)
- Development of arterio-venous fistula(s)
- Development of pseudo aneurysm at puncture site
- Dissection (except coronary dissection)
- Permanent edema (e.g. due to lymphatic congestion at puncture site)
- Embolisation of central or peripheral vessels due to thromboembolism
- Acute closure of coronary vessels
- Stent infection
- Heart failure
- Wrong patient or wrong procedure
- Other

Detailed descriptions for evaluating the secondary objectives are provided in the statistical analysis plan and the cost effectiveness analysis plan.

All procedural complications will be classified according to the NCDR®CathPCI Registry®v4.4 Coder´s Data Dictionary. Dissections in other vascular regions will be adjudicated depending on whether they are life-threatening or not and did prolong the hospital stay by at least 24 hours.

4.2.3 Other Objectives from Pre-Planned Analyses

- Evaluation of Differences in Europe
- Computed Tomography Angiography and Invasive Coronary Angiography Image-based Secondary Outcomes
- Computed Tomography Image-based Secondary Outcomes: Image Quality
- Computed Tomography Image–based Outcomes: Heart Rate and Dose
- Computed Tomography image-based Secondary Outcomes: Plaques
- Invasive Coronary Angiography Secondary Outcomes
- Planned Cross-over in accordance with management recommendations
- Imaging Ischemia tests
- Comparison of Pre-test Probability Calculators

- Predictive Value of DISCHARGE Calculator
- Development of Novel Pre-test Probability Calculator

5. Study Design

This study is a European multicentre prospective pragmatic randomised controlled trial (PRCT) in patients with suspected CAD conducted at 26 clinical centres. The pragmatic approach of the study addresses practical questions about the risks, benefits, and costs of an intervention as they occur in everyday clinical practice.[52]

CT directed clinical management will constitute the intervention group and ICA directed clinical management will be the control group. Thus, a 2-group randomised approach is utilised. ICA will not be withheld from the patients in the intervention group (CT) but will only be carried out depending on the results of CT. Blinding patients towards the groups - CT or ICA - is not possible. A blinded analysis of all outcomes will address whether CT works under the usual conditions and therefore includes all patients. Thus analysis will be performed in the intention-to-treat population.

5.1 Number of Patients

Approximately 3546 men and women age 30 years or older with suspected CAD and scheduled to undergo invasive coronary angiography will be included in this clinical trial and will be analysed according to the intention-to-treat approach. Patients will be randomised to the intervention (CT) or ICA group.

The study will be conducted at 26 clinical sites (hospitals and heart centres) in 16 European countries (Austria, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Spain, United Kingdom). The results of database searches at each of the 26 clinical sites show that about 50% of the 60950 annual ICAs are performed in patients with suspected CAD comprising 27410 patients. Therefore, it will be feasible to enrol the target number of patients.

5.2 Eligibility Criteria

Due to the pragmatic approach of this trial,[1] only minimal inclusion and exclusion criteria are used for study population identification.

Inclusion criteria:

- Patients with suspected coronary artery disease with stable chest pain and intermediate pretest probability (10-60%) of CAD referred for invasive coronary angiography.

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

  - being acute
    (= first appearance within the last 48 hours) or
  - instable
    (= (a) first appearance with Canadian Cardiovascular Society

Angina Grading Scale (CCS, cf. **Table 1**) 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)
angina pectoris

- Patients at least 30 years of age
- Written informed consent

Checking for intermediate pretest probability (10-60%) of disease will be the last step in screening potential patients. It will be performed using a pretest calculator that has been developed at the Charité based on available tools for risk prediction.[55; 56] This calculator uses age, gender, and the patient's clinical presentation of stable chest pain to calculate pretest likelihood 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), a meta-analysis of individual patient data (IPD) of a total of approx. 6,700 cases. This meta-analysis was supported by the German Ministry of Education and Research as part of the joint „clinical study" programme of the ministry and the German Research Foundation (grant number: 01KG1110). At this point in time, the study protocol has been published. [57]

Exclusion criteria:

- Patients who are/were on hemodialysis
- No sinus rhythm
- Pregnancy
- Any medical condition that leads to the concern that participation is not in the best interest of health (e.g., extensive comorbidities)
- Patients who participate in any other randomised/interventional study

Table 1. Classification of angina pectoris according to the Canadian Cardiovascular Society[58]

CCS Class	Description
I	Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina (occurs) with strenuous, rapid or prolonged exertion at work or recreation.
II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
III	Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.

IV	Inability to carry on any physical activity without discomfort–anginal symptoms may be present at rest.

5.3 Duration

The expected duration of the study is from October 2015 (start of enrolment) through September 2019 (final follow-up). Patient recruitment and examinations are from October 2015 through September 2017.

For each patient, it is anticipated that the selection period will last less than 1 day. According to the PRCT design, the number of follow-ups will be minimal in order to avoid interference with usual care. There will be no formal follow-up visits of trial individuals within the DISCHARGE PRCT. Instead, questionnaires (including health status, measures of health-related quality of life, work status, patient preference) will be sent to the patients by mail during the first-year follow-up and several alternative sources (e.g., general practitioners, death registries, and family members) will be utilised for investigating MACE during follow-up. In addition to the final follow-up for MACE, only one exploratory interim analysis will be performed concerning MACE.

6. Methodology

6.1 Interventions

6.1.1 Invasive Coronary Angiography

ICA, as already outlined above, is considered the diagnostic gold standard in confirming or ruling out stenosis of the coronary arteries. All patients participating in the DISCHARGE study will have a referral for ICA based on suspected CAD. The need for this examination was established by the referring physician. However, according to the randomisation schedule, only 50% of the patients enrolled in the study will directly undergo ICA.

In ICA, an X-ray fluoroscopy with administration of contrast medium is performed. For this, a 2 mm flexible plastic tube is threaded to the aortic root of the heart through a punctured artery in the groin or the wrist. When the catheter is advanced to the heart, the coronary arteries and other structures can be depicted by injecting contrast medium through the catheter under fluoroscopy.

In rare cases, the contrast medium can cause mild allergoid reactions (nausea, itching, skin rash, for example). Severe intolerance reactions to the contrast agent (such as impairment of kidney function or allergic shock) are extremely rare as well as other adverse effects. ICA exposes the patient to X-rays. The radiation exposure is about 9-10 mSv, which corresponds to the natural background radiation of 54 to 60 months.

ICA will be performed by cardiologists and cardio-thoracic surgeons.
Detailed information can be found in the electronic case report forms (eCRFs).

6.1.2 Coronary CT Angiography

Two modalities have developed appearing to be suitable to enable noninvasive coronary angiography: CT and magnetic resonance imaging (MRI). Absence of radiation exposure and absence of contrast medium exposure are the two major advantages of MRI. In an earlier study of 130 patients with suspected CAD, 16-row CT and MRI with the standard diagnostic test (ICA) were compared at Charité. CT was found to be significantly superior to MRI in terms of diagnostic accuracy on both the per-patient level and the per-vessel level.[59] The superiority on the patient level was also confirmed in a large meta-analysis of CT (89 studies) and MRI (20 pooled studies).[8]

Based on these results, it seems desirable to answer the question whether the better results achieved with CT can be translated into a reduction of complications and events compared with the gold standard of catheter-based cardiac angiography. Starting in 1998, multislice CT has been developed as an alternative method to ICA. The aim of this alternative method is to examine the arteries that supply the heart muscle (the coronary arteries) with similar reliability but less invasiveness. Earlier studies show that cardiac CT has an accuracy of 95-97% in detecting narrowing (stenosis) of the coronary arteries. Moreover, CT also allows ruling out stenosis with a high degree of probability (so-called negative predictive value) Therefore, CT allows reliably ruling out suspected stenosis (narrowing) without the need for ICA. In order to ensure adequate diagnostic accuracy, each DISCHARGE clinical site will utilise at least 64-slice CT which is state-of-the-art.[8; 9; 60] The CT examination of the heart takes about 15 to 25 minutes. The actual CT scan takes only about 0.2-8 seconds, depending on the CT scanner used. During this time, it is necessary that patients hold their breath for a short period of time. Before CT, the patient's medical records will be reviewed and blood samples may be taken according to local standards. In addition, an ECG will be obtained, unless a patient has a recent ECG (obtained within 1 month before CT). Caffeine is not allowed for 4 hours before the CT examination (coffee, tea, or chocolate, for example). Patients with a heart rate of more than 50 beats/minute (bpm) will be given metoprolol (a betablocker). Alternatively, in case of beta blocker contraindications, ivabradine or calcium channel blockers can be administered. If, after these medications, the heart rate is still above 55 beats per minute just before the CT scan, additional heart-rate control medication will be available (in order to reach the target heart rate of 60 bpm. Ivabradine cannot be given under a heart rate of 60 bpm.

First, non-contrast coronary artery calcium scan (CACS) will be performed. It will be used to determine start and end position of coronary arteries for the subsequent CTA in order to reduce effective dose. However, no patients will be excluded based on high CACS values in the DISCHARGE trial.

Immediately before the CTA examination, nitroglycerine will be given under the tongue to make the coronary arteries wider, which improves their assessment. As with ICA, the CT examination also involves injection of a contrast agent. The contrast agent is an approved agent for CT examinations and will be injected into a vein in the

crook of the elbow. In the DISCHARGE trial, preferably a triphasic injection protocol will be used. Again, in rare cases, the contrast agent can cause mild allergoid reactions (nausea, itching, skin rash, for example). Severe intolerance reactions to the contrast agent (such as impairment of kidney function or allergic shock) are extremely rare as well as other adverse effects.

After the examination, reconstructions for CACS, CTA and noncardiac structures will be made. For reading, workstations that can automatically generate curved multi planar reconstructions (MPRs) will be used and, for interpretation, axial, coronal, sagittal source images, curved MPRs and axial, coronal, and sagittal as well as double-oblique thin-slice maximum intensity projections (MIPs) will be used. For reporting, a modified Society of Cardiovascular Computed Tomography (SCCT) Coronary Segmentation Model with 18 segments based on the American Heart Association (AHA) 17-segment model will be employed.

The same as ICA, CT is also performed with X-rays. The radiation dose is about 1 to 5 mSv and roughly corresponds to the natural background radiation of 6 to 30 months.
Cardiac CT will be performed by board certified radiologists with at least SCCT level II (or equivalent) qualification. Also cardiac CT lab leadership (SCCT level III or similar, such as Q3 Zertifikat der Deutschen Röntgengesellschaft) needs to be shown by all clinical sites.

In order to ensure minimal standards for the performance of CT, a general 10-step guide specifying the most important aspects – patient preparation, examination, reconstruction, reading, reporting - was developed. Based on this guide, vendor- and scanner-specific scan protocols for the participating clinical sites were worked out. (10-Step Guide to Performing Cardiac CT; vendor- and scanner-specific scan protocols: Toshiba, Siemens, GE, and Philips). Further detailed information can be found in the SOP Manual and CTA-related eCRFs.

6.2 Randomisation

Eligible patients will be randomised to receive either CT or ICA (Sop Manual). Allocation will be concealed and equal allocation to the two trial arms will be ensured by block randomisation. In addition, patients will be stratified according to clinical site, and gender in order to minimise covariate imbalance. The randomisation to the intervention (CT) and control group (ICA) will be performed online by using the randomisation tool of the study software secuTrial®.

An intermediate pretest probability (10%-60%) for CAD will be the final inclusion criterion before randomisation. If the patients do not fulfill this, they will undergo ICA as initially planned and the results of this examination will be recorded. No follow-up will be conducted in these patients. In general, an ongoing log for all patients who were screened for the study and reasons for not being enrolled will be maintained (see corresponding eCRFs).

6.3 Withdrawal

All patients who cannot be analysed per protocol, but have signed informed consent

are called drop-outs. Patients who withdraw their participation or who are withdrawn by the principal investigator are also drop-outs and are labelled as withdrawals. Reasons for early withdrawal from a study may include but are not limited to:

1. Patient withdraws consent.
2. Further participation is not in the best interest of the patients health
3. Study ends prematurely.

Patients who withdraw after the diagnostic procedure are considered in the intention-to treat (ITT) analysis. Patients with a randomisation deviation (did not receive diagnostic test they were randomised to) are not considered as drop-outs and are considered as well in the intention-to treat analysis. Withdrawals before the diagnostic procedure, do not count in the ITT analysis.

6.4 Treatment Decisions

Except for basic recommendations based on a combination of current guidelines, the decision-making process concerning treatment options as part of the CT- and ICA-guided management of patients will be made by the local heart team at each individual centre (see below Figure 5. Design of the DISCHARGE pragmatic randomised controlled trial, and SOP Manual), thus reflecting the pragmatic routine practice approach of the DISCHARGE trial.

In the ICA arm of DISCHARGE, the local heart team makes the treatment decisions according to the ESC/EACTS guideline.[61]
In the CT arm of the trial, only patients with high-risk anatomy (left main stenosis or equivalent, proximal LAD [left anterior descending] stenosis, or 3-vessel disease)[61] will be recommended to receive ICA (and fractional flow reserve [FFR], if available) to clarify anatomy and to decide which lesion to revascularise in which way according to the ESC/EACTS guideline.[61] This is recommended because of the imperfect positive predictive value of CT in intermediate risk patients.[12] In patients with 1- or 2-vessel disease in CT, the local heart team will use the best locally available ischemia test (stress echo, SPECT, or stress MRI) before making the decision to perform ICA.[62] In case of <10% ischemic myocardium, only optimal medical therapy (OMT) is recommendend.[63] In case of >10% ischemic myocardium, ICA (and FFR, if available) is recommended before making the final decision for or against revascularisation.[63]
It can be expected that about 80-90% of patients have no obstructive (≥50%) stenosis. These patients will receive guideline-oriented medical therapy and will be immediately discharged.[62; 64; 65]

Also, cardiac and noncardiac secondary findings at CT which can range from being of no consequence to being clinically very relevant and requiring immediate intervention, additional diagnosis, or follow-up (e.g., suspected cancers) will be available to the **local heart team** for treatment decisions[66] in order to ensure that these incidental findings will be used in a beneficial way. Diagnostic and treatment decisions of secondary findings will primarily be made by the local team and depend on the entity of the secondary finding. Incidentally detected lung nodules will be followed up according to Lung CT Screening Reporting and Data System of the American College of Radiology (Lung RADS)[67] modified for DISCHARGE (SOP

Manual).

The local heart team will determine **optimal medical therapy** and **risk factor modification** according to European guidelines[13; 68] and usual care. 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 by which cardiac events can be predicted[69; 70] or high-risk plaque features such as low-attenuation noncalcified plaques (≤50 HU[71] [The threshold might change with intraluminal enhancement]), a positive remodeling index ≥1.1[72-74] (calculated as the vessel cross-sectional area at the site of maximal stenosis divided by the average of proximal and distal reference segments' cross-sectional areas) or the presence of a napkin-ring sign[72; 74] (non-calcified plaque with a central area of low CT attenuation that is apparently in contact with the lumen; and a ring-like higher attenuation plaque tissue surrounding this central area). For details see the **plaque characterisation document** in the SOP Manual. It is recommended to treat patients according to guidelines with clear target values for blood pressure and lipids according to the European guideline on cardiovascular disease prevention[68] and management of stable angina.[13] For risk factor modification in DISCHARGE please check the recommendation "What is CVD prevention" (SOP Manual).

As the DISCHARGE trial concentrates on the assessment of coronary CT angiography in comparison with ICA, it has to be specifically mentioned that **no CT perfusion** or **CT FFR will be allowed** within the trial. The following ischemia tests: are allowed: Echo, MRI, SPECT, PET-CT, and ECG.

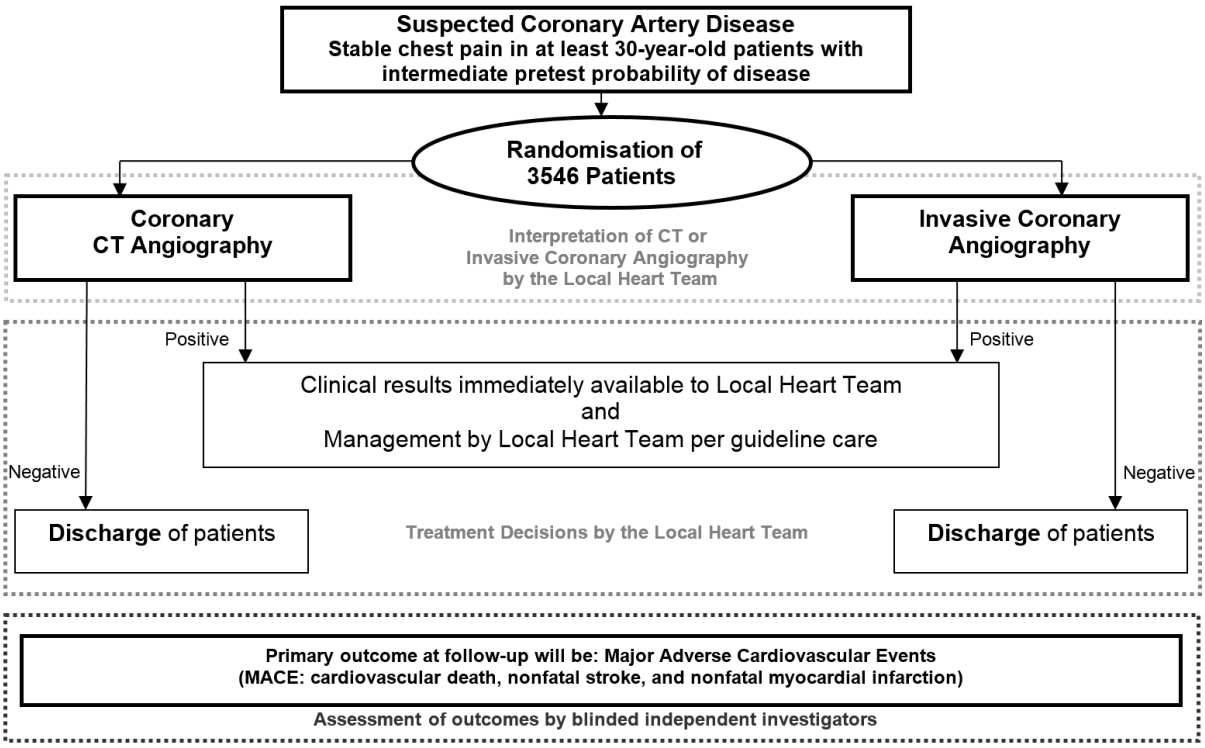


Figure 5. Design of the DISCHARGE pragmatic randomised controlled trial

6.5 Outcome Measures

6.5.1 Primary Outcome Measure MACE

The primary outcome measure is the composite endpoint “major adverse cardiovascular event (MACE)”. It is defined as at least one of the following:

- cardiovascular death
- nonfatal myocardial infarction
- nonfatal stroke

Time Frame: 1 minute after randomisation to CT/ICA diagnosistic procedure and during follow-up
Designated as safety issue: Yes (see section 7.1, pg. 48, 49).
In the following sections, definitions for each of the above listed elements of MACE will be provided:

6.5.1.1 Cardiovascular Death

The standardised definitions for cardiovascular and stroke end point events in clinical trials by the Cardiac Safety Research Consortium[75] will be implemented. According to this definition, cardiovascular death includes death resulting from:

a) Acute myocardial infarction
b) Sudden cardiac death
c) Death due to heart failure
d) Death due to stroke
e) Death due to cardiovascular procedures
f) Death due to cardiovascular hemorrhage
g) Death due to other cardiovascular causes

In the following, the main aspects of the referred document are summarised. For detailed information please see the original article.[75]

a) Death due to acute myocardial infarction
Death due to acute MI refers to death by any cardiovascular mechanism after a MI related to the immediate consequences of the MI.
Death resulting from a procedure to treat an MI or to treat a complication resulting from MI should be considered death due acute MI.
Death resulting from an elective coronary procedure to treat myocardial ischemia or death due to an MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as death due to cardiovascular procedure.

b) Sudden cardiac death
Sudden cardiac death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI

- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- Death after unsuccessful resuscitation from cardiac arrest
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

c) Death due to heart failure
Death due to heart failure (HF) refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology (see document for details).

d) Death due to stroke
Death due to stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke.

e) Death due to cardiovascular procedures
Death due to cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure.

f) Death due to cardiovascular hemorrhage
Death due to cardiovascular hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g. aortic aneurysm) or hemorrhage causing cardiac tamponade.
g) Death due to other cardiovascular causes
Death due to other cardiovascular causes refers to a cardiovascular death not included in the above categories but with a specific, known cause (e.g. pulmonary embolism or peripheral artery disease).

6.5.1.2 Nonfatal Myocardial Infarction

The actual definition of myocardial infarction (MI) of the ESC/ACCF/AHA/WHF Task Force[76] will be implemented. The **Infobox** in **Table 2** briefly summarises the criteria which, under these conditions, constitute the diagnosis for MI. Events are defined as nonfatal if they are not leading to death of the included patient. All fatal events will be recorded and discussed in section 7.3 Cardiovascular death.

Table 2. Infobox. Criteria for acute myocardial infarction

Setting	Criteria
1	Spontaneous MI and MI secondary to an ischemic imbalance: ▪ Detection of a significant rise and/or fall of cardiac biomarker enzymes *Plus* ▪ symptoms of ischemia *OR* ▪ new or presumed new significant ST-Segment-T wave (ST-T) changes or new left bundle branch block (LBBB) in the ECG *OR* ▪ development of pathological Q waves *OR* ▪ imaging evidence of new loss of viable myocardium or new regional wall motion abnormality *OR*

	▪ Identification of an intracoronary thrombus by angiography *or autopsy**
2	*Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block (LBBB), but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased**
3	Percutaneous coronary intervention (PCI) related MI: ▪ significant elevation of cardiac biomarker enzymes in patients with normal baseline value *OR* ▪ rise of biomarker enzyme values >20 % if the baseline values are elevated and are stable or falling. *Plus* ▪ symptoms suggestive of myocardial ischemia *OR* ▪ new ischemic ECG changes *OR* ▪ angiographic findings consistent with a procedural complication *OR* ▪ imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality
4	Stent Thrombosis related MI: ▪ detected by coronary angiography *or autopsy** *Plus* ▪ significant rise and/or fall of cardiac biomarker values
5	Coronary artery bypass graft (CABG) related MI: ▪ significant elevation of cardiac biomarker values *Plus* ▪ new pathological Q waves or new LBBB *OR* ▪ angiographic documented new graft or new native coronary artery occlusion *OR* ▪ imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

**Myocardial infarction resulting in death will be recorded in section 6.5.1.1 Cardiovascular death*

Please note that only symptomatic events are defined as MACE. Asymptomatic events are defined as incidental findings – if they will be detected at all. The latter will be discussed below (see "Silent myocardial infarction").

Biomarker detection of myocardial injury and ECG detection

For detailed information about biomarker detection of myocardial injury and ECG detection please look at the referred consensus document.[76] The following extracts represent the main aspects:

Biomarker detection

- The preferred biomarker of MI is cardiac troponin I or T (cTn)
- If a cTn assay is not available, the best alternative is creatine kinase MB isoform (CKMB).

ECG detection

ECG changes in patients that suffer myocardial infarction may be inscribed in the PR segment, the QRS complex, the ST-segment or the T wave. The following **Table 3** lists ST-T wave criteria for the diagnosis of acute myocardial ischemia that may lead to MI.

Table 3. ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and LBBB)

Changes	Description
ST elevation	New ST elevation at the J point in two contiguous leads with the cut-point: ▪ ≥0.1 mv ▪ exception: V_2-V_3: o ≥0.2mVin men ≥40 years o ≥0.25mV in men <40 years o ≥0.15mV in women
ST depression and T	New horizontal or down-sloping ST depression

wave changes	▪ ≥0,05mV in two contiguous leads *AND/OR* ▪ T-inversion ≥0,1mV in two contiguous leads with prominent R wave or R/S ratio >1

Classification of myocardial infarction
In addition, each nonfatal myocardial infarction will be classified as indicated by the ESC/ACCF/AHA/WHF Task Force (**Table 4**).

Table 4. Universal classification of myocardial infarction

Type	Description
1	**Spontaneous myocardial infarction** Related to atherosclerotic plaque rupture, ulceration, assuring, erosion or dissection with resulting intraluminal thrombus in one or more of the coronary arteries with ensuing myocyte necrosis.
2	**Myocardial infarction secondary to an ischemic imbalance** Myocardial necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand. E.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism etc.
3	***Myocardial infarction resulting in death when biomarker values are unavailable****
4a	**Myocardial infarction related to percutaneous coronary intervention (PCI)**
4b	**Myocardial infarction related to stent thrombosis**
5	**Myocardial infarction related to coronary artery bypass grafting (CABG)**

** Myocardial infarction resulting in death will be recorded in section 6.5.1.1 Cardiovascular death*

Silent myocardial infarction
Silent myocardial infarctions will be treated as incidental findings. When, e.g., a Q wave MI without any symptoms is detected, it will be recorded as an incidental finding and the Clinical Events Committee (CEC) will be informed. Furthermore, temporal aspects of silent myocardial infarctions will be recorded if such data is available. For example, when a patient presents with normal ECG findings at the enrolment stage of the study and a Q wave MI is detected at a later moment within study conduction, the infarction will be recorded as having been occurred during study conduction.

6.5.1.3 Nonfatal Stroke

Unfortunately, no uniform definition of stroke in cooperation with a European medical society exists. Therefore, the definition of stroke by the AHA/ASA[77] was implemented. In the following, the main aspects of the referred document are summarised. For detailed information please see the original article.[77]
Please note that, similar to acute myocardial infarction, only symptomatic events are defined as MACE. Asymptomatic events are defined as incidental findings – if they will be detected at all. The latter will be discussed below (see "Silent CNS infarction").

Definition of ischemic stroke:
An episode of neurological dysfunction caused by focal infarction of the central nervous system (CNS).

Definition of CNS infarction:
CNS infarction is brain, spinal cord or retinal cell death attributable to ischemia,

based on

1. Pathological imaging, or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution; or
2. Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.

CNS infarction includes hemorrhagic infarctions, types I and II; see "Hemorrhagic Infarction."

Hemorrhagic infarction

The term "hemorrhagic stroke" is confusing because it could mean hemorrhage after infarction or primary intracerebral hemorrhage (ICH) or subarachnoidal hemorrhage (SAH). The use of this term should be discontinued. A more standardised approach has been used in clinical trials: hemorrhagic infarction and parenchymal hemorrhage. Hemorrhagic infarction is characterised by its lack of mass effect and is divided into type I and II. Hemorrhagic infarction type I is defined by petechiae of blood along the margins of the infarction, whereas type II has confluent petechiae within the infarction but without a space-occupying effect. These hemorrhagic infarctions typically present with clinical manifestations similar to non-hemorrhagic infarctions and are often treated according to typical ischemic stroke recommendations and there should be considered cerebral infarctions.

In contrast, parenchymal hemorrhage is defined by the presence of mass effect, similar to the ICH definition of a focal collection of blood. Parenchymal hemorrhage type I is a confluent hemorrhage limited to ≤30% of the infracted are with only mild space-occupying effect, and type II is >30% of the infracted are and/or exerts a significant space-occupying effect. These parenchymal hemorrhages may present with signs and symptoms of mass effect and may require reversal of antithrombotic therapy, aggressive antihypertensive therapy, and/or anti-edema therapy, all of which are distinctly atypical for infarctions but are common recommendations for the treatment of ICH. Therefore, parenchymal hemorrhages should be considered ICHs.

Cerebral hemorrhage

Hemorrhages in the CNS will be classified as stroke if they are nontraumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages will not be characterised as stroke. The diagnoses included in cerebral hemorrhage are *intracerebral hemorrhage (ICH), subarachnoidal hemorrhage (SAH)* (both aneurysmal and nonaneurysmal), and *intraventricular hemorrhage*.

Intracerebral hemorrhage (ICH)

Definition of intracerebral hemorrhage:

A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. (Note: Intracerebral hemorrhage includes parenchymal hemorrhages after CNS infarction, types I and II—see "Hemorrhagic Infarction.")

Definition of stroke caused by intracerebral hemorrhage:

Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Subarachnoidal hemorrhage (SAH)

Spontaneous SAH is defined as a stroke because it is a CNS hemorrhage with a

vascular cause that commonly results in permanent injury to the CNS.

Definition of subarachnoid hemorrhage:
Bleeding into the subarachnoid space.
Definition of stroke caused by subarachnoid hemorrhage:
Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space, which is not caused by trauma.

Intraventricular hemorrhage
Intraventricular hemorrhage is considered a subtype of ICH.

Cerebral venous thrombosis
Definition of stroke caused by cerebral venous thrombosis:
Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.

Silent CNS infarction
Silent CNS infarctions will be treated as incidental findings. When, for example, there is imaging evidence of prior cerebral infarction without clinical symptoms, it wil be recorded as an incidental finding and the Clinical Events Committee (CEC) will be informed. Furthermore, temporal aspects of silent CNS infarctions will be recorded if such data is available. E.g., when a patient presents with imaging evidence of no CNS infarction at the enrolment stage of the study and a silent CNS infarction is detected at a later moment within study conduction, the infarction will be recorded as having been occurred during study conduction.

Important note
"At the end of deliberations, the final recommendations for the definition of stroke were not acceptable by the leadership of the European Stroke Organisation and World Stroke Organisation. These organisations declined to participate further in this statement. Their dissent was mainly associated with the inclusion of silent cerebral infarction and silent cerebral hemorrhage within the universal definition of stroke."
According to the consensus of the DISCHARGE Kick-Off-Meeting, these entities will not be defined as MACE in the DISCHARGE trial, anyway. Therefore, the referred document will be implemented.

6.5.1.4 General Considerations

MACE is a composite endpoint. A composite endpoint consists of two or more single events combined in one outcome that should represent an overall clinically relevant and valid measure.[78] Clinical sites will have to pay close attention to the effects not only on the composite endpoint overall, but also on each component of the composite endpoint. As an example, all events will be reported separately in a clear and complete manner which will be assured by the eCRF. More information about composite endpoints can be found in the European Network for Health Technology Assessment Guideline.[78]

6.5.2 Secondary and Other Outcome Measures for Pre-planned Analysis

All details can be found in the SAP, Cost-Effectiveness (CEA) Analysis Plan and on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02400229).

The first secondary end point analysis will be performed after completion of the 1-year follow-up. The data base will be locked for 1-year follow-up data and all diagnostic tests and related procedures will have been performed at this point in time. Thus, there will be no interference of the 1-year follow-up publication with the planned primary outcome analysis of MACE at the 2nd follow-up. The statistical details of the secondary analysis also include the 1-year follow-up analysis. These details are prespecified in the SAP and will include a comparison of the two study groups in regards to patient management and test findings, the comparison of time-to-test, discharged patients without further testing, additional functional tests, rate of obstructive and non-obstructive CAD, diagnostic yield of ICA in both groups, revascularizations, preventive medical therapy, procedural complications (major and minor), patient-reported outcome measures of angina and quality of life.

6.6 Pilot Study

The DISCHARGE PRCT is preceded by a pilot study to gain important data for the work packages Cost-effectiveness Analysis (CEA, WP9) and Health-related Quality of Life (QoL, WP10). This pilot study has three main purposes:

1. To collect data for the main CEA of every clinical site using a micro-costing approach (WP9).
2. To test several quality of life instruments as well as a time trade-off question (WP10) to select the best suitable questionnaires for the main PRCT.
3. Too ensure image quality for CT/ICA and test the 10-steps guide for cardiac CT and the scanner specific CT scan protocols.

The pilot study is neither randomised nor controlled. All patients with stable chest discomfort, at least 30 years of age and with suspected coronary artery disease (CAD) and a referral are suitable for inclusion. Each clinical site has to include 30 patients scheduled for routinely performed cardiac computed tomography angiography (CTA) and 30 patients for invasive coronary angiography (ICA). In comparison to the main PRCT there is no restriction in the pretest probability for CAD, which will be assessed retrospectively.

If locally required, the clinical sites obtained ethical approval for the pilot study. All data should be collected anonymously without written informed consent, since this process is contradictory to anonymous collection. Clinical sites with ethics committees that require to employ written informed consent need to anonymise the data. The pilot study participants do not undergo any follow-up. Paper based case report forms (CRF) were designed to collect the data which is then entered in a digital spreadsheet and sent to the coordinating center for remote monitoring as well as hard copies of these documents for further quality control. A pilot study package was distributed to the clinical sites containing all necessary documents as well as a dedicated comprehensive manual to ensure the correct conduct of the pilot study.
Pilot patients complete the quality of life questionnaire that includes several measures of health-related quality of life (EQ-5D-3L, SF-12-v2, Hospital Anxiety and Depression Scale, WHO-5), [79; 80] and a time trade-off question regarding chest pain. The time trade-off method allows for the assessment of differences in perceptions regarding how different health states impact on life quality, in this case chest pain. This method quantifies preferences by “assessing how much time a patient would be willing to give up to be freed from a reduced health state” [81]. The time-trade-off (TTO) utility is defined as the “number of years left to live symptom-free” (number of years left to live minus the number of years traded for symptom-free living) divided by the “number of years to live with symptoms”. Due to the pragmatic nature of DISCHARGE, it was decided that TTO should be administered via a self-administered questionnaire. The TTO question in the pilot study is based upon a study published by Burström and colleagues in 2006.[82]

In addition, a short from of the Rose Angina questionnaire was included to assess “exertional chest pain”.[83] The patients were asked about the time needed to complete all of the above questions.

At the Charité, a subsample of the pilot study participants take part in a cognitive

interviewing substudy, which was also approved by the ethics committee (EA1/209/14)
The purpose of this substudy is to assess patients' understanding, potential problems with and acceptability of the questionnaire items. This is done using cognitive interviewing, a general method to evaluate the transfer of information through questionnaires. While answering the questions the participants are asked to think aloud so the interviewer can follow the process used to come to an answer. In addition verbal probing techniques are used to test the participants comprehension of specific terms.[84]

The pilot study micro-costing CRFs are filled out by the study personnel observing the scheduled examinations and documenting the participants' age, gender, hospital stay, angina classification and examination results. Further data on staff involvement time, complications and consumables are recorded as well.
All data related to costs for consumables and to the clinical site's local health care system, reimbursement structures, acquisition costs and other costs of hospitalisation will be asked in a second general questionnaire which will be completed yearly during the main PRCT.

For assessing image quality, the clinical sites will submit images from 3 CT and 3 ICA patients. The CT patients need to be examined according to the 10-steps guide for cardiac CT and the scanner specific protocol.

6.7 Adverse Events Monitoring for CT/ICA

Safety monitoring of the CT/ICA examination will be performed by collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of study interventions or study conduct. This will include documentation, reporting and monitoring of adverse events possibly related to study-related procedures; such as CT/ICA contrast agent administration, and medications used for the CT (such as beta-blockers and nitroglycerine). Clinical laboratory tests (e.g., creatinine) will be reviewed. Assessment of allergic reactions will be performed.

7. Safety Considerations

The identification and documentation of adverse events is at the core of the DISCHARGE trial. The primary outcome measure of the DISCHARGE-trial will be the composite endpoint consisting of Major Adverse Cardiovascular Events (MACE). Secondary outcomes include adverse events as well.

7.1 Definitions

The definitions are adopted from ICH-GCP to study specific requirements.

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical trial

subject administered a study procedure and which does probably have a causal relationship with study conduct.

An AE could be diseases, signs or symptoms which occur or worsen after the study procedure.

The following events are considered to be AEs:

- Bleeding or bruising at the site of the incision
- Infection at the incision site
- Mild to moderate allergic reaction or a serious life-threatening allergic reaction to the contrast dye
- Heart attack
- Stroke
- Blood vessel damage (requiring further surgery)
- Death
- Thrombosis

Adverse Events are assessed as follows:

- Mild
- Moderate
- Severe
- If criteria for a serious adverse event (SAE) apply

For every event the causality will be analysed:

- Definite
- Probable
- Possible
- Unlikely
- Unrelated

Serious Adverse Event (SAE)

Serious adverse events are AEs according to the following categories.

1. Fatal
2. Is life threatening?
3. Results in persistent or significant disability or incapacity
4. Is a congenital anomaly or birth defect?
5. Requires inpatient hospitalisation or prolongation of existing hospitalisation with the following exceptions:
    a. Preplanned (prior to study), unless hospitalisation is prolonged
    b. Ambulatory treatment units or <24 hour re-hospitalisations
    c. Hospitalisation for elective procedure

- Emergency room visit
- MACE is an SAE
- any medically important event that may not result in death, be life-threatening, or require hospitalisation when based upon the medical judgement of the investigator may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Major Adverse Cardiovascular Event (MACE)

- Nonfatal myocardial infarction
- Nonfatal stroke
- Cardiovascular death

7.2 Treatment of SAEs and AEs

All AEs should be treated appropriately. Such treatment may include changes in study treatment/procedures including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalisation or any other medically required intervention.

7.3 Assessment of SAEs and AEs

As far as possible, each AE should be evaluated to determine:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study procedure
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; hospitalisation; …)
5. whether it constitutes a serious adverse event (SAE)

7.4 Assessment of Seriousness

Seriousness shall be determined according to the definition above.

Furthermore medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

7.5 Assessment of Intensity

Mild: Symptoms are barely noticeable to the patient or does not cause discomfort. The AE does not affect performance or functioning. Prescription medications are not usually needed for relief of symptoms.

Moderate: Symptoms are of sufficient severity to make the patient uncomfortable. The AE may effect performance of daily activities. Treatment of symptoms may be needed

Severe: Symptoms are of sufficient severity to make the patient uncomfortable. The AE may affect performance of daily activities. Treatment of symptoms may be needed.

7.6 Assessment of Causality

The safety profile and known side effects and expected adverse events related to contrast media have been well described in the literature. Known and anticipated events include, but are not limited to, allergic reaction (mild or severe), anaphylaxis, pruritus, rash, renal impairment, renal failure, contrast-induced nephropathy, vasovagal reaction. Known risks of intravenous line placement include bleeding, infection, tissue or nerve injury, and vasovagal reaction. Known risks related to beta-blocker medication include, but are not limited to, hypotension, bradyarrhythmia, allergic reaction, bronchospasm, and precipitation of reactive airway disease, heart block. Known risks of nitroglycerine use include headache, reduction in blood pressure, hypotension.

Every AE will be assessed regarding the causal relationship to

- underlying disease
- interventional procedure
- other

To assess causality between the study procedure/conduct and the Adverse Event the following definitions apply:

- Definite:
  An Adverse Event that follows a reasonable temporal sequence from the study procedure.
- Probable:
  An Adverse Event that follows a reasonable temporal sequence from the study procedure and for which involvement of other factors such as underlying diseases, complications, concomitant medications and concurrent treatments mayaiso be responsible.
- Possible:
  An Adverse Event that follows a reasonable temporal sequence from the study procedure for which possible involvement of the study procedure may be argued; although factors other than the procedure may be the causative factor including underlying diseases, complications, concomitant drugs and concurrent treatments.
- Unlikely:
  An Adverse Event that does not follow a reasonable temporal sequence from the study procedure or that can be reasonable explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.
- Unrelated:
  An Adverse Event that does not follow a reasonable temporal sequence from the study procedure or that can be reasonable explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments

7.7 Documentation of AEs and SAEs

All SAEs and all AEs need to be documented in the patient's medical chart and in the respective forms of the CRF. The documentation needs to include the type of event, start, duration, severity and causality.
SAEs need to be documented additionally on a separate SAE form.
The Sponsor will carefully document all AEs reported by the Investigator.

7.8 Reporting of SAEs

The Investigator will report any SAE within 24 hours after becoming aware to the KKS Charité via fax:
Central pharmacovigilance KKS Charité
Phone: +49 30 450 553872
Fax: + 49 30 450 7553856
Email: *pharmacovigilance-kks@charite.de*

If required by single national regulation fatal and life-threatening events will be reported by the national investigator to the concerned Ethics Committee (EC) (see approval/favourable opinion of local EC).

7.9 Follow-up of Adverse Events

Once an AE is detected, it should be followed until its resolution or stabilisation, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study, the interventions required to treat it and the outcome.
Follow-up information will be sent to the same address to which the original SAE Report Form is sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.
For a follow-up report, the investigator may be required to collect further information for a detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents.

7.10 Monitoring of Safety Risks

For the monitoring of safety risks and potential harms for the study participants caused by study procedure or study design the sponsor and a Data Safety Monitoring Board (DSMB) will carefully review all (S)AEs (see also section DSMB). In case of any safety issue that might change the risk benefit balance unfavourable the sponsor will take appropriate measures to guarantee the safety of the patients (e.g., adoption of protocol design).

8. Data Management

8.1 Database Set-up

A study specific database will be implemented to store the study data and the appropriate eCRF will be designed and created as well. Therefore a professional software solution - an Electronic Data Capture system (EDC) - will be used for this purpose. This system operates according to the principle of online data capture and is compliant with the code of federal regulations (FDA 21 CFR Part 11) to ensure reliability to the recorded data. It allows the documentation of study data in electronic case report forms (eCRF). The software is specially designed for the data entry according to Good Clinical Practice (GCP). This EDC system offers the major functions: system checks and plausibility, consistency and range checks, Query management tool, Audit Trail to log all activities, which are necessary and helpful for the data entry process.

Due to data safety reasons and to comply with the data privacy protection, the personal data of every patient will be pseudonymised. This ensures the strictly split between the personal data and patient-related dataset (study data). The EDC system automatically generates a pseudonym for every new patient. The pseudonym will be a combination of six alphanumeric characters. All study data of the patient will be linked with this pseudonym. Personal data of the patient will not be saved in the study database at any time.

The participating study centres will enter the data by using the electronic case report forms (eCRF). The eCRF is reachable via the internet at any time. The system uses a secured data connection (with Secure-Sockets-Layer protocol, SSL) to transfer the data from the study centres to the central database.

8.2 Data Management During Study

After the database is created and the eCRF is released the data entry process can be performed by the study centres. The Coordinating Centre of Clinical Studies at Charité (KKS Charité) will ensure the availability of the database and the continuous access to the eCRF.

Furthermore the technical support will be provided for the study centres during the study duration (administration of logins, roles and rights). In addition the database and the eCRF will be adapted due to changes in the study design, if necessary. Due to data availability and data security the study database will be hosted in a secured data centre of the Charité and will be backed up periodically.

In case of scheduled, unscheduled analyses or other needed reports the data will be exported from the database. In a further process these data will be checked, prepared and delivered for these purposes.

8.3 Data Export for Final Statistical Analysis

At the end of the study the entire database will be exported. The final data management process contains plausibility, consistency and range checks of the data. The missing data will be identified as well. If there are any queries, Data Clarification Forms will be generated and will be sent to the respective study centres for clarification. The related data correction will be performed either direct in the eCRF by the study centres or with programmed scripts by the data management team.

After all data management processes are completed, the cleaned data will be available for the statistical analysis. The final data can be delivered in a defined data format like SAS data file (*.sas7bdat), SPSS data file (*.sav), CSV file (*.csv), etc., including a data management report as well.

9. Statistical Analysis

9.1 Justification of Sample Size

This study is designed to show superiority with respect to MACE of CT versus ICA. For sample size calculation a power of at least 80% and a 0.05 two-sided level of significance is assumed.

The primary endpoint is the MACE incidence after a maximum follow-up of 4 years after CT or ICA. For this time to event data an exponential survival distribution is assumed with corresponding exponential parameter λ in each of the two groups. For the CT group we expect an exponential parameter of λ_1=0.00803 (corresponding to a one year MACE incidence of 0.8%, based on Noto TJ et al.,[6] Boden WE et al.,[64] Hulten EA et al.,[85] Serruys PW et al.[86]) and for the ICA group an exponential parameter of λ_2=0.0141 (corresponding to a one-year MACE incidence of 1.4%, based on Noto TJ et al.,[6] Boden WE et al.,[64] Serruys PW et al.,[86] Lichtlen PR et al.,[87] and Papanicolaou MN et al.[88]) yielding a constant hazard ratio of 0.5695. When the sample size in each group is 1773, with a total number of major adverse cardiovascular events required, of 99, an exponential maximum likelihood test of equality of survival curves will have desired power of 80% to detect the difference between the exponential parameter of the CT group and ICA group. Thus in total 3546 patients have to be allocated.

Furthermore, this sample size calculation assumes an accrual period of 2 years, a maximum follow-up time of 4 years, and a common exponential drop-out rate of 0.0513 (5% per year).

Sample size calculation for the pragmatic DISCHARGE trial was performed using nQuery 7.0.

9.2 Data Analysis

The primary endpoint, MACE incidence, will be evaluated in the intention-to-treat population using a Cox proportional hazards model to assess the effect of the investigation group adjusted for gender due to stratified randomisation. To check for robustness, additional analyses with other covariates (e.g. age, education) will be conducted. As a sensitivity analysis a cox proportional hazards model with random effects[89; 90] (frailty model) will be applied. This model is used in order to take variability between study centres and unobserved heterogeneity into account. This unobserved heterogeneity might be for example the result of different therapeutic adherence within each centre.

The **secondary endpoints** will be evaluated by parametric or non-parametric tests according to scaling. Appropriate parameters of effect size (e.g. odds ratios, relative risks, differences of mean values) with confidence intervals will be calculated. Subgroups (gender, age groups, clinical sites) will be analysed exploratively.

Missing values for confounding variables are likely to occur. Thus, multiple imputation methods will be used in order to deal with missing values. Also a sensitivity analysis will be performed to compare results based on the multiple imputations with the complete case setting.

One exploratory analysis will be performed after the occurrence of 50 MACE. Here, a group sequential design with O'Brien-Fleming spending function for time-to-event outcome with a sample size of 3546 was used for planning.[91-93] At this point, also QoL and Cost-Effectiveness will be analysed. The exploratory analysis includes estimation of the survival function (Kaplan-Meier curve) and testing the hypothesis for differences in the hazards between the intervention and the control group applying Cox proportional hazards model. One sided level of significance for the exploratory analysis is set at 0.0026. In case of a significant result the decision concerning continuation of the DISCHARGE trial is in the responsibility of the Steering Committee based on the recommendation of the DSMB (data safety monitoring board).

Further detailed description of statistical analysis and missing values is also provided in the SAP.

To avoid missing values, the clinical database has been programmed accordingly. Also, a timely data entry is required and gets monitored.

9.3 Statistical Process Control

Statistical process control (SPC) is a powerful tool for quality measurement of phenomena over time (dynamic process) and the improvement of processes. SPC applied to measurement data can be used to highlight areas that would benefit from further investigation. These techniques enable the investigator to identify variation within the process. The implementation of SPC usually requires the production of control charts which depends on the type of data to be plotted. For continuous data the *x*-chart will be used, whereas for discrete data the *p*-chart is more appropriate. Both control charts include a plot of the data over time with three additional lines

- the centre line (usually based on the mean)
- and an upper and lower control limit (typically set at ±3 standard deviations from the mean, respectively).[94]

Optionally warning limits (typically set at ±2 standard deviations from the mean)[94] can be included in a control chart. Thus a control chart enables the monitoring of the process level and identification of the type of variation in the process over time with additional rules associated with the control (and warning) limits. SPCs will be implemented for each clinical site.

10. Quality Assurance

10.1 Methods Against Bias

The risk of bias will be minimised in several ways. Essentially, the patient population under investigation is eligible for randomisation to both arms and at all clinical sites both CT and ICA are firmly established. Blinding patients towards 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, to minimise covariate imbalance patients will be stratified according to gender in each clinical site.[95] This central assignment will be implemented online and will be easily accessible by the clinical sites when evaluating eligible patients for randomisation. According to the PRCT design, only low-intensity feedback concerning guideline adherence will be given to the sites and adherence is measured unobtrusively.[1] The blinded analysis of all outcomes will address whether CT works under the usual conditions and therefore includes all patients (intention-to-treat).

10.2 Clinical Monitoring and QA

Monitoring activities will be conducted in accordance with Good Clinical Practices (GCP) as far as applicable for the pragmatic study and the monitoring plan. This is a pragmatic study and thus has monitoring strategies outlined specific to this study design. In general, a risk-based approach will be taken by defining the intensity of monitoring required and implement a system for central monitoring and central review of monitoring reports. On-site monitoring will be replaced by monitoring activities that can be done as well or better remotely (e.g., consistency, completeness and plausibility checks of data, unusual distribution of data within and between sites) by using the EDC system SecuTrial ® (central monitoring). All tests/procedures outlined in the protocol are to be completed at the discretion of the treating physician as part of routine clinical practice.

The monitoring plan defines the minimum requirements for monitoring activities of this study.

Monitoring activities include on-site visits, remote monitoring or telephone contacts. On-site monitoring visits will be documented in Monitoring Visit Reports and should be recorded at the site on a Monitoring Visit Log.

Contact reports can be used to document significant communications with site staff between monitoring visits.

The investigators allow the monitor to have access to all of the study materials needed for source data verification and proper review of the study progress. At all times, the sponsor/investigators/monitors will maintain the confidentiality of the study documents. Furthermore, problems with inconsistent and incomplete data will be discussed. By signing the declaration of informed consent the participants allow access to their documents. With the signature in the protocol, the investigators confirm that auditors and health authority inspectors may have access to the study documentation and accordant medical records. Auditors and inspectors are bound by professional confidentiality and may not pass on any personal information that comes to their knowledge. In the course of audits or inspections, data in the CRF will be compared with the data for medical records. All the documentation held by the investigators within the scope of the clinical trial as well as the drug logs of the study medications will be verified.

10.3 Standard operating procedures (SOPs)

The Standard Operating Procedure (SOPs) manual includes the patient inclusion flow chart, CT-based management, ESC/ EACTS guidelines for revascularisation, CT-based management for lung findings, plaque characterisation document, CVD prevention, cardiac CT readers qualification, and data entry instructions for the eCRF. Also, a general 10-step guide for cardiac CT was developed in order to ensure minimal standards for the performance. Based on this guide, vendor- and scanner-specific scan protocols for the participating clinical sites were worked out (Toshiba, Siemens, Philips, and GE).

10.4 Laboratory Test Results

Laboratory tests are not mandatory. Still, clinically relevant values should be documented and provided in case tests have been carried out. These are, for example, creatinine, glucose, thyroid-stimulating hormone, and myocardial biomarkers.

All laboratory values must be reviewed and appraised by the investigator or research personnel for clinical significance. For any abnormal laboratory value considered to be new since baseline and clinically significant, details must be provided on the Laboratory Adverse Event case report form. This will include whether the event is considered serious, the relationship to the CT/ICA contrast agent or other agents, the action taken, and patient outcome. Significant abnormal values occurring during the study are to be followed until repeatedly measured values return to normal, stabilise, or are no longer considered clinically significant.

10.5 Clinical Events Committee (CEC)

All events will be adjudicated by an independent **clinical events committee (CEC)** which is composed as follows:

Name	Title/Designation	Address and Contact Numbers
Hans-Jürgen Scholze	General Internist	juergen.scholze@yahoo.de
Fabian Knebel	Cardiologist	fabian.knebel@charite.de
Simon Dushe	Cardiac Surgeon	simon.dushe@charite.de
Klemens Ruprecht	Neurologist	klemens.ruprecht@charite.de

The data about the adverse events that belong to the primary endpoint (MACE) will be given to the **CEC** timely after occurrence. All reviews will be blinded. Each **CEC** member reviews the case in a first step on his/her own for a subsequent possible discussion (written, phone, or/and in-person) to seek consensus.

Special eCRFs for MACE and (S)AEs were developed to collect detailed information. A first decision, if the event can be adjudicated to CT/ICA is made by the principal investigators at the clinical site. The role of the **CEC** is thus to confirm or reject the decisions of the principal investigators objectively.

As a basis for decisions the **CEC** members will receive a report that includes the following:

1. Summary of all (S)AEs that could be a MACE.
2. Details from the MACE eCRF
3. Details to enable adjudication and list for decisions if (S)AE, MACE can be adjudicated to ICA/CT as already pre-decided by the principal investigator.

10.6 Data Safety and Monitoring Board (DSMB)

During the course of the “DISCHARGE Trial”, the coordinating centre will carry out periodic data analyses and present data reports to the Data and Safety Monitoring Board **(DSMB)**, [96] who does not participate in the trial. The **DSMB** will semi-annually review the safety data and can give advice to the about necessary changes in the trial conduct to the Coordinator and the steering committee (**SC)**. The review can be unblinded if appropriate and the unblinding can be performed with the clinical database management system.

During the first three months and then semi-annually during subsequent months the **DSMB** will review reports on study performance including recruitment, protocol violations, complications of the CT technology and invasive angiography, the occurrence of patient drop-out and patient lost-to-follow-up, and adverse events associated with the CTA/ICA examination. Examples of the types of tables found in the DSMB report are shown below. During the last year of the trial the **DSMB** will mainly review the trial progress with regard to follow-up and occurrence of cardiovascular events. The **DSMB** will also make the final (blinded) decision about the classification of cardiovascular events and/or complications in case of disagreements or vagueness. Each **DSMB** member reviews the cases in a first step on his/her own for a subsequent possible discussion (written, phone, or/and in-person) to seek consensus. Extraordinary meetings with 7 day written notice may

take place and a meeting after the study when the data from all patients is available.

The following is an outline of the **DSMB** report that will be generated for the conferences:

1. Summary of Main Findings
2. Recent Issues
3. Recruitment Status
4. CRF Status
5. Safety (Serious Adverse Events, Adverse Events following CTA/ICA)
6. Follow-up Results

The DSMB is composed of the following four members:

Name	Title/Designation	Address and Contact Numbers
Universitätsklinikum des Saarlandes		
Danilo Fliser, MD, Prof.	Nephrologist	Street: Kirrberger Straße 100 Town: Homburg/Saar Postal: Code: 66424 Country: Germany Phone: +49 6841 16 23526 Fax: +49 6841 16 23540 E-Mail: Danilo.Fliser@Uniklinikum-Saarland.de
Radiologische Allianz GbR		
Jörn Sandstede, MD, Prof.	Radiologist	Street: Schäferkampsallee 5-7 Town: Hamburg Postal Code: 20357 Country: Germany Phone: +49 40 32 55 52 100 Fax: +49 40 32 55 52 222 E-Mail: joern.sandstede@radiologische-allianz.de
Cardioangiologisches Centrum Bethanien		
Axel Schmermund, MD, Prof.	Cardiologist	Street: Im Prüfling 23 Town: Frankfurt am Main Postal Code: 60389 Country: Germany Phone: +49 69 9450 28 0 Fax: +4 69 4616139 E-Mail: a.schmermund@ccb.de
Georg-August-Universität Göttingen		
Tim Friede, PhD, Prof.	Statistician	Street: Humboldtallee 32 Town: Göttingen Postal Code: 37073 Country: Germany

		Phone: +49 551-39-4991 Fax: +49 551-39-4995 E-Mail: tim.friede@med.uni-goettingen.de

10.7 Steering Committee

The entire project will be overseen by the SC which has delegated authority from all consortium members. It will consist of the work package (WP) leaders and five designated regional representatives of the clinical sites and the coordinator (Marc Dewey).

10.8 External Advisory Board (EAB)

For qualitative assessment, continuous guidance, and additional input throughout the project, several external experts have reviewed this application and will form the **external advisory board (EAB)**.

Name	Title/Designation	Address and Contact Numbers
Dartmouth Institute		
Harold Sox, MD, Prof. (Chair)	Chair of the Institute of Medicine's (www.iom.edu) Committee on Comparative Effectiveness Research Priorities, former Editor-in-chief of the Annals of Internal Medicine	Street: Town: Hannover Postal Code: NH 03755 Country: United States of America Phone: +1 603 653 0897 Fax: E-Mail: hsox@comcast.net
Universitätsklinik Heidelberg, Radiologische Klinik, Diagnostische und Interventionelle Radiologie		
Kauzor	Professor for Diagnostic Radiology at the University of Heidelberg, Medical Director for Diagnostic and Interventional Radiology at the University Hospital of Heidelberg	Street: Im Neuenheimer Feld 110 Town: Heidelberg Postal Code: 69120 Country: Germany Phone: +1 603 653 0897 Fax: E-Mail: hans-ulrich.kauczor@med.uni-heidelberg.de
Institute for Quality and Efficiency in Health Care		
Stefan Sauerland, MD	Head of the department of non-drug interventions of	Street: Im Mediapark 8 (Kölnturm) Town: Köln Postal Code: 50670

	the Institute for Quality and Efficiency in Health Care (IQWiG), Comparative Effectiveness and Cost-Effectiveness Expert	Country: Germany Phone: +49 221 356850 Fax: +49 221 356851 E-Mail: stefan.sauerland@iqwig.de
Leiden University Medical Centre, Department Cardiothoracic Surgery		
Robert JM Klautz, MD, Prof.	Chief of Department of Cardiothoracic Surgery Cardiac Surgery Expert	Street: Albinusdreef 2 Town: Leiden Postal Code: 2333 ZA Country: Netherlands Phone: +31 71 526 4022 Fax: +31 71 526 6965 E-Mail: r.j.m.klautz@lumc.nl
UT Southwestern Medical Center		
Steve Marso, MD, Prof.	Director of Interventional Cardiology, member of the CathPCI registry (www.ncdr.com), Intervention Expert	Street: 5939 Harry Hines Blvd Town: Dallas Postal Code: TX 9047 Country: United States of America Phone: +1 214 645-7500 Fax: +1 214 645 7501 E-Mail: Steven.Marso@utsouthwestern.edu
Cleveland Clinic, Cleveland, Ohio		
Paul Schoenhagen, MD, Prof.	Editor-in-chief of Cardiovascular Diagnosis and Therapy, Department of Diagnostic Radiology and Department of Cardiovascular Medicine, CT Expert	Street: Euclid Avenue Town: Cleveland Postal Code: 9500 Country: United States of America Phone: +1 216 445 7579 Fax: +1 216 636 0822 E-Mail: schoenp1@gmail.com
Carlos Aguiar, MD, Prof.	Vice-President of the Portuguese Society of Cardiology UEMS, Echo expert	Street: Town: Postal Code: Country: Phone: Fax: E-Mail: ctaguiar@sapo.pt
Klinik für Nuklearmedizin Medizinische Hochschule Hannover		
Frank Bengel, MD, Prof.	Director of the Department of	Street: Carl-Neuberg-Str. 1 Town: Hannover

	Nuclear Medicine, Nuclear medicine expert	Postal Code: 30625 Country: Germany Phone: +49 511 532 2577 Fax: +49 511 532 3761 E-Mail: Bengel.Frank@mh-hannover.de
University of Bristol		
Andreas Baumbach, MD, Prof.	Cardiologist	Street: Tyndall Avenue Town: Bristol Postal Code: BS8 1TH Country:United Kingdom Phone: +44 117 342 6573 Fax: E-Mail: Andreas.Baumbach@ubht.nhs.uk
School of Health and Caring Sciences, Linnaeus University		
Joep Perk, MD, Prof.	Chair of the ESC guideline on cardiovascular disease prevention;[68]	Street: Town: Kalmar Postal Code: 391 82 Country: Sweden Phone: +46 772 28 80 00 Fax: +46 480 44 60 32 E-Mail: joep.perk@lnu.se
OLV Ziekenhuis Aalst		
William Wijns, MD, Prof.	Author/Task Force Member of the ESC/EACTS guideline on cardiovascular revascularisation, former ESC chairperson.[61; 97]	Street: Moorselbaan 164 Town: Aalst Postal Code: 9300 Country: Belgium Phone: +32 53 72.44.39 Fax: +32 53 72 45 87 E-Mail: william.wijns@olvz-aalst.be
University of Glasgow, Institute of Health & Wellbeing		
Andrew Briggs, MSc, PhD, Prof.	Health Economics, Cost-Effectiveness Expert	Street: 1 Lilybank Gardens Town: Glasgow Postal Code: G12 8RZ Country: United Kingdom Phone: +44 1413305017 Fax: E-Mail: Andrew.Briggs@glasgow.ac.uk
University of Michigan at Ann Arbor, Radiology		
Ella A Kazerooni, MD, Prof.	Thoracic Radiology, Cardiovascular Radiology, Radiology	Street: 1500 E Medical Center Dr SPC 5868 Town: Ann Arbor Postal: MI 48109 Country: United States of America Phone: (+) 001-

		734-936-4366 Fax: E-Mail: ellakaz@med.umich.edu
University of Bristol, School of Social and Community Medicine		
William Hollingworth, MSc, PhD, Prof.	Health Economics, Cost-Effectiveness Expert	Street: 39 Whatley Road Town: Bristol Postal Code: BS8 2PS Country: United Kingdom Phone: +44 117 9287355 Fax: E-Mail: William.Hollingworth@bristol.ac.uk
Patient Interest Group, Berlin		
Martina Seifert	Patient Interest Group	Weissensee, Berlin

11. Expected Outcomes of the Study

The anticipated impact of the DISCHARGE project will be multiple and will generate beneficial and usable outcomes in a European context on several levels. We predict that the DISCHARGE PRCT, the core of the project, may prove that CT, as the most promising currently available noninvasive imaging modality, utilised as the primary diagnostic strategy in stable chest pain and intermediate pretest probability of CAD is superior to ICA concerning MACE. We further predict that it will lead to better health-related quality of life and increased cost-effectiveness. Special consideration will be given to including and analysing gender aspects and putting emphasis on gender balance throughout the project as it has been shown that the evaluation of chest pain in women is less straightforward than in men because of gender differences in presentation and disease manifestation.[98] It will ensure European regulatory and quality standards concerning the interpretation of CT radiation exposure, good clinical practice, the quality of the data, and clinical treatment guidelines. The results of the DISCHARGE project will provide systematic evidence by applying a pragmatic study design, best reflecting the demand of comparative effectiveness research for routine clinical practice evaluation[99] and including evidence-based medicine (EBM) as well as health technology assessment (HTA) methodology by performing systematic review of evidence and cost-effectiveness analysis. Generalisability of results will be guaranteed by forming a consortium including 30 partners from 18 different European countries. By its collaborative approach of cardiologists, radiologists, and experts in comparative effectiveness research, the DISCHARGE project will enhance communication between these disciplines and facilitate transfer of knowledge. The results of DISCHARGE will have a major impact on influencing standards and guidelines of diagnostic pathways and will also provide information for coverage decisions in Europe concerning the utilisation of CT in the broad population of patients with stable chest pain symptoms and intermediate pretest probability of CAD.

Primarily, stable chest pain patients with intermediate pretest probability of CAD will benefit as the results will enable **early and safe discharge** of the majority using CT

as the initial modality for evaluation. In doing so, unnecessary invasive procedures and hard adverse events will be reduced. Second, health care providers such as physicians and hospitals will be informed about the results of DISCHARGE and will benefit from guideline modifications and information on coverage decisions alike. They will be able to provide more effective imaging strategies utilising CT and will be able to spare scarce resources by implementing a more cost-effective diagnostic workup algorithm. Third, in case of an advantage of CT, the responsible European and national authorities and decision-makers will consider including coronary CT angiography among the reimbursed medical procedures. Thus, the trial results will also have important economic and societal consequences that will be disseminated on the European level to increase its impact.

In summary, the DISCHARGE project will inform patients, health care providers, and decision-makers alike about the effectiveness and cost-effectiveness of CT as the primary diagnostic imaging modality when evaluating stable chest pain symptoms suggesting an intermediate risk of coronary artery disease.

The main impact of the PRCT itself will be to prove that CT, as the most promising currently available noninvasive imaging modality, utilised as the primary diagnostic strategy in the selected broad population of stable chest pain patients with an intermediate pretest probability of CAD is superior to ICA concerning the primary endpoint MACE. The trial will be executed according to a pragmatic design approach thus exploring the effectiveness of CT in comparison to the gold standard ICA in a routine practice and usual care setting and thus leading to clinically meaningful outcomes. The performance of the trial will enhance a close collaboration between the disciplines of radiology and cardiology and will give the great opportunity of laying the foundation to inform patients, health care providers, and decision-makers alike about the most promising new cardiovascular imaging technology by applying a unique multi-national European network cooperation.

In addition to the main impact, an elaborate list of secondary outcomes has been developed to enable a maximum output of the project.

12. Dissemination of Results and Publication Policy

The exploitation and dissemination of results will be planned and procedures and implementation of publications, presentations, and stakeholder information will be addressed in an extra work package.

The dissemination committee **(DC)** initiates, coordinates, and oversee all efforts for dissemination of the results. Dissemination policies and a publication plan will be written. In this way, the efficient and consistent exploitation of the project is ensured. International distribution of findings and raising awareness on outcomes to the health care workforce will be achieved by publication of the results in relevant, high-priority medical journals, presentations at congresses and meetings, and by enforcing collaboration with the professional societies. For the dissemination among policy makers and HTA bodies, the diffusion system of OSTEBA as member of HTA networks including EUnetHTA and INAHTA will be utilised. Patients and the general public will be informed as well to outreach beyond the scientific community.

Raw anonymised data sets can be made available to the scientific community upon request, through the Coordinator to the DISCHARGE DC In cases where the respective results have been published and due time has elapsed, the DC will, in general, support this availability to the scientific community. Single decisions will be made case by case by taking the specifics into consideration.

The 13 members of the **DC** are radiologists, cardiologists and work package leaders and two chairs from radiology and cardiology. The members are not part of the **SC**. The **DC** is the main decision making body for dissemination and the **SC** is only contacted for advice and/or decisions when more serious issues arise.

Name	Title/Designation	Address and Contact Numbers
P02 Medizinische Universität Innsbruck (MUI)		
Guy Friedrich, MD, Prof. (Chair)		Street: Anichstr. 35 Town: Innsbruck Postal Code: 6020 Country: Austria Phone: +4351250481898 Fax: E-Mail: guy.friedrich@tirol-kliniken.at
P10 University College Dublin, National University of Ireland (NUID UCD)		
Jonathan Dodd, MD, Prof. (Co-Chair)		Street: Belfield Campus Town: Dublin Postal Code 4 Country Ireland Phone: +353 87 2987313 Fax: E-Mail: j.dodd@st-vincents.ie

P18 Institut za kardiovaskularne bolesti Vojvodine (IKVBV)		
Nada Čemerlić Adjić, MD, Prof.		Street: Put dr Goldmana 4 Town: Sremska Kamenica Postal Code: 21204 Country: Serbia Phone: +38163433982 Fax: E-Mail: ncemerlica@gmail.com
P23 Aintree University Hospital (AUHT)		
Gershan Davis. MD, Dr.		Street: Longmoor Lane Town: Liverpool Postal Code: L9 7AL Country: United Kingdom Phone: +44 151 529 2974 Fax: +44 151 529 2724 E-Mail: gershan@hotmail.com
P16. Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E)		
Rita Faria, MD	Cardiologist	Street: Rua Conceicao Fernandes Town: Vila Nova De Gaia Postal Code: 4434 502 Country: Portugal Phone: +35 1967216948 Fax: E-Mail: rita.d.faria@gmail.com
P19 Institut Català de la Salut (ICS-HUVH)		
José Rodriguez Palomares, MD, Dr.	Cardiologist	Street: Passeig de Vall d'Hebron 119 Town: Barcelona Postal Code: 08035 Country: Spain Phone: +34934894013 Fax: E-Mail: jfrodriguezpalomares@gmail.com
P06 Kliniken des Landkreises Goppingen GGmbH (KaE)		
Stephen Schröder, MD, Prof.	Chair of the Department of Cardiology	Street: Eichertstrasse 3 Town: Goppingen Postal Code: 73035 Country: Germany Phone: +49 7161 642671 Fax: E-Mail: Stephen.Schroeder@af- k.de

P02 Medizinische Universitaet Innsbruck (MUI)		
Gudrun Feuchtner, MD, Prof.	Radiologist	Street: Anichstr. 35 Town: Innsbruck Postal Code: 6020 Country: Austria Phone: +4351250481898 Fax: Email: gudrun.feuchtner@i-med.ac.at
P14 LIETUVOS SVEIKATOS MOKSLU UNIVERSITETAS (LSMU)		
Antanas Jankauskas. MD, Dr.	Radiologist	Street: Eiveniu str. 2 Town: Kaunas Postal code: 50009 Country: Lithuania Phone: + 37065745548 Fax: E-Mail: jankauskas.antanas@gmail.com
P11 Università degli Studi di Cagliari (UNICA)		
Luca Saba, MD, Prof.	Radiologist	Street: AOU di Cagliari - Polo di Monserrato SS 554 Town: Monserrato (CA) Postal Code: 09042 Country: Italy Phone: +393206202091 Fax: E-Mail: lucasabamd@gmail.com
P27 Fundacion Vasca De Innovacion e Investigacion Sanitarias (Osteba-BIOEF)		
Iñaki Gutiérrez-Ibarluzea, MSc, Dr.	Knowledge Manager and Coordinator of the early awareness and alert system of Osteba, the Basque Office for HTA, Basque Government	Street: Donostia-San Sebastian 1 Town: Vitoria-Gasteiz Postal Code: 01010 Country: Spain Phone: +34945019250 Fax: E-Mail: osteba7-san@ej-gv.es
P28 Universitätsklinikum Jena (UKJ)		
Peter Schlattmann, MD, PhD, Prof. (Affiliated)	Statistician	Street: Bachstraße 18 Town: Jena Postal Code: 07743 Country: Germany Phone: +49 3641 934130 Fax: E-Mail: peter.schlattmann@mti.uni-jena.de

P01 Charité – Universitaetsmedizin Berlin (CHARITE)		
Marc Dewey, MD, PhD, Prof. (Coordinator)	Coordinator	Charité – Universitätsmedizin Berlin Campus Mitte Institut für Radiologie Charitéplatz 1 10117 Berlin Germany Phone: +49-30-450627226 Fax: +49 30 450 7527920 Email: dewey@charite.de

13. Duration of the Project

The first-patient in will be in the first month of the PRCT and the last-patient out will be at the end of month 48 of the PRCT (overall duration: 4 years). Patients will be recruited over a period of 2 years.

Timeline
Recruitment (month 1-24):
The recruitment of eligible patients will be done by medical doctorate candidates and study nurses. Patients will be checked for intermediate pretest probability of disease and will be centrally randomised and stratified (according to site and gender) at each site to either CT angiography or ICA. Recruited patients will fill out the questionnaires after informed consent but *prior* to randomisation.

CT and ICA and patient preference (month 1-24)
The patients will undergo regular CT angiography and ICA and will fill out a patient preference questionnaire[100] afterwards.

Meetings of data safety monitoring board and clinical events committee (month 1-48):
The DSMB will review safety data semi-annually and the clinical events committee will review the possible occurrence of MACE. They will discuss the results internally and will then report directly to the coordinator through the project management office.

Low intensity feedback (month 3-24):
According to the pragmatic design, only low-intensity feedback concerning guideline adherence will be given to the sites by the project management.

First year follow-up (month 13-36):
Due to the pragmatic design, no in-person visits during the first-year follow-up from the patients are planned to avoid interference with the trial. Patients will be sent questionnaires with sections for their medical status (including a possible change in medication), Cost-Effectiveness, and Quality of Life.

Final follow-up (month 37-48):
Due to the pragmatic design, no in-person visits from the patients are mandatory. The patients will be sent patient preference questionnaires and the questionnaire from the first year follow-up. In order to avoid loss to follow-up, several information sources will be used (general practitioners, death registries, and family members) concerning the primary outcome measure of MACE. In addition, they will be given the opportunity to consult the principal investigator in person. For this possible visit, funding has been set aside for patients with low income

14. Problems Anticipated

The PRCT follows usual hospital care and entails the regular risks of cardiac CT and invasive coronary angiography. These risks will be addressed during the informed consent procedure. Thus there are no additional risks as a result of participating in

the study. As for the exposure to radiation, an own work package (WP3) has been defined and the trial will be submitted to the German Federal Office for Radiation Protection for approval.
The main risk of the trial and thus the entire DISCHARGE project is the recruitment rate at the clinical sites to reach a total of 3546 patients. The clinical site partners were chosen very carefully, each one of them being carefully checked for their track record in delivering on clinical trials. They are generally tertiary referral centres and crucial for regional delivery of health care and are not at risk of being restructured or closed down.

The 26 clinical sites in the DISCHARGE consortium performing the trial have a high recruitment potential. Altogether 121900 patients are expected to be referred to them for ICA within the duration of the two year recruitment phase. Out of these patients, approximately 54820 (45%) are estimated to have suspected CAD. Each one of the 26 single sites has a sufficient number of referred patients for ICA. Altogether **only 6.5%** of these patients with suspected CAD need to be recruited. In the case that one clinical site fails to recruit the expected number of patients, any one of the others has the capacity to take over. This may occur due to a late ethical approval and/or a general low recruitment rate. While shifting the number of patients to another clinical site, an appropriate transfer of the salaries and person-months will be taken into account.
Another risk may be the loss of patients during the follow-up phase. To minimise this risk, measures are foreseen (e.g., involvement of family members). Also, in the case patients would like to come in person to the hospital for the final follow-up and cannot afford travelling, after, for example moving to another city, funding has been set aside.

15. Project Management

The project is led by the coordinator Marc Dewey (Heisenberg Prof., consultant radiologist, vice-chair of the radiology department) and the project manager, Adriane Napp (Master of Science in Clinical Trial Management and licensed Clinical Monitor and Database Manager) is an expert in clinical trials. She will thus place an emphasis on overseeing the progress of the Pragmatic Randomised Controlled Trial. She will be strongly supported by the partner INSERM/ ECRIN-ERIC and by Charité-KKS which is a member of the international KKS network and therefore the German partner of ECRIN-ERIC. These institutions will also lead **WP4** “Good Clinical Practice and Surveillance System” and **WP5** “Clinical Data Management” within the DISCHARGE project set-up. Maria Bosserdt and Melanie Estrella replaced Adriane Napp as project managers from 1.2.2018 until the end of the project.

ECRIN-ERIC provides a sustainable, not-for-profit infrastructure with clinical trial units and academic coordinating centres and can support multinational clinical research projects in Europe.

ECRIN–ERIC, led by Christine Kubiak, will be responsible for the on-site monitoring of the clinical trial and safety surveillance and to ensure that the trial is performed efficiently with highest quality and according to GCP and national and international standards. Specifically, this will include the review of ethical and applicable authority

approval and respective notifications, site monitoring, safety reporting, and quality assurance.

The defined services will be performed by ECRIN-ERIC's scientific partners in all non-German DISCHARGE countries. The German clinical sites will be monitored by KKS-Charité under the lead of Corinna Meier-Windhorst.

16. Ethics

The Pragmatic Randomised Controlled Trial (PRCT) will be submitted to all responsible ethics committees and the German Federal Office for Radiation Protection for approval. The patients have been referred to cardiac CT and ICA. In many countries, ICA is the gold standard for patients with stable chest pain and intermediate risk of coronary artery disease. Yet, in countries with less income per capita, cardiac CT is the preferred choice for health care providers (insurances) and has shown to be a very good and gentler alternative. The investigators from the clinical sites have altogether performed over 50 studies with ethical approval from their internal review board (IRB) about cardiac CT and are thus highly experienced.

The study and the pilot study have already been approved by the ethics committee at Charité (No. EA1/294/13 for PRCT and pilot study; No. EA1/209/14 for cognitive interviews).

Important protocol amendments will be communicated to all partners with the request to seek local IRB approval. A scan of the first IRB approval and amendment needs to be provided to Charité by each clinical site for compliance control.

Informed consent will be sought by the investigators from cardiology and radiology for the PRCT. The pilot study only foresees informed consent if requested by the local IRB (see section 6.6 Pilot Study). The researchers from the Institute of Public Health (e.g. physicians, psychologists) will obtain informed consent for the cognitive interviews.

Patient informed consent also includes confidentiality/data protection.

16.1 Ethical Approval PRCT and Pilot Study - Charité

Initial Approval at Charité:

CHARITÉ

Charité | 10117 Berlin

Herrn
Prof. Dr. med. Marc Dewey
Institut für Radiologie

CCM

Ethikkommission
Ethikausschuss 1 am Campus Charité - Mitte

Vorsitzender: Prof. Dr. R. Lebethack

Geschäftsführung: Dr. med. Katja Grochowski
ethikkommission@charite.de

Kommunikationsadresse: Charitéplatz 1, 10117 Berlin
Tel.: 0049-450-517222
Fax: 0049-450-517953

http://ethikkommission.charite.de

Datum: 24.10.2013

Diagnostische Bildgebungstrategien bei Patienten mit stabilem Brustschmerz und mittlerem Risiko einer koronaren Herzerkrankung: Vergleichende Nutzenbewertung existierender Technologien (DISCHARGE)
Antragsnummer: EA1/294/13

Sehr geehrter Herr Professor Dewey,

die von Ihnen eingereichte o.g. Studie wurde durch den Ethikausschuss 1 der Ethikkommission auf der Sitzung am 17.10.2013 beraten.

Die Ethikkommission stimmt dem o.g. Vorhaben zu.

Als Hinweis wird mitgeteilt, dass es nur 1 einzigen primären Endpunkt geben kann, nicht mehrere (Ethikantrag, Punkt 4, Seite 2, Zeile 2).

Es ist zu prüfen, ob eine Strahlen-Haftpflicht-Versicherung gemäß § 24 Abs.1 Nr.10 StrlSchV bzw. § 28 b Abs. 2 Nr. 5 RöV abgeschlossen werden muss, da die Studie nicht ausschließlich an der Charité durchgeführt wird.

Die Ethikkommission bestätigt zur Vorlage beim BfS, dass für das beantragte Vorhaben ein zwingendes Bedürfnis im Sinne des § 28b Absatz 1 Nummer 1 RöV (bzw. § 24 Absatz 1 Nummer 1 StrlSchV) besteht.

Folgende Unterlagen wurden zur Begutachtung eingereicht:

- Ethikantrag, 02.10.13
- Patienteninformation, Version vom 30.09.13
- Einwilligungserklärung, Versionsdatum fehlt
- Zustimmung des Direktors, 25.09.13
- Studienprotokoll, Version 1.0 vom 05.08.13
- Fragebögen

First amendment of ethical approval at Charité:

CHARITÉ

Charité | 10117 Berlin

Herrn
Prof. Dr. med. Marc Dewey
Institut für Radiologie

CCM

Ethikkommission
Ethikausschuss 3 am Campus Charité - Mitte

Vorsitzender: Prof. Dr. R. Uebelhack

Geschäftsführung: Dr. med. Katja Ozegowski
ethikkommission@charite.de

Kommunikationsadresse: Chariteplatz 1, 10117 Berlin
Tel: 0030/450-512252
Fax: 0030/450-512952

http://ethikkommission.charite.de

Datum: 23.10.2014

Diagnostische Bildgebungstrategien bei Patienten mit stabilem Brustschmerz und mittlerem Risiko einer koronaren Herzerkrankung: Vergleichende Nutzenbewertung existierender Technologien (DISCHARGE)
Antragsnummer: EA1/284/13
Vorgang vom 15.10.2014, Eingang am 20.10.2014, per E-Mail am 20.10.2014

Sehr geehrter Herr Professor Dewey,

hiermit bestätigen wir Ihnen den Eingang Ihres Schreibens vom 15.10.2014 mit folgenden Anlagen:

- Ethikantrag, Version vom 16.10.2014
- Patienteninformation, Version vom 09.10.2014
- Einwilligungserklärung, Version vom 09.10.2014

Wir danken für die Kenntnisgabe. Die Ethikkommission erhebt keine Einwände gegenüber den Änderungen.

Mit freundlichen Grüßen

Prof. Dr. med. R. Uebelhack
Vorsitzender

Second amendment of ethical approval at Charité:

CHARITÉ

Charité | 10117 Berlin

Herrn
Prof. Dr. med. Marc Dewey
Institut für Radiologie

CCM

Ethikkommission
Ethikausschuss 1 am Campus Charité - Mitte

Vorsitzender: Prof. Dr. R. Uebelhack

Geschäftsführung: Dr. med. Kaja Grzeszinski
ethikkommission@charite.de

Postanschrift: Charitéplatz 1, 10117 Berlin
Tel.: 0030450 517223
Fax: 0030450-517952

http://ethikkommission.charite.de

Datum: 28.04.2016

Diagnostische Bildgebungsstrategien bei Patienten mit stabilem Brustschmerz und mittlerem Risiko einer koronaren Herzerkrankung: Vergleichende Nutzenbewertung existierender Technologien (DISCHARGE)
Antragsnummer: EA1/294/13
Vorgang vom 22.04.2016, Eingang am 25.04.2016, per E-Mail am 25.04.2016

Sehr geehrter Herr Professor Dewey,

hiermit bestätigen wir Ihnen den Eingang Ihres Schreibens vom 22.04.2016 mit folgender Anlage:

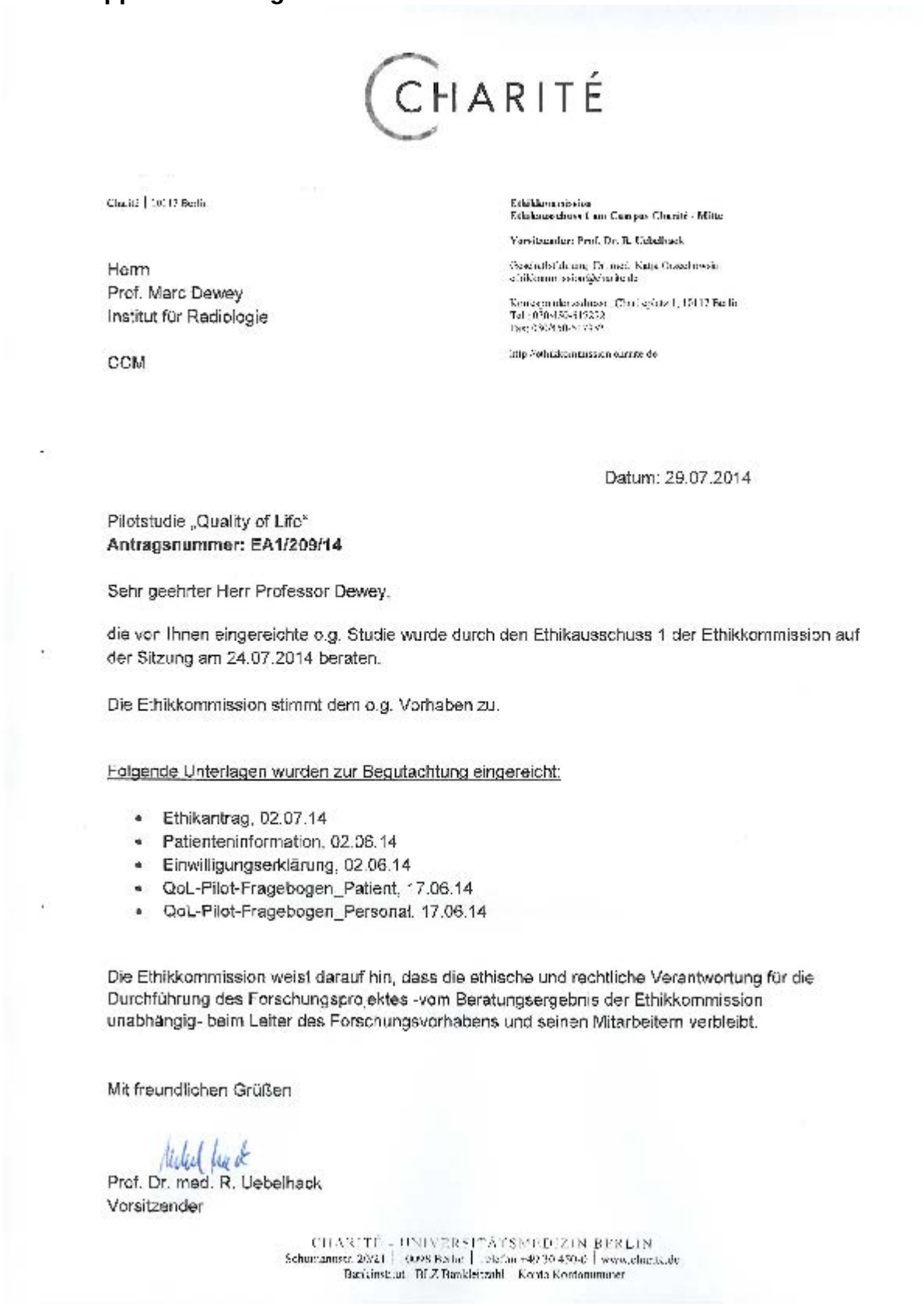
- Clinical study protocol, Version 1.6 vom 01.04.2016

Wir danken für die Kenntnisgabe. Die Ethikkommission erhebt keine Einwände gegenüber den Änderungen.

Mit freundlichen Grüßen

Prof. Dr. med. R. Uebelhack
Vorsitzender

Ethical approval for cognitive Interviews at Charité:



CHARITÉ

Charité | 10117 Berlin

Ethikkommission
Ethikausschuss 1 am Campus Charité - Mitte

Vorsitzender: Prof. Dr. R. Uebelhack

Geschäftsführung: Dr. med. Katja Grasshoff
ethikkommission@charite.de

Kommunikationsadresse: Charitéplatz 1, 10117 Berlin
Tel.: 030/450-518252
Fax: 030/450-518957

http://ethikkommission.charite.de

Herrn
Prof. Marc Dewey
Institut für Radiologie

CCM

Datum: 29.07.2014

Pilotstudie „Quality of Life"
Antragsnummer: EA1/209/14

Sehr geehrter Herr Professor Dewey,

die vor Ihnen eingereichte o.g. Studie wurde durch den Ethikausschuss 1 der Ethikkommission auf der Sitzung am 24.07.2014 beraten.

Die Ethikkommission stimmt dem o.g. Vorhaben zu.

Folgende Unterlagen wurden zur Begutachtung eingereicht:

- Ethikantrag, 02.07.14
- Patienteninformation, 02.06.14
- Einwilligungserklärung, 02.06.14
- QoL-Pilot-Fragebogen_Patient, 17.06.14
- QoL-Pilot-Fragebogen_Personal, 17.06.14

Die Ethikkommission weist darauf hin, dass die ethische und rechtliche Verantwortung für die Durchführung des Forschungsprojektes -vom Beratungsergebnis der Ethikkommission unabhängig- beim Leiter des Forschungsvorhabens und seinen Mitarbeitern verbleibt.

Mit freundlichen Grüßen

Prof. Dr. med. R. Uebelhack
Vorsitzender

CHARITÉ - UNIVERSITÄTSMEDIZIN BERLIN
Schumannstr. 20/21 | 10098 Berlin | Telefon +49 30 450-0 | www.charite.de
Bankinstitut | BLZ Bankleitzahl | Konto Kontonummer

17. Conflicts of Interest

Conflicts of Interest are listed in the full version of the study protocol (www.dischargetrial.eu)

18. Curriculum Vitae

Curriculum vitae are incorporated in the full version of the study protocol (www.dischargetrial.eu)

19. References

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Appendix

Below is the English Version of the initial informed consent form. This will be translated into local languages by the clinical sites and checked for correctness by Charité's project management office. Final versions that also considered the local requirements of the IRB are also collected and checked at Charité to ensure compliance with GCP considering the consistency of informed consent forms in multi-centre trials.

The latest version of the patient information and informed consent at the Charité is attached as well which contains adjustments to new general data protection regulation. All sites have been instructed to adjust their informed consent to their local law accordingly.

1. Patient Informed Consent Form – PRCT

Patient Information - Version 09.10.2014

Title of the study: "Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies (DISCHARGE)"

Dear Patient:

You are invited to participate in our pragmatic clinical DISCHARGE study. This is a European multicentre research study organised by the sponsor Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. Professor Dewey from the Department of Radiology is the coordinator of this study. Three other radiologists of our department are involved in the study: Dr. med. Elke Zimmermann, Dr. med. Matthias Rief and Dr. med. Georg Schütz. The study is conducted in cooperation with the Department of Cardiology (Investigators: PD Dr. med. Michael Laule and Dr. med. Henryk Dreger).

1. What is the aim of the study?

You have been referred for an invasive coronary angiography (ICA, catheter examination). You have a suspected coronary artery disease with stable chest pain and a clinical indication for ICA. This makes you a possible candidate for the DISCHARGE study. The study investigates whether CT is better than a catheter examination of the heart. In order to participate, the probability that you have coronary artery disease (CAD; defined as at least 50% narrowing of the coronary arteries) has to be 10% to 60% - what we refer to as an intermediate pretest probability of CAD. This intermediate pretest probability of CAD will be tested as the last step of the inclusion process for the study. If you have an intermediate pretest probability of 10% to 60% for CAD, you can participate in the study and undergo either ICA or a CT computed tomography (CT) scan of the heart. Which of the two diagnostic tests (ICA or CT) you will undergo will be decided by a random distribution with a 50:50 chance of being assigned (randomised) to CT or ICA. The chance of assignment (randomisation) to either test cannot be influenced in any way by you or the study personnel. Based on the diagnosis made by these tests, further treatment decisions will be made by the local heart team. If you do not have an intermediate pretest probability of 10% to 60% for CAD, you cannot participate in the study and you will **not** be assigned by chance (randomised) to one of the two tests (ICA or CT). Instead you will undergo ICA as planned. The results will be provided to the study sponsor and your personal data will be recorded.

The study is a so-called pragmatic randomised study. This means that the medical care given to

patients who participate in the study reflects the normal clinical situation as much as possible. This is the aim in order to obtain realistic and practical results. It is planned to include a total of 3546 patients into the study at 23 hospitals all over Europe. The Charité will randomise between 128 and 320 patients for the study.

2. Benefits and risks of participating in the study

Because of the low to intermediate pretest probability of CAD (10-60%), as explained above, it can be expected that about **80-90%** of the randomised patients will not have CAD. Following the examination by CT or ICA, patients can be discharged from the hospital unless there are other medical reasons for staying. In the patients who will be examined by CT, the presence of CAD can be ruled out without an invasive examination. This is an advantage for the patients in the CT group. **Some patients** in the CT group may encounter additional advantages. Other diseases such as a pulmonary embolism (blood clot in a lung artery), a hiatal hernia of the esophagus (displacement of a part of the stomach from the abdomen into the chest cavity) or an aortic dissection (tear of the inner layer of the wall of the main artery from the heart) can cause chest pain. These and other diseases of the chest can be reliably detected by CT. The resulting potential advantage is that patients in whom such diseases are detected earlier by CT may benefit from earlier treatment. In most cases, narrowing of the coronary arteries is caused by so-called coronary plaques (deposits in the walls of blood vessels). Such plaques are also identified by CT, and their composition can be assessed. Certain types of such plaques have been shown to bear a higher risk of rupture (plaques that contain a large amount of fat or a lot of calcium, for example). If such a situation is found, this will lead to a recommendation to change medical treatment and/or risk factor modification. Finally, patients may benefit from the fact that the CT findings allow better planning of treatment in those patients who should be treated by reopening of narrowed coronary arteries (with a catheter or surgery). If CT will be shown to be superior, the expected **benefit for future patients** arises, in that a large number of the examinations in patients with stable chest pain and an intermediate probability of CAD may be performed by CT instead of ICA in Germany and in Europe. This is an important advantage given that around 2 million ICAs are considered to be avoidable in Europe each year. In accordance with the pragmatic approach of the DISCHARGE study, participants only have the usual risks of CT or ICA. If one of the usual risks occurs, physicians are available at Charité who can immediately take measures to take care of any undesired effects. It must be noted that CT is expected to identify narrowing of coronary arteries in about 10-20% of the patients. In these patients, additional tests to measure heart perfusion may become necessary as well as a subsequent intervention, percutaneous coronary intervention (PCI) or surgery, for treatment of one or several stenoses. These patients will have a higher radiation exposure and will be given additional contrast medium. This also means that it may take longer in these situations to complete treatment. It may occur that in very seldom cases not all findings can

be diagnosed in the CT group that may have been found in the ICA group. It is to be noted though, that in general more information comes from CT.

3. What are the requirements for study participation?

To participate in the study, patients suspected of having CAD must have been referred for ICA. They must be at least 30 years old and give written informed consent. Other criteria include stable chest pain and an intermediate probability of coronary artery disease (10-60%). Women can participate if they are not pregnant. **Patients cannot participate** if their heart beat is irregular or if they undergo haemodialysis.

To decide whether a patient is suitable for study participation and to ensure optimal care, the investigators will review patients' medical records before and during the study in order to document data that are relevant for the study.

4. How will the study be conducted?

4.1. Preparation

After the investigator has determined that a patient is suitable and after written informed consent has been given, the patient will be checked for presence of 10 – 60% pretest probability for CAD. For this reason the physician will obtain relevant data including personal details, important aspects of the medical history and information about risk factors (elevated fat levels, overweight, smoking etc.) and current medications. . While waiting for their test and before they are informed about the presence of a 10 – 60% pretest probability for CAD, the patients complete questionnaires (on quality of life, for example). If the patient has an intermediate pretest probability of 10% to 60% for CAD he can participate in the study and he will be assigned (randomised) with a 50:50 chance to CT or ICA. Before and after the diagnostic test is conducted the patient will be handed a questionnaire on satisfaction to be completed. If the Patient does not have an intermediate pretest probability of 10% to 60% for CAD, he cannot participate in the study and he will **not** be assigned (randomised) with a 50:50 chance to CT or ICA. Instead he will undergo ICA as planned, the results of which will be provided to the study sponsor and his personal data will be recorded.

4.2.1. Invasive coronary angiography (ICA)

All patients participating in the DISCHARGE study have a referral for ICA (the current standard) based on suspected CAD. The need for this examination was established by our referring physician. However, according to the randomisation schedule, only 50% of the patients enrolled in the study will undergo ICA. In ICA, an X-ray fluoroscopy with administration of contrast medium is performed. In rare cases, the contrast medium can cause mild allergoid reactions (nausea, itching, skin rash, for example). Severe intolerance reactions to the contrast agent (such as impairment of

kidney function or allergic shock) are extremely rare as well as other adverse effects. If such a reaction occurs, immediate treatment is available in the hospital. ICA exposes the patient to X-rays. The radiation exposure is about 9-10 mSv, which corresponds to the natural background radiation of 54 to 60 months. This radiation exposure is clinically indicated because your referring physician decided that ICA is necessary. This radiation exposure is not due to participation in our study.

4.2.2. Computed Tomography (CT)

Starting in 1998, multislice CT has been developed as an alternative method to ICA. The aim of this alternative method is to examine the arteries that supply the heart muscle (the coronary arteries) with similar reliability but less invasiveness. Earlier studies show that cardiac CT has an accuracy of 95-97% in detecting narrowing (stenosis) of the coronary arteries. Moreover, CT also allows ruling out stenosis with a high degree of probability (so-called negative predictive value of 95%). Therefore, CT allows reliably ruling out suspected stenosis (narrowing) without the need for ICA.

The CT examination of the heart takes about 15 to 25 minutes. The actual CT scan takes only about 0.2-8 seconds, depending on the CT scanner used. During this time, it is necessary that patients hold their breath for a short period of time. Before CT, the patient's medical records will be reviewed and blood samples may be taken according to local standards. In addition, an ECG will be obtained, unless a patient has a recent ECG (obtained within 1 month before CT). Caffeine is not allowed for 4 hours before the CT examination (coffee, tea, or chocolate, for example). Patients with a heart rate of more than 50 beats/minute will be given a betablocker. If betablockers cannot be used due to a contraindication, ivabradine will be given. However, ivabradine will not be used if the heart rate is under 60 beats per minute. If, after these medications, the heart rate is still above 55 beats just before the CT scan, additional betablocker could possibly be given by intravenous injection. Immediately before the examination, nitroglycerin will be given under the tongue to make the coronary arteries wider, which improves their assessment. As with ICA, the CT examination also involves injection of a contrast agent. The contrast agent is an approved agent for CT examinations and will be injected into a vein in the crook of the elbow. Again, in rare cases, the contrast agent can cause mild allergoid reactions (nausea, itching, skin rash, for example. Severe intolerance reactions to the contrast agent (such as impairment of kidney function or allergic shock) are extremely rare as well as other adverse effects. If such a reaction does occur, immediate treatment is available in the hospital. CT is also performed with X-rays. The radiation dose is about 1 to 5 mSv and roughly corresponds to the natural background radiation of 6 to 30 months.

4.3. Treatment strategy

The findings of CT or ICA will immediately be made available to the **local heart team** for analysis. The local heart team includes cardiologists, cardiac surgeons and radiologists. Patients will be

discharged immediately if the findings are negative (that is if the examination does not reveal significant (≥ 50%) diameter stenosis of the coronary arteries), unless other medical reasons require further hospitalisation. Risk factor modification and optimal medical therapy may be initiated for the patients based on current European guidelines. If the results are positive (CAD ≥ 50% diameter stenosis is demonstrated) further treatment is based on study recommendations, the hospital's standard procedure, and European guidelines:

a) In the ICA group, the local heart team will decide on further diagnostic and therapeutic measures following the current guidelines of the European Society of Cardiology (ESC) and the European Society of Cardiothoracic Surgery (EACTS) for reopening narrowed coronary arteries.

b) If a patient assigned to the **CT group** of the study, turns out to have high-risk disease (defined as stenosis of the left main coronary artery, stenosis of the proximal LAD, or 3-vessel disease), according to ESC/EACTS guidelines, it is recommended that he or she should have an ICA after CT to confirm that a revascularisation procedure is necessary. In patients in whom the CT scan reveals narrowing of only one or two coronary arteries, the local heart team will perform the best imaging ischemia test available at the hospital (e.g., stress echocardiography, scintigraphy or magnetic resonance imaging) before deciding about whether ICA should be performed. If patients with these CT findings already had a positive ischemia test (>10% of myocardium) before being enrolled in the study, it is recommended to directly proceed to ICA after the CT scan. Incidental CT findings will also be taken into account when the local heart team decides about the patient's further care. The local heart team will decide about measures to modify risk factors in accordance with European guidelines and the usual standard of care. Specifically, cardiac events can be predicted when a patient has noncalcified high risk plaques or has a coronary calcium score according to Agatston (indicator for the calcium burden in blood vessels) of at least 400. In the patients examined by CT, the local heart team will take these high-risk plaque features into account in making their decision concerning guideline-based risk factor modification. It is expected that about 80-90% of the patients in the CT group will not have obstructive stenosis (≥ 50%), i.e., no coronary artery disease. These patients receive guideline-oriented medical therapy and will normally be discharged on the same day.

4.4. Follow-up

It is planned to conduct two follow-up surveys of the patients who participate in the study: the first follow-up survey is planned to be conducted after one year, the second between two and four years after enrollment in the study. The follow-up will be conducted in the form of a questionnaire survey. The questionnaires (covering topics such as quality of life and patient satisfaction, for example) will be mailed to the patients by the Charité (Dept. of Radiology). Completing and returning the questionnaires is very important for the success of our study. Therefore, all patients are asked to carefully complete the questionnaires and provide correct information. Please kindly

inform the study centre about any change of address, email address, or phone number, so we can contact you. In addition, your referring physician will be informed about your participation in this study. In order to obtain missing information (e.g., in case of a change of address), we ask you to authorise/ release from medical confidentiality obligation the following persons/third parties in order to provide data that are relevant for the study: your first-degree relatives, your general practitioner/cardiologist, your health insurer and any involved authorities (e.g., population registries, public health agencies, statistical authorities) and the respective affiliated physicians of these authorities. Your rights to confidentiality of your data will be protected any time. You can always contact us directly by telephone should you have questions concerning your treatment or the questionnaires. Should you note a change in your well-being or symptoms, contact your local medical services and inform us as well. The questionnaires used in the follow-up survey correspond to the questionnaires you are asked to complete immediately after having consented to participation in the study. In this way, we hope to minimise your efforts and the time required for completing the questionnaires. For your convenience, we will enclose self-addressed, stamped envelopes for returning the completed questionnaires to the Charité. Your data will be collected and stored at the xx and transmitted to the coordinating centre at Charité, Berlin, Germany (see next section).

5. What will happen to my data?

Information on data protection

The study will be conducted in accordance with current data protection laws. Any personal data relating to you that we collect and send to the central study database at Charité - Universitätsmedizin Berlin and AGMednet are pseudonymised. This means that the persons handling the data cannot trace them back to individual participants.

With your signature on the informed consent form, you agree to the storage and processing of person-related data for the purpose of the above-named study by the investigator and his or her co-workers.

Person-related data include your name, data of birth, sex, ethnicity, data on your physical and mental health, and other personal data that are collected during the study or at follow-up with, for example, questionnaires.

The investigator will use your person-related data for administration and conduct of the study as well as for research and statistical analysis.

The original informed consent form with your nonpseudonymised personal data will be filed at the investigator's study centre.

Data collected by the local investigator at the study centre during the study will be transmitted in pseudonymised form to the coordinator, Prof. Dr. med. Marc Dewey - Charité - Universitätsmedizin Berlin, Campus Mitte, Dept. of Radiology and Neuroradiology, Charitéplatz 1, 10117 Berlin, Germany.

Study-related data (questionnaires, patient forms, medical documentation) will be stored for processing, analysis and scientific investigation in the local study centre (Charité, Berlin, Humboldt-Universität, Charitéplatz 1, 10117 Berlin, Germany, phone: ++49 (0)30 450-627264). The local principal investigator is responsible for data collection, processing, and transmission. The image

data will be stored on behalf of Charité at AGMednet, Inc.,2 Atlantic Avenue, Boston, Massachusetts 02110, phone: 855-246-3363.

In the study centre, data will be processed in pseudonymised form. To this end, the investigator assigns a code to the datasets (pseudonymisation of the data). This code is used when your data are transmitted to the central database. The key to the code that allows tracing the data back to you is only available to the local principal investigator and other staff authorised by him. All documents that allow identification of your person will be handled with strict confidence.

All person-related data that are kept by the investigator can be reviewed by the coordinator Prof. Dr. med. Marc Dewey and/or his or her representatives and specific study personnel (e.g., monitors, auditors), who will not be able to them trace back to the individual participant and will be bound to confidentiality. These reviews may become necessary to ensure that the study is conducted properly and/or to ensure the quality of the study-related data.

You have been informed that the data/details concerning your health that we collect for the study and which are documented on questionnaires and on electronic media can be transmitted pseudonymised to the following parties:

a) the responsible monitoring authority (in the present study: German Federal Office for Radiation Protection, Salzgitter) for the purpose of checking whether the study is conducted properly and for assessing study results and adverse events;

b) the sponsor = coordinating study centre (Charité, Berlin, Humboldt-Universität, Charitéplatz 1, 10117 Berlin, Germany; phone ++49 (0)30 450 527353) for scientific analysis and for conducting the follow-up survey; on behalf of Charité at AGMednet, Inc.,2 Atlantic Avenue, Boston, Massachusetts 02110, phone: 855-246-3363

You are free to withdraw your consent to the processing of your data at any time during the study. In this case, no new data will be collected and your stored personal data and the corresponding key will be deleted or destroyed unless there are legal regulations that require storage for certain periods.

You have the right to know which personal data are stored. You can request correction of your person-related data in case of inaccuracies. If you wish to make a request, please contact your investigator, who will then immediately provide the information you wish to have.

After the end of the study, your data must be kept on file for another 10 years (according to the German regulation for procedures involving the use of X-rays). After this 10-year period, your person-related data will be deleted unless there are other legal or contractual regulations that require us to store the data for even longer periods.

Please note that the results of the study may be published in medical journals; in this case your identity will be hidden and it will not be possible to trace any published results back to you.

6. Will there be costs for me when I participate in the study?

No costs will arise and you will receive no payment.

7. Who can decide about removing me from the study?

There are some circumstances that may result in excluding you from the further study. This decision is made by the investigator, and you have no influence on the decision. Reasons for excluding you may be that further participation is not in the best interest of your health or that the study ends prematurely.

8. Will I be insured during the study?

Participants in the DISCHARGE Study, who will be randomised into the cardiac CT or ICA group, will be insured by ECCLESIA. A maximum coverage of 500,000 Euro is put in place. Fault-based damage (caused by the clinic staff) will be covered through the business liability insurance of the respective clinic for the entire duration of the study. The patient is responsible to notify the clinical site about possible radiation-induced damage. Coverage (e.g., for lost wages or pain) as a result of damage to persons will only be paid if it is covered by ECCLESIA.

9. What else do I need to know?

Please note that the results of the study may be published in a medical journey. This will be done without revealing your identity. You need not participate in this study to receive standard medical care. If you do not participate in the study, you will undergo ICA.

During your participation in the study, please follow the physicians' instructions and immediately report to them any change in your health.
Participation in this study is entirely voluntary. Please read and sign the attached Informed Consent form. You can withdraw consent at any time without giving a reason. If you do not wish to participate, this has no consequences for your further treatment or for the relationship to your doctor. You will continue to receive the best medical care. We expect the study to improve future diagnostic management and treatment of coronary artery disease.

10. Who will answer my questions?

Do you have any questions? We are always available to answer any questions you may have concerning this written information and the examinations. The following questions have been discussed:

……..

……..

At the Department of Radiology (Charitéplatz 1, 10117 Berlin), your investigator, **Prof. Dr. med. M. Dewey** (phone: **030 450-627 353),** or the study centre (phone: **030 450-627 264**) will be available to answer your questions.

If you do not have further questions, please sign the attached Informed Consent form and enter the date of your consent. You will be handed a copy of this patient information and of the signed Informed Consent form. We thank you for taking the time to consider participation in this study.

I confirm that I have read and understood this patient information. A copy has been handed to me.

_____ _____

Berlin (date) (Patient’s signature)

Informed Consent Version 09.10.2014

Title of the study: " Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies (DISCHARGE)"

Please read this Informed Consent form carefully. Do not hesitate to ask us if anything is unclear or if you wish to have further information.

Hereby I,
First name:
Last name:
Date of birth:

confirm that Mr./Ms./Mrs./Dr./Prof. has informed me, both orally and in writing, about the nature, significance, scope and risks of the scientific investigation in the DISCHARGE study conducted by the Department of Radiology at Charité. I had sufficient time to ask questions and seek clarification from the investigator.

I understand that my participation in the study is entirely voluntary and that I may discontinue my participation at any time without giving a reason. This will not in any way affect my further treatment.

I am aware that if I do not fulfill the final inclusion criterion of an intermediate pretest probability (10% - 60%) for CAD I cannot participate in the study and I **will undergo ICA** as planned. I agree that the results as well as my personal data will be recorded and analysed. I am aware that no follow-up will be conducted if I cannot participate in the study.

If I fulfill the final inclusion criterion of an intermediate pretest probability (10% - 60%) for CAD I want to participate in the study for the comparison of computed tomography (CT) and ICA. I am aware that I will be assigned by chance to one of the two diagnostic tests and their subsequent patient management strategies. The chances are 50:50 that I will receive a CT examination or ICA.I authorise my treating and referring physicians (family doctor, cardiologist) to provide the clinical study centre (Charité, Berlin) with information regarding my exact diagnosis and the further development of my medical status during the follow-up period of the study. I also agree that they pass on copies of relevant medical records. I authorise/ release from medical confidentiality obligation my first-degree relatives, my treating family physician/cardiologist, my health insurer and all relevant authorities (e.g., population registries, health authorities, statistical authorities), including affiliated physicians of these authorities to provide the local investigator of the Charité with confidential data that are relevant for the study. I also authorise the clinical study center to inform the above mentioned parties about my participation in the study.

Specifically, I have read and understood the written patient information (dated October 9, 2014) and I have been handed a copy of the information and of this informed consent. I agree to the use of X-rays in my examinations. I explicitly confirm that I consent that the responsible German authority (the German Federal Office for Radiation Protection) will be

notified about my participation in this study and the resulting radiation exposure. With regard to my study participation and the resulting radiation exposure, this authority can review my personal data. My consent to reporting the received radiation exposure is irrevocable. This does not apply to medical data. I am aware that a copy of this Informed Consent form will be kept in the files. This will be done in strict compliance with legal regulations concerning the protection of data and I explicitly agree to this procedure.

Informed consent concerning data handling

1) I am aware that all data concerning me will be stored in computerised and pseudonymised form during the course of the study. This will be done by the local study centre (Charité, Department of Radiology, Charitéplatz 1, 10117 Berlin, Germany) with strict adherence to data protection regulations. My personal data (name and address, for instance) will be strictly separated from my other data. Only the local investigator has access to my personal data.

2) All analyses performed that involve my data will be done using the data in pseudonymised form (this means that the data cannot be traced back to me). I have been informed that my study-related data will be handled in accordance with the regulations for the confidentiality of data and data protection laws.

3) I confirm that I agree to the documentation of my study-related data/details concerning my health and to the storage of these data in electronic form. These data can be transmitted in pseudonymised form to the following persons and other third parties:

a) the sponsor = coordinating study centre (Charité, Berlin, Humboldt-Universität, Charitéplatz 1, 10117 Berlin, Germany; phone ++49 (0)30 450 527353) for scientific analysis and for conducting the follow-up survey; on behalf of Charité at AGMednet, Inc.,2 Atlantic Avenue, Boston, Massachusetts 02110, phone: 855-246-3363

b) the state monitoring authorities (Landesamt für Arbeitsschutz, Gesundheitsschutz und Technische Sicherheit), the highest federal authority (Bundesamt für Strahlenschutz) and the ethics committee, if they request these data for verification of study results and adverse events.

4) All person-related data that are kept by the local investigator can be reviewed by the coordinator Prof. Dr. med. Marc Dewey and/or his or her representatives and specific study personnel (e.g., monitors, auditors), who will not be able to them trace back to the individual participant and will be bound to confidentiality. These reviews may become necessary to ensure that the study is conducted properly and/or to ensure the quality of the study-related data. For this purpose, I authorise the investigator to disclose the required information.

5) You have the right to know which personal data are stored. You can request correction of your person-related data in case of inaccuracies. If you wish to make a request, please contact your investigator, who will then immediately provide the information you wish to have.

6) You are free to withdraw your consent to the processing of your data at any time during the study. In this case, no new data will be collected and your stored personal data and the corresponding key will be deleted or destroyed unless there are legal regulations that require storage for certain periods.

7) After the end of the study, your data must be kept on file for another 10 years (according to the German regulation for procedures involving the use of X-rays). After this 10-year period, your person-related data will be deleted unless there are other legal or contractual regulations that require us to store the data for even longer periods.

I consent to undergoing the examination in the setting of the above-referenced study.

_____ _____

Berlin (date) (Patient's signature)

I confirm that I have explained the nature, significance, scope and risks of this study. Both written and oral information has been provided. The patient has been handed a copy of the

written information and of this informed consent form.

Berlin (date)	(Investigator’s signature)

Patienteninformation – Version: 30.01.2020

Studientitel: "Diagnostische Bildgebungsstrategien bei Patienten mit stabilem Brustschmerz und mittlerem Risiko einer koronaren Herzerkrankung: Vergleichende Nutzenbewertung existierender Technologien (DISCHARGE)"

Sehr geehrte Patientin, sehr geehrter Patient,
vielen Dank für ihr Interesse an der pragmatischen klinischen Studie DISCHARGE. Diese europäische multizentrische Forschungsstudie wird von der Charité in Berlin koordiniert (Sponsor: Institut für Radiologie, Charité, Charitéplatz 1, 10117 Berlin). Am Institut für Radiologie der Charité sind neben dem Studienleiter, Prof. Dr. med. Marc Dewey, als Studienärzte an dieser Studie beteiligt: Dr. med. Elke Zimmermann, Dr. med. Matthias Rief, Dr. med. Georg Schütz. Die Studie findet in Zusammenarbeit mit der Klinik für Kardiologie (Studienärzte: PD Dr. med. Michael Laule, Dr. med. Henryk Dreger) statt.

1. Was ist das Ziel der Studie?

Sie haben eine Indikation zu einer invasiven Koronarangiografie (Herzkatheter). Außerdem liegen bei Ihnen stabile Brustschmerzen vor, für die eine koronare Herzkrankheit (KHK = mindestens 50%ige Verengung der Herzkranzgefäße) als Ursache vermutet wird. Somit kommen sie als Teilnehmer für die DISCHARGE Studie in Betracht, bei der entweder ein Herzkatheter oder eine Computertomografie (CT) durchgeführt wird. Auf der Diagnose durch eines dieser Verfahren beruhen die Entscheidungen zur weiteren Vorgehensweise und Behandlung durch das lokale Herzteam. In dieser Studie soll die Überlegenheit der CT gegenüber dem Herzkatheter untersucht werden. Ob sie in die Studie aufgenommen werden können, richtet sich nach der Wahrscheinlichkeit für das Vorliegen einer KHK. Liegt die Wahrscheinlichkeit für das Vorliegen einer KHK bei ihnen zwischen 10% bis 60%, was wir als mittlere Prätestwahrscheinlichkeit bezeichnen, können sie in die Studie aufgenommen und durch ein zufälliges Losverfahren mit einer 50:50 Chance dem CT oder dem Herzkatheter zugeteilt (randomisiert) werden. Es besteht keine Möglichkeit der Einflussnahme auf diese Zufallsverteilung durch sie oder das Studienpersonal. Liegt bei ihnen keine mittlere Prätestwahrscheinlichkeit von 10% bis 60% für eine KHK vor, können sie nicht in die Studie aufgenommen werden und bei ihnen wird, wie geplant, ein Herzkatheter durchgeführt, dessen Ergebnisse durch das Studienteam bei ihrem behandelnden Arzt erfragt und dokumentiert werden.

Bei der Studie handelt es sich um eine randomisierte pragmatische Studie. Dies bedeutet, dass die medizinische Versorgung der Patienten innerhalb der Studie, soweit wie möglich, den normalen klinischen Alltag widerspiegeln soll, um möglichst realistische und praktikable Studienergebnisse erzielen zu können. Insgesamt sollen 3546 Patienten in 23 europäischen klinischen Zentren in die Studie aufgenommen werden. Für die Charité ist die Randomisierung von 128 bis maximal 320 Patienten geplant.

2. Nutzen und Risiken der Teilnahme an der Studie

Auf Grund der mittleren Wahrscheinlichkeit (10-60%) für das Vorliegen einer KHK kann erwartet werden, dass ca. **80-90%** der randomisierten Patienten keine KHK aufweisen. Nach Durchführung der CT oder des Herzkatheters kann dann der Patient, soweit keine anderen medizinischen Gründe vorliegen, entlassen werden. Bei den Patienten, die in die CT-Gruppe randomisiert wurden, ist dieser Ausschluss einer KHK ohne invasive Untersuchung möglich. Darin besteht ein Vorteil für die Patienten. Für **einzelne Patienten** der CT-Gruppe ergeben sich eventuell weitere Vorteile. Erkrankungen wie die Lungenarterienembolie (Blutgerinnsel in den Lungenarterien), eine axiale Gleithernie der Speiseröhre (in den Brustkorb verlagerter Magenanteil) aber auch die Aortendissektion (Riss der Innenwand der Hauptschlagader) können zu Brustschmerzen führen und sind mit der CT in den mit dargestellten Regionen sicher zu erkennen. Daraus ergibt sich der Vorteil, dass derartige Erkrankungen durch die Untersuchung im Rahmen der Studie früher erkannt und damit zügiger behandelt werden können. Verengungen in den Herzkranzgefäßen werden meist durch sogenannte koronararterielle Plaques (Ablagerungen in den Gefäßwänden) hervorgerufen. Diese können mit der CT ebenfalls erkannt und bezüglich ihrer Zusammensetzung charakterisiert werden. Besondere Typen dieser Plaques haben ein größeres Risiko zu ruptuieren (z.B. Plaques mit einem großen Gehalt an Fett oder viel Kalzium). In einer solchen Situation können Änderungen der Medikation oder Risiko-Faktor-Modifikationen vorgenommen werden um einer Ruptur vorzubeugen. Außerdem wird die Art der Wiedereröffnung von möglichen Verengungen der Herzkranzgefäße (mittels Katheter vs. chirurgisch) durch die Erkenntnisse aus der CT maßgeblich beeinflusst und könnte zu Vorteilen führen. Der voraussichtliche **Vorteil für zukünftig betroffene Personen** entsteht, wenn sich die CT als überlegen im Vergleich zum Herzkatheter mit den jeweils dazugehörigen Behandlungsplänen darstellt. In diesem Fall wäre es denkbar, dass ein bedeutender Anteil der heutzutage in Deutschland und Europa invasiv mit Katheter durchgeführten Untersuchungen von Patienten mit stabilem Brustschmerz und mittlerer Wahrscheinlichkeit für eine koronare KHK nicht-invasiv durch die CT mit insgesamt geringeren Risiken für die Patienten durchgeführt werden könnte. Dies ist deshalb bedeutsam, da etwa 2 Millionen Herzkatheteruntersuchungen in Europa jährlich als vermeidbar angesehen werden. Gemäß dem pragmatischen Vorgehen in der DISCHARGE

Studie existieren nur die üblichen Risiken der CT sowie des Herzkatheters. Bezogen auf die Einzeluntersuchung ergeben sich somit keine zusätzlichen Risiken für die Patienten durch die Teilnahme. Im Falle des Auftretens der üblichen Risiken stehen an der Charité die entsprechenden Maßnahmen der Versorgung zur Verfügung. Es ist zu bedenken, dass etwa bei 10-20% der Patienten eine Verengung der Herzkranzgefäße in der CT zu erwarten ist. Dann kann ein anschließender Herzkatheter, nach möglichen weiteren kardiologischen Funktionstests, zur interventionellen Behandlung der Stenose(n) notwendig werden. Hierdurch werden diese Patienten einer erhöhten Strahlenexposition und zusätzlichem Kontrastmittel im Vergleich zur Nichtteilnahme an der Studie ausgesetzt. Der Diagnose- und Behandlungspfad verlängert sich entsprechend. In äußerst seltenen Fällen kann es vorkommen, dass Stenosen der Herzkranzgefäße in der CT-Gruppe nicht erkannt werden, die in der Herzkatheter-Gruppe erkannt worden wären. Allerdings können in der CT-Untersuchung weitere diagnostische Daten gewonnen werden, die zu einem zusätzlichen therapeutischer Nutzen führen können.

3. Welche Voraussetzungen gibt es zur Teilnahme?

An der Studie **können** Patienten mit einer Indikation zur Herzkatheteruntersuchung teilnehmen, bei denen eine mittlere Wahrscheinlichkeit für das Vorliegen einer koronaren Herzerkrankung (10-60%) besteht, die einen stabilen Brustschmerz als Symptomatik aufweisen, die des Weiteren mindestens 30 Jahre alt sind und ihr schriftliches Einverständnis zur Teilnahme geben. Frauen können an der Untersuchung teilnehmen, wenn eine Schwangerschaft ausgeschlossen wurde bzw. die Menopause eingetreten ist oder die Gebärmutter operativ entfernt wurde. **Nicht teilnehmen** können Patienten, bei denen kein regelmäßiger Herzschlag vorliegt, oder die eine dialysepflichtige Nierenerkrankung aufweisen. Zur Feststellung der Eignung als auch um eine bestmögliche Versorgung zu gewährleisten, wird vor als auch während der Studie Einsicht in die medizinischen Unterlagen der Patienten genommen und studienrelevante Daten dokumentiert.

4. Wie ist der Ablauf der Studie und was müssen Sie bei Teilnahme beachten?

4.1. Vorbereitungen

Nachdem die Eignung der Patienten durch den Studienarzt festgestellt worden ist und die Einwilligung der Patienten vorliegt, wird die Wahrscheinlichkeit für das Vorhandensein einer koronaren Herzkrankheit (KHK = mindestens 50%ige Verengung der Herzkrankgefäße) vom Studienarzt geprüft. Da es sich um die Wahrscheinlichkeit vor dem Vorliegen von Ergebnissen aus dem CT oder Herzkatheter handelt, wird auch von der sog.

Prätestwahrscheinlichkeit gesprochen Hierzu werden persönliche Daten des Patienten erhoben sowie Informationen zur Krankheitsgeschichte, zu Risikofaktoren (erhöhte Fettwerte, Übergewicht, Rauchen etc.) und verordneten Medikamenten aufgenommen. Während der Studienarzt die Wahrscheinlichkeit für das Vorliegen einer KHK errechnet füllen die Patienten Fragebögen (z.B. zur Lebensqualität) aus. Liegt eine Prätestwahrscheinlichkeit von 10% bis 60% für das Vorhandensein einer koronaren Herzkrankheit (KHK = mindestens 50%ige Verengung der Herzkranzgefäße) vor, wird der Patient in die Studie aufgenommen und durch ein zufälliges Losverfahren mit einer 50:50 Chance dem CT oder dem Herzkatheter zugeteilt (randomisiert). Vor und nach den jeweiligen Untersuchungen werden Fragebogen u.a. zur Zufriedenheit der Patienten ausgegeben und vom Patienten ausgefüllt. Liegt beim Patienten keine Prätestwahrscheinlichkeit von 10% bis 60% für eine KHK vor, wird dieser nicht in die Studie aufgenommen und bei ihm wird, wie geplant, ein Herzkatheter durchgeführt, dessen Ergebnisse durch das Studienteam bei dem behandelnden Arzt erfragt und mit den vom Patienten erteilten Daten dokumentiert werden.

4.2.1. Herzkatheter

Bei allen Patienten, die an der DISCHARGE Studie teilnehmen, liegt eine medizinische Notwendigkeit (Indikation) für einen Herzkatheter (derzeitiger Goldstandard für die Diagnostik der KHK) vor. Diese wurde durch ihren behandelnden Arzt festgestellt. Auf Grund der Randomisierung wird der Herzkatheter jedoch nicht bei jedem Patienten durchgeführt. Die Darstellung der Herzkranzgefäße erfolgt unter Einbringung von Kontrastmittel bei gleichzeitiger Röntgendurchleuchtung. Durch das Röntgenkontrastmittel kann es selten zu leichten allergischen Reaktionen (z.B. Brechreiz, Juckreiz, Hautausschlag) kommen. Ein weiteres Risiko durch die Kontrastmittelgabe ist eine Verschlechterung der Nierentätigkeit. Andere Nebenwirkungen sind sehr selten. Sollten sie dennoch auftreten, können die Patienten unmittelbar daraufhin behandelt werden. Bei der Herzkatheteruntersuchung wird der Patient mit Röntgenstrahlung untersucht. Diese beträgt etwa 9-10 mSv, was einer natürlichen Strahlenexposition von etwa 54 bis 60 Monaten entspricht. Diese Strahlenexposition im Herzkatheter beruht auf der Indikationsstellung durch Ihren behandelnden Arzt und ist nicht durch die Teilnahme an der Studie bedingt.

4.2.2. Darstellung der Herzkranzgefäße (Koronararterien) mittels CT

In den letzten Jahren (beginnend 1998) ist mit der Mehrschicht-CT eine Methode entwickelt worden, die die zuverlässige Darstellung der Herzkranzgefäße (Koronararterien) als Alternative zum Herzkatheter erlaubt. Die Genauigkeit bei der Erkennung von Patienten mit Verengungen an den Herzkranzgefäßen betrug in bisherigen Untersuchungen ca. 95-97%. Das Vorhandensein von Stenosen (Einengungen) bei Patienten kann des Weiteren mit einer hohen Sicherheit ausgeschlossen werden (sog. negativer Vorhersagewert: 95%). Mit einer

der neuesten Gerätegenerationen, die in dieser Studie zur Anwendung kommen wird, wird diese Genauigkeit weiter verbessert. Somit ist es möglich, mit der CT zuverlässig das Vorhandensein von Einengungen bei Patienten mit Verdacht auf Stenosen (Einengungen) ohne die Notwendigkeit eines Herzkatheters auszuschließen. Die Untersuchung im CT dauert etwa 15 bis 25 Minuten. Davon macht die reine Untersuchungszeit nur ca. 0,2-8 Sekunden je nach CT-Gerät aus. In dieser Zeit ist es notwendig, dass der Patient seinen Atem kurz anhält. Vor der CT werden die medizinischen Akten der Patienten gesichtet und bei Bedarf werden Blutproben entnommen. Ein EKG wird ebenfalls aufgenommen, wenn es nicht bereits innerhalb der letzten 30 Tage angefertigt wurde. Für 4 Stunden vor der CT-Untersuchung dürfen keine koffeinhaltigen Produkte (z.B. Kaffee, Tee oder Schokolade) zu sich genommen werden. Bei einer Herzfrequenz von über 50 Schlägen pro min wird den Patienten ein Betablocker verabreicht. Sollten Betablocker wegen z.B. einer Kontraindikation nicht verabreicht werden können, kann ein anderes Medikament zur Senkung der Herzfrequenz oral verabreicht werden. Ivabradin wird nicht bei einer Herzfrequenz von unter 60 Schlägen pro min gegeben. Sollte die Herzfrequenz vor der Untersuchung im CT weiterhin über 55 Schlägen pro min liegen, werden gegebenenfalls zusätzlich intravenöse herzfrequenzsenkende Medikamente verabreicht. Unmittelbar vor der Untersuchung wird dem Patienten zur Erweiterung der Herzkranzgefäße und somit besseren Beurteilbarkeit das Medikament Nitroglycerin unter die Zunge gegeben. Ebenso wie beim Herzkatheter erhält der Patient während der Untersuchung im CT eine Kontrastmittelinjektion mit einem zugelassenen Kontrastmittel für die CT über die Ellenbeugenvene. Auch hier besteht die seltene Möglichkeit, dass der Patient allergisch reagiert, was sich z. B. in Übelkeit, Juckreiz oder roten Hautflecken äußern kann. Schwere Unverträglichkeitsreaktionen (wie z.B. eine Beeinträchtigung der Nierentätigkeit oder eines allergischen Schocks) sind jedoch extrem selten. Sollten sie dennoch auftreten, können die Patienten unmittelbar daraufhin behandelt werden. Bei der CT wird auch Röntgenstrahlung genutzt. Dabei entspricht die Strahlenexposition von ca. 1 bis 5 mSv etwa der natürlichen Strahlenexposition von 6 bis 30 Monaten.

4.3. Behandlungsstrategie

Die Untersuchungsresultate stehen dem **lokalen Herzteam** umgehend für die Auswertung zur Verfügung. Dieses besteht aus Fachärzten der Kardiologie, Herzchirurgie und Radiologie. Bei einem negativen Befund der Untersuchung, also wenn keine signifikante Stenose der Herzkranzgefäße (≥ 50%ige Stenose der Koronararterien) gefunden werden konnte, werden die Patienten direkt entlassen, soweit keine anderen medizinischen Gründe vorliegen. Gegebenenfalls wird eine Anpassung der medikamentösen Therapie und der Risikofaktoren anhand aktueller europäischer Leitlinien empfohlen und initiiert. Bei einem positiven Befund (≥ 50%ige Verengung der Koronararterien) basiert die Weiterbehandlung

auf der lokalen Standardbehandlung und europäischen Leitlinien:

a) Im **Herzkatheterarm** der Studie wird das lokale Herzteam Entscheidungen gemäß der aktuellen Leitlinien der Europäischen Gesellschaft für Kardiologie (ESC) und der Europäischen Gesellschaft für kardiothorakale Chirurgie (EACTS) für die Wiedereröffnung von verengten Gefäßen treffen.

b) Zeigt sich im **CT-Arm** der Studie, dass bei Patienten eine Hochrisiko-Anatomie vorliegt, dazu gehört eine Stenose der linken oder proximalen Koronararterie (LAD) oder einer 3-Gefäßerkrankung und somit gemäß der ESC/EACTS Leitlinien eine klare Indikation zur Wiedereröffnung vorliegt, wird eine anschließende Herzkatheteruntersuchung empfohlen, um die Notwendigkeit hierfür zu bestätigen. Bei Patienten mit 1- oder 2-Gefäßerkrankung im CT wird das lokale Herzteam zuerst den besten lokal verfügbaren Ischämietest (zum Nachweis einer Minderdurchblutung) zur Anwendung bringen (z.B. Stress-Echokardiografie, Szintigrafie oder Magnetresonanztomografie), bevor die Entscheidung für einen nachfolgenden Herzkatheter getroffen wird. Liegt bereits vor dem Einschluss in die Studie ein positiver Ischämietest (>10% des Myokards) vor, so wird direkt nach dem CT die Herzkatheteruntersuchung empfohlen. Auch nichtkardiale Zufallsbefunde im Zuge der CT werden bei der Entscheidung der nachfolgenden Behandlung durch das lokale Herzteam mit berücksichtigt. Das lokale Herzteam wird die Modifikation der Risikofaktoren nach europäischen Leitlinien und den üblichen Versorgungsstandards festlegen. Kardiale Ereignisse können speziell durch einen koronaren Kalziumscore nach Agatston (Indikator für die Belastung der Gefäße mit Kalkablagerungen) von mindestens 400 und der Anwesenheit von nichtverkalkten Plaques vorhergesagt werden. Das lokale Herzteam wird diese Hochrisiko-Plaquecharakteristika für Patienten im CT-Arm der Studie mit in den Entscheidungsprozess über leitlinienorientierte Risikofaktormodifikation einbeziehen. Es ist insgesamt zu erwarten, dass etwa 80-90% der Patienten mit mittlerer Prätestwahrscheinlichkeit keine obstruktive (≥ 50%) Stenose (keine koronare Herzerkrankung) haben werden. Diese Patienten erhalten leitlinienorientierte medizinische Therapie und werden in der Regel noch am selben Tag entlassen.

4.4. Nachbefragung (Follow-up)

Bei Patienten die in die Studie aufgenommen und dem CT-Arm oder Herzkatheterarm zugeteilt (randomisiert) werden, sind zwei Nachbeobachtungen vorgesehen: das erste Mal nach 1 Jahr und ein zweites Mal innerhalb von maximal 4 (und minimal 2) Jahren nach Beginn der Studienteilnahme. Diese Nachbeobachtungen werden durch das Ausfüllen von Fragebögen (z.B. zur Lebensqualität und zur Patientenzufriedenheit), die postalisch oder per E-Mail von der Charité zugestellt werden, durch die Patienten erfolgen. Die Teilnahme an den Nachbefragungen ist essentiell für den Studienerfolg und die Patienten werden gebeten,

sich hieran mit korrekten Informationen zu beteiligen und der Studienzentrale Änderungen ihrer Kontaktdaten (Adresse, E-Mail, Telefonnummer) bekannt zu geben. Ebenso werden wir ihren behandelnden Hausarzt/Kardiologen dieser Patienten über die Teilnahme an der Studie informieren. Zum Einholen eventuell fehlender Informationen (z.B. durch Umzug) möchten wir Sie außerdem bitten, Ihre Angehörigen ersten Grades, Ihren behandelnden Hausarzt/Kardiologen sowie ihre Krankenkasse und alle entsprechenden Behörden und Ämter (z.B. Meldeamt, Bezirksamt, Gesundheitsamt, statistisches Landesamt) inklusive hier eingebundener Ärzte von der Schweigepflicht bezüglich der studienrelevanten Daten zu entbinden. Ihre datenschutzrechtlichen Belange bleiben immer gewahrt. Sie können sich auch direkt telefonisch an uns wenden, wenn Sie Fragen zur Behandlung oder den Fragebögen haben. Sollte sich an Ihrem Wohlbefinden oder Symptomen etwas verändern, nutzen sie bitte ihren lokalen Gesundheitsdienstleister (z.B. Hausarzt oder Krankenhaus) und kontaktieren sie auch uns. Die Fragebögen der Nachbefragung entsprechen den Fragebögen, die die Patienten unmittelbar nach Ihrer Zustimmung zur Teilnahme zu Beginn der Studie ausfüllen werden. Dadurch erhoffen wir uns, dass das Ausfüllen der Fragebögen für Sie möglichst einfach und mit geringem Aufwand durchführbar ist. Die Rücksendung der Fragebögen erfolgt mittels beiliegender bereits frankierter Umschläge direkt an die Charité.

5. Was geschieht mit den Daten?

Aufklärung über den Datenschutz

Wir verarbeiten zum Zwecke der Durchführung der Studie personenbezogene Daten. Neben den Sie identifizierenden Daten erheben wir insbesondere Informationen zu Ihrer Gesundheit. Dazu gehören auch radiologische Bilddaten. Die Daten, die wir über Untersuchungen mit medizinischer Dokumentation gewinnen und weitere, die wir per Fragebögen, Patientenbögen, medizinische gewinnen werden zum Zweck der Auswertung, Verarbeitung und Analyse in der Studienzentrale (Charité, Berlin, Humboldt-Universität, Charitéplatz 1, 10117 Berlin, Tel. 030 450-627264) gespeichert. Verantwortlich für die Datenerhebung, -verarbeitung und -nutzung ist der Studienleiter. Das Studienteam wird Ihre personenbezogenen Daten für Zwecke der Verwaltung und Durchführung der Studie sowie für Zwecke der Forschung und statistischen Auswertung verwenden. Die Daten werden in pseudonymisierter Form verarbeitet, gespeichert und übermittelt (d. h. es kann ohne eine Entschlüsselungsliste keine Verbindung zwischen Ihren Daten und Ihrer Person hergestellt werden,. Hierzu versieht der Studienarzt die Daten mit einer Codenummer, die er auf einer separaten Liste mit Ihren Identifizierenden Daten und dem Code speichert (Codeschlüssel). Auf den Codeschlüssel, der es erlaubt, die studienbezogenen Daten mit Ihnen in Verbindung zu bringen, haben nur der Studienleiter, der Studienarzt und von ihnen autorisierte Mitarbeiter Zugriff. Sämtliche Aufzeichnungen, anhand derer Sie identifiziert werden können, werden streng vertraulich behandelt. Ihre sich auf der Einwilligungserklärung befindlichen personenbezogenen Daten verbleiben im Original beim Studienleiter im Studienzentrum.
Ihre Daten werden in pseudonymisierter Form an folgende Institutionen übermittelt:
a) die zuständige Überwachungsbehörde (hier: Bundesamt für Strahlenschutz, Salzgitter) zur Überprüfung der ordnungsgemäßen Durchführung der Studie, zur Bewertung von Studienergebnissen und unerwünschter Ereignisse;

b) einen Datenhoster zur Speicherung der Bilddaten (AG Mednet AGMednet, Inc.,2 Atlantic Avenue, Boston, Massachusetts 02110, phone: 855-246-3363). Nach Beendigung der Studie werden die Daten an der Charité auf einem Bilddatenserver gespeichert (Forschungsdaten Picture Archiving and Communication System (FPACS)) und vom Datenhoster der AG Mednet gelöscht.
Um sicherzustellen, dass die Studie ordnungsgemäß durchgeführt wird und/oder die Qualität der studienbezogenen Daten gewährleistet ist können Vertreter der Studienzentrale (z. B. Monitore, Auditore) die pseudonymisierten Daten im Studienzentrum einsehen. Hierzu bitten wir Sie um Entbindung von der ärztlichen Schweigepflicht. Die Erklärung können Sie jederzeit ohne Angaben von Gründen und ohne Nachteile für Ihre weitere Behandlung widerrufen.
Ihre Daten werden im Sinne der Aufbewahrungsfristen der Stahlenschutzverordnung nach Beendigung oder Abbruch der Studie für 30 Jahre aufbewahrt.Sie haben ein Recht auf Auskunft, Berichtigung, Sperrung oder Löschung über die von ihnen gespeicherten Daten. Bitte wenden Sie dafür an das Studienteam.
Sie können ihre Einwilligungserklärung jederzeit ohne Angabe eines Grundes widerrufen. Dann werden ihre Daten gelöscht oder sofern gesetzliche oder vertragliche Aufbewahrungsfristen entgegenstehen gesperrt und nach Ablauf des Aufbewahrungszeitraumes gelöscht.
Im Falle eines Widerrufs der Teilnahmeerklärung hat dieses keine Auswirkungen auf die vor dem Widerruf durchgeführte Verarbeitung und auch keine Auswirkungen, soweit die Verwirklichung der Forschungszwecke unmöglich gemacht oder ernsthaft beeinträchtigt wird, die weitere Verarbeitung zur Wahrung schutzwürdiger Interessen der weiteren in das Vorhaben eingeschlossenen Personen erforderlich ist oder zur Nachvollziehbarkeit der Exposition der in das Forschungsvorhaben eingeschlossenen Personen erforderlich ist (gemäß § 134 Abs. 5 der Strahlenschutzverordnung.

***Nutzung der Daten zu zukünftigen Forschungszwecken:** Ihre personenbezogenen Daten sollen über die Verwendung im Rahmen dieser Studie hinaus zum Zwecke der gemeinsamen Forschung auf dem Fachgebiet (Koronare Herzkrankheiten) auf einer gemeinsamen Datenbank pseudonymisiert aufbewahrt werden. Radiologische Bilddaten werden auf dem Bilddatenserver FPACS der Charité aufbewahrt, weitere erhobene Daten auf der elektronischen Studiendatenbank (eCRF) sowie der Health Data Plattform der Charité. Hierzu erfragen wir Ihre gesonderte Einwilligung (OPT IN). Sie können sich diesbezüglich jederzeit zu den aktuellen Verwendungen und Forschungspartnern über die folgende Seite informieren: www.dischargetrial.eu. Zugang zu den pseudonymisierten Daten hat nur, wer einen Antrag unter ausdrücklicher Darlegung des Zwecks und der Befugnis an das Verbreitungskomitee der DISCHARGE Studie gestellt hat und von diesem bewilligt worden ist.*

Neben der Speicherung auf der Health Data Plattform der Charité sollen die Bilddaten und klinischen Daten auch für sogenannte Challenges verwendet werden. Bei einer Challenge handelt es sich um den Wettbewerb verschiedener (möglicher Weise auch gewerblicher) Forschungsgruppe auf dem Fachgebiet (Radiologie, Koronare Herzkrankheit), die versuchen mit automatisierter Software die klinischen Fragestellung auf den radiologischen Bildern zu lösen. Die Daten werden dazu auf Webseiten der Studie (www.dischargetrial.eu) und für derartige Challenges (https://grand-challenge.org/challenges/) zum download Verfügung stellt. Hiermit sollen verschiedene klinische Fragestellungen wie die Erfassung von Organgrenzen auf Bilddaten, die Abgrenzung von gesunden und krankhaften Arealen, der Einstufung von Veränderungen in Krankheitsgruppen, die Messung von Bildwerten sowie die Vorhersage von für die Patienten relevanten klinischen Ereignissen im Verlauf. Es ist nicht vollständig auszuschließen, dass mit diesen Daten Patienten identifiziert werden können durch Ärzte, bei denen diese Patienten bereits in Behandlung waren. Ansonsten wird das Risiko für eine Identifizierung mit den Bilddaten und klinischen Daten durch das Löschen von patientenindividuellen und damit potenziell identifizierenden Merkmalen in den Daten bestmöglich reduziert.

Die Daten, die wir in der Datenbank für zukünftige Forschungszwecke aufbewahren, sollen für einen unbegrenzten Zeitraum aufbewahrt werden. Verantwortlich für die Datenbank ist der Studienleiter Prof. Dr. med. Marc Dewey. Rückfragen stellen Sie bitte über Ihr einschließendes Prüfzentrum, da nur dieses Ihre Identität feststellen kann. Das zuständige Prüfzentrum wird Ihre Anfrage pseudonymisiert an die Registerstelle weiterleiten und Ihnen die Antwort zukommen lassen. Da wir die Verwendung der Daten für noch nicht genau definierte Forschungszwecke planen, werden diese nicht in ein Drittland ohne Sicherstellung eines angemessenen Datenschutzniveaus garantieren.

Bitte beachten Sie, dass die Ergebnisse der Studie in der medizinischen Fachliteratur veröffentlicht werden können, wobei Ihre Identität jedoch nicht bekannt wird, weil wir die personenbeziehbaren Daten entfernen.

***Rechtsgrundlage:** Die Rechtsgrundlage zur Verarbeitung der Sie betreffenden personenbezogenen Daten bildet bei klinischen Studien Ihre freiwillige schriftliche Einwilligung gemäß DSGVO (siehe auch: die Deklaration von Helsinki (Erklärung des Weltärztebundes zu den ethischen Grundsätzen für die medizinische Forschung am Menschen) und -soweit zutreffend für die Studie- die Leitlinie für Gute Klinische Praxis).*
Bezüglich Ihrer Daten haben Sie folgende Rechte, die Sie gegenüber dem Verantwortlichen geltend machen können:
***Einwilligung:** Sie haben das Recht, ihre Einwilligung zur Verarbeitung personenbezogener Daten jederzeit zu widerrufen. Im Falle des Widerrufs müssen Ihre personenbezogenen Daten gelöscht werden (Artikel 17, Absatz 3 lit. c) DSGVO).*
***Recht auf Auskunft:** Sie haben das Recht auf Auskunft über die Sie betreffenden personenbezogenen Daten, die im Rahmen der klinischen Studie erhoben, verarbeitet oder ggf. an Dritte übermittelt werden (einschließlich einer kostenfreien Kopie).*
***Recht auf Berichtigung:** Sie haben das Recht, Sie betreffende unrichtige personenbezogene Daten berichtigen zu lassen (Artikel 16 DSGVO).*
***Recht auf Löschung:** Sie haben das Recht auf Löschung Sie betreffender personenbezogener Daten, z.B. wenn diese Daten für den Zweck, für den sie erhoben wurden, nicht länger benötigt werden (Artikel 17 DSGVO).*
***Recht auf Einschränkung der Verarbeitung:** Unter bestimmten Voraussetzungen haben Sie das Recht, eine Einschränkung der Verarbeitung zu verlangen, d.h. die Daten dürfen nur gespeichert, aber nicht verarbeitet werden. Dies müssen Sie beantragen (Artikel 18 DSGVO).*
***Recht auf Datenübertragbarkeit:** Sie haben das Recht, die Sie betreffenden personenbezogenen Daten, die Sie dem Verantwortlichen für die Studie bereitgestellt haben, zu erhalten. Damit können Sie beantragen, dass diese Daten (strukturiert und in einem gängigen Format auf einem tragbaren elektronischen Datenträger) entweder Ihnen oder einem anderen von Ihnen benannten (weiteren) Verantwortlichen für die Datenverarbeitung im Sinne der DSGVO übermittelt werden können (Artikel 20 DSGVO).*
***Widerspruchsrecht:** Sie haben das Recht, jederzeit gegen konkrete Entscheidungen oder Maßnahmen zur Verarbeitung der Sie betreffenden personenbezogenen Daten Widerspruch einzulegen. Eine Verarbeitung (neuer Daten) findet anschließend nicht mehr statt, es sei denn, die Verarbeitung ist gesetzlich weiterhin gefordert (z.B. wie im Arzneimittelgesetz, AMG) (Artikel 21 DSGVO).*
***Möchten Sie diese Rechte in Anspruch nehmen, wenden Sie sich bitte an** Ihren Prüfer oder an den Datenschutzbeauftragten Ihres Prüfzentrums.*
***Einschränkungen:** Wir möchten Sie an dieser Stelle darauf hinweisen, dass die aufgeführten Rechte eingeschränkt werden können, wenn diese Rechte die Verwirklichung der Forschungszwecke unmöglich machen oder ernsthaft beinträchtigen und die Beschränkung für die Erfüllung der Forschungszwecke notwendig ist – bezüglich des Rechts auf Löschen gilt (Artikel, 17 Absatz 3 DSGVO). Ihre Rechte auf Auskunft, Datenübertragbarkeit und Berichtigung fehlerhaft verarbeiteter Daten bestehen nicht, sofern die Auskunftserteilung einen unverhältnismäßigen Aufwand erfordern würde oder technisch*

unmöglich ist. Ob Ihre Rechte eingeschränkt werden können bedarf einer konkreten Abwägung.
Einwilligung zur Verarbeitung personenbezogener Daten und Recht auf Widerruf dieser *Sie haben das* ***Recht, Beschwerde bei einer Aufsichtsbehörde einzulegen****, wenn Sie der Ansicht sind, dass die Verarbeitung der Sie betreffenden personenbezogenen Daten gegen die DSGVO verstößt.*

Für die Datenverarbeitung verantwortliche Person:
Der Sponsor der Studie, das Institut für Radiologie, Charité, Charitéplatz 1, 10117 Berlin, vertreten durch den Studienleiter Prof. Dr. med. Marc Dewey, ist für die Datenverarbeitung verantwortlich.
Datenschutzbeauftragte/r des Prüfzentrums und Sponsors:
Behördliche Datenschutzbeauftragte der Charité
Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin
Telefon 030 450 580015 , E-Mail datenschutz@charite.de
Datenschutz-Aufsichtsbehörde des Prüfzentrums und Sponsors:
Die Berliner Beauftragte für Datenschutz und Informationsfreiheit
Friedrichstr. 219 , 10969 Berlin
Telefon 030 13889-0, E-Mail mailbox@datenschutz-berlin.de

6. Entstehen für Sie Kosten durch die Teilnahme an der Studie?

Ihnen entstehen durch die Studienteilnahme keine Kosten und es erfolgt keine Vergütung.

7. Wer entscheidet, ob Sie aus der Studie ausscheiden?

Unter gewissen Umständen könnte es möglich sein, dass der Studienarzt entscheidet, Ihre Teilnahme an der klinischen Studie vorzeitig zu beenden, ohne dass Sie auf die Entscheidung Einfluss haben. Die Gründe hierfür können z. B. sein, dass Ihre weitere Teilnahme an der klinischen Studie ärztlich nicht mehr vertretbar ist, oder die Studie frühzeitig beendet wird.

8. Sind Sie während der Studie versichert?

Für die Teilnehmer der Studie, die in den CT-Arm oder Herzkatheterarm randomisiert werden wurde bei der ECCLESIA eine Probandenversicherung abgeschlossen. Die Deckungssumme beträgt 500.000 Euro. Über die Betriebshaftpflichtversicherung des jeweiligen Klinikums besteht Versicherungsschutz im Falle von verschuldensabhängigen (durch das Klinikpersonal verursachten) Schäden für die gesamte Dauer der Studie. Dem Patienten obliegt die Mitteilung von möglichen strahlungsinduzierten Schäden an das Studienzentrum. Eine Vergütung (z.B. für verloren gegangenen Lohn oder für Schmerzen) in Folge einer Personenschädigung erfolgt nur wenn diese durch die Probandenversicherung abgedeckt ist.

9. Worauf müssen Sie noch achten?

Bitte beachten Sie, dass die Ergebnisse der Studie in der medizinischen Fachliteratur

veröffentlicht werden können, wobei Ihre Identität jedoch anonym bleibt. Sie müssen nicht an dieser Studie teilnehmen, um die reguläre medizinische Versorgung zu erhalten. Ihre Alternative zur Teilnahme an dieser Studie ist die reguläre medizinische Versorgung.

Während Ihrer Teilnahme bitten wir Sie, sich an die Anordnungen der Ärzte zu halten und Veränderungen des gesundheitlichen Wohlbefindens umgehend an diese zu übermitteln. Die Teilnahme an der Studie geschieht ausschließlich auf freiwilliger Basis. Im Falle Ihrer Zustimmung bitten wir Sie, die Einwilligung zu unterschreiben. Sie können Ihre Zustimmung ohne Begründung jederzeit zurückziehen. Eine Weigerung wird in keinem Fall Konsequenzen für die weitere Behandlung bzw. die Beziehung zu Ihrem Arzt haben. Sie werden selbstverständlich weiterhin nach bestem Wissen und Gewissen medizinisch versorgt werden. Wir erhoffen uns eine Verbesserung des zukünftigen diagnostischen und therapeutischen Behandlungsprozederes der koronaren Herzerkrankung.

10. An wen kann ich mich wenden, wenn ich weitere Fragen habe?

Gibt es Fragen Ihrerseits? Fragen zu diesem Aufklärungsbogen und zum Untersuchungsgang werden wir Ihnen jederzeit gern beantworten. Fragen, die besprochen wurden:

.....
.....

Bei Fragen steht Ihnen am Institut für Radiologie (Charitéplatz 1, 10117 Berlin) Ihr Studienarzt: Herr **Prof. Dr. med. M. Dewey** (Telefon: **030 450-627 353)**, bzw. die Studienzentrale (Telefon: **030 450-627 264**) zur Verfügung. Falls Sie keine weiteren Fragen haben lesen und unterzeichnen Sie bitte die beiliegende Einwilligungserklärung und fügen Sie das Datum Ihrer Einwilligung ein. Sie erhalten eine Kopie dieser Patienteninformation und der unterschriebenen Einwilligungserklärung ausgehändigt. Wir bedanken uns, dass Sie sich die Zeit genommen haben, diese Studie in Betracht zu ziehen.

Hiermit bestätige ich, dass ich diese Patienteninformation gelesen, verstanden und ein Exemplar erhalten habe.

Berlin (Datum)	(Unterschrift der Patientin / des Patienten

Einwilligungserklärung

Studientitel: "Diagnostische Bildgebungsstrategien bei Patienten mit stabilem Brustschmerz und mittlerem Risiko einer koronaren Herzerkrankung: Vergleichende Nutzenbewertung existierender Technologien (DISCHARGE)"

Bitte lesen Sie die Patienteninformation und die Einwilligungserklärung sorgfältig durch. Bitte fragen Sie bei allen Unklarheiten oder wenn Sie weitere Informationen wünschen.

Hiermit erkläre ich, Vorname: _____ Name: _____ Geburtsdatum: _____

dass ich durch _____ mündlich und schriftlich über Wesen, Bedeutung, Tragweite und Risiken der wissenschaftlichen Untersuchung im Rahmen der Studie DISCHARGE, die vom Institut für Radiologie und Kardiologie der Charité durchgeführt wird, informiert wurde und ausreichend Gelegenheit hatte, Fragen hierzu in einem Gespräch mit dem Studienarzt zu klären. Ich weiß, dass meine Teilnahme an der Studie freiwillig ist und dass ich diese Einwilligung jederzeit ohne Angabe von Gründen widerrufen kann, ohne dass mir Nachteile entstehen.

Ich habe verstanden, dass ich nicht an der Studie teilnehmen kann, falls der Studienarzt keine mittlere Prätestwahrscheinlichkeit von 10% bis 60% für eine KHK bei mir feststellt. Ich bin mit bewusst, das in diesem Fall, wie geplant, eine Herzkatheteruntersuchung bei mir durchgeführt wird, dessen Ergebnisse und Kopien von, in diesem Zusammenhang relevanten, medizinischen Dokumenten durch das Studienteam bei meinem behandelnden Arzt erfragt und mit den von mir erteilten Daten (z.B. Fragebogen zur Lebensqualität) dokumentiert werden. Ich bin mir bewusst, das keine Nachbeobachtung bei mir stattfindet, da ich nicht an der Studie teilnehmen kann.

Soweit der Studienarzt bei mir eine mittlere Prätestwahrscheinlichkeit von 10% - 60% für eine KHK feststellt erkläre ich mich bereit, an der Studie zum Vergleich von Computertomografie (CT) mit der Herzkatheteruntersuchung teilzunehmen. Ich bin mir bewusst, dass die Entscheidung, ob der Behandlungspfad dann auf der CT bzw. der Herzkatheteruntersuchung beruht, allein nach einem Zufallsverfahren getroffen wird, und dass ich eine 50:50 Chance habe, dem einen oder anderen Behandlungspfad zugeteilt zu werden. Ich erkläre mein Einverständnis, dass meine behandelnden Ärzte die genaue Diagnose und die weitere medizinische Entwicklung in der Nachbeobachtungsphase der Studie an die Studienzentrale (Charité, Berlin) übermitteln und Kopien von, in diesem Zusammenhang relevanten, medizinischen Dokumenten aushändigen dürfen. Für die Nachbeobachtung und zum Einholen eventuell fehlender Informationen (z.B. durch Umzug) entbinde ich meine Angehörigen ersten Grades, meinen behandelnden Hausarzt/Kardiologen sowie meine Krankenkasse und alle entsprechenden Behörden und Ämter (z.B. Meldeamt, Bezirksamt, Gesundheitsamt, statistisches Landesamt) inklusive hier eingebundener Ärzte von der

Schweigepflicht bezüglich der Studien relevanten Daten. Mit der Anwendung von Röntgenstrahlen an meiner Person bin ich einverstanden. Ich erkläre ausdrücklich mein Einverständnis an der Mitteilung meiner Teilnahme und der durch die Anwendung erhaltenen Strahlenexposition an die zuständige Bundesbehörde. Die zuständige Bundesbehörde (Bundesamt für Strahlenschutz) kann Einsicht in persönliche Daten nehmen, soweit es die Teilnahme an der Studie und die dabei aufgetretene Strahlenexposition betrifft. Das Einverständnis zur Mitteilung der erhaltenen Strahlenexposition ist unwiderruflich. Medizinische Daten sind davon nicht betroffen. Ich bin darüber informiert, dass eine Kopie dieser Erklärung in den Akten entsprechend den gesetzlichen Vorschriften der Vertraulichkeit aufbewahrt wird und stimme dem ausdrücklich zu.

Ich erkläre mich damit einverstanden, dass das Studienteam meine personenbezogenen Daten (z.B. Name, Geburtsdatum) zum Zweck der o.g. Studie erheben, verarbeiten und nutzen darf. Ich erkläre mich weiterhin damit einverstanden, dass meine erhobenen Daten in weiteren Studien verarbeitet und genutzt werden dürfen, wenn auf dem Forschungsgebiet der koronaren Herzkrankheit neue Erkenntnisse vorliegen, wie neue Bildmarker.
Ich wurde anhand des Informationsblattes ausführlich und verständlich darüber aufgeklärt, dass meine in der Studie erhobenen Daten, insbesondere Angaben über meine Gesundheit, sowie radiolgische Bilddaten zu den in dem Informationsblatt zur Studie beschriebenen Zwecken erhoben und in pseudonymisierter Form elektronisch gespeichert und ausgewertet werden.

Mir ist bekannt, dass ich von der Studienleitung jederzeit Auskunft, Berichtigung und Löschung meiner Daten/Proben verlangen kann und Beschwerde bei einer Datenschutzbehörde einlegen. Hierzu wende ich mich an den Studienleiter/in, der/die allein meine Daten re-identifizieren kann. Insbesondere auch einer (Teil-) Anonymisierung meiner personenbezogenen Daten zum Zwecke der Veröffentlichung oder Weitergabe an Kooperationspartner stimme ich zu. Mir ist bewusst, dass das Anonymisieren dazu führen kann, dass eine Rückverfolgung der Datenverarbeitung ausgeschlossen ist, so dass dann meine Rechte auf Auskunft, Berichtigung oder Löschung nicht mehr durchgesetzt werden können.

§ 134 Abs. 5 Strahlenschutzverordnung: Ich wurde darüber aufgeklärt, im Falle eines Widerrufs der Teilnahmeerklärung keine Auswirkungen auf die vor dem Widerruf durchgeführte Verarbeitung und auch keine Auswirkungen, soweit die Verwirklichung der Forschungszwecke unmöglich gemacht oder ernsthaft beeinträchtigt wird, die weitere Verarbeitung zur Wahrung schutzwürdiger Interessen der weiteren in das Vorhaben eingeschlossenen Personen erforderlich ist oder zur Nachvollziehbarkeit der Exposition der in das Forschungsvorhaben eingeschlossenen Personen erforderlich ist.

Ich bin einverstanden, dass meine Daten in pseudonymisierter Form übermittelt werden an:
a) die zuständige Überwachungsbehörde (hier: Bundesamt für Strahlenschutz, Salzgitter) zur Überprüfung der ordnungsgemäßen Durchführung der Studie, zur Bewertung von Studienergebnissen und unerwünschter Ereignisse;
b) einen Datenhoster zur Speicherung der Bilddaten (AG Mednet AGMednet, Inc.,2 Atlantic Avenue, Boston, Massachusetts 02110, phone: 855-246-3363). Mir ist bekannt, dass Bilddaten grundsätzlich nicht anonym sind also ein Personenbezug herstellbar ist und dass der Hoster seinen Sitz in einem Land hat, in dem kein angemessenes, der DSGVO vergleichbares Datenschutzniveau besteht.Trotzdem stimme ich der Datenverarbeitung zu.

Ich habe die mir vorgelegte Patienteninformation mit Datum vom 30.01.2020 verstanden und eine Ausfertigung derselben und dieser Einwilligungserklärung erhalten.

_____ _____

Berlin (Datum) (Unterschrift der Patientin / des Patienten)

Ich habe den Patienten über Wesen, Bedeutung, Tragweite und Risiken der o.g. Studie mündlich und schriftlich aufgeklärt.

Berlin (Datum) (Unterschrift des Studienarztes)

2. Patient Information Pilot Study

Participant Information

Purpose of the study
You are being asked to participate in a research study. The purpose of the study is to assess the quality of life in patients with stable angina/chest pain. Quality of life is about how you perceive your health, your ability of pursuing everyday activities and your well-being. In this study we compare different questionnaires of quality of life in 18 European countries. We want to know how long it takes participants to complete these questionnaires and whether there are differences between countries. The study is funded by the European Union.

Description of the research
You will receive a short questionnaire about how you perceive your health. Additionally the study personnel will ask you some questions about your symptoms and medical status. The diagnostic procedure and its result will be documented. Independently we may document the estimated costs of your hospitalisation.

Potential risks and discomfort
You may feel some anxiety and stress while answering questions during the study.

Voluntary participation
Participation in this study is voluntary. If you decide not to participate, this will not affect your ability to receive medical care at the hospital or to receive any benefits to which you are otherwise entitled. You may discontinue participation during the study at any time without penalty or loss of benefits to which you are otherwise entitled.

Contact person
If you have any questions, please contact:

Contact address: to be completed
Thank you for your participation.
Write signature page if necessary

3. Patient Informed Consent – Cognitive Interviews

This form is only available in German, since it the study is only being performed at Charité.
Other clinical centers can conduct the study upon request and would need to translate the informed consent form into local language.

Studientitel: Pilotstudie - Quality of Life

Sehr geehrte Patientin, sehr geehrter Patient,

hiermit bieten wir Ihnen die Teilnahme an einer wissenschaftlichen Studie an! Sollten Sie sich entschließen an der Studie teilzunehmen, helfen Sie uns die Erfassung der gesundheitsbezogenen Lebensqualität von Patienten mit Brustschmerz zu verbessern. Diese Studie wird von der Charité in Berlin koordiniert. Sponsor ist das Institut für Radiologie der Charité - Universitätsmedizin Berlin.

Ziel der Studie

Gegenstand der Studie ist die Erfassung der gesundheitsbezogenen Lebensqualität bei Patienten mit Brustschmerz. Lebensqualität beinhaltet verschiedene Aspekte: Es geht darum wie Sie Ihre Gesundheit einschätzen, wie gut Sie Ihren üblichen Tätigkeiten im Alltag nachgehen können und wie ihr psychisches Wohlbefinden ist. Wir vergleichen in dieser Studie Fragebögen zur Lebensqualität, in 18 europäischen Ländern. Insgesamt werden in 23 klinischen Zentren jeweils 60 Patienten den Fragebogen ausfüllen und zu diesem befragt. Ziel der Studie ist es herauszufinden, wie lange das Ausfüllen dieser Fragebögen dauert und inwieweit dieser verbessert werden kann, damit der Fragebogen in einer validierten Form in einer späteren Studie genutzt werden kann.

Ablauf der Studie

Sie erhalten einen Fragebogen zum Ausfüllen. Während Sie den Fragebogen ausfüllen, werden Sie von dem Studienmitarbeiter gebeten Ihre Meinung und Ihre Probleme bei den einzelnen Fragen zu formulieren. Im Anschluss wird Ihnen der Studienmitarbeiter einige Fragen zur Einschätzung Ihres Brustschmerzes stellen. Die Gespräche werden dabei mit einem digitalen Aufnahmegerät aufgenommen. Nach dem Interview wird der Studienmitarbeiter bei ihrem behandelnden Arzt dokumentieren welche diagnostische Prozedur Sie im Rahmen Ihrer klinischen Versorgung erhalten werden oder bereits erhalten haben (entweder eine Computertomographie oder Koronarangiografie) sowie den klinischen

Schweregrad ihres Brustschmerzes. Hier bitten wir sie die Beteiligten von der ärztlichen Schweigepflicht zu befreien. Die Fragebögen und Tonaufzeichnungen der Interviews werden im Nachgang ausgewertet um den Fragebogen für eine spätere Studie zu verbessern.

Dauer der Teilnahme

Das Ausfüllen des Fragebogens und das Interview mit dem/der Studienmitarbeiter/in dauern ca. eine Stunde.

Mögliche Risiken

Risiken durch das Ausfüllen der Fragebogen oder die Teilnahme an dem Interview sind nicht bekannt.

Datenschutz

Durch Ihre Unterschrift auf der Einwilligungserklärung erklären Sie sich damit einverstanden, dass das Studienteam unter Berücksichtigung der geltenden Datenschutzgesetze Ihre personenbezogenen Daten (z.B. Name, Geburtsdatum) zum Zweck der o.g. Studie erheben, verarbeiten und nutzen dürfen. Die verantwortliche Stelle und Sponsor der Studie ist die Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin. Ihre Daten (Ausgefüllter Fragebogen, Tonaufzeichnung des Interviews, erhobene Daten von ihrem behandelnden Arzt) werden zum Zweck der Verbesserung des Fragebogens zur gesundheitsbezogenen Lebensqualität erhoben und in der Studienzentrale (Institut für Radiologie) gespeichert. Ihre Daten werden dabei in pseudonymisierter Form (d.h. es kann keine Verbindung zwischen ihren Daten und ihrer Person hergestellt werden) verarbeitet und genutzt. Hierzu versieht die Studienleitung die Daten mit einem Teilnehmercode (Pseudonymisierung). Nur der Studienleiter und von diesem autorisierte Mitarbeiter haben Zugriff auf diese Codenummer. Aus der Tonaufzeichnung werden nach der Auswertung des Interviews alle personenbezogenen Begriffe (z.B. Person- oder Ortsnamen, Adressen) gelöscht. Dann werden die Tonaufnahmen auf einem externen Datenträger in der Studienzentrale gespeichert. Die personenbezogenen Daten auf der Einwilligungserklärung verbleiben im Original beim Studienleiter. Eine Übermittlung ihrer Daten an Dritte findet nicht statt. Alle erteilten Daten inklusive der Tonaufzeichnungen werden für einen Zeitraum von 10 Jahren aufbewahrt und danach vernichtet. Bitte beachten Sie, dass die Ergebnisse der Studie in der medizinischen Fachliteratur veröffentlicht werden können, wobei Ihre Identität jedoch anonym bleibt. Sie haben ein Recht auf Auskunft, Berichtigung, Sperrung oder Löschung über die von ihnen gespeicherten Daten. Bitte wenden Sie sich dafür an das Studienteam.

Sie können ihre Einwilligungserklärung jederzeit ohne Angabe eines Grundes widerrufen. In diesem Fall werden ihre Daten gelöscht oder sofern gesetzliche oder vertragliche Aufbewahrungsfristen entgegenstehen gesperrt und nach Ablauf des Aufbewahrungszeitraumes gelöscht.

Freiwilligkeit der Teilnahme

Ihre Teilnahme an dieser Studie ist freiwillig. Sie können jederzeit ohne Nennung von Gründen und ohne Nachteile für Ihre derzeitige oder künftige medizinische Behandlung Ihre Teilnahme abbrechen.

Versicherung

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An wen kann ich mich wenden, wenn ich weitere Fragen habe?

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_____ _____

Berlin (Datum) (Unterschrift des Studienleiters)

Summary of changes – Study Protocol

Revision Chronology:

Version Date	Version Number	Adjustments
05 Aug 2013	Version 1.0	For ethical approval in the format of the European Union grant proposal.
	Internal Draft Versions 1.1-1.5	Draft version 1.1: Format adjusted according to SPIRIT/WHO. Patient informed consent (dated 9 October 2014) was approved by Charité ethics committee. Draft Version 1.2: Overall revision and addition of major clinical aspects. Draft Version 1.3: Incorporation of recommendations from ECRIN, updated participating clinical sites and outreach activities, completed SPIRIT and WHO check list items, included Measurement section, shifted and shortened text from Safety section. Draft Version 1.4: Added more details to Statistical sections to show that the interim analysis does not produce bias, also added secondary/other outcomes list. Draft Version 1.5: Draft Version 1.4 was slightly revised for consistency and clear phrasing before recruitment.
01 Apr 2016	Version 1.6.*	Slight revision of Draft Version 1.5, from before the start of recruitment, for further clarification, e.g., consistent phrasing.
15 Jan 2019	Version 1.7	Adjustments were made in section 4.2.2 on classification of procedural complications according to the NCDR®CathPCI Registry®v4.4 Coder´s Data Dictionary and on the timeframe for major and minor adverse cardiovascular events. Recording of project management change from Adriane Napp to Maria Bosserdt and Melanie Estrella on Feb. 1, 2018 as well as other personnel changes.
09 Nov 2020	Version 1.8	Adjustments were made in section 2.6.3 regarding addition of team members, Peter Martus and Konrad Neumann, as well as for the interim analysis in section 6.5.2.

*This version of the Study Protocol was inserted in this Protocol Appendix as the initial version as it was formatted according to SPIRIT/WHO and thus more easily comparable to the final version 1.8.

STATISTICAL ANALYSIS PLAN

Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies

The "DISCHARGE" Study

A pragmatic randomized controlled trial (PRCT) evaluating the superiority of CT over ICA concerning effectiveness in stable chest pain patients with intermediate pretest probability of coronary artery disease

Charité – Universitätsmedizin Berlin

Table of Contents

Abbreviations

AE	Adverse Event
ACC	American College of Cardiology
AHA	American Heart Association
ASA	American Stroke Association
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society Angina Grading Scale
COME-CCT	Collaborative Meta-analysis of cardiac CT
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed Tomography
CTA	CT Angiography
DISCHARGE	Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
ESC	European Society of Cardiology
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
ICA	Invasive Coronary Angiography

ICH	International Conference on Harmonization
ITT	Intention-to-Treat
KKS Charité	Coordinating Center of Clinical Studies at Charité
LM	Left Main Coronary Artery
LV	Left Ventricle
MACE	Major Adverse Cardiovascular Event
MCS	Mental Component Summary
MI	Myocardial Infarction
MICE	Minor Adverse Cardiovascular Event
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association (Functional Classification)
PCI	Percutaneous Coronary Intervention
PCS	Physical Component Summary
PET	Positron Emission Tomography
PP	Per-Protocol
PRCT	Pragmatic Randomized Controlled Trial
QoL	Quality of Life
RE	Emotional health-related role limitations (Role-Emotional)
RP	Physical health-related role limitations (Role-Physical)
SAE	Serious Adverse Event
SD	Standard Deviation
SF-12v2	Quality of Life Questionnaire Short Form 12 Version 2
SPECT	Single Photon Emission Computed Tomography
VAS	Visual Analogue Scale
VD	Vessel Disease
WHF	World Heart Foundation

Signature page

In signing this page, I am confirming that I have reviewed and approve this analysis plan.

Prof. Peter Schlattmann

(Planning statistician) Date

digital unterschrieben von peter schlattmann
DN: cn=peter schlattmann, o=uniwestfälischklinikum ams, ou=ams,
email=peter.schlattmann@med.uni-jena.de, c=de
Datum: 2020.11.06 13:03:03 +01'00'

Prof. Peter Martus

(Conduct of main outcomes statistical analysis) Date

Nov 6 2020

Dr. Konrad Neumann

(Conduct of patient reported outcomes statistical analysis) Date

Nov 6 2020

Prof. Marc Dewey

(PI of the DISCHARGE trial) Date

Marc Dewey Digital unterschrieben von Marc Dewey
Datum: 2020.11.06 18:42:02 +01'00'

1 Background

Coronary artery disease (CAD) is the leading cause of death in high-income countries. Invasive coronary angiography (ICA) is the reference standard for the diagnosis of CAD and allows immediate interventional therapy. Coronary computed tomography (CT) is the most accurate diagnostic test for CAD currently available.

The primary hypothesis of the DISCHARGE trial is that CT is superior to ICA for major adverse cardiovascular events after 2nd follow-up in a broad population of stable chest pain patients with intermediate pretest probability (10-60%) of CAD. This will be assessed using a pragmatic randomized controlled design in order to generate practical and usable outcomes for clinical decision-making according to comparative effectiveness research methodology.

2 Study Objectives

2.1 Primary Objective

The primary objective of this trial is to evaluate the comparative effectiveness of CT and ICA in patients with stable chest pain and intermediate pretest probability (10-60%) of coronary artery disease. The superiority hypothesis of CT over ICA is evaluated based on MACE (MACE = Major Adverse Cardiovascular Events; as defined in chapter 11.1, time frame: 1 minute after randomization to CT/ICA diagnosis/procedure and until the 2nd follow-up, 24-56 months) as the primary end point. Primary outcome measures as well as secondary outcome measures, which were prespecified before the start of the trial are listed at https://clinicaltrials.gov/ct2/show/NCT02400229. The analysis plan for the primary outcome is shown in Table 1 in Chapter 3.2 and a description of the primary end point is shown in Table 2 in Chapter 7.1.

2.2 Secondary Objectives

Secondary objectives of the DISCHARGE trial were prespecified before the start of the trial at https://clinicaltrials.gov/ct2/show/NCT02400229. These secondary objectives are identified using numbers in parentheses in this chapter and Tables 3-17. A description and how these secondary objectives are operationalized can be found in chapter 7.1 and 7.2.

Secondary objectives of the DISCHARGE trial as specified in the study protocol will be:

1. to evaluate the occurrence of MACE in individual composites according to specified secondary objectives defined before the start of the DISCHARGE trial (# of

secondary objectives on NCT 02400229: 126, 127)* as well as MACE in subgroups (24, 25, 116, 125) as well as subgroups defined by quintiles of pretest probability of CAD (Table 2)

2. to compare the CT and ICA group with respect to MICE (MICE = Minor Adverse Cardiovascular Event; as defined in chapter 11.2, time frame: 1 minute after randomization to CT/ICA diagnosis/procedure and until the 2nd follow-up) (7)
3. to identify and document major and minor procedural complications as defined in study protocol section 4.2.2 (time frame: occur during the procedure or within 48 hours post last related index procedure; relevant procedures are CT, ICA, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and functional tests) (28-37
4. to evaluate the influence of CT and ICA on angina pectoris (26)
5. to evaluate and to compare incidental findings in CT and ICA group and potential benefits and harms of findings (38, 39, 40, 41, 42, 43)
6. to evaluate patient's acceptance/preference of CT and ICA (85, 86)
7. to assess radiation exposure of CT and ICA (87, 88)
8. to estimate and to compare cost-effectiveness of CT and ICA (98, 99, 100, 101, 102, 103, 104, 110, 111)
9. to evaluate and compare Health-Related Quality of Life (HRQoL, secondary outcome and predictor), socioeconomic status (working condition as predictor and outcome), and lifestyle in the CT and ICA group (outcome and predictor) (17, 39, 113, 115, 118)
10. to assess and to determine gender differences (28, 29, 31, 33, 34, 35, 36, 116, 117, 119, 120, 121, 122, 123, 124)

Numbers in parentheses correspond to the number of prespecified secondary objectives defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229. Further details of these secondary end points are shown in Tables 3-17.

3 Study Design

3.1 Overview

This study is a European multicenter prospective pragmatic randomized controlled trial (PRCT) in patients with suspected CAD. The pragmatic approach of the study addresses practical questions about the risks, benefits, and costs of a CT- and ICA-directed strategy as they would occur in everyday clinical practice.[1]

CT directed clinical management will constitute the intervention group and ICA directed clinical

management will be the control group. Thus, a 2-group randomized approach is utilized. Planned ICA will be recommended for patients in the CT group if indicated by positive CT results. Thus, both strategies might be labelled as “ICA first” vs. “CT first followed by ICA if indicated”. Blinding patients towards the diagnostic tests - CT or ICA - is not possible. A blinded analysis of all outcomes will be performed as described in the study protocol section 10.5.

3.2 Sample Size

To show superiority of CT versus ICA with respect to MACE, a sample size of approximately 3546 men and women aged 30 years or older with suspected CAD and scheduled to undergo invasive coronary angiography will be needed.

For sample size calculation a power of at least 80% and a 0.05 two-sided level of significance is assumed. The primary endpoint will be the MACE incidence until the 2nd follow-up. For this time to event data an exponential survival distribution is assumed with corresponding exponential parameter λ in each of the two groups. For the CT group we expect an exponential parameter of λ_1=0.00803 (corresponding to a one year MACE incidence equal to 0.8%, based on Noto TJ et al. [2], Boden WE et al. [3], Hulten EA et al. [4], Serruys PW et al. [5]) and for the ICA group an exponential parameter of λ_2=0.0141 (corresponding to a one-year MACE incidence equal to 1.4%, based on Noto TJ et al.[2], Boden WE et al.[3], Serruys PW et al.[5], Lichtlen PR et al.[6], Papanicolaou MN et al.[7]) yielding a constant hazard ratio of 0.5695. When the sample size in each group is 1773, with a total number of major adverse cardiovascular events required, E, of 99, an exponential maximum likelihood test of equality of survival curves will have the desired power of 80% to detect the difference between the exponential parameter of the CT group and the ICA group. Thus in total 3546 patients have to be allocated.

Furthermore, this initial sample size calculation assumed an accrual period of 2 years, a minimum and maximum 2nd follow-up time of 2 and 4 years, respectively. Conservatively, a common exponential drop-out rate of 0.0513 (5% per year) was assumed. The accrual period was extended, after review and approval of the European Commission, from the planned 2 years to 3.5 years to enable recruitment of the planned patient number. Thus, the 2nd follow-up times were updated and will now range between 24 and 56 months.

In order to perform one interim analysis, a group sequential design with O’Brien-Fleming spending function for time-to-event outcome with sample size 3546 will be used. The analysis plan below (see Table 1) shows the number of events E required at each analysis. Publication of the interim MACE analysis will be allowed if all patients have been recruited and undergone the diagnostic strategies. A symmetric two-sided group sequential design with 80 % power and

2.5 % one-sided type I error leads to:

Table 1: Analysis plan for group sequential design with O'Brien-Fleming spending function

Analysis	E(vents)	Z	Nominal p	Spend
Interim	50	2.80	0.0028	0.0026
Final	100	1.98	0.0240	0.0224
Total				0.0250

(E – number of events required at each analysis; Z – standard normal test-statistic; p – one-sided p-value for Z; Spend - Incremental error spending at each given analysis)

In the case of the interim analysis, the two-sided level of significance for the final analysis of the primary endpoint at the 2nd follow-up is set at 0.048.

Sample size estimation was performed using nQuery 7.0 and the R package *gsDesign* for group sequential design to perform an interim analysis was used. For precise recalculation of 2nd follow-up times after extension of the accrual period from 2.0 to 3.5 years with approval by the European Commission, we performed a simulation written in the statistical computer language R with N=1,000,000 runs.

3.3 Inclusion/Exclusion Criteria

Due to the pragmatic approach (Thorpe KE [8]) of the DISCHARGE trial, only minimal inclusion and exclusion criteria are used for study population identification.

3.3.1 Inclusion Criteria

- Patients with suspected coronary artery disease with stable chest pain and intermediate pretest probability (10-60%) of CAD referred for invasive coronary angiography.

  "Stable chest pain" is defined as **not**
  - being acute (= first appearance within the last 48 hours) or unstable angina pectoris =
    - (a) first appearance with Canadian Cardiovascular Society Angina Grading Scale Class (CCS) 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)
- Patients of at least 30 years of age
- Written informed consent

The pretest probability 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 the probability of CAD. It was developed on the basis of the results of the COME-CCT project ("Collaborative Meta-analysis of Cardiac CT"; www.coronaryrisk.org, by Haase R et al. [9]).

3.3.2 Exclusion Criteria

- Patients who are or were on hemodialysis
- No sinus rhythm
- Pregnancy
- Any medical condition that leads to the concern that participation is not in the best interest of health (e.g., extensive comorbidities)
- Participation in any other interventional/ randomized study

4 Study Scheme

The first-patient in will be in the first month of the PRCT and the last-patient out will be at the end of month 66 of the PRCT (overall duration: 5.5 years).

The patient's timeline and time points where data will be collected can be taken from the following graphical presentation in Figure 1.

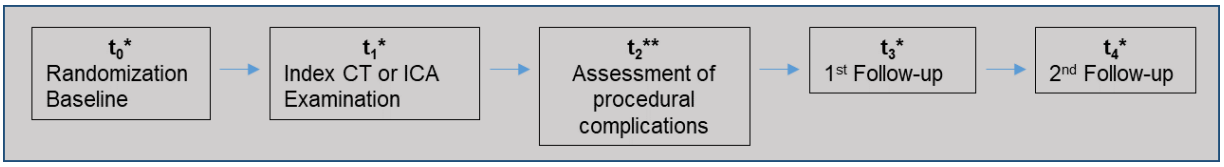

Figure 1: Timeline of the study

*Time frame for MACE/ MICE: from randomization (t_0) to CT/ICA diagnosis/procedure (t_1), follow-up for procedural complications (t_2) and during long-term follow-up until t_3 and t_4. The 1st follow-up (t_3) will be conducted after 1 year and the 2nd follow-up (t_4) will be conducted after 24 to 56 months.

**Time frame for procedural complications (t_2): Occur during the procedure or within 48 hours after the last procedure in the related patient management path following the initial index tests (CT or ICA), i.e. CT, ICA, ischemia test, PCI, and CABG.

5 Study Centers

26 clinical sites (hospitals and heart centers) in 16 European countries (Austria, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Spain, United Kingdom) consented for trial participation.

6 Assurance of Data Quality

The European Clinical Research Infrastructure Network (ECRIN) was responsible for the coordination of clinical monitors visiting the clinical sites (except Germany, which was coordinated by KKS Charité) to ensure adherence to protocol and compliance with ICH-GCP. On-site clinical monitoring was performed by ECRIN according to the monitoring plan in the study protocol and remote monitoring was performed by the coordinating center. The clinical data management team of the Coordinating Center of Clinical Studies at Charité (KKS Charité) was responsible for electronic data recording and preparation. Within the clinical monitoring process (done centrally and on-site) data were checked and proofed concerning consistency, completeness, range and plausibility. Unusual distribution of data within and between clinical sites were detected, checked and queried by project management.

7 Outcomes and Study Variables

This section defines the specific measurement variable, measurement scale, method of aggregation and time point for primary (7.1) and secondary (7.2) end points that will be compared between the CT and ICA group. In section 7.3 pre-planned analyses of other objectives are summarized along with the study variables, if appropriate. The outcomes will be evaluated by the respective work packages which are denoted.

7.1 Primary End Point

The primary outcome measure is the occurrence of MACE which is a composite endpoint that will comprise at least one of the following entities:

- Cardiovascular death
- Nonfatal myocardial infarction
- Nonfatal stroke

In detail, the primary outcome is defined during the time frame 1 minute after randomization to CT or ICA until the first occurrence of any MACE-event up to the 2nd follow-up (t_4).

Table 2: Major adverse cardiovascular events*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
MACE (composite = primary endpoint) and single components				**WP 11**				
1	Occurrence of - Cardiovascular death† - Nonfatal myocardial infarction †† - Nonfatal stroke††† †According to Definitions for Cardiovascular Endpoint Events in Clinical Trials by Hicks et al. [10] ††According to the Third Universal Definition of Myocardial Infarction by Thygesen et al. [11] †††According to Updated Definition of Stroke for the 21st Century by Sacco et al. [12]	Rate	Time-to-event	x	x	x	x	x
Explorative subgroup analyses: - *Quintiles of pretest probability** - *Age (under 45, 45-65, over 65 years) (24) (125)* - *Gender (male versus female) (116)* - *Body Mass Index (BMI) (under 25, 25-30, over 30) (25) (125)* - *Smoking status (never, former, current)** - *Angina type groups (125)* - *CT plaque characteristic groups: high risk versus other plaques versus no plaques (125)* *Different composites of MACE definitions to be analyzed as secondary end points including competing risk analysis:* - *Composite endpoint: definition of MACE as* o *a) vascular death or Myocardial Infarction (MI) (126)* o *b) cardiac death or MI (126)* o *c) Nonfatal myocardial infarction or nonfatal stroke or cardiovascular death or major procedural complications (as defined in study protocol section 4.2.2) or transient ischemic attack** - *Occurrence of myocardial infarction (procedural and non-procedural) and stroke (127)* - *Occurrence of myocardial infarction based on a secondary definition of nonfatal myocardial infarction according to the Fourth Universal Definition of Myocardial Infarction* [13]							

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

7.2 Secondary End Points

For each of these secondary end points, not only a 2-sided significance test is applied but also the 95% confidence interval of the difference, hazard or odds ratios will be given for the comparison of the two groups. Each subgroup analysis will be accompanied by a statistical test of interaction between study group and subgroup factor.

7.2.1 Main Secondary End Points

Table 3: Minor cardiovascular events*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
MICE (composite) and single components				**WP 11**				
2	Occurrence of - coronary revascularization following new, non-index related ICA in a later management path (7) - peripheral artery revascularization (7) - hospitalization for chest pain/ discomfort (7) - emergency department visit for chest pain/ discomfort (7) - transient ischemic attack (7) - congestive heart failure (7)	Rate	Time-to-event	x	x	x	x	x
Explorative subgroup analyses according to MICE: - *Quintiles of pretest probability** - *Age (under 45, 45-65, over 65 years) (24)* - *Gender (male versus female) (116)* - *Body Mass Index (BMI) (under 25, 25-30, over 30) (25)*								

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 4: Procedural Complications*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Procedural Complications				**WP 11**				
Major Complications: Any (composite) and single components								
3	• Occurrence of major procedural complications as defined in study protocol section 4.2.2 (death, nonfatal myocardial infarction, nonfatal stroke, further complications prolonging hospitalization by at least 24 hours, dissection (coronary, aorta) (35), cardiogenic shock (37), cardiac tamponade (37), retroperitoneal bleeding (37), cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation) (35), cardiac arrest) - Also occurrence of adverse events due to medication (28) - Occurrence of adverse events related to venous or arterial puncture (29) - Association of experience of examiners on events, duration of the exams, contrast agent amount used for diagnosis and intervention and exposure of radiation. (33)	Proportion	Nominal		x	x	x	
Minor Complications: Any (composite) and single components								
4	• Occurrence of minor procedural complications as defined in study protocol section 4.2.2 (hematoma at the puncture site (29), secondary bleeding at the puncture site (29), bradycardia, angina without infarction (36), allergoid contrast agent reaction (28), stent migration (36), hypotension requiring treatment (28), headache (28), hyperthyroidism (28), skin tissue and nerve injuries (29), extravasate (29), contrast-induced nephropathy (CIN) (31), infections (32), femoral arterial	Proportion	Nominal		x	x	x	

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	occlusion (or arterial access vessel) or dissection (35), new requirement for dialysis (37), DVT/pulmonary embolism (37), closure or injury of vessels (35), injury of the heart (e.g. valve or myocardium) (35), perforation (37), gastrointestinal bleeding (37), genital-urinary bleeding (37), other major bleeding (37), red blood cell (RBC)/Whole blood transfusion (37), twisting or rupture of the catheter parts (35), other equipment mishaps (e.g. retained foreign body guidewire fracture) (37), development of arterio-venous fistula(s) (35), development of pseudo aneurysm at puncture site (35), dissection (except coronary dissection) (35), permanent edema (e.g. due to lymphatic congestion at puncture site) (35), embolization of central or peripheral vessels due to thromboembolism (35), acute closure of coronary vessels (36), stent infection, heart failure (37), wrong patient or wrong procedure (37), other (37)) - Also occurrence of adverse events due to medication (28) - Contrast induced nephropathy (31) - occurrence of adverse events related to venous or arterial puncture (29) - Influence of experience of examiners on events (33)							
Explorative subgroup analyses as defined for MACE in Table 2 *Additional analysis: Major and minor complications of ICA procedure in the CT and ICA group*								

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 4.1: Procedural complications, findings, and characteristics of procedures*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Characteristics of diagnostic procedures, findings, recommendations and management of patients after CT or ICA				**WP 11**				
5	Stenosis (no stenosis, <20%, 20 to 50%, >50%, number of stenoses, most severe stenosis per patient) in both groups as well as agreement in diagnostic findings (kappa) and management between CT and ICA in patients receiving both*	Proportion	Ordinal		x	x	x	
6	Non-diagnostic segments (number, location): comparison of prevalence and patient as well as technical factors, binary in marginal analyses, GEE, leading to such uninterpretable findings or exams (46)	Proportion	Ordinal		x	x	x	x
7	Obstructive CAD (one vessel, two vessels, three vessels or Left Main disease)* Extent of CAD (Segment involvement score, Segment stenosis score, high-risk anatomy and non-high risk anatomy) and also extent of CAD in dependence of patients' socioeconomic status (income, education, occupation, job situation, gender) (19) Accuracy and agreement of automated analysis systems (56)	Proportion Mean Accuracy	Nominal Metric Percent		x	x	x	x
8	Composite outcome: Rate of coronary artery anomalies (benign and malignant) and rate of myocardial bridging seen on CTA and ICA and the clinical implications of these at follow-up as well as influence on Major Adverse Cardiovascular Events (MACE) and MICE (10) Prevalence of sinus node artery being a side branch of Left Coronary Artery (LCX) or Right Coronary Artery RCA by core lab reading and the risk of CAD on CT and ICA	Proportion	Nominal		x	x	x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	as well as MICE and MACE (48) Prevalence of left, intermediate, and right coronary distribution type by core lab and site reading and the risk of CAD (as significant) on CT and ICA at baseline and MICE and MACE (49)							
9	Performing Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG) in a management path related to the index test (CT or ICA) (8, 12, 15, 16) - Completeness of revascularization for Percutaneous Coronary Intervention single vessel vs multivessel Percutaneous Coronary Intervention and Coronary Artery Bypass Graft; stent use (bare metal vs drug eluting) (22) - Information on surgical procedures i.e. isolated Coronary Artery Bypass Graft, Coronary Artery Bypass graft with valve replacement, Coronary Artery Bypass Graft with aortic surgery (23)	Proportion	Binary		x	x	x	x
10	Performing ICA, PCI or CABG in a later management path not indicated in the index test (CT or ICA) (8, 12, 15, 16) - Completeness of revascularization for Percutaneous Coronary Intervention single vessel vs multivessel Percutaneous Coronary Intervention and Coronary Artery Bypass Graft; stent use (bare metal vs drug eluting) (22) - Information on surgical procedures i.e. isolated Coronary Artery Bypass Graft, Coronary Artery Bypass graft with valve replacement, Coronary Artery	Proportion	Binary		x	x	x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	Bypass Graft with aortic surgery (23) - Rate of follow-up Invasive Coronary Angiographies and Percutaneous Coronary Interventions related to the index test (CT or ICA) after initial Computed Tomography/Invasive Coronary Angiography and up to 1st and 2nd follow-up (70) - Additional treatments during follow-up by clinical site (104)							
11	Undergoing further cardiac diagnostics (see chapter 11.4) 48h after the final procedure related to the test randomized to (11, 12) and additional tests: Differences in adverse events might lead to a different use of diagnostic tests during the follow-up phase. Therefore, data about cost-effective differences of examinations, not being mandatory according to the study protocol, will be collected. (103)	Proportion	Binary		x	x	x	x
12	Undergo further cardiac diagnostics (see chapter 11.4) in a later management path not related to the index test in a later management path (CT or ICA) (11, 12)	Proportion	Binary				x	x
13	Performing coronary revascularization (15)	Proportion	Binary		x	x	x	x
14	Performing coronary revascularization (PCI and CABG) (16) Improvement of selection of distal coronary segments used for Coronary Artery Bypass Surgery-anastomosis by Computed Tomography in comparison to Invasive Coronary Angiography alone (especially heavy calcification detection) as assessed by the cardiac surgeons (50)	Proportion	Binary		x	x	x	x
15	Treatment recommendations after index tests*	Proportion	Nominal		x			

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	- consider other cardiac or non-cardiac reasons for pain - Preventive medical therapy (PMT) defined as statin (primary definition) or statin plus antiplatelet (secondary definition - risk factor modification - perform best locally available imaging ischemia test - ICA and treatment according to ESC/ EATS guideline							
16	Time from randomization to ICA (20) and also to CT (including a per-site analysis)*	Median	Metric	x	x			
17	Time from randomization to first coronary revascularization (including a per-site analysis) (21)	Median	Metric	x	x	x	x	x
18	Duration of the exams (in min)*	Median	Metric		x	x		
19	Length of initial hospital stay* and days in hospital per patient by clinical site during follow up (102)	Mean/ Median	Metric		x	x	x	x
20	Comparison of procedural complications in: - Outpatient versus inpatient ICA rates after adjusting for risk factors (34) - Femoral versus radial approach ICA (34) - Different closure devices versus manual compression (34) - Patient acceptance*	Proportion	Nominal		x	x		
21	Complications related to ICA: e.g. cardiac arrhythmia, closure or injury of vessels, etc. (35) and procedural complications during or after revascularization (36)	Proportion	Nominal		x	x		
22	Occurrence of other adverse events (AE) and serious adverse events (SAE) (37)	Proportion	Nominal		x	x		

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 5: Health-related Quality of Life (HRQoL)*

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
Health-related Quality of Life (HRQoL)				**WP 10**				
23	SF-12v2: Physical Component Summary (PCS) (113)	Mean	Metric	x*			x	X
24	SF-12v2: Mental Component Summary (MCS) (113)	Mean	Metric	x*			x	X
25	EQ 5D-3L: Health profile (113)	Proportion	Ordinal	x*			x	X
26	EQ 5D-3L: Visual Analogue Scale (VAS), overall self-rated health (113)	Mean	Metric	x*			x	X
27	EQ 5D-3L: Index values (113)	Mean	Metric	x*			x	X
28	Hospital Anxiety and Depression Scale (HADS): Depression Subscale (113)	Mean	Metric	x*			x	X
29	HADS: Anxiety subscale (113)	Mean	Metric	x*			x	X
* for baseline adjustment								

Explorative subgroup analyses for main papers at t3 and t4:

- *Gender (113), Age (under 45, 45-65, over 65 years)**
- *Angina type at baseline (typical angina, atypical angina, non-anginal chest discomfort and other chest discomfort) (113)*
- *CAD diagnosis (obstructive CAD, non-obstructive CAD, no CAD)**
- *Major or minor procedural complications (any versus none)**
- *Patient groups according to treatment paths (Revascularization: any revascularizations until the follow ups, Medical Treatment alone: defined as Medical Treatment until the follow ups)**
- *MACE (yes/no) at t_4 (113)*

Explorative subgroup analyses for secondary papers:

- *Quintiles of pretest probability*, Baseline chest pain intensity (0-3, 4-6, 7-10) based on the strongest episode within the past 12 months (113)*
- *Socioeconomic status*, Country of origin, European region (i.e. south vs. north)**
- *Chronic illness (i.e. rheumatoid arthritis, diabetes)**
- *Lifestyle*, Incidental findings**
- *Type and quantity of plaques in the CT arm**
- *Patients with obstructive CAD who do or do not undergo ischemia-guided recommendations*, Patients without obstructive CAD and with or without potential etiologies identified explaining patient's symptoms*, Patients who underwent conservative versus invasive treatment strategies (matched analysis for the extent of CAD and ischemia).**

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 5.1: Further pre-specified analyses of HRQoL (WP 10)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
30	Associations between pre-diagnostic HRQoL and: - Socio-economic variables* - Cardiac risk factors and Lifestyle* - Treatment Regimens (adherence to therapy recommendation as covariate: statin alone, statin plus antiplatelet, statin plus antiplatelet plus risk factor modification or any combination with risk factor modification (17) - Family History* Analyses will be stratified by gender*			x	x	x		
31	Change and predictors of change in HRQoL over time in the complete sample (stratified by randomized group status in case change in HRQoL differs between groups). - Socio-economic variables* - Cardiac risk factors and Lifestyle* - Treatments* - Family History* Analyses will be stratified by gender and differences regarding HRQoL, lifestyle and socioeconomic status at baseline as well as in regards to changes of these factors seen at the two follow-up time points in the two randomized groups and in male and female patients with and without CAD on testing (118)			x			x	X
32	Comparison of HRQoL in participants across European regions at baseline and over time*			x			x	X
33	Comparison of different measures of HRQoL (113) (115)			x			x	x

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Cost-effectiveness:

Cost-effectiveness and cost-utility analysis will be presented separately in specific SAP.

Table 6: Radiation exposure*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Radiation Exposure and Contrast Agent				**WP 3**				
34	Effective radiation dose measured as - dose length product and - dose area product during CT (for Coronary Artery Calcium (CAC) Score and CT) and ICA (87) and reduction of radiation exposure by using coronary artery calcium score information (88)	Mean	Metric		x	x	x	x
35	Cumulative radiation dose (87)	Mean	Metric		x	x	x	x
36	Amount of contrast medium (in ml) used for entire procedure (CT or ICA) and the cumulative contrast agent amount in the two study group (14)	Mean	Metric		x	x	x	x
*Explorative subgroup analysis: Gender for radiation dose (117) and for contrast amount**								

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 7: Angina Pectoris*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Influence of CT and ICA strategy on Chest Pain				**WP 11**				
37	Occurrence of chest pain in the past 4 weeks and occurrence of exertional chest pain in the past 4 weeks as determined by the Rose questionnaire – short form*	Proportion	Nominal				x	x
38	Intensity of chest pain: Reduction of angina pectoris intensity in the two study groups (26)*	Median	Ordinal	x			x	x

Explorative subgroup analyses for main papers at t3 and t4:

- *Age (under 45, 45-65, over 65 years)*, Gender**
- *Angina type at baseline (typical angina, atypical angina, non-anginal chest discomfort and other chest discomfort)**
- *CAD diagnosis (obstructive CAD, non-obstructive CAD, no CAD)**
- *Major procedural complications (any versus none)**
- *Minor procedural complications (any versus none)**
- *Patient groups according to treatment paths (Revascularization: any revascularizations until the follow ups, Medical Treatment alone: defined as Medical Treatment until the follow ups)**
- *MACE (yes/no) at t_4**

Explorative subgroup analyses for secondary papers:

- *Quintiles of pretest probability**
- *Baseline chest pain intensity (0-3, 4-6, 7-10) based on the strongest episode in the past 12 months**
- *Socioeconomic status*, Country of origin, European region (i.e. south vs. north)**
- *Chronic illness (i.e., rheumatoid arthritis, diabetes)**
- *Lifestyle*, Incidental findings**
- *Type and quantity of plaques in the CT arm**
- *Patients with obstructive CAD who do or do not undergo ischemia-guided recommendations (26), Patients without obstructive CAD and with or without potential etiologies identified explaining patient's symptoms (26), Patients who underwent conservative versus invasive treatment strategies (matched analysis for the extent of CAD and ischemia (26).*

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229. For self-reported angina endpoints, we have pre-specified "occurrence of angina in the past 4 weeks" at the follow-ups as the primary angina variable (pre-specified principal patient-reported angina end point).

7.2.2 Other Secondary Outcomes

Table 8: Incidental Findings*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Incidental Findings				**WP 11**				
39	Comparison of findings of non-coronary cardiac causes of symptoms (e.g. aortic dissection, valve disease, pericarditis) and potential benefits and harms of findings. Analysis of prevalence non-coronary cardiac causes of symptoms and influence of non-coronary cardiac findings on Major Adverse Cardiac Events, non-cardiac events and HRQoL (38, 39)	Proportion	Nominal		x	x	x	x
40	Any non-cardiac findings (e.g. thrombus, pulmonary embolism, pleural effusion, pneumonia, hiatal hernia) and potential benefits and harms of findings. Analysis of prevalence of non-cardiac findings, causes of symptoms and influence of non-cardiac findings on MACE, non-cardiac events and HRQoL (38, 39)	Proportion	Nominal		x	x	x	x
41	Findings of malignancy in nodules seen on CT (40)	Proportion	Nominal		x	x	x	x
42	Risk prediction for lung cancer by McWilliams et al. (41)				x	x	x	x
43	Death from cancer, competing risk analysis (42)	Rate	Time-to-event				x	x
44	Conducting unnecessary follow-up procedures (examinations, biopsies, surgeries done based on non-coronary findings) (43)	Proportion	Nominal				x	x

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 9: Patients' acceptance and preference*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Patients' acceptance and preference according to the procedures that the patient underwent				**WP 6**				
45	Patients' acceptance ("preference questionnaire") (85)				x†	x†		
46	Patients' acceptance of informed consent, preparation and procedural aspects of the test performed (86)				x†	x†		
47	Satisfaction with the trial (rate the information about the study in general) (85)	Proportion	Ordinal		x†	x†	x	
48	Satisfaction with preparation and information prior to examination (86)	Proportion	Ordinal		x†	x†		
49	Satisfaction with performance of the performed examination (86)	Proportion	Ordinal		x†	x†	x	
50	Assessment of maximum pain during examination (VAS 0 – 100) (86)	Mean	Metric		x†	x†		
51	Patients' acceptance of management after CT or ICA of patients who could not be discharged directly (86)	Proportion	Ordinal		x†	x†		
* at timepoints when examinations are performed								
Explorative subgroup analyses: Gender, patients without significant stenosis seen on the initial test randomized to, patients with significant stenosis seen on CT and a) ICA not recommended or done e.g., because of imaging ischaemia results or b) ICA done (85, 86)								

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

7.2.3 Gender Aspects

First, gender is a baseline characteristic that may influence outcomes independently or modify effects of intervention on outcome. These aspects will be examined by gender subgroup analyses for the primary and secondary endpoints as described above (7.2.1 and 7.2.2).

Second, demographic and baseline characteristics as well as prevalence and characteristics of CAD in men and women will be analyzed and compared.

Third, gender will be analyzed along with CAD variables (coronary stenosis, coronary plaque) in prognostic models for MACE and MICE.

Fourth, among women, the impact of specific female cardiovascular risk factors (see below) on prevalence and type of CAD, diagnostic safety and accuracy of ICA/CT and prognosis will be assessed.

The following table describes planned analyses regarding the gender aspect.

Table 10: Variables used in gender analyses (WP 7)*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Prevalence and characteristics of CAD in European women and men								
52	Independent variable: Gender (119) Dependent variables / outcomes: • Demographic and Baseline Characteristics* • CAD variables: - Rate of coronary artery disease and coronary stenosis (by CT and/or ICA): patient-by-patient normal, non-obstructive and >50% stenosis and – defined as vessel disease (1VD, 2VD, 3VD or LM) (119) - Coronary plaque (by CT): coronary plaque assessment, including calcified, mixed and non-calcified plaque, remodeling index, ring-sign, spotty calcification (120)			x	x		x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	Gender differences of myocardial resting blood flow / tissue characteristics determined by cardiac CT using parameters such as regional and global TPR, AD, PI, perfusion defects, myocardial calcification, myocardial fatty infiltration, myocardial thinning. (121)							
Gender related differences of safety and diagnostic accuracy/yield by ICA or CT								
53	Independent variables: • Diagnostic procedure (CT, ICA) • Gender Dependent variables / outcomes: • Procedural complications (28, 29, 31, 33, 34, 35, 36) • Gender differences in radiation exposure: Radiation dose received for all performed invasive / non-invasive diagnostic procedures, for each type of procedure (ICA, PCI, CT, SPECT, PET) and for each diagnostic strategy (CT and ICA) (117) • Index diagnostic conclusion: CAD with indication for revascularization, CAD with indication for antianginal medical therapy, no CAD (119) • Coronary revascularization proportion of patients undergoing PCI or CABG* • pulmonary findings of cardiac CT (in the CT group) a) signs of pulmonary congestion: Ground-Glass Opacification (GGO), Pleural effusions, interlobular transudate high density pulmonary attenuation index b) pulmonary emphysema			x	x	x	x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	(with/without CAD), low density pulmonary attenuation index c) Pulmonary embolism (major, minor) (123) structural cardiac CT findings including parameters such as LV-mass, volumes and dimensions of Left Ventricle (LV), Left Atrium (LA), Right Ventricle (RV), Right Atrium (RA) and blood pressure (124)							
Gender related differences of prognosis as predicted by either CT or ICA								
54	Independent / predictor variables: • Gender (116) • CAD variables - Coronary stenosis (by CT or ICA): patient-by-patient normal, non-obstructive and >50% stenosis and – defined as vessel disease (1VD,2VD,3VD or LM) (119) - Coronary plaque (by CT): coronary plaque assessment, including calcified, mixed and non-calcified plaque, remodeling index, ring-sign, spotty calcification (120) Dependent variables / outcomes: • MACE* • MICE*			x	x		x	x
Gender related differences of true positive findings								
55	Independent / predictor variables: • Diagnostic procedure (CT, ICA)* • Gender (116) Dependent variables / outcomes: Diagnostic value of CT in men vs women - frequency of true positive findings in patients referred for ICA - i.e. frequency of revascularization in			x	x		x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	patients referred for ICA based on CT with and without ischemia testing, CT findings, Ischemia testing findings, ICA (122)							

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Baseline characteristics including cardiovascular risk factors in women includes age at first menstrual cycle, age at menopause (in women after menopause), early menopause (<40 years), duration in years of contraceptive medication treatment, hysterectomy y/n - if Y age at Hysterectomy, Oophorectomy y/n - If Y age at Oophorectomy, number of pregnancies, number of child births, age at first childbirth, premature birth (before week 37) Y/N - If Y age at birth, breastfeeding Y/N - if Y number of months, heart or medical problems during pregnancy Y/N - If Y type, pregnancy with (gestational) hypertension Y/N, pregnancy with preeclampsia Y/N, pregnancy induced diabetes Y/N. Baseline demographics for both women and men includes age, BMI, conventional CVD risk factors, ethnicity, marital status, socio-economic variables, geographic location, symptom status and HRQol.

7.4 Pre-planned Analyses for Other Objectives

Table 11: Analysis of Differences in Europe (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
56	Likelihood of receiving PCI in different European countries (1)			x			x	x
57	Rates of PCI and use of intracoronary techniques in different European countries (2)			x			x	x
58	Patient management in different European countries (3)			x			x	x
59	Follow-up strategies in different European countries (4)			x			x	x
60	European differences in occurrence and extent of CAD in regards to city versus rural lifestyle (5) as well as PMT and risk factor modification*			x			x	x
61	European and local differences in patient consent (i.e. patient participation and withdrawal) of sites (6)			x			x	x
62	Geographical distribution of risk factors for MACE and MICE, cardiovascular events and cardiac events (18)			x			x	x

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 12: Image-based Outcomes for CT and ICA group (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
63	Image quality in CT and ICA groups and analysis of interobserver variability (site versus core lab) of reading for coronary stenosis and plaques (44)				x	x	x	x
64	Percent diameter stenosis (45) and correlation between percent diameter stenosis by CT with invasive FFR and correlation of non-invasively estimated FFR by CT with invasive FFR after CT/ICA (47)					x	x	x

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 13: Image Quality and Image-based Outcomes in CT group (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
65	Relation of plaque characterization and quantification by core lab and MACE and MICE (51)						x	x
66	Image quality of CT by core lab read and flow and concentration of contrast agent used intravenously (52)				x	x	x	
67	Coronary artery dimension (53)				x	x	x	
68	Noise in CT imaging (54)				x	x	x	
69	Factors that influence image quality: BMI, gender, origin of patient, number of detector rows, heart rate, 80-100-120-135-140 kV, different mA settings, acquisition type (55). The relationship between these factors and frequency of non-diagnostic segments will be assessed.* Evaluation of the 10-step guide to cardiac CT (57)				x	x	x	
70	Semi-qualitative analysis: Composite outcome (intensity, noise, signal to noise, contrast and signal to noise in some regions of interest) (58)				x	x	x	
71	Qualitative analysis: Composite outcome (levocardiography effect and some regions of interest) (59)				x	x	x	
72	Heart rate reduction achieved by DISCHARGE beta-blocker protocol (also in subgroups: e.g. gender, age, subgroups of patients with contraindication to beta blockers or no adherence to protocol ,…) (60, 61) and conscious sedation (62)				x	x	x	
73	Correlation of extent of CAD and high calcium score (63)				x	x	x	
74	Characterization of plaques by CT core lab				x	x	x	

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
	in relation to cardiac risk factors (64)							
75	Differences in plaque characteristics (type and composition) and analysis of potential influence by geographical origin of the patient, after adjustment for other cardiac risk factors. (65)				x	x	x	
76	Comparison of CT and intracoronary techniques (66)				x	x	x	
77	Influence of statin treatment on plaque development (67)				x	x	x	

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 14: Outcomes of ICA procedure (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
78	Correlation of effective dose and diagnostic proportion (i.e. those without non-diagnostic test results) with weight and BMI (68)				x		x	x
79	Correlation of effective dose and contrast agent medium used for ICA with severity of CAD (69)				x		x	x
80	Correlation of the number of projections for the right and left coronary artery with effective dose of ICA (71)				x		x	x
81	Rates of left ventriculography performed (72)				x		x	x

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 15: Planned invasive diagnostic testing in accordance with management recommendations (WP 6)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
82	Rates of invasive testing with ICA in the CT group based on positive and negative CT imaging findings as well as patients receiving the test not randomized to (73)					x	x	
83	Comparison of patients with planned ICA in the CT group based on positive or negative CT imaging findings to patients not receiving ICA even if indicated by CT findings and patients switching over to the test not randomized and not recommended by findings of the index test to regarding patient-reported health status, MACE, MICE (74)				x	x	x	x
84	Analysis of influence of prior CT (versus no CT) on ICA and PCI in terms of duration, radiation exposure, amount of contrast agent used for ICA in matched patients from both study groups (13)				x	x		

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 16: Ischemia tests (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
85	Correlation of CT and/or ICA results with the results of ischemia tests (exercise ECG, stress echo, stress SPECT, stress PET, stress MRI, FFR, before or after index CT or ICA testing) (11) (75)			x		x	x	x
86	Correlation between imaging ischemia tests and invasive Fractional Flow Reserve if done (76)			x		x	x	x
87	Rates of (imaging) ischemia tests recommended (77) Rate of PCI / CABG recommended and performed after CTA and positive or negative imaging ischemia tests in comparison to the ICA arm (81)			x		x	x	x
88	Comparison of diagnostic accuracy of (imaging) ischemia tests for the detection of CT- or ICA-defined CAD and prediction of MACE, MICE (78, 79)			x		x	x	x
89	Correlation between (imaging) ischemia results and coronary stenosis as well as plaque composition and characterization findings by CT (80)			x		x	x	x
90	Correlation of the results of study-CT, recommended (imaging) ischemia test and ICA in patients with respective study course (82)			x		x	x	x
91	Occurrence of procedural events in (imaging) ischemia testing (83)			x		x	x	x
92	Correlation of intensity and reduction of angina pectoris with (imaging) test results (84)			x		x	x	x

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 17: Comparison of Pretest Probability Calculators and Event Predictors (WP 11)*

No	*Steps of analysis*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
93	Validation of the CAD DISCHARGE and COME-CCT pretest probability calculators. (90, 92) Comparison of the ability of the calculators to predict CAD in different genders (91)			x	x		x	x
94	Potential advantage of calculators in combination with chest discomfort guidelines to triage patients most effectively based on pretest probability in comparison to the DISCHARGE approach of CT including calcium scoring and CTA for management decision making about risk factor modification and revascularization (93)			x	x		x	x
95	Predictive value of the DISCHARGE calculator in patients who could not be included in the trial due to their very low pretest probability (< 10%) or very high pretest probability (> 60%). (94, 95)			x	x		x	x
96	Development of a novel pretest probability calculator based on age, gender, symptoms, and cardiac risk factors and/or exercise ECG or imaging ischemia results of patients in DISCHARGE with CT and/or ICA results being the reference standard for the definition of CAD for this novel calculator; comparison of this novel calculator with the simple DISCHARGE pretest probability calculator for diagnostic test selection (96) Further: Ability to predict MACE and MICE (97)			x	x		x	x
97	Validation of different questionnaires to predict Major and Minor Adverse Cardiac Events: Validation of the Rose Angina questionnaire including pain scale and the			x	x		x	x

No	Steps of analysis	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	InterHeart Risk Score (IHRS) to predict MACE and MICE in both trial groups (27)							

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

8 Analysis Sets

8.1 Definitions

The following analysis sets will be considered:

- **Intention-to-Treat (ITT) analysis set**
  The ITT analysis set includes all randomized patients in the groups to which they were randomly assigned, i.e. CT or ICA. Patients who withdraw or are withdrawn by study physician before procedure will be excluded. Furthermore, missing follow-up information for the primary endpoint will be treated as censored.

- **Per-Protocol (PP) analysis set**
  The PP analysis set is defined as a subset of the ITT analysis set of only those patients who attempt to undergo ICA or CT as randomized, and excludes patients who received the test they were not randomized to as the index test ('change of study arm'). Furthermore, patients with a negative CT who received ICA will be excluded and also patients with ICA as the index test who received an additional CT, which was not recommended to be done in the protocol, will be excluded.

- **Safety analysis set**
  The safety analysis set includes all patients who undergo at least one investigation. Data will be analyzed in groups according to the diagnostic test procedure (CT or ICA) the patients undergo first as the index test. For each event, the relation to the first test patients undergo as well as to further procedures will be assessed. An additional analysis will be performed in patients who received both CT and ICA.

8.2 Applications

Analysis for the primary and secondary end points will be performed primarily for the ITT analysis set and secondarily for the PP analysis set. Procedural complications, MACE and MICE will be additionally analysed for the safety analysis set.

8.3 Major Protocol Violations

Major protocol violations are defined as:

1) patients who were randomized to an intervention but did not receive any intervention because they withdrew or were withdrawn.
2) patients who did not receive the intervention they were randomized to.

In case of major protocol violations due to 1) clinical sites are requested to recruit further patients and these patients will not be included in the ITT analysis. For major protocol violations due to 2) patients will be taken into account in the ITT analysis set.

Protocol violations will be checked on complete data for all patients prior to defining the analysis populations. The decision will be based on the blinded raw data listings and the protocol violations and deviations tracked by Project Management.

Major protocol violations will be summarized by type of violation and by investigation group and overall.

9 Treatment of Missing Values

Missing values of the primary endpoint MACE and other time-to-event data (e.g. time until the occurrence of MICE, coronary revascularization, …) will be treated as censored observation. Missing values for confounding variables are likely to occur. Thus, multiple imputation methods will be used in order to deal with missing values. For adverse events, i.e. major and minor procedural complications as well as major and minor adverse cardiovascular events, no imputation will performed. Also a sensitivity analysis will be performed to compare results based on the multiple imputations with the complete case setting.

10 Statistical Analysis

10.1 General Principles

Data will be summarized by each intervention group and for pooled intervention groups. For both continuous variables (e.g. age) and ordinal variables (e.g. severity of symptoms) descriptive statistics will be presented (mean, standard deviation, median, 25th and 75th percentiles, range and number of patients with data). For categorical variables (e.g. sex) frequencies, percentages and number of patients with data will be presented. The denominator for the percentages will be the number of patients with non-missing data. Descriptive analysis will be done primarily on available data. The same analysis can be done using MI data, but only if differences are relevant. Relevance will be determined between Investigators and Statisticians. Data will be analyzed according to measurement scale and distribution.

Listings of individual patient's data will be provided by KKS Charité.

The statistical output for the primary endpoint will be validated independently by Peter Martus and another statistician, Konrad Neumann, who is responsible for patient-reported outcome statistics and vice versa.

Statistical testing will be performed using a two-sided significance level of 0.05 (5%) or – if indicated - a one-sided level of 0.025 (2.5%), unless otherwise specified. For symmetrical distributions and effects with expected orientation (if stated in advance), both approaches are equivalent.

10.2 Patients' Availability

The number of patients who provided informed consent and were randomized will be summarized. The number of subjects included in the ITT and PP analysis sets will be included in the table. Attendance at each defined time point, including missed time points, discontinuations, lost to follow-up and percentage accountability will be summarized. A list of patients who withdraw early will be provided. It will include the reason and timing of the withdrawal. Similarly, the reason any patient was excluded from an analysis set will also be provided. In addition, major known protocol deviations will be noted for individual patients; a summary table may also be provided.

The patient's availability will be displayed in a Consolidated Standards of Reporting Trials (CONSORT) diagram. The number of screened patients who fulfilled trial inclusion criteria, and

the number included in the primary and secondary analyses, as well as reasons for exclusions in primary and secondary analyses will be reported.

10.3 Demographic and Baseline Characteristics

All demographic and baseline characteristics captured in the eCRF will be summarized by investigation group and across the whole trial. Demographic data including, but not limited to age, gender, ethnicity, income, marital status, profession and work status, and baseline characteristics including, but not limited to BMI, blood pressure, angina type, smoking, concomitant medication, NYHA-class, hypertension, family history of CAD, diabetes, cardiac history will be reported.

Data will be presented by adequate statistical measures as described in paragraph 10.1.

10.4 Primary Analysis

The primary endpoint will be MACE incidence until the occurrence of MACE within the time window from randomization until the 2nd follow-up. This event time will be analyzed using techniques from survival time analysis. Kaplan Meier curves for the CT- and ICA-group will be generated. The event-rate at 2nd follow-up and the 95% confidence interval will be presented for each group. The primary analysis in the ITT will be done without adjusting for pretest probability of obstructive CAD in the two groups. A sensitivity analysis will include pretest probability of obstructive CAD.

Differences between the two groups with respect to the primary endpoint will be finally tested at a two-sided significance level of nominal 0.048 due to alpha-spending for interim analysis to preserve the overall significance level of 5%. The primary statistical hypothesis to be tested is that under the proportional hazards assumption (i.e., HR = $h_{CT}(t) / h_{ICA}(t)$ = constant, $t \geq 0$) there is no difference in the hazards for MACE between the two investigation groups, i.e.:

$$H_0: HR = 1 \quad \text{vs.} \quad H_A: HR \neq 1$$

Here, $h_{CT}(t)$ and $h_{ICA}(t)$ ($t \geq 0$) denote the hazard functions for MACE for the two groups. For proving the above hypotheses a Cox proportional hazards model including investigation group adjusted for gender due to stratified randomization will be applied. Results of this first Cox proportional hazards model will be presented as hazard ratio together with 95% confidence

interval accounting for alpha spending.

To adjust for pretest probability and the variables contributing to pretest probability (age, gender, angina type), an additional Cox proportional hazards model will be used to test for differences between the two groups. In case of a non-convergent model (too many covariates) forward variable selection will be applied.

As a sensitivity analysis, a Cox proportional hazards model with random effects for center (i.e. frailty models [14]) will be applied. This model will be used in order to take variability between study centers and unobserved heterogeneity into account. This unobserved heterogeneity might be e.g. the result of different therapeutic adherence within each center. The relative effect of CT versus ICA will be presented as hazard ratio together with 95% confidence interval.

Checking the proportional hazards assumption will be done using goodness of fit test based on Schoenfeld residuals.[15] In case the proportional hazards assumption is not fulfilled a parametric regression model will be chosen.

10.5 Secondary Analyses

The secondary endpoints will be evaluated:

- by means of parametric (unpaired or paired t-test, (RM-)ANOVA) or non-parametric (Kruskal-Wallis test, Mann-Whitney-U test or Friedman test, Wilcoxon signed-rank test) tests according to scaling and distribution
- by means of linear or generalized mixed models for longitudinal data (e.g. HRQoL-data)
- by means of Chi^2-test for comparison of proportions between different groups
- logistic regression models for binary outcome data
- Kaplan Meier method and Cox proportional hazard models for censored data, competing risk analysis if adequate
- by means of correlation analysis (Pearson, Spearman, Sommers-d, Kendall-tau) according to scaling
- by means of Kappa-coefficient or Intraclass-Correlation for agreement consideration
- by a statistical test of interaction between study group and subgroup factor for each subgroup analysis.

Appropriate parameters of group-specific outcomes (e.g., rates, prevalences, mean or median values) and effect size (e.g., relative risks, odds ratios, difference of mean or median) with 95% confidence intervals will be calculated.

Since the time between baseline and follow-up is not fixed in this pragmatic trial, in sensitivity analyses, the true time interval involving endpoints at t3 and t4 (Figure 1) will be adjusted for.

If indicated, subgroup analyses will be performed in appropriate models (Cox proportional hazard model, logistic regression model) including interaction terms between intervention and other pre-specified covariates (see 7.1 and 7.2).

Although all HR**QoI endpoints** are secondary endpoints, the VAS (EQ3D) and the physical component score (PCS) of the SF12v2 are defined as variables of primary interest (pre-specified principal patient-reported QOL end points). For self-reported **angina endpoints**, we have pre-specified "occurrence of angina in the past 4 weeks" at the follow-ups as the primary angina variable (pre-specified principal patient-reported angina end point).

HRQoL analyses will be carried out at baseline (t_0), at one year follow-up (t_3) and at the 2nd follow-up (t_4). Beside the QoI variables also the change of the variables between t_0 and t_3, between t_0 and t_4 and between t_3 and t_4 will be compared between groups defined by the factors randomization groups (CT and ICA). Furthermore, we will compare the study groups ICA and CT in the pre-defined subgroups (see Tables 5 and 7). From the DISCHARGE pilot we know that the HRQoL endpoints are nearly symmetrically distributed. Hence, we may assume that for all QoI outcomes the normality assumption will be satisfied and parametric statistical methods can be applied. Hence, group comparisons will be carried out using univariate linear mixed effects models with study group, age, gender and angina type at baseline as independent variables and the HRQoL variables as dependent variables. A random intercept will be added to the model equations in order to account for possible study site (center) effects. The scheduled time between baseline (t_0) and the 1st follow-up (t_3) is one year and the time until 2nd follow-up (t_4) is 24-56 months. Since we expect that the time between t_0 and $t_{3/4}$ can influence QoI outcomes we will adjust all QoI scores at t_3 and t_4 with respect to the time between t_0 and t_3 and between t_0 and t_4. The choice of the model used for these adjustments will depend on the distribution of the time between t_0 and t_3 and between t_0 and t_4, respectively. Missing values at t_0, t_3 and t_4 will be treated by multiple imputation with at least m=100 imputation samples. The imputation models contain all HRQoL variables and the baseline characteristics such as gender, age, randomization group and angina type.

10.6 Safety Analyses

Safety will be evaluated by tabulations of adverse events (AEs) and will be presented with descriptive statistics at examination and during follow-up ($t_{2\text{-}4}$) for each investigation group.
A tabulation of Serious Adverse Events (SAEs) will be provided by patient within groups.

10.7 Analysis at 1st follow-up

The first secondary end point analysis will be performed after completion of the 1-year follow-up (t_3). The data base will be locked for 1-year follow-up data and all diagnostic tests and related procedures will have been performed at this point in time. Thus, there will be no interference of the 1-year follow-up publication with the planned primary outcome analysis of MACE at the 2nd follow-up (t_4). The statistical details of the secondary analysis also include the 1-year follow-up analysis. These details are prespecified in this SAP and will include a comparison of the two study groups in regards to patient management and test findings, the comparison of time-to-test, discharged patients without further testing, additional functional tests, rate of obstructive and non-obstructive CAD, diagnostic yield of ICA in both groups, revascularizations, preventive medical therapy, procedural complications (major and minor), patient-reported outcome measures of angina and quality of life.

11 Scales and Definition for Clinical Evaluations

11.1 Protocol Definition of MACE

MACE is defined as at least one of the following:

- Cardiovascular death
- Nonfatal myocardial infarction
- Nonfatal stroke

Protocol definition of cardiovascular death

The standardized definitions for end points in clinical trials developed by the joint Writing Committee to Develop Cardiovascular Endpoint Data Standards of the American College of Cardiology/American Heart Association (ACC/AHA) will be implemented.[10] These definitions for cardiovascular endpoint events in clinical trials were initially included as an unpublished document in the DISCHARGE study protocol as Hicks et al. (2014: Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations) and are updated in this SAP after full journal publication by Hicks et al. for the ACC/AHA Committee. According to this definition, all deaths will be rated and classified as cardiovascular, non-cardiovascular or undetermined. Cardiovascular deaths are defined as all deaths excluding death for which the

underlying cause is exclusively non-cardiovascular. As introduced by Hicks et al.[10] cardiovascular death includes death resulting from:

a) Acute myocardial infarction
b) Sudden cardiac death
c) Death due to heart failure
d) Death due to stroke
e) Death due to cardiovascular procedures
f) Death due to cardiovascular hemorrhage
g) Death due to other cardiovascular causes

Protocol definition of nonfatal myocardial infarction

The actual definition of myocardial infarction (MI) of the joint European Society of Cardiology/ American College of Cardiology/American Heart Association/World Heart Foundation (ESC/ACC/AHA/WHF) Task Force will be implemented.[11] Events are defined as nonfatal if they are not leading to death of the patient.

Protocol definition of nonfatal stroke

The definition of stroke by the American Heart Association/American Stroke Association (AHA/ASA) was implemented.[12]

11.2 Protocol Definition of MICE

The composite endpoint MICE is defined as at least one of the following:

- Coronary revascularization following new, non-index related ICA
- Peripheral artery revascularization
- Hospitalization for chest pain/ discomfort
- Emergency department visit for chest pain/ discomfort
- Transient ischemic attack
- Congestive heart failure

11.3 Protocol Definition of Procedural Complications

See study protocol section 4.2.2.

11.4 Definition of Further Cardiac Diagnostics

Further cardiac diagnostics include the performance of

- Additional CT or ICA (including additional tests in ICA: FFR [functional], IVUS and OCT [anatomical])
- Electrocardiogram (ECG)
- Exercise ECG
- Stress echocardiogram
- Stress magnetic resonance imaging
- SPECT
- PET-CT

11.5 Patient Reported Outcomes (Angina and HRQoL)

Angina

At baseline and all follow-ups, patients are asked to rate the occurrence and intensity of their chest pain. **Exertional and non-exertional angina** are assessed using the short version of the Rose questionnaire. In addition, patients are asked to rate the **intensity** of their strongest episode of angina in the past 12 months on a 10-point scale ranging from 0 (no pain) to 10 (maximum pain). Intensity ratings are grouped into low (0-3), medium (4-6) and high (7-10) angina intensity.
At each follow-up, patients are asked when their **last episode of chest pain** had occurred. The primary angina endpoint “occurrence of angina within the past 4 weeks” will be derived from this information.

Short Form-12v2 (SF-12v2)

The SF-12v2 is a generic measure of health status which encompasses an eight-scale profile of functional health and well-being, as well as two physical and mental health summary measures.[16] In DISCHARGE, we use the standard (4-week) recall form of the SF-12v2.

The eight domains of functioning are: Physical Functioning, physical health-related role limitations (Role-Physical, RP), Bodily Pain, General Health, Vitality, Social Functioning, emotional health-related role limitations (Role-Emotional, RE) and Mental Health. These are further aggregated in two component summary measures: physical component summary

(PCS) and mental component summary (MCS).

The eight health domain scores as well as the summary component scores will be transformed to t-scores according to the SF-12v2 user's manual (Maruish ME[16]). The *standard* scoring algorithm (based on the SF-12v2 2009 US general population normative sample) will be applied rather than country-specific SF-12v2 scoring algorithms, because a) country-specific algorithms are only available for some but not all countries represented in DISCHARGE and b) a comparison of DISCHARGE participants' SF-12v2 scores to normative sample data is not the aim of this study, but rather the assessment of intervention effects on HRQoL. For calculation of the two dimensions PCS and MCS of the SF-12v2 we will use the software Optum™-PRO CoRE with the scoring method "Maximum Data Recovery". From the DISCHARGE pilot where the same Qol outcomes were evaluated we know that the skewness of the distributions of all metrical Qol outcomes is small. Hence we report as for all metrical Qol outcomes means and standard deviations for the scores PCS and MCS and may assume that the normality assumption is true.

Furthermore, we will report the proportion of patients with PCS / MCS scores below one standard deviation of the US general population normative sample as part of the health-related quality of life secondary outcomes of DISCHARGE.

EuroQoL (EQ-5D-3L)

The EQ-5D-3L was developed by the EuroQol group as a subjective measure of health status. The questionnaire consists of two parts. The first part assesses current health-related quality of life in five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, each of which can take one of three responses (no problems/some or moderate problems/extreme problems). The second part consists of the EQ visual analogue scale (VAS): a standard vertical 20 cm visual analogue scale (similar to a thermometer). Participants are asked to rate how good or bad their own health is today, on a scale from 0 (Worst imaginable health state) to 100 (best imaginable health state).

The EQ-5D-3L allows for the presentations of health profiles along the five functional dimensions (no problems, some problems and extreme problems). This allows for calculating percentages of patient groups with some or extreme problems in each domain. Further**,** health states can be presented, e.g. health state 11212 represents a patient who indicates some problems (=2) on the usual activities and anxiety/depression dimensions and no problems (=1) on the other dimensions. These health states can be converted to a single index value using (one of) the available EQ-5D-3L value sets. These value sets have been derived using Visual

Analogue Scale (VAS) or time trade-off (TTO) valuation techniques from the general population. Value sets for the EQ-5D-3L are available for all countries participating in DISCHARGE.[16, 17]

We will report the health states (proportion of participants with some or extreme problems in each of the five functional domains), and means, standard deviations for the visual analogue scale and the index value.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) assesses the presence and severity of symptoms of anxiety and depression. The depression and anxiety subscales each contain seven questions. Several cut-offs for possible “clinical caseness” have been proposed, most often, a score of 8 on either subscale will be considered a cut-off for a depressive or anxiety disorder, respectively. Several studies have validated this instrument for use in somatically ill patients. We will report means and standard deviations for the two subscales as well as the proportion of participants with a score of >= 8 (cut-off for elevated depressive / anxiety symptoms, respectively).

12 Software

Data manipulation, statistical summaries and statistical analyses will be performed using SAS software, Version 9.4 or higher for Windows (Copyright© 2014 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.). Some analysis may be carried out in SPSS (IBM, version 26 or higher) and R version 3.2.0 or higher.[18]

13 Scientific Concomitant Program

Within the study several further scientific objectives will be considered:

- Pretest Probability Calculator:
  - To compare several pretest probability calculators
  - To investigate the predictive value of the DISCHARGE calculator
  - To develop a novel pretest probability calculator
- Development of 10-steps guide to performing cardiac CT and scanner specific protocols
- Development of CT quality criteria for image quality and radiation exposure

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STATISTICAL ANALYSIS PLAN

Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies

The "DISCHARGE" Study

A pragmatic randomized controlled trial (PRCT) evaluating the superiority of CT over ICA concerning effectiveness in stable chest pain patients with intermediate pretest probability of coronary artery disease

Charité – Universitätsmedizin Berlin

Table of Contents

Abbreviations

AE	Adverse Event
ACC	American College of Cardiology
AHA	American Heart Association
ASA	American Stroke Association
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society Angina Grading Scale
COME-CCT	Collaborative Meta-analysis of cardiac CT
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed Tomography
CTA	CT Angiography
DISCHARGE	Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
ESC	European Society of Cardiology
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
ICA	Invasive Coronary Angiography

ICH	International Conference on Harmonization
ITT	Intention-to-Treat
KKS Charité	Coordinating Center of Clinical Studies at Charité
LM	Left Main Coronary Artery
LV	Left Ventricle
MACE	Major Adverse Cardiovascular Event
MCS	Mental Component Summary
MI	Myocardial Infarction
MICE	Minor Adverse Cardiovascular Event
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association (Functional Classification)
PCI	Percutaneous Coronary Intervention
PCS	Physical Component Summary
PET	Positron Emission Tomography
PP	Per-Protocol
PRCT	Pragmatic Randomized Controlled Trial
QoL	Quality of Life
RE	Emotional health-related role limitations (Role-Emotional)
RP	Physical health-related role limitations (Role-Physical)
SAE	Serious Adverse Event
SD	Standard Deviation
SF-12v2	Quality of Life Questionnaire Short Form 12 Version 2
SPECT	Single Photon Emission Computed Tomography
VAS	Visual Analogue Scale
VD	Vessel Disease
WHF	World Heart Foundation

Signature page

In signing this page, I am confirming that I have reviewed and approve this analysis plan.

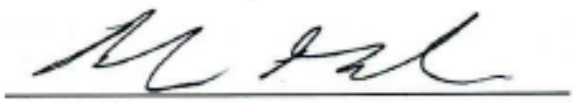
Prof. Peter Schlattmann

(Planning statistician) Date

Digital unterschrieben von Peter Schlattmann
DN: cn=Peter Schlattmann, o=Jena University Hospital, ou=Institute Medical Statistics, Informatic and Data Science, email=peter.schlattmann@med.uni-jena.de, c=DE
Datum: 2021.12.07 16:07:21 +01'00'

Prof. Peter Martus

(Conduct of main outcomes statistical analysis) Date



6.12.21

Dr. Konrad Neumann

(Conduct of patient reported outcomes statistical analysis) Date

DR. Konrad Neumann

Digital unterschrieben von DR. Konrad Neumann
Datum: 2021.12.08 10:25:36 +01'00'

Prof. Marc Dewey

(PI of the DISCHARGE trial) Date

Marc Dewey

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Datum: 2021.12.07 16:16:57 +01'00'

1 Background

Coronary artery disease (CAD) is the leading cause of death in high-income countries. Invasive coronary angiography (ICA) is the reference standard for the diagnosis of CAD and allows immediate interventional therapy. Coronary computed tomography (CT) is the most accurate noninvasive diagnostic test for CAD currently available.

The primary hypothesis of the DISCHARGE trial is that CT is superior to ICA for major adverse cardiovascular events after 2nd follow-up in a population of stable chest pain patients with intermediate pretest probability (10-60%) of CAD. This will be assessed using a pragmatic randomized controlled design based on the European guidelines available at the time of study conduct[1,2,1, 3] in order to generate practical and usable outcomes for clinical decision-making according to comparative effectiveness research methodology. European and US guidelines published after conduct of trial could not be considered in the study design and methods.[4,5]

2 Study Objectives

2.1 Primary Objective

The primary objective of this trial is to evaluate the comparative effectiveness of CT and ICA in patients with stable chest pain and intermediate pretest probability (10-60%) of coronary artery disease. The superiority hypothesis of CT over ICA is evaluated based on MACE (MACE = Major Adverse Cardiovascular Events; as defined in chapter 11.1, time frame: from randomization to CT/ICA until the 2nd follow-up as the primary outcome). Primary outcome measures as well as secondary outcome measures, which were prespecified before the start of the trial are listed at https://clinicaltrials.gov/ct2/show/NCT02400229. The analysis plan for the primary outcome is shown in Tables 1 and 2 in Chapter 3.2 and a description of the primary outcome is shown in Table 3 in Chapter 7.1.

2.2 Secondary Objectives

Secondary objectives of the DISCHARGE trial were prespecified before the start of the trial at https://clinicaltrials.gov/ct2/show/NCT02400229. These secondary objectives are identified using numbers in parentheses in this chapter and Tables 4-19. A description of how these secondary objectives are operationalized can be found in chapter 7.2 and an overview of scales and statistical comparison is provided in Table 20.
Secondary objectives of the DISCHARGE trial as specified in the study protocol will be:

1. to evaluate the occurrence of MACE in individual composites according to specified secondary objectives defined before the start of the DISCHARGE trial (# of secondary objectives on NCT 02400229: 126, 127)* as well as MACE in subgroups (24, 25, 116, 125) as well as subgroups defined by quintiles of pretest probability of CAD (Table 3)
2. to compare the CT and ICA group with respect to MICE (MICE = Minor Adverse Cardiovascular Event; as defined in chapter 11.2, time frame: from randomization to CT/ICA diagnosis/procedure and until the 2nd follow-up) (7) as well in MICE subgroups (24, 25, 116) as well in subgroups as defined by quintiles of pretest probability of CAD (Table 4)
3. to identify and document major and minor procedural complications as defined in study protocol section 4.2.2 (time frame: occur during the procedure or within 48 hours post last related index procedure; relevant procedures are CT, ICA, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and additional functional tests) (28-37) (Table 5 and Table 5.1)
4. to evaluate the influence of CT and ICA on angina pectoris (26) (Table 8)
5. to evaluate and to compare incidental findings in CT and ICA group and potential benefits and harms of findings (38, 39, 40, 41, 42, 43) (Table 9)
6. to evaluate patient's acceptance/preference of CT and ICA (85, 86) (Table 10)
7. to assess radiation exposure of CT and ICA (87, 88) (Table 7)
8. to estimate and to compare cost-effectiveness of CT and ICA (98, 99, 100, 101, 102, 103, 104, 110, 111) (in separate SAP for cost-effectiveness analysis)
9. to evaluate and compare Health-Related Quality of Life (HRQoL, secondary outcome and predictor), socioeconomic status (working condition as predictor and outcome), and lifestyle in the CT and ICA group (outcome and predictor) (17, 39, 113, 115, 118) (Table 6 and Table 6.1)
10. to assess and to determine gender differences (28, 29, 31, 33, 34, 35, 36, 116, 117, 119, 120, 121, 122, 123, 124) (Table 11)

*Numbers in parentheses correspond to the number of prespecified secondary objectives defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229. Further details of these secondary outcomes are shown in Tables 4-19.

3 Study Design

3.1 Overview

This study is a European multicenter prospective pragmatic randomized controlled trial (PRCT) in patients with suspected CAD clinically referred for ICA. The pragmatic approach of the study

addresses practical questions about the risks, benefits, and costs of a CT- and ICA-directed strategy as they would occur in everyday clinical practice.[6]

CT directed clinical management will constitute the intervention group and ICA directed clinical management will be the control group. Thus, a 2-group randomized approach is utilized. Thus, both strategies might be labelled as “ICA first” vs. “CT first followed by ICA if indicated”. Blinding patients towards the diagnostic tests - CT or ICA - is not possible. A blinded adjudication of all outcomes will be performed as described in the study protocol section 10.5 and 10.6.

3.2 Sample Size

To show superiority of CT versus ICA with respect to MACE, a sample size of approximately 3546 men and women aged 30 years or older with suspected CAD and clinically referred to undergo ICA will be needed.

For sample size calculation a power of at least 80% and a 0.05 two-sided level of significance is assumed. The primary endpoint will be the MACE incidence until the 2nd follow-up. For this time to event data an exponential survival distribution is assumed with corresponding exponential parameter λ in each of the two groups. For the CT group we expect an exponential parameter of λ_1=0.00803 (corresponding to a one year MACE incidence equal to 0.8%, based on Noto TJ et al.[7], Boden WE et al.[8], Hulten EA et al.[9], Serruys PW et al.[10]) and for the ICA group an exponential parameter of λ_2=0.0141 (corresponding to a one-year MACE incidence equal to 1.4%, based on Noto TJ et al.[7], Boden WE et al.[8], Serruys PW et al.[10], Lichtlen PR et al.[11], Papanicolaou MN et al.[12]) yielding a constant hazard ratio of 0.5695. When the sample size in each group is 1773, with a total number of major adverse cardiovascular events required, E, of 99, an exponential maximum likelihood test of equality of survival curves will have the desired power of 80% to detect the difference between the exponential parameter of the CT group and the ICA group (**Table 1,** Napp AE et al.[13]).

Table 1: 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 randomized patients to the CT and the ICA groups, E number of events

Thus in total 3546 patients have to be allocated. In the study protocol, an interim analysis after 50 MACE have occurred was planned using a group sequential design (**Table 2**). In this group sequential design 80% power and a total 5% two-sided type I error were fixed. Corresponding to **Table 2**, the level of significance for the interim analysis of the primary outcome was 0.0052 and the level of significance for the final analysis of the primary endpoint at the 2nd follow-up was set at 0.048 (two-sided) leading to 50 and 99 events required (**Table 2**).

Table 2: Analysis plan for the group sequential design for an interim and final analysis with O'Brien-Fleming spending function

Analysis	E(vents)	Z	Nominal p	Spend
Interim	50	2.80	0.0052	0.0052
Final	99	1.98	0.048	0.0448
Total				0.05

(E – number of events required at each analysis; Z – standard normal test-statistic; p – two-sided p-value for Z; Spend - Incremental error spending at each given analysis) Note that this Table uses two-sided p-values instead of one sided p-values as presented in Napp AE et al.[13].

Publication of the interim analysis was allowed if all patients had been recruited and undergone the diagnostic strategies. The interim analysis has been performed as planned and the results have been presented to the DSMB. The two-sided p-value in this interim analysis was larger than 0.0052 (equivalent to a one-sided 0.0026).

In case less than 99 events will have occurred with completion of the 2nd follow up, the final analysis will be conducted based on the number of observed and verified events. Furthermore, the initial sample size calculation assumed an accrual period of 2 years and a minimum and maximum 2nd follow-up time of 2 and 4 years (median of 3 years), respectively. Conservatively, a common exponential drop-out rate of 0.0513 (5% per year) was assumed. The accrual period was extended, after review and approval of the required funding by the European Commission, from the planned 2 years to 3.5 years to enable recruitment of the planned patient number. Thus, the 2nd follow-up times were updated to adjust for the longer accrual period and the 2nd follow-up will occur after a median of 3.5 years after randomization.

Sample size estimation was performed using nQuery 7.0 and the R package *gsDesign* for group sequential design to perform an interim analysis was used. For precise recalculation of 2nd follow-up times after extension of the accrual period from 2.0 to 3.5 years with approval by the European Commission, we performed a Monte-Carlo simulation written in the statistical computer language R with N=1,000,000 runs, which demonstrated that the updated 2nd follow-up times maintain the desired power of 80%. The database will be locked on Dec 10th, 2021.

3.3 Inclusion/Exclusion Criteria

Due to the pragmatic approach (Thorpe KE[14]) of the DISCHARGE trial, only minimal inclusion and exclusion criteria are used for study population identification.

3.3.1 Inclusion Criteria

- Patients with suspected coronary artery disease with stable chest pain and intermediate pretest probability (10-60%) of CAD referred for invasive coronary angiography.

  "Stable chest pain" is defined as **not**
  - being acute (= first appearance within the last 48 hours) or
    instable angina pectoris =
    (a) first appearance with Canadian Cardiovascular Society Angina Grading Scale Class (CCS) III or IV[15],
    (b) progressive with at least 1 CCS Class to at least CCS Class III or, now at rest for at least 20 min)
- Patients of at least 30 years of age
- Written informed consent

The pretest probability 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 the probability of CAD. It was developed on the basis of the results of the COME-CCT project ("Collaborative Meta-analysis of Cardiac CT"; www.coronaryrisk.org, by Haase R et al.[16]).

3.3.2 Exclusion Criteria

- Patients who are/were on hemodialysis
- No sinus rhythm
- Pregnancy
- Any medical condition that leads to the concern that participation is not in the best interest of health (e.g., extensive comorbidities)
- Patients who participate in any other randomized/interventional study

4 Study Scheme

The first-patient in was in the first month of the PRCT and the last-patient out was originally planned at the end of month 48 of the PRCT (24 months of recruitment followed by 2 years of

follow-up with resulting minimal 24 months and maximal 48 month follow-up, respectively and median follow-up time of 36 month). After the extension of the recruitment of the PRCT to reach the required patient number the actual overall duration of the PRCT has been prolonged to 72 month (42 months recruitment period followed by a median follow-up of 3.5 years). The patient's timeline and time points where data will be collected can be taken from the following graphical presentation in **Figure 1**.

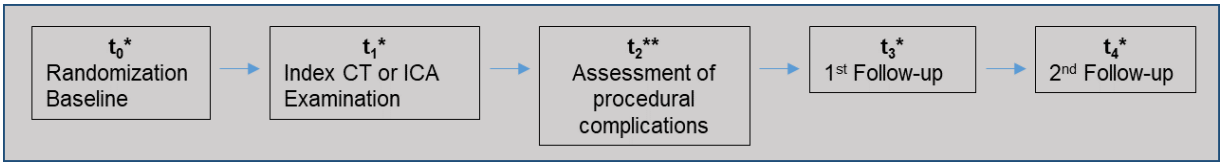

Figure 1: Timeline of the study

*Time frame for recording of MACE/MICE: from randomization (t_0) to CT/ICA diagnosis/procedure (t_1), follow-up for procedural complications (t_2) and during long-term follow-up until t_3 and t_4. The 1st follow-up (t_3) will be conducted after 1 year and the 2nd follow-up (t_4) will be conducted after a median of 3.5 years.

**Time frame for recording of procedural complications (t_2): Occur during the procedure or within 48 hours after the last procedure in the related patient management path following the initial index tests (CT or ICA), i.e. CT, ICA, ischemia test, PCI, and CABG.

5 Study Centers

26 clinical sites (hospitals and heart centers) in 16 European countries (Austria, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Spain, United Kingdom) consented for trial participation.

6 Assurance of Data Quality

The European Clinical Research Infrastructure Network (ECRIN) was responsible for the coordination of clinical monitors visiting the clinical sites (except Germany, which was coordinated by KKS Charité) to ensure adherence to protocol and compliance with ICH-GCP. On-site clinical monitoring was performed by ECRIN according to the monitoring plan in the study protocol and remote monitoring was performed by the coordinating center. The clinical data management team of the Coordinating Center of Clinical Studies at Charité (KKS Charité) was responsible for electronic data recording and preparation. Within the clinical monitoring process (done centrally and on-site) data were checked and proofed concerning consistency, completeness, range and plausibility. Unusual distribution of data within and between clinical sites were detected, checked and queried by project management.

7 Outcomes and Study Variables

This section defines the specific measurement variable, measurement scale, method of aggregation and time point for primary (7.1) and secondary (7.2) outcomes that will be compared between the CT and ICA group. In section 7.3 pre-planned analyses of other objectives are summarized along with the study variables, if appropriate. The outcomes will be evaluated by the respective work packages which are denoted.

7.1 Primary Outcome

The primary outcome measure is the occurrence of MACE which is a composite endpoint that comprises the occurrence of the first of the following entities:

- Cardiovascular death
- Nonfatal myocardial infarction
- Nonfatal stroke

In detail, the primary outcome is defined during the time frame from randomization until the first occurrence of any MACE-event up to the 2nd follow-up (t_4).

Table 3: Major adverse cardiovascular events from randomization until follow-up*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
MACE (composite = primary endpoint) and single components				**WP 11**				
1	Occurrence of - Cardiovascular death† - Nonfatal myocardial infarction †† - Nonfatal stroke††† †According to Definitions for Cardiovascular Endpoint Events in Clinical Trials by Hicks et al.[17] ††According to the Third Universal Definition of Myocardial Infarction by Thygesen et al.[18] †††According to Updated Definition of Stroke for the 21st Century by Sacco et al.[19]	Rate	Time-to-event	x	x	x	x	x

Explorative subgroup analyses:

- *Quintiles of pretest probability**
- *Age (< 45, 45-65, > 65 years) (24) (1) (125) and additionally in ages groups as defined in the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain[5] (< 65, 65-75, > 75)**
- *Gender (male versus female) (116)*
- *Body Mass Index (BMI) (< 25, 25-30, > 30) (25) (125) and additionally in BMI groups as defined in the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain[5] (≤40 and >40)**
- *Smoking status (never, former, current)**
- *Angina type groups (125)*
- *Diabetes**
- *CT plaque characteristic groups: high risk versus other plaques versus no plaques (125)*
- *ICA referral categories as defined by the 2013 ESC guidelines on the management of stable coronary artery disease of the European Society of Cardiology[1]**

Different composites of MACE definitions to be analyzed as secondary outcomes including competing risk analysis:

- *Composite endpoint: definition of MACE as*
  - *a) vascular death or Myocardial Infarction (MI) (126)*
  - *b) cardiac death or MI (126)*
  - *c) Nonfatal myocardial infarction or nonfatal stroke or cardiovascular death or major procedural complications (as defined in study protocol section 4.2.2) or transient ischemic attack**
  - *d) All-cause death or MI or stroke**
- *Occurrence of myocardial infarction (procedural and non-procedural) and stroke (127)*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
	- *Occurrence of myocardial infarction based on a secondary definition of nonfatal myocardial infarction according to the Fourth Universal Definition of Myocardial Infarction*[20]							

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 3A – Major adverse cardiovascular events, explorative analysis (change of time point zero in a landmark analysis from randomization to the actual conduct of the initial index Test t_1 and consideration of events until follow-up)*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
MACE (composite = primary endpoint) and single components				**WP 11**				
1	Occurrence of - Cardiovascular death† - Nonfatal myocardial infarction †† - Nonfatal stroke††† †According to Definitions for Cardiovascular Endpoint Events in Clinical Trials by Hicks et al.[17] ††According to the Third Universal Definition of Myocardial Infarction by Thygesen et al.[18] †††According to Updated Definition of Stroke for the 21st Century by Sacco et al.[19]	Rate	Time-to-event		x	x	x	x

* In order to exclude MACE during waiting time after randomization until initial index test.

7.2 Secondary Outcomes

For each of these secondary outcomes, not only a 2-sided significance test is applied but also the 95% confidence interval of the difference, hazard ratios or odds ratios will be given for the comparison of the two groups. Each subgroup analysis (subgroups are further specified in table 3 – 8, 10, 13, 14, 17 and section 7.2.3) will be accompanied by a statistical test of interaction between study group and subgroup factor.

7.2.1 Main Secondary Outcomes

Table 4: Minor cardiovascular events*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
MICE (composite) and single components				**WP 11**				
2	Occurrence of - coronary revascularization following new, non-index related ICA in a later management path (7) - peripheral artery revascularization (7) - hospitalization for chest pain/ discomfort (7) - emergency department visit for chest pain/ discomfort (7) - transient ischemic attack (7) - congestive heart failure (7) MICE will be analyzed in a time-to-event model considering the first of the above which occurs. Additionally, combinations of MICE at the same time point are counted separately for Poisson regression.	Rate	Time-to-event	x	x	x	x	x
Explorative subgroup analyses according to MICE: - *Quintiles of pretest probability** - *Age (< 45, 45-65, > 65 years) (24) and additionally in ages groups as defined in the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain[5] (< 65, 65-75, > 75)** - *Gender (male versus female) (116)* - *Body Mass Index (BMI) (< 25, 25-30, > 30) (25) and additionally in BMI groups as defined in the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and*								

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	*Diagnosis of Chest Pain[5] (≤40 and >40)**							
	- *Diabetes**							
	- *ICA referral categories as defined by the 2013 ESC guidelines on the management of stable coronary artery disease of the European Society of Cardiology[1]**							

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 5: Procedural Complications*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Procedural Complications				**WP 11**				
Major Complications: Any (composite) and single components								
3	• Occurrence of major procedural complications as defined in study protocol section 4.2.2 (death, nonfatal myocardial infarction, nonfatal stroke, further complications prolonging hospitalization by at least 24 hours, dissection (coronary, aorta) (35), cardiogenic shock (37), cardiac tamponade (37), retroperitoneal bleeding (37), cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation) (35), cardiac arrest)	Proportion	Nominal		x	x	x	
Minor Complications: Any (composite) and single components								
4	• Occurrence of minor procedural complications as defined in study protocol section 4.2.2 (hematoma at the puncture site (29), secondary bleeding at the puncture site (29), bradycardia, angina without infarction (36), allergoid contrast agent reaction (28), stent migration (36), hypotension requiring treatment (28), headache (28), hyperthyroidism (28), skin tissue and nerve injuries (29), extravasate (29), contrast-induced nephropathy (CIN) (31), infections (32), femoral arterial occlusion (or arterial access vessel) or dissection (35), new requirement for dialysis (37), DVT/pulmonary embolism (37), closure or injury of vessels (35), injury of the heart (e.g. valve or myocardium) (35), perforation (37), gastrointestinal bleeding (37), genital-urinary bleeding (37), other major bleeding (37), red blood cell (RBC)/Whole blood transfusion (37), twisting or rupture of the catheter parts	Proportion	Nominal		x	x	x	

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	(35), other equipment mishaps (e.g. retained foreign body guidewire fracture) (37), development of arterio-venous fistula(s) (35), development of pseudo aneurysm at puncture site (35), dissection (except dissections that are considered major procedure-related complications) (35), permanent edema (e.g. due to lymphatic congestion at puncture site) (35), embolization of central or peripheral vessels due to thromboembolism (35), acute closure of coronary vessels (36), stent infection, heart failure (37), wrong patient or wrong procedure (37), other (37))							
Explorative subgroup analyses as defined for MACE in Table 3 *Additional analysis: Major and minor complications of ICA procedure in the CT and ICA group*								

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 5.1: Procedural complications, findings, and characteristics of procedures*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Characteristics of diagnostic procedures, findings, recommendations and management of patients after CT or ICA				**WP 11**				
5	Stenosis (no stenosis, <20%, 20 to 50%, >50%, number of stenoses, most severe stenosis per patient) in both groups as well as agreement in diagnostic findings (kappa) and management between CT and ICA in patients receiving both*	Proportion	Ordinal		x	x	x	
6	Non-diagnostic segments (number, location): comparison of prevalence and patient as well as technical factors, binary in marginal analyses, GEE, leading to such uninterpretable findings or exams (46)	Proportion	Ordinal		x	x	x	x
7	Obstructive CAD (one vessel, two vessels, three vessels or Left Main disease)* Extent of CAD (Segment involvement score, Segment stenosis score, high-risk anatomy and non-high risk anatomy) and also extent of CAD in dependence of patients' socioeconomic status (income, education, occupation, job situation, gender) (19) Accuracy and agreement of automated analysis systems (56)	Proportion Median (IQR)/ Mean (SD) Accuracy	Nominal Metric Percent		x	x	x	x
8	Composite outcome: Rate of coronary artery anomalies (benign and malignant) and rate of myocardial bridging seen on CTA and ICA and the clinical implications of these at follow-up as well as influence on Major Adverse Cardiovascular Events (MACE) and MICE (10) Prevalence of sinus node artery being a side branch of Left Coronary Artery (LCX) or Right Coronary Artery RCA by core lab	Proportion	Nominal		x	x	x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	reading and the risk of CAD on CT and ICA as well as MICE and MACE (48) Prevalence of left, intermediate, and right coronary distribution type by core lab and site reading and the risk of CAD (as significant) on CT and ICA at baseline and MICE and MACE (49)							
9	Performing Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG) in a management path related to the index test (CT or ICA) (8, 12, 15, 16) - Completeness of revascularization for Percutaneous Coronary Intervention single vessel vs multivessel Percutaneous Coronary Intervention and Coronary Artery Bypass Graft; stent use (bare metal vs drug eluting) (22) - Information on surgical procedures i.e. isolated Coronary Artery Bypass Graft, Coronary Artery Bypass graft with valve replacement, Coronary Artery Bypass Graft with aortic surgery (23)	Proportion	Binary		x	x	x	x
10	Performing ICA, PCI or CABG in a later management path not indicated in the index test (CT or ICA) (8, 12, 15, 16) - Completeness of revascularization for Percutaneous Coronary Intervention single vessel vs multivessel Percutaneous Coronary Intervention and Coronary Artery Bypass Graft; stent use (bare metal vs drug eluting) (22) - Information on surgical procedures i.e. isolated Coronary Artery Bypass Graft, Coronary Artery Bypass graft	Proportion	Binary		x	x	x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	with valve replacement, Coronary Artery Bypass Graft with aortic surgery (23) - Rate of follow-up Invasive Coronary Angiographies and Percutaneous Coronary Interventions related to the index test (CT or ICA) after initial Computed Tomography/Invasive Coronary Angiography and up to 1st and 2nd follow-up (70) - Additional treatments during follow-up by clinical site (104)							
11	Undergoing further cardiac diagnostics (see chapter 11.4) 48h after the final procedure related to the index test randomized to (11, 12) and additional tests: Differences in adverse events might lead to a different use of diagnostic tests during the follow-up phase. Therefore, data about cost-effective differences of examinations, not being mandatory according to the study protocol, will be collected. (103)	Proportion	Binary		x	x	x	x
12	Undergo further cardiac diagnostics (see chapter 11.4) in a later management path not related to the index test in a later management path (CT or ICA) (11, 12)	Proportion	Binary				x	x
13	Performing coronary revascularization (15)	Proportion	Binary		x	x	x	x
14	Performing coronary revascularization (PCI and CABG) (16) Improvement of selection of distal coronary segments used for Coronary Artery Bypass Surgery-anastomosis by Computed Tomography in comparison to Invasive Coronary Angiography alone (especially heavy calcification detection) as assessed by the cardiac surgeons (50)	Proportion	Binary		x	x	x	x

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
15	Treatment recommendations after index tests* - consider other cardiac or non-cardiac reasons for pain - Preventive medical therapy (PMT) defined as statin (primary definition) or statin plus antiplatelet (secondary definition - risk factor modification - perform best locally available imaging ischemia test - ICA and treatment according to ESC/ EATS guideline	Proportion	Nominal		x			
16	Time from randomization to ICA (20) and also to CT (including a per-site analysis)*	Median (IQR)/ Mean (SD)	Metric	x	x			
17	Time from randomization to first coronary revascularization (including a per-site analysis) (21)	Median (IQR)/ Mean (SD)	Metric	x	x	x	x	x
18	Duration of the exams (in min)*	Median (IQR)/ Mean (SD)	Metric		x	x		
19	Length of initial hospital stay* and days in hospital per patient by clinical site during follow up (102)	Median (IQR)/ Mean (SD)	Metric		x	x	x	x
20	Comparison of procedural complications in: - Outpatient versus inpatient ICA rates after adjusting for risk factors (34) - Femoral versus radial approach ICA (34) - Different closure devices versus manual compression (34) - Patient acceptance* - Diabetes* - ICA referral categories as defined by the 2013 ESC guidelines on the	Proportion	Nominal		x	x		

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
	management of stable coronary artery disease of the European Society of Cardiology[1]*							
21	Complications related to ICA: e.g. cardiac arrhythmia, closure or injury of vessels, etc. (35) and procedural complications during or after revascularization (36)	Proportion	Nominal		x	x		
22	Occurrence of other adverse events (AE) and serious adverse events (SAE) (37)	Proportion	Nominal		x	x		

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 6: Health-related Quality of Life (HRQoL)*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Health-related Quality of Life (HRQoL)				**WP 10**				
23	SF-12v2: Physical Component Summary (PCS) (113)	Median (IQR)/ Mean (SD)	Metric	x*			x	X
24	SF-12v2: Mental Component Summary (MCS) (113)	Median (IQR)/ Mean (SD)	Metric	x*			x	X
25	EQ 5D-3L: Health profile (113)	Proportion	Ordinal	x*			x	X
26	EQ 5D-3L: Visual Analogue Scale (VAS), overall self-rated health (113)	Median (IQR)/ Mean (SD)	Metric	x*			x	X
27	EQ 5D-3L: Index values (113)	Median (IQR)/ Mean (SD)	Metric	x*			x	X
28	Hospital Anxiety and Depression Scale (HADS): Depression Subscale (113)	Median (IQR)/ Mean (SD)	Metric	x*			x	X
29	HADS: Anxiety subscale (113)	Median (IQR)/ Mean (SD)	Metric	x*			x	X

* for baseline adjustment

Explorative subgroup analyses for main papers at t3 and t4:

- *Gender (113), Age (< 45, 45-65, > 65 years)* and additionally in ages groups as defined in the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain[5] (< 65, 65-75, > 75)**
- *Angina type at baseline (typical angina, atypical angina, non-anginal chest discomfort and other chest discomfort) (113)*
- *CAD diagnosis (obstructive CAD, non-obstructive CAD, no CAD)**
- *Major or minor procedural complications (any versus none)**
- *Patient groups according to treatment paths (Revascularization: any revascularizations until the follow ups, Medical Treatment alone: defined as Medical Treatment until the follow ups)**
- *MACE (yes/no) at t_4 (113)*
- *Body Mass Index (BMI) (< 25, 25-30, > 30) (25) and additionally in BMI groups as defined in the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain[5] (≤40 and >40)**
- *Diabetes**

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
- *ICA referral categories as defined by the 2013 ESC guidelines on the management of stable coronary artery disease of the European Society of Cardiology[1]**								
Explorative subgroup analyses for secondary papers:								
- *Quintiles of pretest probability*, Baseline chest pain intensity (0-3, 4-6, 7-10) based on the strongest episode within the past 12 months (113)*								
- *Occurrence of chest pain in the past 4 weeks at t3 (for t3 QoL) and t4 (for t4 QoL)*								
- *Socioeconomic status*, Country of origin, European region (i.e. south vs. north)**								
- *Chronic illness (i.e. rheumatoid arthritis, diabetes)**								
- *Lifestyle*, Incidental findings**								
- *Type and quantity of plaques in the CT arm**								
- *Patients with obstructive CAD who do or do not undergo ischemia-guided recommendations*, Patients without obstructive CAD and with or without potential etiologies identified explaining patient's symptoms*, Patients who underwent conservative versus invasive treatment strategies (matched analysis for the extent of CAD and ischemia).**								

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 6.1: Further pre-specified analyses of HRQoL (WP 10)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
30	Associations between HRQoL and: - Socio-economic variables* - Cardiac risk factors Occurrence of chest pain in the past 4 weeks at t3 (for t3 HRQoL) and t4 (for t4 HRQoL)*, and Lifestyle* - Treatment Regimens (adherence to therapy recommendation as covariate: statin alone, statin plus antiplatelet, statin plus antiplatelet plus risk factor modification or any combination with risk factor modification (17) - Family History of premature coronary artery disease in women or men* Analyses will be stratified by gender*	Pearson and Spearman correlation coefficients, linear regression coefficients derived from general linear models including /SE	Various (outcome metric, covariates categorical, ordinal or metric)	x			x	x
31	Change and predictors of change in HRQoL over time in the complete sample (stratified by randomized group status in case change in HRQoL differs between groups). - Socio-economic variables* - Cardiac risk factors Occurrence of chest pain in the past 4 weeks at t3 (for t3 HRQoL) and t4 (for t4 HRQoL)*, and Lifestyle* - Treatments* - Family History of premature coronary artery disease in women or men* Analyses will be stratified by gender and differences regarding HRQoL, lifestyle and socioeconomic status at baseline as well as in regards to changes of these factors seen at the	Regression coefficient/SE will be derived from linear mixed models including random intercepts for patients and investigating contrasts t4-t0 and t3-t0. Interactions with study group will be tested	Metric	x			x	x

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
	two follow-up time points in the two randomized groups and in male and female patients with and without CAD on testing (118)							
32	Comparison of HRQoL in participants across European regions (North: Denmark, Latvia, Finland; Central: Germany, Austria; East: Czech Republic, Hungary, Lithuania, Poland, Romania, Serbia; South: Italy, Portugal, Spain; West: United Kingdom, Ireland) at baseline and over time*	Cross sectional: effects from analysis of variance including pairwise comparisons (Tukey B) longitudinal analysis: regression coefficients/SE from linear mixed models	Metric	x			x	x
33	Comparison of different measures of HRQoL (113) (115)	Pearson correlation analysis of measurements and their differences over time	Metric	x			x	x

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Cost-effectiveness:

Cost-effectiveness and cost-utility analysis will be described separately in a specific SAP.

Table 7: Radiation exposure*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Radiation Exposure and Contrast Agent				**WP 3**				
34	Effective radiation dose measured as - dose length product and - dose area product during CT (for Coronary Artery Calcium (CAC) Score and CT) and ICA (87) and reduction of radiation exposure by using coronary artery calcium score information (88) • Association of experience of examiners on events, duration of the exams, contrast agent amount used for diagnosis and intervention and exposure of radiation. (33)	Median (IQR)/ Mean (SD)	Metric		x	x	x	x
35	Cumulative radiation dose (87)	Median (IQR)/ Mean (SD)	Metric		x	x	x	x
36	Amount of contrast medium (in ml) used for entire procedure (CT or ICA) and the cumulative contrast agent amount in the two study group (14) • Association of experience of examiners on events, duration of the exams, contrast agent amount used for diagnosis and intervention and exposure of radiation. (33)	Median (IQR)/ Mean (SD)	Metric		x	x	x	x
*Explorative subgroup analysis: Gender for radiation dose (117) and for contrast amount**								

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 8: Angina Pectoris*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Influence of CT and ICA strategy on Chest Pain				**WP 11**				
37	Occurrence of chest pain in the past 4 weeks and occurrence of exertional chest pain in the past 4 weeks as determined by the Rose questionnaire – short form*	Proportion	Nominal				x	x
38	Intensity of chest pain: Reduction of angina pectoris intensity (on the scale from 0 to 10) in the two study groups (26)*	Median	Ordinal	x			x	x

Explorative subgroup analyses for main papers at t3 and t4:

- *Age (< 45, 45-65, > 65 years)* and additionally in ages groups as defined in the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain[5] (< 65, 65-75, > 75)*, Gender**
- *Angina type at baseline (typical angina, atypical angina, non-anginal chest discomfort and other chest discomfort)**
- *CAD diagnosis (obstructive CAD, non-obstructive CAD, no CAD)**
- *Major procedural complications (any versus none)**
- *Minor procedural complications (any versus none)**
- *Patient groups according to treatment paths (Revascularization: any revascularizations until the follow ups, Medical Treatment alone: defined as Medical Treatment until the follow ups)**
- *MACE (yes/no) at t_4**
- *Body Mass Index (BMI) (< 25, 25-30, > 30) (25) and additionally in BMI groups as defined in the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain[5] (≤40 and >40)**
- *Diabetes**
- *ICA referral categories as defined by the 2013 ESC guidelines on the management of stable coronary artery disease of the European Society of Cardiology[1]**

Explorative subgroup analyses for secondary papers:

- *Quintiles of pretest probability**
- *Baseline chest pain intensity (0-3, 4-6, 7-10) based on the strongest episode in the past 12 months**
- *Socioeconomic status*, Country of origin, European region (i.e. south vs. north)**
- *Chronic illness (i.e., rheumatoid arthritis, diabetes)**
- *Baseline elevated depressive symptoms (HADS-D score >=8)*, Lifestyle*, Incidental findings**
- *Type and quantity of plaques in the CT arm**
- *Patients with obstructive CAD who do or do not undergo ischemia-guided recommendations (26), Patients without obstructive CAD and with or without potential etiologies identified*

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	explaining patient's symptoms (26), Patients who underwent conservative versus invasive treatment strategies (matched analysis for the extent of CAD and ischemia (26).							

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229. For self-reported angina endpoints, we have pre-specified "occurrence of angina in the past 4 weeks" at the follow-ups as the primary angina variable (pre-specified principal patient-reported angina outcome).

7.2.2 Other Secondary Outcomes

Table 9: Incidental Findings*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Incidental Findings				**WP 11**				
39	Comparison of findings of non-coronary cardiac causes of symptoms (e.g. aortic dissection, valve disease, pericarditis) and potential benefits and harms of findings. Analysis of prevalence non-coronary cardiac causes of symptoms and influence of non-coronary cardiac findings on Major Adverse Cardiac Events, non-cardiac events and HRQoL (38, 39)	Proportion	Nominal		x	x	x	x
40	Any non-cardiac findings (e.g. thrombus, pulmonary embolism, pleural effusion, pneumonia, hiatal hernia) and potential benefits and harms of findings. Analysis of prevalence of non-cardiac findings, causes of symptoms and influence of non-cardiac findings on MACE, non-cardiac events and HRQoL (38, 39)	Proportion	Nominal		x	x	x	x
41	Findings of malignancy in nodules seen on CT (40)	Proportion	Nominal		x	x	x	x
42	Risk prediction for lung cancer by McWilliams et al. (41)[21]	Rate	Ordinal		x	x	x	x
43	Death from cancer, competing risk analysis (42)	Rate	Time-to-event				x	x
44	Conducting unnecessary follow-up procedures (examinations, biopsies, surgeries done based on non-coronary findings) (43)	Proportion	Nominal				x	x

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 10: Patients' acceptance and preference*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Patients' acceptance and preference according to the procedures that the patient underwent				**WP 6**				
45	Patients' acceptance ("preference questionnaire") (85)	Median	Ordinal		x†	x†		
46	Patients' acceptance of informed consent, preparation and procedural aspects of the test performed (86)	Median	Ordinal		x†	x†		
47	Satisfaction with the trial (rate the information about the study in general) (85)	Proportion	Ordinal		x†	x†	x	
48	Satisfaction with preparation and information prior to examination (86)	Proportion	Ordinal		x†	x†		
49	Satisfaction with performance of the performed examination (86)	Proportion	Ordinal		x†	x†	x	
50	Assessment of maximum pain during examination (VAS 0 – 100) (86)	Median (IQR)/ Mean (SD)	Metric		x†	x†		
51	Patients' acceptance of management after CT or ICA of patients who could not be discharged directly (86)	Proportion	Ordinal		x†	x†		
† at timepoints when examinations are performed								
Explorative subgroup analyses: 31), patients without significant stenosis seen on the initial test randomized to, patients with significant stenosis seen on CT and a) ICA not recommended or done e.g., because of imaging ischemia results or b) ICA done (85, 86)								

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

7.2.3 Gender Aspects

First, gender is a baseline characteristic that may influence outcomes independently or modify effects of intervention on outcome. These aspects will be examined by gender subgroup analyses for the primary and secondary endpoints as described above (7.2.1 and 7.2.2).

Second, demographic and baseline characteristics as well as prevalence and characteristics of CAD in men and women will be analyzed and compared.

Third, gender will be analyzed along with CAD variables (coronary stenosis, coronary plaque) in prognostic models for MACE and MICE.

Fourth, among women, the impact of specific female cardiovascular risk factors (see below) on prevalence and type of CAD, diagnostic safety and accuracy of ICA/CT and prognosis will be assessed.

The following table describes planned analyses regarding the gender aspect.

Table 11: Variables used in gender analyses (WP 7)*

No	*Measurement Variable*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
Prevalence and characteristics of CAD in European women and men (Hypothesis 1)								
52	Independent variable: Gender (119) Dependent variables / outcomes: • Demographic and Baseline Characteristics* • CAD variables: - Rate of coronary artery disease and coronary stenosis (by CT and/or ICA): patient-by-patient normal, non-obstructive and >50% stenosis and – defined as vessel disease (1VD, 2VD, 3VD or LM) (119) - Coronary plaque (by CT): coronary plaque assessment, including calcified, mixed and non-calcified plaque, remodeling index, ring-sign, spotty calcification (120) Gender differences of myocardial resting	Proportion Proportion/ Median (SD) Proportion Proportion Proportion/	Binary Nominal /Metric Ordinal Nominal Nominal	x	x		x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	blood flow / tissue characteristics determined by cardiac CT using parameters such as regional and global TPR, AD, PI, perfusion defects, myocardial calcification, myocardial fatty infiltration, myocardial thinning. (121)	Median	/ Metric					
Gender related differences of safety and diagnostic accuracy/yield by ICA or CT (Hypotheses 2 and 3)								
53	Independent variables: • Diagnostic procedure (CT, ICA) • Gender	Proportion	Nominal	x	x	x	x	x
	Dependent variables / outcomes: • Procedural complications (28, 29, 31, 33, 34, 35, 36)	Proportion	Nominal					
	• Gender differences in radiation exposure: Radiation dose received for all performed invasive / non-invasive diagnostic procedures, for each type of procedure (ICA, PCI, CT, SPECT, PET) and for each diagnostic strategy (CT and ICA) (117)	Median (SD)	Metric					
	• Index diagnostic conclusion: CAD with indication for revascularization, CAD with indication for antianginal medical therapy, no CAD (119)	Proportion	Nominal					
	• Coronary revascularization proportion of patients undergoing PCI or CABG*	Proportion	Nominal					
	• pulmonary findings of cardiac CT (in the CT group) a) signs of pulmonary congestion: Ground-Glass Opacification (GGO), Pleural effusions, interlobular transudate high density pulmonary attenuation index b) pulmonary emphysema (with/without CAD), low density	Proportion	Nominal					

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	pulmonary attenuation index c) Pulmonary embolism (major, minor) (123) structural cardiac CT findings including parameters such as LV-mass, volumes and dimensions of Left Ventricle (LV), Left Atrium (LA), Right Ventricle (RV), Right Atrium (RA) and blood pressure (124)							
Gender related differences of prognosis as predicted by either CT or ICA (Hypothesis 4)								
54	Independent / predictor variables: • Gender (116) • CAD variables - Coronary stenosis (by CT or ICA): patient-by-patient normal, non-obstructive and >50% stenosis and – defined as vessel disease (1VD,2VD,3VD or LM) (119) - Coronary plaque (by CT): coronary plaque assessment, including calcified, mixed and non-calcified plaque, remodeling index, ring-sign, spotty calcification (120) Dependent variables / outcomes: • MACE* • MICE* • EQ 5D-3L: Index values (113) • Occurrence of chest pain in the past 4 weeks	Proportion Proportion Rate Rate	Nominal Time-to-event Time-to-event	x	x		x	x
Gender related differences of true positive findings (Hypothesis 3)								
55	Independent / predictor variables: • Diagnostic procedure (CT, ICA)* • Gender (116) Dependent variables / outcomes: Diagnostic value of CT in men vs women - frequency of	Proportion	Nominal	x	x		x	x

No	Measurement Variable	Measure	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	true positive findings in patients referred for ICA - i.e. frequency of revascularization in patients referred for ICA based on CT with and without ischemia testing, CT findings, Ischemia testing findings, ICA (122)							

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Baseline characteristics including general cardiovascular risk factors defined above as well as specific cardiovascular risk factors in women including age at first menstrual cycle, age at menopause (in women after menopause), early menopause (<40 years), duration in years of contraceptive medication treatment, hysterectomy y/n - if Y age at Hysterectomy, Oophorectomy y/n - If Y age at Oophorectomy, number of pregnancies, number of child births, age at first childbirth, premature birth (before week 37) Y/N - If Y age at birth, breastfeeding Y/N - if Y number of months, heart or medical problems during pregnancy Y/N - If Y type, pregnancy with (gestational) hypertension Y/N, pregnancy with preeclampsia Y/N, pregnancy induced diabetes Y/N. Baseline cardiovascular demographics for both women and men includes but is not limited to age, BMI, conventional CVD risk factors, ethnicity, marital status, socio-economic variables, geographic location, symptom status and HRQol.

7.3 Pre-planned Analyses for Other Objectives

Table 12: Analysis of Differences in Europe (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
56	Likelihood of receiving PCI/CABG in different European countries (1) or regions (North: Denmark, Latvia, Finland; Central: Germany, Austria; East: Czech Republic, Hungary, Lithuania, Poland, Romania, Serbia; South: Italy, Portugal, Spain; West: United Kingdom, Ireland)*	Rate	Metric	x			x	x
57	Rates of PCI and use of intracoronary techniques in different European countries (2) or regions (North: Denmark, Latvia, Finland; Central: Germany, Austria; East: Czech Republic, Hungary, Lithuania, Poland, Romania, Serbia; South: Italy, Portugal, Spain; West: United Kingdom, Ireland)*	Rate/ Proportion	Time-to-event/ Nominal	x			x	x
58	Patient management in different European countries (3) or regions as described above	Proportion	Nominal	x			x	x
59	Follow-up strategies in different European countries (4) or regions as described above	Proportion	Nominal	x			x	x
60	European differences in occurrence and extent of CAD in regards to city versus rural lifestyle (5) as well as PMT and risk factor modification* for regions as described above	Proportion	Nominal	x			x	x
61	European and local differences in patient consent (i.e. patient participation and withdrawal) of sites (6) or regions as described above	Proportion	Nominal	x			x	x
62	Geographical distribution of risk factors for MACE and MICE, cardiovascular events and cardiac events (18) for regions as described above	Proportion / Rate	Nominal / Time-to-event	x			x	x

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 13: Image-based Outcomes for CT and ICA group (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
63	Image quality in CT and ICA groups and analysis of interobserver variability (site versus core lab) of reading for coronary stenosis and plaques (44): • Interobserver variability (site versus core lab) of reading for coronary artery calcium scoring in CTA for stenosis and plaques in CT and ICA and for CT calcium scanning: including analysis of patient subgroups • Accuracy of plaque and stenosis detection and quantification as well as characterization using existing probing and segmentation software	Median (IQR)/ Mean (SD)/ Cohen's Kappa, Chi-square test, binary or ordinal logistic regression, Agreement (Bland-Altman method)	Ordinal/ Metric		x	x	x	x
64	Percent diameter stenosis (45) and correlation between percent diameter stenosis by CT with invasive fractional flow reserve (FFR) and correlation of non-invasively estimated FFR by CT with invasive FFR after CT/ICA (47): • Analyses of the correlation between quantitative flow ratio (QFR) and CT-FFR in patients with suspected coronary artery disease • Inter- and intraobserver agreement in quantification of CT-FFR and QFR in patients with suspected coronary artery disease • Analyses of the accuracy for prediction of clinically indicated coronary revascularization with CT-FFR and QFR compared to stenosis quantification on CTA and ICA • Analysis of CT-FFR and QFR in	Correlation (Pearson), Cohen's Kappa, Chi-square test, binary or ordinal logistic regression, Agreement (Bland-Altman method)	Metric			x	x	x

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
	relation to functional test results*							

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators. Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 14: Image Quality and Image-based Outcomes in CT group (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
65	Relation of plaque characterization and quantification by core lab and MACE and MICE (51)	Regression coefficient/ SE	Metric				x	x
66	Image quality of CT by core lab read and flow and concentration of contrast agent used intravenously (52)	Regression coefficient/ SE	Metric		x	x	x	
67	Coronary artery dimension (mm) (53)	Diameter	Metric		x	x	x	
68	Noise in CT imaging (quantified) (54)	Median (IQR)/ Mean (SD)	Metric		x	x	x	
69	Factors that influence image quality: BMI, gender, origin of patient, number of detector rows, heart rate, 80-100-120-135-140 kV, different mA settings, acquisition type (55). The relationship between these factors and frequency of non-diagnostic segments will be assessed.* Evaluation of the 10-step guide to cardiac CT (57)	Regression coefficient/ SE	Metric		x	x	x	
70	Semi-qualitative analysis: Composite outcome (intensity, noise, signal to noise, contrast and signal to noise in some regions of interest) (58)	Median (IQR)/ Mean (SD)	Metric		x	x	x	
71	Qualitative analysis: Composite outcome (levocardiography effect and some regions of interest) (59)	Median (IQR)/ Mean (SD)	Metric		x	x	x	
72	Heart rate reduction achieved by DISCHARGE beta-blocker protocol (also in subgroups: e.g. gender, age, subgroups of patients with contraindication to beta blockers or no adherence to protocol ,…) (60, 61) and conscious sedation (62)	Median (IQR)/ Mean (SD) Plus Regression coefficient/ SE	Metric		x	x	x	
73	Correlation of extent of CAD and high calcium score (63):	Correlation (Pearson),	Metric		x	x	x	

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
	• Analysis of prevalence and extent of CAD (obstructive disease and plaques) in correlation to high calcium score • Analysis of stress test results in correlation to high calcium score (>400)* • Exclusion of any CAD in correlation to a zero calcium score, potential of defining a threshold with high predictive value	Kappa						
74	Characterization of plaques and stenosis by CT core lab in relation to cardiac risk factors and baseline patient characteristics (64)	Regression coefficient/ SE	Metric		x	x	x	
75	Differences in plaque characteristics (type and composition) and analysis of potential influence by geographical origin of the patient, after adjustment for other cardiac risk factors. (65)	Regression coefficient/ SE	Metric		x	x	x	
76	Comparison of CT and intracoronary techniques (66)	Regression coefficient/ SE	Metric		x	x	x	
77	Influence of statin treatment on plaque development (67)	Regression coefficient/ SE	Metric		x	x	x	

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 15: Outcomes of ICA procedure (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
78	Correlation of effective dose and diagnostic proportion (i.e. those without non-diagnostic test results) with weight and BMI (68)	Correlation (Pearson), Kappa, Chi-square test, binary or ordinal logistic regression	Ordinal		x		x	x
79	Correlation of effective radiation dose and contrast agent amount used for ICA with severity of CAD on ICA (69)	Correlation (Pearson), Kappa, Chi-square test, binary or ordinal logistic regression	Ordinal		x		x	x
80	Correlation of the number of projections for the right and left coronary artery with effective dose of ICA (71)	Correlation (Pearson), Kappa, Chi-square test, binary or ordinal logistic regression	Ordinal		x		x	x
81	Rates of left ventriculography performed (72)	Rates	Ordinal		x		x	x

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 16: Planned invasive diagnostic testing in accordance with management recommendations (WP 6)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
82	Rates of invasive testing with ICA in the CT group based on positive and negative CT imaging findings as well as patients receiving the test not randomized to (73) and rates of unnecessary ICA performed (no obstructive CAD diagnosed in stress test including MRI or without PCI/CABG)	Proportions	Nominal			x	x	
83	Comparison of patients with planned ICA in the CT group based on positive or negative CT imaging findings to patients not receiving ICA even if indicated by CT findings and patients switching over to the test not randomized and not recommended by findings of the index test to regarding patient-reported health status, MACE, MICE (74)	Mean differences (health status) Hazard Ratios (MACE), Relative Risks (MICE) each including SEs	Nominal		x	x	x	x
84	Analysis of influence of prior CT on ICA and PCI in terms of duration, radiation exposure, amount of contrast agent used in patients randomized to CT in comparison to patients randomized to ICA (13).	Median (IQR)/ Mean (SD)	Metric		x	x		

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 17: Ischemia tests (WP 3)*

No	*Pre-planned analyses*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
85	Correlation of CT and/or ICA results with the results of ischemia tests (exercise ECG, stress echo, stress SPECT, stress PET, stress MRI, FFR, before or after index CT or ICA testing) (11) (75) and in different ICA referral subgroups[1]	Rates	Ordinal Metric	x		x	x	x
86	Correlation between imaging ischemia tests and invasive Fractional Flow Reserve (FFR) if done (76)	Rates	Ordinal Metric	x		x	x	x
87	Rates of (imaging) ischemia tests recommended (77) Rate of PCI / CABG recommended and appropriate revascularization (PCI / CABG) performed after CTA and positive or negative imaging ischemia tests in comparison to the ICA arm (81)	Rates	Ordinal Metric	x		x	x	x
88	Comparison of diagnostic accuracy of (imaging) ischemia tests for the detection of CT- or ICA-defined CAD and prediction of MACE, MICE (78, 79)	Agreement, Accuracy	Ordinal Metric	x		x	x	x
89	Correlation between (imaging) ischemia results and coronary stenosis as well as plaque composition and characterization findings by CT (80)	Rates	Ordinal Metric	x		x	x	x
90	Correlation of the results of study-CT, recommended (imaging) ischemia test and ICA in patients with respective study course (82)	Rates	Ordinal Metric	x		x	x	x
91	Occurrence of procedural events in (imaging) ischemia testing (83)	Rates	Ordinal Metric	x		x	x	x
92	Correlation of intensity and reduction of angina pectoris with (imaging) CS (84)	Rates	Ordinal Metric	x		x	x	x

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 18: Comparison of Pretest Probability Calculators and Event Predictors (WP 11)*

No	*Steps of analysis*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
93	Validation of the CAD DISCHARGE and COME-CCT pretest probability calculators. (90, 92) Comparison of the ability of the calculators to predict CAD in different genders (91)	Agreement/ Accuracy/ ROC	Metric	x	x		x	x
94	Potential advantage of calculators in combination with chest discomfort guidelines to triage patients most effectively based on pretest probability in comparison to the DISCHARGE approach of CT including calcium scoring and CTA for management decision making about risk factor modification and revascularization (93)	Agreement/ Accuracy/ ROC	Metric	x	x		x	x
95	Predictive value of the DISCHARGE calculator in patients who could not be included in the trial due to their very low pretest probability (< 10%) or very high pretest probability (> 60%). (94, 95)	Agreement/ Accuracy/ ROC	Metric	x	x		x	x
96	Development of a novel pretest probability calculator based on age, gender, symptoms, and cardiac risk factors and/or exercise ECG or imaging ischemia results of patients in DISCHARGE with CT and/or ICA results being the reference standard for the definition of CAD for this novel calculator; comparison of this novel calculator with the simple DISCHARGE pretest probability calculator for diagnostic test selection (96) Further: Ability to predict MACE and MICE (97)	Agreement/ Accuracy/ ROC	Metric	x	x		x	x
97	Validation of different questionnaires to predict Major and Minor Adverse Cardiac Validation of different questionnaires to	Agreement/ Accuracy/ ROC	Metric	x	x		x	x

No	*Steps of analysis*	*Measure*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
	predict Major and Minor Adverse Cardiac Events: Validation of the Rose Angina questionnaire including pain scale and the modified InterHeart Risk Score (IHRS; baseline: InterHeart cholesterol risk score) to predict MACE and MICE in both trial groups (27).							

* Numbers in parentheses correspond to the number of prespecified secondary analyses defined before the start of the DISCHARGE trial at https://clinicaltrials.gov/ct2/show/NCT02400229.

Table 19: Deep Learning (DL), Radiomics, and Fractal Analysis of Coronary Calcium Score, Coronary CT and IC Angiography, Coronary Artery Plaques, Pericoronary Inflammation, Coronary Artery Flow, and Myocardial Tissue and Myocardial Perfusion*

No	*Steps of analysis*	*Measure and analysis method*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
98	Coronary Calcium Score: development and validation of the diagnostic and predictive value of DL and radiomics models of coronary and noncoronary calcifications for coronary disease and clinical outcomes (MACE and MICE) including the importance of explainabillity and integration of human reader input into DL models and the interpretation of radiomics (including fractal analysis) texture findings.	Development Learning sample (2/3 of total sample). Validation: Validation sample using ROC analysis, Poisson (MICE) and Cox regression analysis including score values as parameters	Metric	x	x		x	x
99	Coronary Angiography: development and validation of the diagnostic and predictive value of DL and radiomics models of CT and invasive coronary angiography for coronary disease and clinical outcomes (MACE and MICE) including the importance of explainabillity and integration of human reader input into DL models and the interpretation of radiomics (including fractal analysis) texture findings.	Addition of covariate "change of Score by interpretation of human readers" in the model of 98, comparison of classification rates and AUROC between models with and without human readers	Metric	x	x		x	x
100	Coronary Artery Plaques: development and validation of the diagnostic and predictive value of DL (including graph DL) and radiomics models of coronary artery plaques and (peri-)coronary	identical to No 99	Metric	x	x		x	x

No	Steps of analysis	Measure and analysis method	Scale	Timepoint				
				t_0	t_1	t_2	t_3	t_4
	inflammation for coronary disease and clinical outcomes (MACE and MICE) including the importance of explainabillity and integration of human reader input into DL models and the interpretation of radiomics (including fractal analysis) texture findings.							
101	Coronary Artery Flow: development and validation of the diagnostic and predictive value of DL and radiomics models of coronary artery flow (e.g. fractional flow reserve, quantitative flow ratio) for coronary disease and clinical outcomes (MACE and MICE) including the importance of explainabillity and integration of human reader input into DL models and the interpretation of radiomics (including fractal analysis) texture findings.	identical to 99	Metric	x	x		x	x
102	Myocardial Tissue and Perfusion: development and validation of the diagnostic and predictive value of fractal analysis, DL, and radiomics models of myocardial tissue and perfusion for coronary disease and clinical outcomes (MACE and MICE) including the importance of explainabillity and integration of human reader input into models and the interpretation of findings.	identical to 99	Metric	x	x		x	x
103	Comprehensive Cardiac Analysis and Risk Prediction: development and validation of the diagnostic and predictive value of comprehensive models (integrating 98-102 above) for coronary disease and clinical outcomes (MACE and MICE) including the	identical to 99	Metric	x	x		x	x

No	*Steps of analysis*	*Measure and analysis method*	*Scale*	*Timepoint*				
				t_0	t_1	t_2	t_3	t_4
	explainabillity and integration of human reader input into DL models.							

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clincialtrials.gov but were predefined in this SAP before the release of any study data to statisticians and investigators.

The following **Table 20** summarizes all analyses planned for the primary and secondary endpoints with the related scales and comparisons.

Table 20: Overview of Scales and Statistical Comparisons of all Primary and Secondary Endpoints

Table	*Title*	*Measurement Variable No*	*Scale*	*Comparison between arms*
3 and 3A	Major adverse cardiovascular events	1	Time-to-event	Kaplan Meier, Cox Model, cumulative incidence
4	Minor cardiovascular events	2	Time-to-event	Kaplan Meier, Cox Model, cumulative incidence, competing risks
5	Procedural Complications	3,4	Nominal	Chi-square test binary or polytomous logistic regression
5.1	Procedural complications, findings, and characteristics of procedures	5,6	Ordinal	Chi-square test ordinal logistic regression
		7	Nominal Metric Percent	Nominal: chi-square test binary or polytomous logistic regression, Metric: t-test and general linear model, Percent (agreement) Kappa Measure
		8,15,20-22	Nominal	Chi-square test binary or polytomous logistic regression
		9-14	Binary	Chi-square test binary logistic regression
		16-19	Metric	Mann-Whitney test, cumulative incidence (in case of censoring)
6	Health-related Quality of Life (HRQoL)	23,24,26-29	Metric	Linear mixed effect model
		25	Ordinal	Ordinal logistic GEE model
6.1	Further pre-specified analyses of HRQoL (WP 10)	30	various (outcome metric, covariates categorical, ordinal or metric)	Linear mixed effect model
		31	Metric	Linear mixed effect model
		32	Metric	ANOVA, Linear mixed effect model
		33	Metric	Pearson correlation analysis

7	Radiation exposure	34-36	Metric	t-test, general linear model
8	Angina Pectoris	37	Nominal	Chi-square test binary logistic regression
		38	Ordinal	Chi-square test ordinal logistic regression
9	Incidental Findings	39-41,44	Nominal	Chi-square test, cumulative incidence (in case of censoring)
		42	Ordinal	Sensitivity, specificity, ROC analysis
		43	Time-to-event	Kaplan Meier, Cox Model, cumulative incidence, competing risks
10	Patients' acceptance and preference	45-47-49,51	Ordinal	Chi-square test ordinal logistic regression
		50	Metric	t-test and general linear model
11	Variables used in gender analyses (WP 7)	52-55	Binary, Ordinal, Metric, Nominal, Time-to-event	Same methods as used in comparison of study arms
12	Analysis of Differences in Europe (WP 3)	56	Metric	Anova, Kruskal Wallis test, logistic regression and Cox model with dummy variables
		57,62	Time-to-event/ Nominal	Anova, Kruskal Wallis test, logistic regression and Cox model with dummy variables
		58-61	Nominal	Anova, Kruskal Wallis test, logistic regression and Cox model with dummy variables
13	Image-based Outcomes for CT and ICA group (WP 3)	63-64	Ordinal/ Metric	Chi-square test, binary or ordinal logistic regression, Agreement (Bland-Altman method), Cohen's kappa
14	Image Quality and Image-based Outcomes in CT group (WP 3)	65-77	Metric	Confidence intervals for proportions, medians, and means
15	Outcomes of ICA procedure (WP 3)	78-81	Ordinal	Chi-square test, binary or ordinal logistic regression
16	Planned invasive diagnostic testing in accordance	82-84	Nominal/ Metric	Kappa Measure

	with management recommendations (WP 6)			
17	Ischemia tests (WP 3)	85-92	Ordinal/ Metric	Metric: t-tests and general linear model, binary/ordinal chi-square tests and binary/ordinal logistic regression
18	Comparison of Pretest Probability Calculators and Event Predictors (WP 11)	93-97	Metric	Agreement (Bland-Altman method), Pearson correlations
19	Deep Learning (DL), Radiomics, and Fractal Analysis	98-103	Metric	For comparison of different prediction models: Agreement (Bland-Altman method), Accuracy, ROC, Pearson correlations, Kappa, F1-score (segmentation)

8 Analysis Sets

8.1 Definitions

The following analysis sets will be considered:

- **Intention-to-Treat (ITT) analysis set**

  The ITT analysis set includes all randomized patients in the groups to which they were randomly assigned, i.e. CT or ICA. Patients who withdraw or are withdrawn by study physician before procedure and randomized patients found to have not fulfilled eligibility criteria (randomization in error) will be excluded. The intention of the exclusion of such withdrawals before diagnostic procedure from the ITT analysis set, which was specified in the study protocol, was to avoid bias in between-group comparisons because of evidence from earlier smaller randomized trials suggesting higher patient withdrawal rates before procedures after randomization to ICA (5.8% and 11.0%) compared to randomization to CT (0.6% and 4.7%).[22,23] This approach was also implemented to avoid underestimating MACE rates and decreased estimated effect size and power. Furthermore, missing follow-up information for the primary endpoint will be treated as censored.

- **Per-Protocol (PP) analysis set**

  The PP analysis set is defined as a subset of the ITT analysis set of only those patients who attempt to undergo ICA or CT as randomized, and excludes patients who received the test they were not randomized to as the index test (‘change of study arm’). Furthermore, patients with a negative CT who received ICA will be excluded and also patients with ICA as the index test who received an additional CT, which was not recommended to be done in the protocol, will be excluded.

- **Safety analysis set**

  The safety analysis set includes all patients who undergo at least one investigation. Data will be analyzed in groups according to the diagnostic test procedure (CT or ICA) the patients undergo first as the index test. For each event, the relation to the first test patients undergo as well as to further procedures will be assessed. An additional analysis will be performed in patients who received both CT and ICA.

8.2 Applications

Analysis for the primary and secondary outcomes will be performed primarily for the ITT analysis set and secondarily for the PP analysis set. Procedural complications, MACE and MICE will be additionally analyzed for the safety analysis set.

8.3 Major Protocol Violations

Major protocol violations are defined as:

1) patients who were randomized to an intervention but did not receive any intervention because they withdrew or were withdrawn.
2) patients who did not receive the intervention they were randomized to.

In case of major protocol violations due to 1) clinical sites are requested to recruit further patients and these patients will not be included in the ITT analysis. For major protocol violations due to 2) patients will be taken into account in the ITT analysis set.

Protocol violations will be checked on complete data for all patients prior to defining the analysis populations. The decision will be based on the blinded raw data listings and the protocol violations and deviations tracked by Project Management.

Major protocol violations will be summarized by type of violation and by investigation group and overall.

9 Treatment of Missing Values

Missing values of the primary endpoint MACE and other time-to-event data (e.g. time until the occurrence of MICE, coronary revascularization) will be treated as censored observation. Missing values for confounding variables are likely to occur. Thus, multiple imputation methods will be used in order to deal with missing values in secondary outcomes (see Section 10.5). Missing values at t_0, t_3 and t_4 will be treated by multivariate imputation by chained equations as implemented in the R-package "mice"[24]. This multiple imputation algorithm generates at least m=100 imputation samples. The imputation methods depend on the measurement level (scale) of the target variable. It uses predictive mean matching (pmm) for metrical, logistic regression for binary and polytomous logistic regression for ordinally scaled variables. The imputation models contain all HRQoL variables, angina, and important baseline characteristics such as gender, age, and angina type at baseline as independent variables. In case of instable models, not all variables will be used. For adverse events, i.e. major and minor procedural complications as well as major and minor adverse cardiovascular events, no imputation will be performed. We do not impute a missing value if the reason for the missing value is the patient's death. Also a sensitivity analysis will be performed to compare results based on the multiple imputations with the complete case setting.

10 Statistical Analysis

10.1 General Principles

Data will be summarized by each intervention group and for pooled intervention groups. For both continuous variables (e.g. age) and ordinal variables (e.g. severity of symptoms) descriptive statistics will be presented (range and number of patients with data for each variable, mean and standard deviation for normally distributed variables, median, 25th and 75th percentiles for ordinal or nonnormally distributed variables). Normal distribution will be assessed by the criterion skewness and kurtosis between -1 and +1. For categorical variables (e.g. sex) frequencies, percentages and number of patients with data will be presented. The denominator for the percentages will be the number of patients with non-missing data. Descriptive analysis will be done primarily on available data. The same analysis can be done using multiple imputation data, but only if differences are relevant. Relevance of these differences will be determined between Investigators and Statisticians. Data will be analyzed according to measurement scale and distribution.

Listings of individual patient's data will be provided by KKS Charité. The statistical output for the primary endpoint will be generated by Peter Martus and validated independently by Konrad

Neumann, who is responsible for patient-reported outcome statistics. Only for this analysis p-values will be given and significance statements will be formulated in the main publication. Statistical testing will be performed using a two-sided significance level of 0.048 (4.8%) in the main publications. For all other analyses in the main publication point estimates and two-sided 95% confidence limits for the relevant parameters (rates, proportions, hazard ratios, means, medians, correlation coefficients, regression coefficients, areas under the ROC curve, Kappa values, Bland Altman limits of agreement) will be given. In secondary analyses p-values will be reported if in accordance with journal policy.

10.2 Patients' Availability

The number of patients who provided informed consent and were randomized will be summarized. The number of subjects included in the ITT and PP analysis sets will be included in the table. The assignment of populations (c.f. section 8.3) will be done using a blind data review in which outcome is not disclosed. Patients not treated in the study arm they were randomized to will be assigned to the ITT population but not to the PP population. Attendance at each defined time point, including missed time points, discontinuations, lost to follow-up and percentage accountability will be summarized. A list of patients who withdraw early will be provided. It will include the reason and timing of the withdrawal. Similarly, the reason any patient was excluded from an analysis set will also be provided. In addition, major known protocol deviations will be noted for individual patients; a summary table may also be provided. These violations will be defined in advance, however, in the course of the review new criteria might be added.

The patient's availability will be displayed in a Consolidated Standards of Reporting Trials (CONSORT) diagram. The number of screened patients who fulfilled trial inclusion criteria, and the number included in the primary and secondary analyses, as well as reasons for exclusions in primary and secondary analyses will be reported.

10.3 Demographic and Baseline Characteristics

All demographic and baseline characteristics captured in the eCRF will be summarized by treatment arm and across the whole trial. Baseline characteristics include but are not limited to age, gender, type of chest pain, pretest probability of obstructive CAD, cardiovascular risk factors, pulmonary risk factors, cigarette smoking, BMI, cardiovascular medications, ICA referral categories, patient reported outcomes at baseline as angina intensity and health related quality of life. Furthermore, demographic characteristics including, but not limited to partner or marital status, education and work status, cigarette smoke exposure, alcohol

consumption and nutrition and ethnicity will assed, as well further baseline characteristics including, but not limited to blood pressure, concomitant medication, NYHA-class, hypertension, family history of CAD, diabetes, cardiac history.

Data will be presented by adequate statistical measures as described in paragraph 10.1.

10.4 Primary Analysis

The primary endpoint will be MACE incidence until the occurrence of MACE within the time window from randomization until the 2nd follow-up. This event time will be analyzed using techniques from survival time analysis. Kaplan Meier curves for the CT- and ICA-group will be generated. The event-rate at 2nd follow-up and the 95% confidence interval will be presented for each group. The primary analysis in the ITT will be done without adjusting for pretest probability of obstructive CAD in the two groups. A sensitivity analysis will include pretest probability of obstructive CAD.

Differences between the two groups with respect to the primary endpoint will be finally tested at a two-sided significance level of nominal 0.048 due to alpha-spending for interim analysis to preserve the overall significance level of 5%. The primary statistical hypothesis to be tested is that under the proportional hazards assumption (i.e., $HR = h_{CT}(t) / h_{ICA}(t) = \text{constant}, t \geq 0$) there is no difference in the hazards for MACE between the two investigation groups, i.e.:

$$H_0: HR = 1 \quad \text{vs.} \quad H_A: HR \neq 1$$

Here, $h_{CT}(t)$ and $h_{ICA}(t)$ $(t \geq 0)$ denote the hazard functions for MACE for the two groups. For proving the above hypotheses a Cox proportional hazards model including investigation group adjusted for gender due to stratified randomization will be applied. Results of this first Cox proportional hazards model will be presented as hazard ratio together with 95% confidence interval accounting for alpha spending.

To adjust for pretest probability and the variables contributing to pretest probability (age, gender, angina type), additional Cox proportional hazards models will be used to test for differences between the two groups. In case of non-convergent models (too many covariates) forward variable selection will be applied.

As a sensitivity analysis, a Cox proportional hazards model with random effects for site (i.e. frailty models[25]) will be applied. This model will be used in order to take variability between study centers and unobserved heterogeneity into account. This unobserved heterogeneity might be e.g. the result of different therapeutic adherence within each center. The relative effect of CT versus ICA will be presented as hazard ratio together with 95% confidence interval.

Study center will be included as random factor only if results are stable. These will be inspected by standard convergence criteria and inspection of parameter estimates in the several model estimation steps.

Checking the proportional hazards assumption will be done using goodness of fit test based on Schoenfeld residuals.[26] In case the proportional hazards assumption is not fulfilled a parametric regression model and a model using time dependent covariates will be chosen.

10.5 Secondary Analyses

In secondary analyses p-values will be reported if in accordance with journal policy.

The secondary endpoints will be evaluated:

- by means of parametric (unpaired or paired t-test, (RM-)ANOVA) or non-parametric (Kruskal-Wallis test, Mann-Whitney-U test or Friedman test, Wilcoxon signed-rank test) tests according to scaling and distribution
- by means of linear mixed models or binary logistic GEE models for clustered and longitudinal data (e.g. HRQoL-data)
- by means of Chi^2-test for comparison of proportions between different groups
- logistic regression models for binary outcome data
- Kaplan Meier method and Cox proportional hazard models for censored data, competing risk analysis if adequate
- by means of correlation analysis (Pearson, Spearman, Sommers-d, Kendall-tau) according to scaling
- by means of Kappa-coefficient or Intraclass-Correlation for agreement consideration
- by a statistical test of interaction between study group and subgroup factor for each subgroup analysis.
- MICE are analyzed using Poisson regression with the natural logarithm of follow-up time as offset.

Appropriate parameters of group-specific outcomes (e.g., rates, prevalences, mean or median values) and effect size (e.g., relative risks, odds ratios, difference of mean or median) with 95% confidence intervals will be calculated.

Since the time between randomization and 2^{nd} follow-up is not fixed in this pragmatic trial, in sensitivity analyses, the true time interval involving endpoints at t3 and t4 (Figure 1) will be adjusted for.

If indicated, subgroup analyses will be performed in appropriate models (Cox proportional

hazard model, logistic regression model) including interaction terms between intervention and other pre-specified covariates (see 7.1 and 7.2).

Among HRQol endpoints the VAS (EQ3D) and the physical component score (PCS) of the SF12v2 are defined as variables of primary interest (pre-specified principal patient-reported QOL outcomes). For self-reported angina endpoints, we have pre-specified “occurrence of angina in the past 4 weeks” as the primary angina variable (pre-specified principal patient-reported angina outcome). This will be reported for the two follow-up time points.

HRQoL analyses will be carried out at baseline (t_0), at 1-year follow-up (t_3) and at the 2nd follow-up (t_4). Beside the Qol variables also the change of the variables between t_0 and t_3, between t_0 and t_4 and between t_3 and t_4 will be compared between groups defined by the factors randomization groups (CT and ICA). Furthermore, we will compare the study groups ICA and CT in the pre-defined subgroups (see Tables 6 and 8). From the DISCHARGE pilot we know that the HRQoL endpoints are nearly symmetrically distributed.[27] Hence, we may assume that for all Qol outcomes the normality assumption will be satisfied, and parametric statistical methods can be applied. Hence, group comparisons will be carried out using univariate linear mixed effects models with study group, age, gender and angina type at baseline as independent variables and the HRQoL variables as dependent variables. The statistical model treats possible site effects as random since the study sites are a sample from many heart centers all over Europe. This two-level approach seems more appropriate than the alternative approach to treat site effects as fixed. For a thorough treatment of whether site effects are fixed or random, we will apply methods described by Brown and Prescott.[28]

Group comparisons of patient-reported angina as the dependent variable will be performed using a logistic generalized estimating equation model (GEE) with independent working correlation structure and with randomisation group, age, gender, angina type at baseline, and time from baseline to follow-up as independent variables. Similar to the linear mixed effects model the GEE model accounts for correlations arising from possible site effects. Since we expect that the time between t_0 and $t_{3/4}$ can influence Qol outcomes we will adjust all Qol scores at t_3 and t_4 with respect to the time between t_0 and t_3 and between t_0 and t_4. The choice of the model used for these adjustments will depend on the distribution of the time between t_0 and t_3 and between t_0 and t_4, respectively. Missing values at t_0, t_3 and t_4 will be treated by multiple imputation. For more details on the imputation method see Section 9.

An overview of all analyses planned for the primary and secondary endpoints is summarized in **Table 20**.

10.6 Safety Analyses

Safety will be evaluated by tabulations of adverse events (AEs) and will be presented with descriptive statistics at examination and during follow-up ($t_{2\text{-}4}$) for each investigation group.
A tabulation of Serious Adverse Events (SAEs) will be provided by patient within groups.

11 Scales and Definition for Clinical Evaluations

11.1 Protocol Definition of MACE

MACE is defined as at least one of the following:

- Cardiovascular death
- Nonfatal myocardial infarction
- Nonfatal stroke

Protocol definition of cardiovascular death

The standardized definitions for endpoints in clinical trials developed by the joint Writing Committee to Develop Cardiovascular Endpoint Data Standards of the American College of Cardiology/American Heart Association (ACC/AHA) will be implemented.[17] These definitions for cardiovascular endpoint events in clinical trials were initially included as an unpublished document in the DISCHARGE study protocol as Hicks et al. (2014: Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations) and are updated in this SAP after full journal publication by Hicks et al. for the ACC/AHA Committee. According to this definition, all deaths will be rated and classified as cardiovascular, non-cardiovascular or undetermined. Cardiovascular deaths are defined as all deaths excluding death for which the underlying cause is exclusively non-cardiovascular. As introduced by Hicks et al.,[17] cardiovascular death includes death resulting from:

a) Acute myocardial infarction
b) Sudden cardiac death
c) Death due to heart failure
d) Death due to stroke
e) Death due to cardiovascular procedures
f) Death due to cardiovascular hemorrhage
g) Death due to other cardiovascular causes

Protocol definition of nonfatal myocardial infarction

The actual definition of myocardial infarction (MI) of the joint European Society of Cardiology/ American College of Cardiology/American Heart Association/World Heart Foundation (ESC/ACC/AHA/WHF) Task Force will be implemented.[18] Events are defined as nonfatal if they are not leading to death of the patient.

Protocol definition of nonfatal stroke

The definition of stroke by the American Heart Association/American Stroke Association (AHA/ASA) was implemented.[19]

11.2 Protocol Definition of MICE

The composite endpoint MICE is defined as at least one of the following:

- Coronary revascularization following new, non-index related ICA
- Peripheral artery revascularization
- Hospitalization for chest pain/ discomfort
- Emergency department visit for chest pain/ discomfort
- Transient ischemic attack
- Congestive heart failure

11.3 Protocol Definition of Procedural Complications

See study protocol section 4.2.2.

11.4 Definition of Further Cardiac Diagnostics

Further cardiac diagnostics include the performance of

- Additional CT or ICA (including additional tests in ICA: FFR [functional invasive test], IVUS and OCT [anatomical tests])
- Electrocardiogram (ECG)

Additional noninvasive functional tests:

- Exercise ECG
- Stress echocardiography
- Stress magnetic resonance imaging
- Stress SPECT
- Stress PET-CT

11.5 Patient Reported Outcomes (Angina and HRQoL)

Angina

At baseline and all follow-ups, patients are asked to rate the occurrence and intensity of their chest pain. **Exertional and non-exertional angina** are assessed using the short version of the Rose questionnaire. In addition, patients are asked to rate the **intensity** of their strongest episode of angina in the past 12 months on an 11-point scale ranging from 0 (no pain) to 10 (maximum pain). Intensity ratings are grouped into low (0-3), medium (4-6) and high (7-10) angina intensity.
At each follow-up, patients were asked if they had chest pain/discomfort in the last 12 month (for FU1) or since the first follow-up (for FU2), respectively and if so, when their **last episode of chest pain/discomfort** had occurred. The primary angina endpoint "occurrence of angina within the past 4 weeks" will be derived from this information.

Short Form-12v2 (SF-12v2)

The SF-12v2 is a generic measure of health status which encompasses an eight-scale profile of functional health and well-being, as well as two physical and mental health summary measures.[29] In DISCHARGE, we use the standard (4-week) recall form of the SF-12v2.

The eight domains of functioning are: Physical Functioning, physical health-related role limitations (Role-Physical, RP), Bodily Pain, General Health, Vitality, Social Functioning, emotional health-related role limitations (Role-Emotional, RE) and Mental Health. These are further aggregated in two component summary measures: physical component summary (PCS) and mental component summary (MCS).

The eight health domain scores as well as the summary component scores will be transformed to t-scores according to the SF-12v2 user's manual.[29] The *standard* scoring algorithm (based on the SF-12v2 2009 US general population normative sample) will be applied rather than country-specific SF-12v2 scoring algorithms, because a) country-specific algorithms are only available for some but not all countries represented in DISCHARGE and b) a comparison of DISCHARGE participants' SF-12v2 scores to normative sample data is not the aim of this study, but rather the assessment of intervention effects on HRQoL. For calculation of the two dimensions PCS and MCS of the SF-12v2 we will use the software Optum™-PRO CoRE with the scoring method "Maximum Data Recovery". From the DISCHARGE pilot where the same QoI outcomes were evaluated we know that the skewness of the distributions of all metrical QoI outcomes is small.[27] Hence we report as for all metrical QoI outcomes means and standard deviations for the scores PCS and MCS and may assume that the normality assumption is true.

Furthermore, we will report the proportion of patients with PCS / MCS scores below one standard deviation of the US general population normative sample as part of the health-related quality of life secondary outcomes of DISCHARGE.

EuroQoL (EQ-5D-3L)

The EQ-5D-3L[30] was developed by the EuroQol group as a subjective measure of health status. The questionnaire consists of two parts. The first part assesses current health-related quality of life in five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, each of which can take one of three responses (no problems/some or moderate problems/extreme problems). The second part consists of the EQ visual analogue scale (VAS): a standard vertical 20 cm visual analogue scale (similar to a thermometer). Participants are asked to rate how good or bad their own health is today, on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

The EQ-5D-3L allows for the presentations of health profiles along the five functional dimensions (no problems, some problems and extreme problems). This allows for calculating percentages of patient groups with some or extreme problems in each domain. Further**,** health states can be presented, e.g. health state 11212 represents a patient who indicates some problems (=2) on the usual activities and anxiety/depression dimensions and no problems (=1) on the other dimensions. These health states can be converted to a single index value using (one of) the available EQ-5D-3L value sets. These value sets have been derived using Visual Analogue Scale (VAS) or time trade-off (TTO) valuation techniques from the general population. Value sets for the EQ-5D-3L are available for all countries participating in DISCHARGE.[29, 31]

We will report the health states (proportion of participants with some or extreme problems in each of the five functional domains), and means, standard deviations for the visual analogue scale and the index value.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) assesses the presence and severity of symptoms of anxiety and depression. The depression and anxiety subscales each contain seven questions.[32] Several cut-offs for possible “clinical caseness” have been proposed, most often, a score of 8 on either subscale will be considered a cut-off for a depressive or anxiety disorder, respectively. Several studies have validated this instrument for use in somatically ill patients.[33, 34] We will report means and standard deviations for the two subscales as well as the proportion of participants with a score of >= 8 (cut-off for elevated depressive / anxiety symptoms, respectively).

12 Software

Data manipulation, statistical summaries and statistical analyses will be performed using SAS software, Version 9.4 or higher for Windows (Copyright© 2014 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.). Some analysis may be carried out in SPSS (IBM, version 26 or higher) and R version 3.2.0 or higher.[35]

13 Scientific Concomitant Program

Within the study several further scientific objectives will be considered:

- Pretest Probability Calculator:
  - To compare several pretest probability calculators
  - To investigate the predictive value of the DISCHARGE calculator
  - To develop a novel pretest probability calculator
- Development of 10-steps guide to performing cardiac CT and scanner specific protocols
- Development of CT quality criteria for image quality and radiation exposure

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Summary of changes to the Statistical Analysis Plan of the DISCHARGE trial

Name of Trial: Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies

ClinicalTrials.gov Identifier: NCT02400229

Statistical Analysis Plan Version	**Signature Date**
Original Version	November 6, 2020
Final Revised Version	December 8, 2021

This document details changes to the DISCHARGE Statistical Analysis Plan.
The Statistical Analysis Plan (SAP) was developed with the DISCHARGE trial leader and statisticians of the study. Necessary changes to the original version were made in the 2nd version prior to database lock and data analysis.

Section 2.2 Secondary Objectives
Addition of Table 19, addition of diabetes mellitus and ICA referral criteria to Table 3 and Table 4 for explorative subgroup analyses for MACE and MICE, respectively.

Section 3.2 Sample Size
Addition of a table (Table 1 included in the study design publication, which was published by Napp et al.[1]) to explain power calculation.
A section on updated power calculation was inserted which adjusted for the actual duration of the 2nd follow-up period after extension of the trial was approved by the European Commission.
The original table for the analysis plan (now Table 2) was adjusted for 2-sided p-values as described in the Study Protocol.

Section 4 Study Scheme
The timeline of the trial was adjusted to actual study duration.

Section 7.1 Primary Endpoint
Addition of subgroup analyses for age, BMI, diabetes mellitus, and ICA referral categories.
Addition of Table 3A to present a landmark explorative analysis for MACE.

Section 7.2.1 Main Secondary End Points

In Table 4, the analysis of MICE was described further as a time-to-event model, and further subgroup analyses for age, BMI, diabetes mellitus, and ICA referral categories were added.
In Table 5.1, No 20 diabetes mellitus and ICA referral categories were added as subgroup analyses.

In Table 6, age, BMI, diabetes mellitus, and ICA referral categories were added as further subgroup analyses, also the occurrence of chest pain in the last 4 weeks. In Table 6.1, the occurrence of chest pain in the last 4 weeks was added to No 30 and No 31. For No 32, European regions were specified in detail. Previously missing measures and scales were added to Table 6 and 6.1.

In Table 7, measures were adjusted and No 34 and No 36 extended for analysis of association of examiner's experience with events, duration of the exams, contrast agent amount used for diagnosis and intervention, and radiation exposure.

In Table 8, age, BMI, diabetes mellitus, and ICA referral categories were added as subgroup analyses, as were elevated depressive symptoms at baseline *(HADS-D score >=8)*.

In Table 9, for No 42, previously missing measures and scales were added.

In Table 10, for No 45 and No 46, previously missing measures and scales were added.
7.2.3. was further extended by 4 additional hypotheses and, in Table 11, previously missing measures and scales were added.

In Table 12, previously missing measures and scales were added and, for No 56 and No 57, European regions were specified in detail.

In Table 13, previously missing measures and scales were added and, for No 63 and 64, further subgroup analyses added.

In Table 14, previously missing measures and scales were added and, for No 73 and No 74, further subgroup analyses added.

In Table 15, previously missing measures and scales were added.

In Table 16, previously missing measures and scales were added.

In Table 17, previously missing measures and scales were added.

In Table 18, previously missing measures and scales were added.

Addition of new Table 19, in which all radiomics analyses were now described; addition of an overview of all scales and comparisons in additional Table 20.

Section 9 Treatment of Missing Values

This section was updated to include more details on the imputation method at each time point, the statistical program used, and independent variables.

Section 10.1 General Principle

For primary endpoint analysis, a p-value will be given in the main publication. For all other analyses in the main publication, point estimates and two-sided 95% confidence limits for the relevant parameters will be given. In secondary analyses, p-values will be reported if in accordance with journal policy.

Section 10.2 Patients' Availability

In this section, it was noted that the unchanged definition of the ITT population (section 8.1) should be applied.

Section 10.4 Primary Analysis

We clarified that study center will be included as random factor only if results are stable. This will be assessed by applying standard convergence criteria and inspection of parameter estimates in the model estimation steps.

Section 10.5 Secondary Analyses

We provided more detailed information on models used (linear mixed models and binary logistic GEE models).

Analysis of MICE was described in greater detail.

Former Section 10.7 Analysis at 1st Follow-up

Analysis description was deleted as interim results at 1st follow-up up were not published.

Section 14 References

Additional references were added.

Formal and wording changes

Pg. 2-3 Table of Content adjusted.

Section 1 Background wording adjustments.

Section 2 Study Objectives wording adjustments.

Section 3.1 Overview wording adjustments.

Section 3.3 Inclusion/Exclusion Criteria wording adjustments.

Section 7.1 Primary End Point wording adjustments.

Section 7.2 Secondary End Points wording adjustments.

Section 10.3 Demographic and Baseline Characteristics wording adjustments.

Section 10.5 Secondary Analyses wording adjustments.

Section 11.1 Protocol Definition of MACE wording adjustments.

Section 11.5 Patient-Reported Outcomes

References

1. Napp AE, Haase R, Laule M, Schuetz GM, Rief M, Dreger H, et al. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. Eur Radiol. 2017;27(7):2957-68.