FINAL REPORT

Grant Agreement number:	603266
Project acronym:	**DISCHARGE**
Project title:	Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies
Funding Scheme:	Collaborative Project (small or medium-scale integrating project)
Period covered:	from 01/02/2014 to 31/01/2020
Project coordinator name:	Dr. Marc Dewey
Organisation name:	CHARITE – UNIVERSITAETSMEDIZIN BERLIN

List of abbreviations

AE	Adverse event
CAD	Coronary artery disease
CEA	Cost-effectiveness analysis
CEC	Clinical events committee
CT	Computed tomography
CTA	CT angiography
DC	Dissemination committee
DSMB	Data safety and monitoring board
EAB	External advisory board
ECR	European Congress of Radiology
eCRF	Electronic case report form
EUnetHTA	European Network for Health Technology Assessment
ICA	Invasive coronary angiography
INAHTA	International network of Agencies for HTA
HTA	Health technology assessment
MACE	Major adverse cardiovascular events
MICE	Minor cardiovascular events
PRCT	Pragmatic randomised controlled trial
SAP	Statistical analysis plan
SAE	Serious adverse event
SC	Steering Committee
SOP	Standard operation procedure
WP	Work package

Content

1. Final publishable 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 (CTA)** is the most accurate diagnostic test for CAD currently available, excellent for the exclusion of disease with high certainty. CTA 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.

Although diagnostic accuracy of CTA has been confirmed in several studies in the recent past, there is little evidence of the effectiveness in a large population of patients with an intermediate pretest probability. We expect our results to support the hypothesis that CTA is also effective in this important patient population.

To evaluate this, the DISCHARGE project with a 5-year duration was implemented by a multinational European consortium. The project was prolonged by 12 month by the EU to a total duration of 6 years. The core of the project is the DISCHARGE trial, a **pragmatic randomised controlled trial (PRCT)**. The primary hypothesis is that CTA is superior to ICA for **major adverse cardiovascular events (MACE)**, including cardiovascular death, nonfatal 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 is assessed by 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 includes 26 clinical sites from 16 European countries, which recruited 3883 patients of which 3667 were randomised to either CTA or ICA ensuring broad geographical representation. Further areas of interest are radiation exposure, cost-effectiveness analysis (CEA), quality of life (QoL), systematic review of evidence and health technology assessment and gender differences. All of these aspects are assessed in separate work packages, which are supported by a statistician and his staff and are led by experts in the field.

Although ICA is a well-known and widely spread diagnostic test, being conducted by experienced physicians, it remains an invasive test with a low but evident chance of adverse events (AEs). Our research hypothesis is that replacing a certain amount of ICA examinations by CTA, being a non-invasive test, leads to **reduced AE rates**. Adverse events can be subdivided into non-serious and serious adverse events (SAE). MACE are an important subcategory of SAE because of their severity and therefore the need of fast and intensive treatment. Therefore, the occurrence of MACE is the primary endpoint. We expect that the rate of MACE is lower in patients, receiving CTA in comparison with patients, being diagnosed by using ICA.

From the economic point of view, our hypothesis is that CTA is **cost-effective** compared to invasive coronary angiography (ICA) since patients with a low to intermediate pretest probability are likely to have negative results, gained by the cheaper CTA, making a more expensive ICA obsolete. We take into account, that CTA is obsolete in patients with CAD, requiring treatment by ICA. We assume that the potential savings by avoiding ICA in patients without CAD exceed additional costs, caused by diseased patients, requiring ICA after CT for treatment. This leads to potential savings on a macroeconomic level. Currently, there are 2 million ICA examinations with negative results in the EU. By using CTA as a non-invasive and cheaper diagnostic alternative, a reasonable amount of possible savings becomes evident.

Because of these two explanations, we expect our results to support the hypothesis that the supplement of ICA by CTA will lead to relevant savings for health care systems and with that, for national economies.

While the 1 year follow-up was completed by January 2020 in regard to MACE, the second follow-up is still ongoing. Thus no final results are available.

2. Summary of project context and objectives

Currently ca. 2 million ICA examinations are performed annually in the Europe, which yield negative results. Only 40% of patients undergoing ICA actually have obstructive CAD. ICA is the reference standard for the diagnosis of CAD, the leading cause of death in high-income countries. This diagnostic method allows immediate therapy of obstructed coronary arteries. Although ICA is a well-known and widely spread diagnostic test, being conducted by experienced physicians, it has relatively rare but considerable risks since it is an invasive test with a low but evident chance of AEs. CTA is the most accurate diagnostic test for CAD currently available, excellent for the exclusion of disease with high certainty.

By using CTA as a non-invasive and cheaper diagnostic alternative, a reasonable amount of possible savings becomes evident: It may become the most effective strategy to reduce the negative ICAs by enabling early and safe discharge of the majority of patients with an intermediate risk of CAD. In addition, CTA, being a non-invasive test, leads to reduced AE rates. Adverse events can be divided into non-serious and serious adverse events (SAE). Major adverse cardiovascular events (MACE) are an important subcategory of SAE because of their severity and therefore the need of fast and intensive treatment. Therefore, the occurrence of MACE is the primary endpoint.

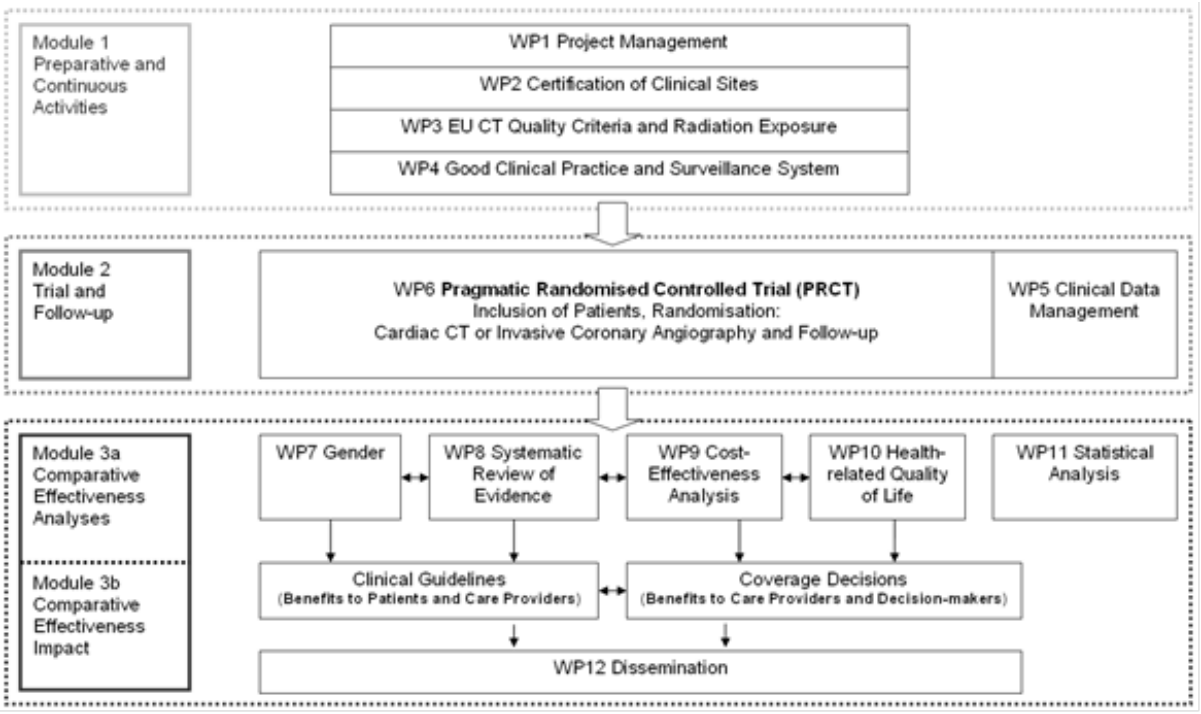
We expect that the rate of MACE is lower in patients, receiving CTA in comparison with patients, being diagnosed using ICA. We take into account, that CT is obsolete in patients with CAD, requiring treatment by ICA. We assume that the potential savings by avoiding ICA in patients without CAD exceed additional costs, caused by diseased patients, requiring ICA after CTA for treatment. This leads to potential savings on a macroeconomic level.

To evaluate the above hypotheses the DISCHARGE project with a 5-year duration was implemented by a multinational European consortium. The project was prolonged by 12 to a total number 6 years by the EU. The core of the project is the DISCHARGE trial, a pragmatic randomised controlled trial (PRCT). The primary hypothesis is that CTA is superior to ICA for MACE 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. The results of the PRCT will provide the basis for clinical decision-making according to comparative effectiveness research methodology.

The trial includes 26 clinical sites from 16 European countries, which recruited 3883 patients of which 3667 were randomised to either CTA or ICA ensuring broad geographical representation. Further areas of interest are radiation exposure, cost-effectiveness analysis (CEA), quality of life (QoL), systematic review of evidence and health technology assessment (HTA) as well as gender differences. All of these aspects are assessed in separate work packages, which are led by experts in the field who are supported by a statistician and his staff.

Twelve work packages (WPs) grouped in 3 modules have been defined in DISCHARGE to reach the aimed at objectives. Module 1 includes preparative and continuous activities, module 2 contains the trial and the follow-up. Module 3 was further split in two submodules: module 3a contains comparative effectiveness analyses and module 3b focuses comparative effectiveness impact.

Figure 1. Work packages, modules, and work flow within the DISCHARGE project



WP1 Project Management

Project management has to oversee and coordinate the project in accordance with the coordinator and consortium council. It functions as interface between the European Commission and all partners and established boards. Management procedures include the preparation of meetings, minutes, reports and audits as well as handling finances in the project.

WP2 Certification of Clinical Sites

Main objective of this WP is to guarantee the quality of the work performed by all clinical sites in the trial. To reach this goal, all investigators and their staff have to be trained in standard operating procedures (SOPs) for the general conduct of the trial as well as the correct use of the electronic clinical database. In addition, all clinical sites have to provide proof of the certification of their CT reading supervisors.

WP3 EU CT Quality Criteria and Radiation Exposure

This WP ensures quality of image acquisition and radiation protection. It provides information on patient exposure and radiation risk for the models that will be needed for quality of life assessment (WP10). Innovative progress will be accomplished by establishment of “European quality criteria for image quality and radiation exposure in coronary CT angiography”. These criteria can be considered as a comprehensive array of clinical and safety parameters with regard to image quality, radiation exposure and radiation risk in CTA and ICA.

WP4 Good Clinical Practice and Surveillance

Good clinical practice and surveillance are implemented to ensure the conduct of the trial is in accordance with the study protocol and the principles of ICH-GCP and applicable legal and regulatory requirements. To check adherence to given protocols as well as safety requirements on-site and remote monitoring activities are performed.

WP5 Clinical Data Management

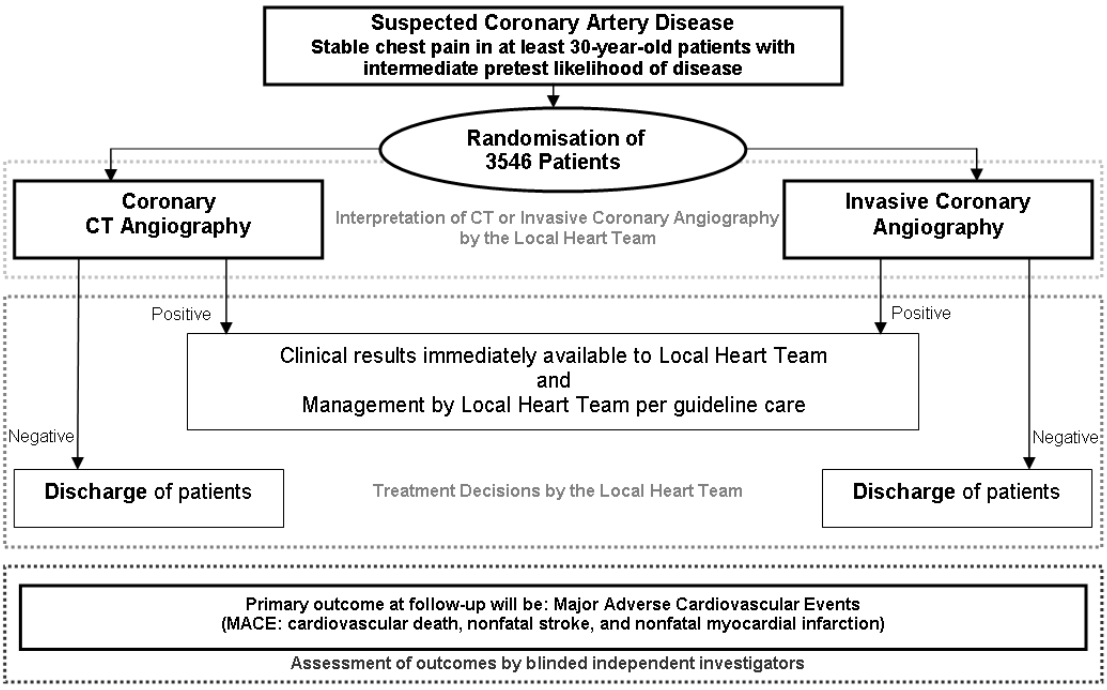
In this WP an electronic clinical study database which operates according to the principle of online data capture has to be established that is compliant with the code of federal regulations (FDA 21 CFR Part 11) to ensure reliability to the recorded data. The system allows documentation of study data in electronic case report forms (eCRF). Furthermore,

administration of the data base as well as providing technical support as well as reports are part of this WP.

WP6 Pragmatic randomised Controlled Trial (PRCT)

A PRCT was designed to test the hypothesis that CTA is superior to ICA concerning the primary outcome of MACE after a maximum follow-up of 4 years in stable chest pain patients with intermediate pretest likelihood of CAD. Secondary outcomes assessed include cost-effectiveness, radiation exposure, cross-over to CTA or ICA, gender differences, and health-related quality of life. For this, it is planned that 3546 patients at 26 clinical sites in 16 European countries with stable chest pain and an intermediate pretest likelihood (10-60%) of CAD will be randomised to receive either CTA or ICA. Allocation concealment and equal allocation to the two trial arms will be ensured by block randomisation with central assignment online. In addition, patients will be stratified according to gender, site, symptoms (typical, atypical, chest pain, no pain) and age in order to minimize covariate imbalance. Due to the pragmatic nature of the trial, the number of follow-ups will be minimal (after 1 year for an exploratory analysis and after a maximum of 4 years (final follow-up) for MACE. For the final follow-up, several information sources will be used (general practitioners, death registries, and family members) to investigate MACE. In addition, patient preference concerning CTA and ICA will be evaluated. The preparatory and accompanying activities for the DISCHARGE PRCT are presented in WP1-5.

Figure 2. Design of the DISCHARGE pragmatic randomised controlled trial



WP7 Gender

Gender will be thoroughly explored in this project. Specific guidelines in women on how to interpret clinical presentation of chest pain syndromes and thus to plan appropriate subsequent diagnostic evaluation will be developed based on data generated in the DISCHARGE trial. The DISCHARGE trial will be the largest multi-center, international study compiling a substantial amount of data on gender related differences of stable ischemic heart disease. Based on collected CT imaging data a detailed description of gender related differences of coronary patho-anatomy and corresponding clinical outcome will be developed.

WP8 Systematic Review of Evidence

The systematic review of evidence will use evidence from the PRCT and combine it with data from economic evaluation, gender analysis and quality of life. For that purpose, EUnetHTA core model will be considered as framework to include all the aspects required for clinical and coverage decisions. Furthermore, this project will explore the use of GRADE methodology in

coverage decisions. This method is explored by different health technology assessment (HTA) agencies in Europe. The recommendations will be elaborated taking into account the target stakeholder by adapting the information to each requirement.

WP9 Cost-Effectiveness Analysis

An estimation of the costs from the perspectives of health care providers and patients will be assessed. Cost-effectiveness of CTA vs. ICA using MACE as benefit measure will also be assessed. In addition, the ratio between the cost of each technology and the benefit it produces in terms of Quality of Life should be estimated. Furthermore, a comparison and consolidation of cost-effectiveness results between European countries will be performed.

WP10 Health-related Quality of Life

This WP investigates patient-reported outcomes such as QoL in patients undergoing CTA and ICA. The effect of the interventions on patients' QoL in addition to clinical events will be a major determinant for the potential inclusion of CTA into clinical guidelines or recommendations. As QoL varies in different subgroups, such as between men and women or between regions, the assessment in different European countries/sites and populations will allow for adjustment.

WP11 Statistical Analysis

The task of WP 11 is to plan the set up of the trial and the evaluation of the results of the PRCT in regard to the statistical analysis, including the primary endpoint. Furthermore, statistical support will be provided to WP7-10. In addition, a new statistical methodology for analysis of time to event data will be developed.

WP12 Dissemination

Aim of this WP is to disseminate the progress generated by the other WPs and to explore different ways of providing information to stakeholders, as meetings, webpage, abstracts to meetings to facilitate the implementation of the recommendations for coverage and clinical practice. In addition, the quality of the scientific dissemination will be ensured by establishing rules and procedures for dissemination.

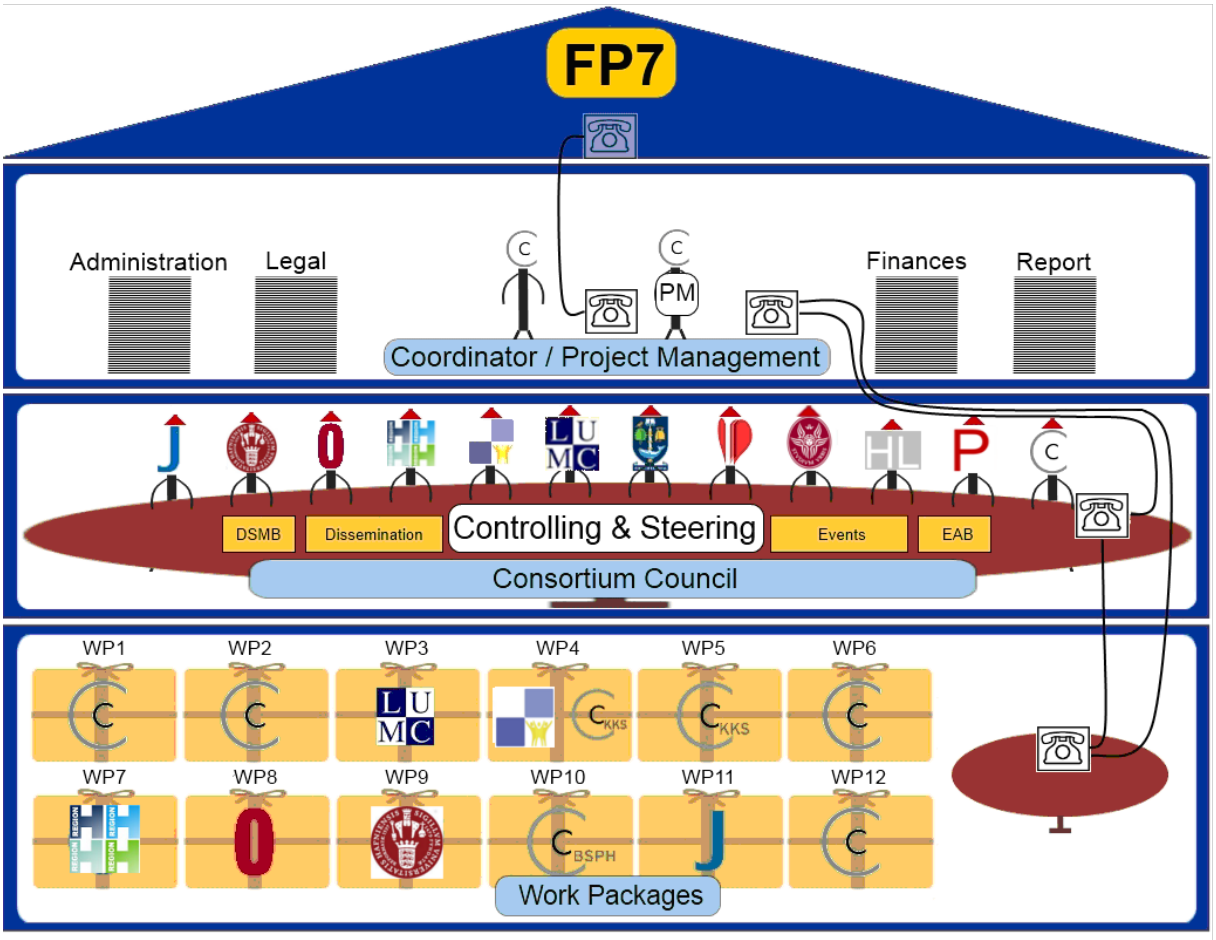
3. Main scientific and technical (S&T) results/foregrounds

Since the DISCHARGE trial is not completed as the 1 year follow-up was completed in January 2020 in regard to MACE while final follow-up is still ongoing until April 2021, final results are not available at the moment. The first main publication about MACE as well as minor cardiovascular events (MICE), procedural complications and initial CTA and ICA management is planned for submission after the occurrence of 50 MACE as an interim safety analysis.

The following was achieved in the project so far:

Management (WP1) in the project was performed as required. In person as well as telephone meetings were organized for clinical and scientific partners as well as for the boards, the dissemination committee (DC), the steering committee (SC) and the external advisory board (EAB). Further boards in the project included the data safety monitoring board (DSMB) and the clinical events committee (CEC) which reviewed safety parameters as occurring adverse events (AEs). Minutes were taken at meetings, required reports generated, deliverables collected and financial tasks performed. Project management organized patients shifts of low to high recruiting sites to reach to final patient target number. Budget of affected sites was shifted accordingly. Furthermore project management handed in a 3. amendment to the grant agreement which resulted in a prolongation of the project for 1 more year to a total project length of 6 years.

Figure 3. Graphical overview of the management structure



The management structure of the DISCHARGE project represented as a "house" under the roof of the European Commission and the 7. Framework Research Programme.

The **certification of clinical sites (WP2)** ensured high quality of CTA performance in the trial. The investigators were trained in standard operating procedures (SOP) and the use of the

electronic clinical data management system and corresponding electronic cases report forms (eCRF). All sites provided proof of certification of the CT reading supervisors. In addition, two 1-week cardiac CTA training workshops were conducted at the Charité.

In order to develop optimised **EU CT quality criteria and radiation exposure (WP3)** the compliance to the cardiac CT protocol "10-Step Guide to Performing Cardiac CT" developed for the DISCHARGE trial was monitored closely. Differences in adherence were assessed and evaluated in regard to image quality and radiation exposure of the patients. For details see D3.2 "Final report on adherence to trial quality criteria by participating sites".

Good clinical practice and surveillance (WP4) was implemented to ensure the conduct of the trial was in accordance with the study protocol and principles of ICH-GCP and applicable legal and regulatory requirements. On-site and remote monitoring activities were performed to check adherence to given protocols as well as safety requirements at all participating clinical sites. For details see D4.7 "Period 5: Monitor and safety reports".

An electronic data capture system was established and maintained continuously for **clinical data management (WP5)**. Technical support was provided for the sites. Data was processed and exported for selected reports. The final export of cleaned data will be performed after the completion of the final follow-up.

The **pragmatic randomised controlled trial (PRCT) (WP6)** was performed at 26 clinical sites in 16 European countries. 3883 patients were recruited in the trial of which 3667 were randomised to either to CT angiography or ICA. 3536 randomised patients were included in the Intention-to-Treat (ITT) population. Patient preference questionnaires were filled out by the patients after the procedure and will be analysed. The safety data was reviewed semi-annually by a data safety monitoring board (DSMB), MACE were additionally rated by a Clinical Events Committee (CEC). The recruitment ended on 01/31/2019. All patients have undergone the 1-year follow up by 01/31/2020 in regard to MACE. An interim safety analysis is planned for publication after 50 MACE focusing on short term safety as radiation exposure and procedural complications, as well as first analysis of MACE and MICE. After all patients have undergone the final follow-up, which will be completed by the end of April 2021, the data will be evaluated for the planned primary and secondary outcomes for comparative effective analyses.

Potential **gender (WP7)** differences will be analysed once final data will be available in regard to imaging acquisition, radiation load, plaque burden, CEA, QoL and radiation exposure. The ratio of men and women included in the trial has been balanced by stratification to site and CTA or ICA group. Overall more women than men were randomised in DISCHARGE.

Systematic Review of Evidence (WP8) was performed to elaborate recommendations for clinical practice on the role of CTA in the management of patients with stable angina. A systematic review of the literature was performed. As soon as final results of the trial will be available they will be included in the final recommendations for guidelines producers with the GRADE method. For details see D8.3 "Mini-HTA" and D8.4" D8.4"Recommendations for practice (CPG) and coverage following GRADE method". A manuscript on the definition of MACE has been prepared by Inaki Gutierrez, which will be submitted to Lancet.

A methodology for a **cost-effectiveness analysis (CEA) (WP9)** was established. A manuscript on this matter was prepared by Kristian Schultz Hansen which will be submitted. Final CEA will be performed once the final follow-up will also be completed. An extrapolation of an exploratory CEA provides first evidence that there is a high probability that the CTA intervention is cost-effective compared to the ICA intervention. For details, see D9.3 "Results from exploratory CEA". A study on micro-costing depicting the health care providers´ perspective based on results of the preceding pilot study is in progress. Since the second follow-up of the PRCT is still ongoing, no final results are available.

Quality of life (QoL) (WP10) of the patients undergoing the trial was assessed for both intervention groups in the pilot study, at baseline (before randomisation) and at follow-up. The comparison of QoL at the pilot study is completed and was just accepted for publication by Health and Quality of Lifes Outcome on 1 March 2020. Exploratory analysis were performed for QoL at baseline and first year follow-up, for details see D10.3 "Analyses of QoL at baseline

and the exploratory follow-up".Final analysis will be performed once data will be available after the completion of the final follow-up.

The **statistical analysis (WP11)** of the PRCT was prepared and specified in detail in a statistical analysis plan (SAP). For details see D11.4 "Statistical analysis for all WPs". In addition, a new model for between-patient-variability in survival analysis was developed. An abstract with the title "Novel discrete mixture modeling in survival analysis without covariate" of this new method was presented by Annegret Mucha and Peter Schlattmann at a meeting of "Deutsche Region der Internationalen Biometrischen Gesellschaft" in Frankfurt (Main) in Germany from March 25th-28th, 2018. The manuscript with the title "Nonparametric finite mixture models for survival analysis" was subsequently submitted to the Biometrical Journal and is currently under review.

Dissemination (WP12) of results was prepared by the preparation of dissemination policies as well as publication plans. Manuscripts were written and submitted for the pilot study on CTA image quality, pre-test probability for prediction of obstructive coronary artery disease and quality of life. An analysis on image quality of the pilot study was published in European Radiology in December 2019. An analysis on health-related quality of life, angina type and coronary artery disease in patients with stable chest pain was just accepted for publication in Health and Quality of Life Outomes and will be published Open Access. A paper on the design of the PRCT was previously published in European Radiology in 2017. Overall, 10 main papers are planned for submission to major journals about MACE, MICE, cost effectiveness analysis, quality of life and gender. For details see D12.4 "Publication Plan Step 3". Patients and stakeholders will be informed about the results of the PRCT and novel guidelines via selected contacts, project homepage and information material as described in D8.5 "Output tailored to stakeholders" and D12.9 "Brochures for patients, social networks discussions", respectively. Relating to the General Data Protection Regulation (GDPR) which is applicable in the European Union since May 2018 the clinical sites were asked to update their patient information and informed consent in accordance to their local applicable regulations. In addition, the sites were asked to include a opt-in section for extended use of research data so that data retrieved in the DISCHARGE trial can also be used for other further related research projects in the field (radiology, coronary artery disease) if the patients decide to agree to this option.

List of publications:

Journal articles:

Adriane Napp, Robert Haase, Michael Laule, Georg M. Schuetz, Matthias Rief, Henryk Dreger, Gudrun Feuchtner, Guy Friedrich, Miloslav Špaček, Vojtěch Suchánek, Klaus Fuglsang Kofoed, Thomas Engstroem, Stephen Schroeder, Tanja Drosch, Matthias Gutberlet, Michael Woinke, Pál Maurovich-Horvat, Béla Merkely, Patrick Donnelly, Peter Ball, Jonathan D. Dodd, Martin Quinn, Luca Saba, Maurizio Porcu, Marco Francone, Massimo Mancone, Andrejs Erglis, Ligita Zvaigzne, Antanas Jankauskas, Gintare Sakalyte, Tomasz Harań, Malgorzata Ilnicka-Suckiel, Nuno Bettencourt, Vasco Gama-Ribeiro, Sebastian Condrea, Imre Benedek, Nada Čemerlić Adjić, Oto Adjić, José Rodriguez-Palomares, Bruno Garcia del Blanco, Giles Roditi, Colin Berry, Gershan Davis, Erica Thwaite, Juhani Knuuti, Mikko Pietilä, Cezary Kępka, Mariusz Kruk, Radosav Vidakovic, Aleksandar N. Neskovic, Ignacio Díez, Iñigo Lecumberri, Jacob Geleijns, Christine Kubiak, Anke Strenge-Hesse, The-Hoang Do, Felix Frömel, Iñaki Gutiérrez-Ibarluzea, Gaizka Benguria-Arrate, Hans Keiding, Christoph Katzer, Jacqueline Müller-Nordhorn, Nina Rieckmann, Mario Walther, Peter Schlattmann, Marc Dewey, The DISCHARGE Trial Group. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. *Eur Radiol* 2017; 27(7):2957-2968

Gianluca de Rubeis, Adriane E. Napp, Peter Schlattmann, Jacob Geleijns, Michael Laule, Henryk Dreger, Klaus Kofoed, Mathias Sørgaard, Thomas Engstrøm, Hans Henrik Tilsted, Alberto Boi, Michele Porcu, Stefano Cossa, José F. Rodríguez-Palomares, Filipa Xavier Valente, Albert Roque, Gudrun Feuchtner, Fabian Plank, Cyril Štěchovský, Theodor Adla,

Stephen Schroeder, Thomas Zelesny, Matthias Gutberlet, Michael Woinke, Mihály Károlyi, Júlia Karády, Patrick Donnelly, Peter Ball, Jonathan Dodd, Mark Hensey, Massimo Mancone, Andrea Ceccacci, Marina Berzina, Ligita Zvaigzne, Gintare Sakalyte, Algidas Basevičius, Małgorzata Ilnicka-Suckiel, Donata Kuśmierz, Rita Faria, Vasco Gama-Ribeiro, Imre Benedek, Teodora Benedek, Filip Adjić, Milenko Čanković, Colin Berry, Christian Delles, Erica Thwaite, Gershan Davis, Juhani Knuuti, Mikko Pietilä, Cezary Kepka, Mariusz Kruk, Radosav Vidakovic, Aleksandar N. Neskovic, Iñigo Lecumberri, Ignacio Diez Gonzales, Balazs Ruzsics, Mike Fisher, Marc Dewey, Marco Francone, The DISCHARGE Trial Group. Pilot study of the multicentre DISCHARGE Trial: image quality and protocol adherence results of computed tomography and invasive coronary angiography. Eur Radiol 2019, published online 16 December 2019

Nina Rieckmann, Konrad Neumann, Sarah Feger, Paolo Ibes, Adriane Napp, Daniel Preuß, Henryk Dreger, Gudrun Feuchtner, Fabian Plank, Vojtěch Suchánek, Josef Veselka, Thomas Engstrøm, Klaus F. Kofoed, Stephen Schröder, Thomas Zelesny, Matthias Gutberlet, Michael Woinke, Pál Maurovich-Horvat, Béla Merkely, Patrick Donnelly, Peter Ball, Jonathan D. Dodd, Mark Hensey, Bruno Loi, Luca Saba, Marco Francone, Massimo Mancone, Marina Berzina, Andrejs Erglis, Audrone Vaitiekiene, Laura Zajanckauskiene, Tomasz Harań, Malgorzata Ilnicka Suckiel, Rita Faria,Vasco Gama-Ribeiro, Imre Benedek, Rodean Ioana, Filip Adjić, Nada Čemerlić Adjić, José Rodriguez-Palomares, Bruno Garcia del Blanco, Katriona Brooksbank, Damien Collison, Gershan Davis, Erica Thwaite, Juhani Knuuti, Antti Saraste, Cezary Kępka, Mariusz Kruk,Theodora Benedek, Mihaela Ratiu, Aleksandar N. Neskovic, Radosav Vidakovic, Ignacio Diez, Iñigo Lecumberri, Michael Fisher, Balasz Ruzsics, William Hollingworth, Iñaki Gutiérrez-Ibarluzea, Marc Dewey, Jacqueline Müller-Nordhorn. Health-related qualify of life, angina type and coronary artery disease in patients with stable chest pain. Health Qual Life Outcomes, accepted for publication, Open Access Publication

Abstracts of presentations at scientific meetings:

Robert Haase presented an abstract with the title “A pragmatic randomised controlled trial of the comparative effectiveness of computed tomography versus invasive coronary angiography for the management of stable chest pain patients: Methods of the multicentre DISCHARGE trial” at the European Society of Radiology (ECR) in Vienna on March 4, 2015.

Gianluca de Rubeis presented an abstract with the title “The multicentre DISCHARGE trial pilot study: Image quality and protocol adherence results” at the European Society of Radiology (ECR) in Vienna on March 3, 2016.

Sarah Feger presented an abstract with the title “Comparison of pretest probability with prevalence of obstructive coronary artery disease using invasive coronary angiography or computed tomography angiography” at the European Society of Radiology (ECR) in Vienna on March 2, 2017.

Annegret Mucha and Peter Schlattmann presented an abstract with the title “Novel discrete mixture modeling in survival analysis without covariate” at a meeting of “Deutsche Region der Internationalen Biometrischen Gesellschaft” in Frankfurt (Main) in Germany from March 25th-28th, 2018. Viktoria Wieske presented an abstract with the title **“**Perspectives of radiologists and cardiologists about the severity of health events in the multicentre DISCHARGE trial - on behalf of the DISCHARGE investigators**”** at the European Society of Radiology (ECR) in Vienna on February 28, 2019.

Manuscripts undergoing review:

A manuscript about the pilot study results on clinical pre-test probability for prediction of obstructive coronary artery disease by Sarah Feger et. al. is under review at European Radiology.

Manuscripts in preparation:

A manuscript on the methodology for CEA has been prepared by Kristian Schultz-Hansen, which will be submitted.

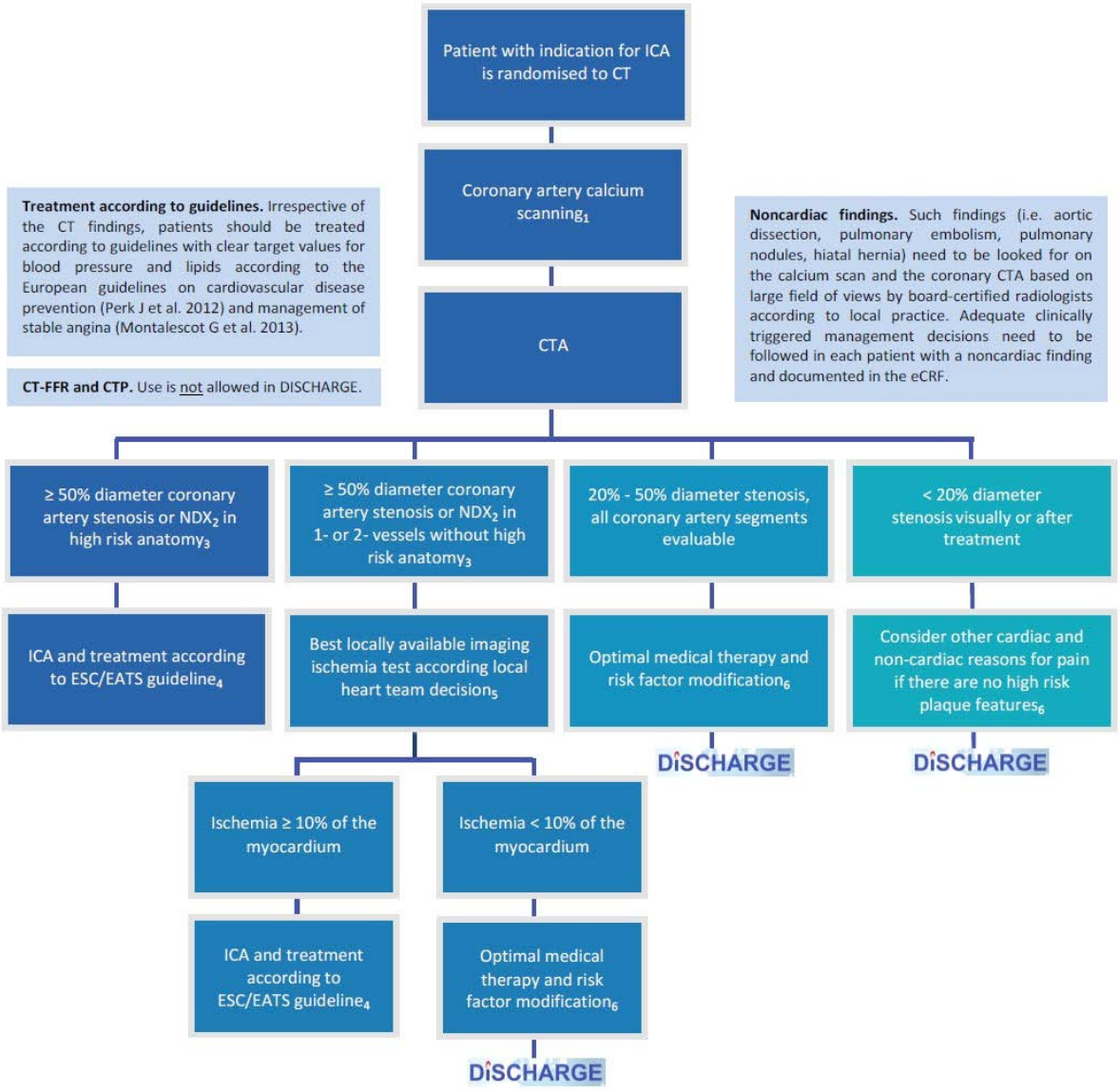
A manuscript on the definition of MACE has been prepared by Inaki Gutierrez, which will be submitted to Lancet.

A manuscript on the adaptation of Lung-RADS to cardiac CT by Jonathan Dodd et. al. was prepared, which will be submitted.

An manuscript on the results of a survey on the professional and patient view on the rating of MACE by Viktoria Wieske et. al. is in progress.

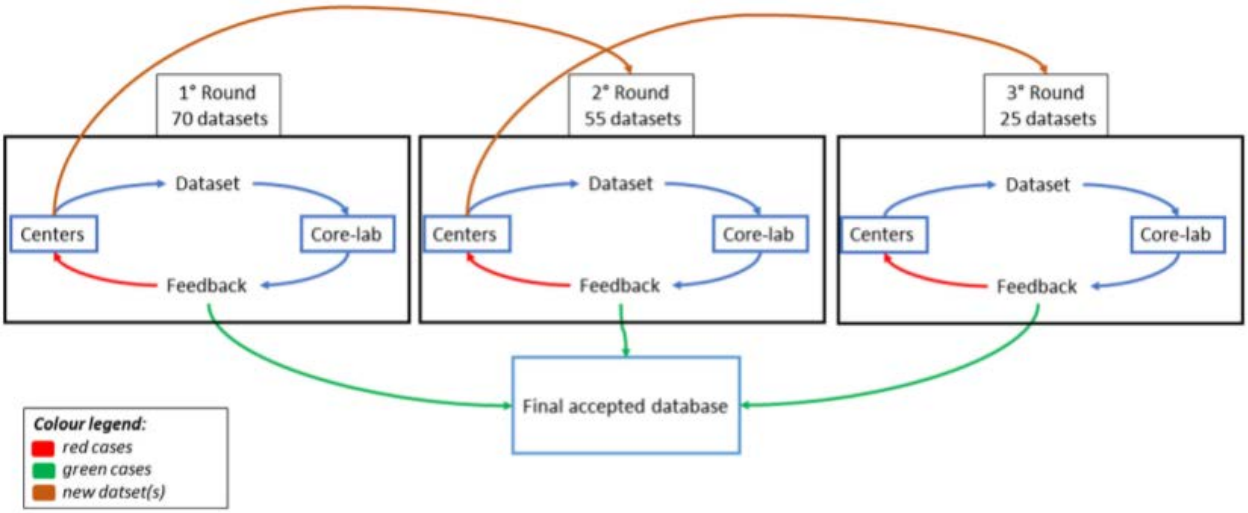
An manuscript on the results of a micro costing analysis of the pilot study data by Paolo Ibes et. al. is in progress.

Figure 4. Overview of CTA based patient management in DISCHARGE as published in A. Napp Eur et. al. Radiol (2017) 27:2957-2968



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

Figure 5. Scheme of quality assessment of the protocol adherence of CT angiography in the DISCHARGE pilot study as published in G. De Rubeis et. al. Eur Radiol (2019)



Scheme 1 The "round" (black box) algorithm showing the flow of the study (arrows)

Figure 6. Results of a detailed quality criteria analysis of available CT angiography datasets of the DISCHARGE pilot study as published in G. De Rubeis et. al. Eur Radiol (2019)

Table 1 Detailed quality criteria analysis of the all available CCTA datasets

General protocol part	Protocol adherence parameters	Number and percentage
Exclusion criteria[a]	Stent	3 (2%)
	Age < 30 years	1 (0.7%)
CACS scan	Performed	139 (92.7%)
	Scan length on the z-axis (< 16 cm)	126 (90.6%)
	Slice thickness (3 mm)	126 (90.6%)
	Slice increment (3 mm)	108 (77.7%)
	IR and FBP recon	47 (33.8%)
CCTA scan	FOV (< 20 cm)	129 (86.0%)
	Scan length on the z-axis has to be reduced by using CACS scan as a mask	120 (80.0%)
	Slice thickness (≤ 0.8 mm)	146 (97.3%)
	Slice increment (≤ 0.5 mm)	139 (92.7%)
	IR and FBP recon	57 (38.0%)
	Sharply coronary arteries visualization	133 (88.7%)
	Kidney not displayed	147 (98.0%)
	Aortic arch not displayed	149 (99.3%)
Non-cardiac structure scan	FOV (> 32 cm)	106 (70.7%)
	Slice thickness (1 mm)	103 (68.7%)
	Slice increment (1 mm)	98 (65.3%)
	Images based on CACS scan row data	84 (56%)
	Images based on CTA scan row data	121 (80.7%)
	IR and FBP recon°	46 (30.7%)

CACS, coronary artery calcium score; *IR*, iterative reconstruction; *FBP*, filtered back projection; *CCTA*, cardiac *CT* angiography; *FOV*, field of view

[a] The exclusion criteria are 4: age < 30 years, pregnancy, dialysis, and known coronary artery disease (CAD).

°Iterative and filtered back reconstruction should be provided for all acquisitions including CACS, CCTA, and non-cardiac structure retro-reconstruction

Figure 7. Results of an analysis of the health-related quality of life of the DISCHARGE pilot study as will be published in N. Rieckmann et.al. Health Qual Life Outcomes (accepted for publication 1 March 2020)

Table 2 Health-related quality of life measures

	Total sample	Gender			Angina Classification					Diagnostic Outcome		
		Men	Women	*p*	Typical Angina Pectoris	Atypical Angina Pectoris	Non-anginal chest discomfort	Other chest discomfort	*p**	ObstructiveCAD	No obstructive CAD	*p*
SF-12 Physical Health	43.1 (9.3)	44.2 (9.2)	41.8 (9.3)	0.001	41.2 (8.8)^{abc}	43.3 (9.1)^{ade}	46.2 (9.0)^{bd}	46.4 (11.4)^{ce}	< 0.001	41.9 (8.9)	43.7 (9.4)	0.072
SF-12 Mental Health	45.7 (9.8)	47.0 (9.8)	44.1 (9.7)	< 0.001	44.5 (9.5)^{ab}	45.1 (9.9)^{cd}	47.6 (10.1)^{ace}	51.4 (8.7)^{bde}	< 0.001	45.6 (10.0)	45.7 (9.8)	0.117
EQ-5D-3 L Visual Analogue Scale	66.3 (18.8)	67.7 (18.3)	64.5 (19.3)	0.010	64.0 (18.1)^{ab}	65.6 (19.4)^{cd}	69.6 (18.8)^{ace}	76.6 (16.8)^{bde}	< 0.001	64.1 (18.3)	67.2 (19.0)	0.111
EQ-5D-3 L Utility Score	0.69 (0.21)	0.71 (0.20)	0.66 (0.21)	< 0.001	0.65 (0.21)^{ab}	0.68 (0.20)^{cd}	0.74 (0.20)^{ac}	0.79 (0.22)^{bd}	< 0.001	0.67 (0.20)	0.69 (0.21)	0.230
HADS Depression	5.9 (3.95)	5.5 (3.8)	6.4 (4.1)	< 0.001	6.5 (4.0)^{ab}	6.1 (3.7)^{cd}	4.8 (3.8)^{ac}	4.6 (4.5)^{bd}	< 0.001	6.0 (4.0)	5.8 (4.0)	0.380
HADS Anxiety	7.5 (4.21)	6.9 (4.0)	8.2 (4.3)	< 0.001	8.3 (4.1)^{a}	7.5 (4.1)^{a}	6.5 (4.0)^{a}	4.6 (4.5)^{a}	< 0.001	7.3 (4.1)	7.6 (4.2)	0.861

Unadjusted values are presented as mean ± SD. p-values are based upon multiple imputation analyses and adjusted for age and gender where appropriate. Possible site effects were accounted for by mixed model analysis

* Pairwise comparisons: angina classification groups with a common superscript differ significantly ($p < 0.05$). After applying a Bonferroni correction, some of the comparisons between patients with other or non-anginal chest discomfort and atypical angina pectoris do not reach statistical significance

Measures (possible range in parenthesis): SF-12 Physical and Mental Health (0–100), EQ-5D-3 L Visual Analogue Scale (0–100), EQ-5D-3 L Utility Score (−0.0734–1) and HADS Depression and Anxiety (0–21)

4. Potential impact and main dissemination activities and exploitation results

4.1 Impact of gender aspects

In the DISCHARGE project women are involved in project management, as work package leader, as task leader in work packages and as principal investigator (PI) in the clinical trial. Women are involved as work package leader in 5 WPs (1, 2, 4, 10) and as task leaders in 50% of all work packages (WP1, 2, 4, 8, 10, 12). They are involved as PI at 10 of the 26 clinical sites. Furthermore, women are members of the project specific boards: 5 women are member of the steering committee, 6 women are member of the dissemination committee.

Gender was included as a separate work package in the project in order to assess all potentially relevant differences relating to gender in regard to imaging acquisition, radiation load, plaque burden, CEA, QoL and radiation exposure. The ratio of men and women included in the trial has been balanced by stratification to site and CTA or ICA group. Overall more women than men were randomised in DISCHARGE (1987 women, 1549 men of the ITT population). Thus, the DISCHARGE is the first cardiovascular randomised controlled trial, which has included more women than men.

4.2 Impact of ethical issues in the PRCT

In order to ensure the safety of the patients undergoing the trial adherence to given protocols was monitored closely by the coordinating site and on-site monitors in order to ensure the patients safety as well as their best possible treatment.

In addition, the Data Safety Monitoring Board (DSMB) is informed semi-annually about all AEs and SAEs, which occur in the trial. The DSMB reviews the reported AEs in a blinded fashion and gives advice about required changes of classifications. By 17.1.2019 when the 8. and latest DSMB report was generated, 651 AEs were reported by the clinical sites in total. MACE were additionally rated by a Clinical Events Committee (CEC).

4.3 Efforts to involve other actors and spread awareness

In the work package dissemination key stakeholders have been identified. They include key stakeholder (citizens, patients, clinicians, managers), policy makers, patient interest groups, specific networks and scientific societies (listed in D12.5). To inform stakeholders as well as DISCHARGE partners a homepage was set up and updated at www.dischargetrial.eu with an external area for the public and an internal one for the DISCHARGE partners. All partners contributed to informing stakeholders by producing information material in their local languages.

Published results of the DISCHARGE trial in peer reviewed journals study will be forwarded to the selected organisations with appropriate text templates. We will approach patient organisations through EHN (http://www.ehnheart.org) and European Patients Forum (EPF, http://www.eu-patient.eu/). In addition, we will contact scientific organisations and patient organisations stated by the clinical sites as well as Health Technology Assessment Agencies. Guideline development will be pursued at the production level.

4.4 Disseminations of the results of the PRCT

101 dissemination activities were performed by all partners in the consortium during the project. They include articles published in the popular press or web sites, oral presentation to a scientific event or wider public, creation of flyers and other activities.

Rules and procedures for dissemination have been established in cooperation with the dissemination committee in dissemination policies. In addition, publication plans have been generated listing the planned publications of the results of the project (D12.2, 12.3, 12.4).

A paper on the design of the DISCHARGE study was published in European Radiology in 2017. It is available under https://www.ncbi.nlm.nih.gov/pubmed/27864607. Robert Haase presented an abstract on the design of the DISCHARGE PRCT at the European Congress of Radiology (ECR) in 2015 previously.

A analysis of CT image quality by Gianluca de Rubeis et. al. was published by European Radiology. It is available under https://www.ncbi.nlm.nih.gov/pubmed/31844958. Gianluca de Rubeis presented the abstract with the title “The multicentre DISCHARGE trial pilot study: Image quality and protocol adherence results” at the European Society of Radiology (ECR) in Vienna on March 3, 2016 previously.

An analysis on health-related quality of life, angina type and coronary artery disease in patients with stable chest pain by Nina Rieckmann et. al. was just accepted for publication in Health and Quality of Life Outomes. It will be published Open Access.

Currently one manuscript about the pilot study results on clinical pre-test probability for prediction of obstructive coronary artery disease by Sarah Feger et. al. is under review at European Radiology. Sarah Feger has also presented her results of the pilot study of the DISCHARGE trial on pre-test probability for prediction of obstructive coronary artery disease at the high impact session Clinical Trials in Radiology (CTiR) in Vienna previously on 2.3.2017.

An abstract on the results of a survey on the professional and patient view on the rating of MACE by Viktoria Wieske et. al. was also presented at the ECR 2019 in the CTiR session. The preparation of a manuscript for publication is in progress.

Other presentations at the CTiR session at the ECR in Vienna included presentations of results of the monocentric predecessor trial of DISCHARGE, the CAD-Man study, on CEA and patient preference comparison (2019), gender analysis and statin adherence and serum lipid levels (2018). Results on kidney injury after contrast agent administration of the CAD-Man trial were also presented at the American Society of Nephrology (ASN) 2017 in New Orleans.

Peter Schlattmann´s team presented a new developed statistical method for between-patient-variability in survival which was developed as part of WP11 “Statistical Analysis” at the annual meeting of the “Deutsche Region der Internationalen Biometrischen Gesellschaft” in Frankfurt (Main) in Germany on March 25th, 2018. The manuscript with the title “Nonparametric finite mixture models for survival analysis” was subsequently submitted to the Biometrical Journal and is currently under review.

Another manuscript was prepared on the adaptation of Lung-RADS to cardiac CT by Jonathan Dodd et. al. which will be submitted.

A manuscript on the methodology of CEA has been prepared by Kristian Schultz-Hansen, which will be submitted.

An manuscript on the results of a micro costing analysis of the pilot study data by Paolo Ibes et. al. is in progress.

A manuscript on the definition of MACE has been prepared by Inaki Gutierrez, which will be submitted to Lancet.

The first main publication about MACE as well as MICE, procedural complications and initial CTA and ICA management is planned for submission after the occurrence of 50 MACE as interim safety analysis. Overall, 10 main papers are planned for submission to major journals about MACE, MICE, cost effectiveness analysis, quality of life and gender (for details see D12.4).

4.5 Socioeconomic impact of the project

From the economic point of view, our hypothesis is that CTA is cost-effective compared to ICA since patients with a low to intermediate pretest probability are likely to have negative results, gained by the cheaper CTA, making a more expensive ICA obsolete. We take into account, that CTA is obsolete in patients with CAD, requiring treatment by ICA. We assume that the

potential savings by avoiding ICA in patients without CAD exceed additional costs, caused by diseased patients, requiring ICA after CTA for treatment. This leads to potential savings on a macroeconomic level. Currently, there are 2 million ICA examinations with negative results in the EU. By using CTA as a non-invasive and cheaper diagnostic alternative, a reasonable amount of possible savings becomes evident.

Although ICA is a well-known and widely spread diagnostic test, being conducted by experienced physicians, it remains an invasive test with a low but evident chance of AEs. Our research hypothesis is that replacing a certain amount of ICA examinations by CTA, being a non-invasive test, leads to reduced AE rates. Adverse events can be divided into non-serious AES and SAE. MACE are an important subcategory of SAE because of their severity and therefore the need of fast and intensive treatment. Therefore, the occurrence of MACE is the primary endpoint. We expect that the rate of MACE is lower in patients, receiving CTA in comparison with patients, being diagnosed by using ICA.

Because of these two explanations, we expect our results to support the hypothesis that the supplement of ICA by CTA will lead to relevant savings for health care systems and with that, for national economies.

While the 1 year follow-up was completed by January 2020 in regard to MACE, the second follow-up is still ongoing. Thus no final results are available.

Stefan Sauerland, member of the External Advisory Board (EAB) of DISCHARGE has reported that the German Institute for Quality and Efficiency in Health Care (IQWiG) has just started a pre-assessment project on coronary CT (or MRI) as an alternative to invasive coronary angiography in patients with low or medium pre-test probability of coronary heart disease. The aim of this project is to estimate the quantity and quality of high-quality evidence on these two diagnostic interventions. As a possible consequence of this pre-assessment, the Federal Joint Committee (G-BA) could start a formal health technology assessment (HTA). This assessment of G-BA (including a second report of IQWiG) would last two years, but could ultimately lead to a positive reimbursement decision on coronary CT scanning in 2022.

5. Public website address and contact details

5.1 Website of the project

The DISCHARGE **public website** (https://www.dischargetrial.eu) is updated regularly. It contains local contact information of participating clinical sites for patients interested in participation of the trial, contact of the coordinator and project manager, names of the advisory board members and partners, a short description of the beneficiaries, a short description of the project, articles and latest news on the project.

The DISCHARGE **internal website** includes contact details of the consortium, project managers, a long description of the project (PartB), templates, meeting agenda and minutes, documents from the Commission and latest news for beneficiaries on the project.

5.2 Coordinator contact details

Marc Dewey, MD, PhD,
Charité – Universitätsmedizin Berlin
Institut für Radiologie
Charitéplatz 1
10117 Berlin
Germany
e-mail: marc.dewey@charite.de

5.3 The DISCHARGE Consortium

Participant No.		Participant Organisation Name	Country
1. Coor-dinator		CHARITE – UNIVERSITAETSMEDIZIN BERLIN (CHARITE)	Germany
2		MEDIZINISCHE UNIVERSITAET INNSBRUCK (MUI)	Austria
3.		UNIVERSITAIR ZIEKENHUIS ANTWERPEN (UZA), Withdrawal	Belgium
4.		FAKULTNI NEMOCNICE V MOTOLE (FN Motol)	Czech Republic
5.		REGION HOVEDSTADEN (REGIONH)	Denmark
6.		ALB Fils Kliniken (ALB)	Germany
7.		UNIVERSITAET LEIPZIG (ULEI)	Germany

Participant No.		Participant Organisation Name	Country
8.		SEMMELWEIS EGYETEM (SE)	Hungary
9.		South Eastern Health and Social Care Trust (SET)	Ireland
10.		UNIVERSITY COLLEGE DUBLIN, NATIONAL UNIVERSITY OF IRELAND, DUBLIN (St. Vincent's University Hospital, SVUH)	Ireland
11.		UNIVERSITA DEGLI STUDI DI CAGLIARI (UNICA)	Italy
12.		UNIVERSITA DEGLI STUDI DI ROMA LA SAPIENZA (UNIROMA)	Italy
13.		Paula Stradiņa Klīniskā universitātes slimnīca (PSKUS)	Latvia
14		LIETUVOS SVEIKATOS MOKSLU UNIVERSITETAS (LSMU)	Lithuania
15.		WOJEWODZKI SZPITAL SPECJALISTYCZNY WE WROCLAWIU (WSS)	Poland
16.		Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE (CHVNG/E)	Portugal
17.		S.C.Cardio Med S.R.L (CAM)	Romania
18.		Institut za kardiovaskularne bolesti Vojvodine - Sremska Kamenica (IKVBV)	Serbia
19.		***INSTITUT CATALA DE LA SALUT (ICS-HUVH)***	Spain
20.		OSTERGOTLANDS LAN (OSTERGOTLANDS LAN), Withdrawal	Sweden

Participant No.		Participant Organisation Name	Country
21.		Kantonsspital St. Gallen (KSSG), Withdrawal	Switzerland
22.		University of Glasgow (Glasgow)	UK
23.		Aintree University Hospital NHS Foundation Trust (AUHT)	UK
24.		INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM), Withdrawal	France
25.		ACADEMISCH ZIEKENHUIS LEIDEN - LEIDS UNIVERSITAIR MEDISCH CENTRUM (LUMC)	The Netherlands
26.		FUNDACION VASCA DE INNOVACION E INVESTIGACION SANITARIAS (Osteba-BIOEF)	Spain
27.		Ceske Vysoke Uceni Technicke v Praze (CVUT), Withdrawal	Czech Republic
28.		Universitätsklinikum Jena (UKJ)	Germany
29		Turku University Hospital / Turku PET Centre (TURKU)	Finland
30		The Institute of Cardiology in Warsaw (IKARD)	Poland
31		University of Medicine and Pharmacy Targu-Mures (UMFTGM)	Romania
32		Faculty of Medicine, University of Belgrade (MFUB)	Serbia
33		Osakidetza-Basque Health Service (Osakidetza)	Spain
34		ECRIN	France
35		Københavns Uiversitet (UCPH)	Denmark

Participant No.		Participant Organisation Name	Country
36		ROYAL LIVERPOOL AND BROADGREEN UNIVERSITY HOSPITALS NHS TRUST (RLUHT)	UK