Health Economics Analysis Plan of the DISCHARGE Trial: a pragmatic, multicenter, superiority trial in Europe to assess whether computed tomography (CT) improves outcomes in patients with stable chest pain clinically referred for invasive coronary angiography (ICA)

Trial Registration number: NCT02400229, clinicaltrials.gov

Trial Protocol version: this document has been written based on information contained in the trial protocol v1.8 dated November 9, 2020 and the statistical analysis plan (SAP) of the trial v2 dated November 30, 2021.

Trial HEAP version: 2.0, dated February 12, 2026

Website: www.dischargetrial.eu

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Content section

Glossary of terms and abbreviations

ACE: angiotensin-converting enzyme

ARB: angiotensin-receptor blocker

CABG: coronary artery bypass grafting

CEA: cost-effectiveness analysis

CUA: cost-utility analysis

CT: computed tomography

CTA: computed tomography angiography

DISCHARGE: Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease

DRG: diagnosis-related group

ECG: electrocardiogram

ECRIN: European Clinical Research Infrastructure Network

EMD: emergency department

FFR: fractional flow reserve

GDP: gross domestic product

ICA: invasive coronary angiography

ICPM: International Classification of Procedures in Medicine

ICU: intensive care unit

ITT: intention to treat

IMC: intermediate care unit

KKS: Koordinierungszentrum für klinische Studien

MACE: major adverse cardiovascular events

MICE: minor adverse cardiovascular events

MRI: magnetic resonance imaging

NLST: national lung screening trial

PCI: percutaneous coronary intervention

PP: per protocol

PPP: purchasing power parities

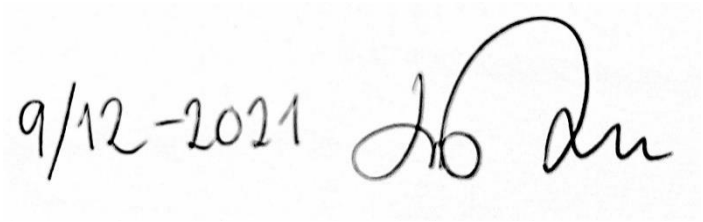
PET: positron emission tomography

QALY: quality-adjusted life year

RCT: randomized controlled trials

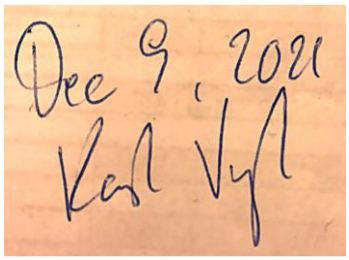
SPECT: single-photon emission CT

Signatures for version 1.0



Date: 9-12-2021 Kristian Schultz Hansen

Study health economics experts: Dr Laura Elina Pirhonen and Dr Kristian Schultz Hansen



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Study statistician: Professor Peter Martus

Date: 22 March 2026, Marc Dewey

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Summary of changes to the Health Economics Analysis Plan

Health Economics Analysis Plan Version	Signature Date
Original Version	December 9, 2021
Final Revised Version	February 12, 2026

This section details changes to the DISCHARGE Health Economics Analysis Plan (HEAP) in response to DFG reviewer comments (MO 5273/1-1) and the inclusion of DISCHARGE EXTEND (DE 1361/35-1) 10-year follow-up data.

The HEAP 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 data analysis.

Key structural changes:

1. Primary analysis changed from fully pooled to country-specific (7 countries, ≥200 patients)
2. Secondary analysis changed from geographic regions to 6 healthcare system groups with hierarchical Bayesian partial pooling
3. Decision tree + Markov model framework added for lifetime extrapolation
4. Three-tier extrapolation framework (12 candidate survival models) added
5. DISCHARGE EXTEND 10-year follow-up integrated (10-year CEA + prospective validation)

Signatures for version 2.0

Date: __12-Feb-2026__ _____

Junior study health economics expert: Dr. Mahmoud Mohamed

1. Introduction

The health economics analysis plan (HEAP) of the DISCHARGE trial is in accordance with the study protocol, the methods and design publication (Napp et al., 2017), and the statistical analysis plan (SAP) of the trial. The DISCHARGE trial HEAP will also adhere to the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine (Neumann & Sanders, 2017; Sanders et al., 2016).

The structure and content of the DISCHARGE HEAP was informed by the Delphi Expert Consensus Study recommendations for trial-based economic evaluations (Thorn et al., 2021), which was coordinated by Professor William Hollingworth as senior author who is also a member of the external advisory board (EAB) of the DISCHARGE trial. Following these specific recommendations for HEAP as part of randomized controlled trials (RCTs) will help prevent bias in our trial-based economic evaluations by ensuring to provide all items that are considered essential in a HEAP and that are required for planning of the economic evaluation in a prespecified fashion before trial completion and unblinding.

Publication of the economics analyses of the DISCHARGE trial will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Husereau et al., 2013) and will include the 24-item CHEERS checklist of items to include when reporting economic evaluations of health interventions in cost-effectiveness analyses (CEA).

2. Background and aims of the trial

DISCHARGE compares the effectiveness of a diagnostic imaging strategy guided by computed tomography (CT) or by invasive coronary angiography (ICA) with regards to major adverse cardiovascular events (MACE) as the primary outcome in patients with stable chest pain and suspected coronary artery disease (CAD) who are clinically referred for ICA to 26 European sites in 16 European countries. The details of the study have been described in the methods and design publication (Napp et al., 2017) and the study protocol and statistical analysis plan (SAP), which will be published together with the clinical main trial publication.

Cost-effectiveness studies applying decision analytical modeling suggest that CT is a cost-effective option compared to ICA in patients with a low-to-intermediate pretest likelihood of CAD (Dewey & Hamm, 2007; Genders et al., 2015; Halpern et al., 2010); other modeling studies have indicated that CT might be more cost-effective than cardiac functional (stress) tests such as SPECT (Lee et al., 2015; Min et al., 2010) while CT had similar costs as functional tests in the PROMISE trial (Mark et al., 2016) as well as lower diagnostic costs compared with ICA until 1 year in the CONSERVE trial (Chang et al., 2019). A cost-effectiveness analysis comparing CT and ICA strategies based on costs and longer-term outcomes generated from a randomized controlled trial could provide additional valuable insights (Genders et al., 2013).

The present document details the health economic analyses conducted alongside the DISCHARGE trial. DISCHARGE tested the superiority of a patient management strategy guided by CT in regards to MACE as compared with patient management guided by ICA; both randomization groups received patient management recommendation based on the diagnostic test findings in accordance with the three relevant European guidelines applicable at the time of study conduct (Montalescot et al., 2013; Perk et al., 2012; Windecker et al., 2014). Further details about the secondary objectives of the trial, the design and hypotheses and the trial population are provided in the study protocol and SAP. Recruitment commenced on October 3, 2015 and finished on April 12, 2019. The follow-up periods will consist of an interim 1-year and a second follow-up after a median of 3.5 years. The main clinical results were published in NEJM (DISCHARGE Trial Group et al., 2022). The DFG-funded DISCHARGE EXTEND

(DE 1361/35-1) provides 10-year long-term follow-up of all 3,561 patients (data available at the end of 2028), enabling a 10-year cost-effectiveness analysis and prospective validation of lifetime extrapolation models.

3. Economic approach/overview

3.1 Aims of the economic evaluation

The aim of the health economic evaluations of the DISCHARGE trial is to address the question "What is the cost-effectiveness of a diagnostic imaging strategy guided by CT compared with ICA in patients with stable chest pain and intermediate pretest probability of CAD?".

3.2 Objectives of economic evaluation

The **primary objective** of the health economic evaluation is to estimate the long-term cost-effectiveness of CT versus ICA for patients referred for ICA with stable chest pain from the perspective of the health care sector over the period of clinical trial-wide follow-up data until a median of 3.5 years.

This objective achievable through 5 analyses:

1. Primary: 7 country-specific ICERs (≥200 patients each)
2. Secondary: 6 healthcare system groups with hierarchical Bayesian partial pooling
3. Lifetime extrapolation via decision tree + Markov model with 12 candidate survival models across three tiers
4. 10-year CEA using observed DISCHARGE EXTEND outcomes
5. Prospective validation of all 12 pre-registered models against 10-year data

A **secondary objective** is to estimate the cost-effectiveness of CT versus ICA for patients referred for ICA with stable chest pain from the societal perspective.

The **tertiary objective** of the health economic evaluations is to estimate cost-effectiveness of CT versus ICA for patients referred for ICA with stable chest pain from the perspective of the health care provider using micro-costing data for costs and angina in the last 4 weeks at 1st follow-up; this objective will include break-even analyses.

Lastly, the study enables a cost-effectiveness analysis of the effects (measured as benefits and harms) as well as costs of lung nodule detection by CT for lung cancer detection and treatment following the specific recommendations used in the DISCHARGE trial for this purpose (Haase et al., 2020) and will follow the role model analysis provided by the NLST (Black et al., 2014).

3.3 Overview of economic analysis

The within-trial economic analysis will be performed using individual patient level data from the DISCHARGE trial. The analytical approaches will take the form of cost-effectiveness and cost-utility analysis (CUA). The primary analysis produces 7 independent country-specific ICERs for countries with ≥200 patients, using each country's own clinical effectiveness, resource use, and DRG cost data. The

secondary analysis clusters 16 countries into 6 healthcare system groups, applying DRG tariffs from a single representative country per group within a hierarchical Bayesian partial pooling framework (Manca, Rice, et al., 2005; Nixon & Thompson, 2005). In both analyses, the NMB will complement the ICER using country-specific WTP/QALY thresholds. WTP thresholds will be weighted by the level of participation from each country, reflecting regional differences between Western and Eastern Europe. Specifically, for Western European countries such as Denmark, the United Kingdom, Spain, Germany, Ireland, Italy, Austria, Finland, and Portugal, the cost-effectiveness threshold per QALY will typically range from $20,000 to $50,000, with some countries like Denmark and UK having higher thresholds closer to $30,000–$50,000 per QALY (Pichon-Riviere et al., 2023). In contrast, for Eastern European countries like Hungary, Romania, Serbia, Latvia, Czech Republic, Poland, Lithuania, and others, the thresholds will be lower, ranging from $300 to $3,000 per QALY, reflecting more constrained healthcare budgets and a lower willingness to pay for health improvements (Pichon-Riviere et al., 2023).

3.4 Jurisdictions

The trial is conducted in 16 European countries. For an overview of reimbursement to health care providers and the organization of the health care systems, see **Appendix A**. In a multi-country study such as the DISCHARGE trial, there will be differences in the way health care services are financed across participating countries with higher direct payment by patients in some countries than in others. The costs borne by the health care sector in different countries will therefore differ even for similar services. To ensure comparability of costs of health care services across countries from a health sector perspective, we will include the full value of resources required to perform health care services irrespective of who directly pays for the service. The primary analysis consists of fully split, country-specific CEAs (Fully split with multicountry costing) for 7 countries with ≥200 patients (Hungary, Denmark, Romania, United Kingdom, Spain, Germany, Serbia). The secondary analysis clusters the 16 countries into 6 healthcare system groups (Partially pooled with one-country costing) based on: (i) public financing strength, (ii) out-of-pocket payment burden, (iii) healthcare system maturity (DRG implementation), and (iv) economic development (GDP per capita PPP, 2018) **(Table 1),** following Böhm et al. (2013) and Wendt et al. (2009) (**Table 2**); In case unit cost data is not available for a country, unit cost data for this country will be substituted with the costing methodology of the country with the closest health care sector set-up (**Appendix A**). In case clinical effectiveness data or resource use data is not available for a site, this site will be excluded from the primary health economic evaluation. The advantage of the planned fully split health economics analysis with multicountry costing data are the following: maintaining the patient-level relationship between clinical effectiveness data and resource use data, maintaining the patient-level relationship between resource use and cost, and allowing consistency between reporting of clinical effectiveness in economic and clinical publications (Reed et al., 2005).

Table 1: Country Classification based on Healthcare Systems and Income Leve

Country	Group	GDP per capita PPP 2018 ($)	Public Coverage (%)	Out-of-Pocket (%)	System Type	DRG Implementation	Population Coverage
Denmark	Group 1	$57,545	84%	14%	Tax-funded NHS	Pre-2010	Universal
United Kingdom	Group 1	$47,005	79%	16%	Tax-funded NHS	1990s	Universal
Ireland	Group 1	$81,686	73%	12%	Tax-funded NHS-type	Pre-2010	Universal
Germany	Group 2	$54,439	76%	12%	Social Insurance (Bismarck)	Pre-2010	Universal
Austria	Group 2	$55,706	75%	18%	Social Insurance (Bismarck)	Pre-2010 (LKF)	Universal
Finland	Group 3	$49,334	62%	20%	Municipal Tax + Insurance	Pre-2010 (NordDRG)	Universal
Italy	Group 3	$42,838	74%	24%	Regional NHS	Pre-2010	Universal
Spain	Group 3	$40,139	71%	24%	Regional Tax-funded NHS	Pre-2010	Universal
Czech Republic	Group 4	$40,290	85%	15%	Social Insurance	2020 (CZ-DRG 3.0)	Universal
Portugal	Group 4	$34,041	65%	27%	Tax NHS + subsystems	Pre-2010	Universal
Hungary	Group 4	$31,560	73%	27%	Social Insurance	Pre-2010	Universal
Poland	Group 4	$31,430	60%	30%	Mandatory Insurance (NFZ)	Pre-2010 (negotiated)	Universal
Lithuania	Group 5	$35,729	72%	27%	Insurance Fund	2012	Universal
Latvia	Group 5	$29,489	55%	45%	NHS-type	Post-2010 (mixed)	Universal
Romania	Group 6	$28,413	67%	19% + informal	Social Insurance	2014 (specific tariffs)	85%
Serbia	Group 6	$17,555	58%	42% + informal	Social Insurance	2019 (partial)	Significant gaps

Table 2: Terminology for methodological approaches to multinational economic evaluations

Source of clinical effectiveness data	Source of resource use data	Type of analysis		Costing methodology		Classification
All participating countries	All countries	Fully pooled	→	Multicountry	→	Fully pooled with multicountry costing
			→	One country	→	Fully pooled with one-country costing
All participating countries	One country or subset of countries	Partially split	→	Multicountry*	→	Partially split with multicountry costing
			→	One country	→	Partially split with one-country costing
One country or subset of countries	One country or subset of countries	Fully split	→	Multicountry*	→	Fully split with multicountry costing
			→	One country	→	Fully split with one-country costing

Table 1 is taken from (Reed et al., 2005). For the primary economic analysis, we plan to use a fully split analysis with multi-country costing data. If cost data from some countries/sites are missing, we will use data from similar countries or exclude the country/site.

The cost-effectiveness analyses from a societal perspective entail incorporating the costs of all resources required, irrespective of who bears the costs including the health sector and patients. It will include transport costs of patients and productivity losses (days out of work, limitations on non-work daily activities, etc.).

3.5 Perspectives

The primary economic analysis will be from the perspective of the health care sector. The health care sector perspective is chosen as the primary perspective because this perspective is most commonly used in European economic evaluation guidelines (Garcia-Mochon et al., 2021) and because analysis from the societal perspective involves higher uncertainty in regards to data quality and more comprehensive assumptions. The secondary and tertiary analysis will include the societal perspective and the perspective of the health care provider. The analysis of lung nodule management will also take the societal perspective.

3.6 Time horizons

The primary objective from the health care sector perspective will compare the costs and consequences of each randomization group over the follow-up until a median of 3.5 years after randomization. An additional time horizon is added exploiting the DISCHARGE EXTEND data, which is a 10-year follow-up of all 3,561 DISCHARGE patients. This enables both a 10-year CEA and prospective validation of lifetime extrapolation models (see section 6)

The secondary objective from the societal perspective will compare the costs and consequences of each randomization group including decision analytical modeling data for the lifetime horizon.

The tertiary objective from the health care provider perspective will cover costs during the initial diagnostic tests which patients are randomized to (CT or ICA) and the subsequent initial patient management.

4. Economic data collection and management

4.1 Statistical software

Statistical analyses will be performed using SAS software version 9.4 (SAS Institute Inc.), SPSS for Windows version 26 (IBM), and the statistical programming language *R* version 4.0.3. Primary analysis will be conducted using R. Hierarchical Bayesian models will be implemented in Stan/JAGS via R. Machine learning survival models (DeepSurv, DeepHit) will use Python (pycox/scikit-survival). Decision analytical modeling will be performed using R (heemod/BCEA packages).

4.2 Identification of resources

The following items of health care resource use that may differ between randomization groups will be measured: health service resource use and personal expenditure on health care. The following items will be considered for health care resource data collection during the initial patient management including procedures and operations directly following the initial tests randomized to (CT or ICA) and the subsequent follow-up patient management in regard to related health care costs (**List 1 and 2**). Cost categories for the economic evaluation from a health care sector perspective include the value of all the resources incurred in the health sector such as the initial CT or ICA diagnostic test, additional diagnostic procedures (ECG, non-invasive or invasive functional tests such as stress echocardiography, stress SPECT, stress MRI, stress PET, FFR), hospitalizations (normal ward, EMD, IMC, ICU), treatment procedures (PCI or CABG), and medications. If several of these items are covered by a single payment that cover hospital cases or care episodes with one fee e.g. through a diagnosis-related group (DRG), these groups will be used for the assessment. Any of these items will be included if performed as health care services in the hospital or outside the hospital sector. If DRGs cover both the inpatient and outpatient sector, these groups will be used for the assessment. For the patient management resources only related medical costs for coronary artery disease care or any care required for MACE or minor cardiovascular events (MICE) but not cost unrelated to such care will be considered. Self-payments (out-of-pocket) by patients for coronary artery disease care or any care required for MACE or MICE will be considered.

List 1: Initial patient management resources (in- or outpatient) for the primary analysis

- CT (including calcium score scan and CTA)
- ICA (with or without IVUS and/or OCT)
- ECG (after randomization)
- Noninvasive or invasive functional tests
    - Stress ECG
    - Stress echocardiography
    - Stress SPECT
    - Stress MRI
    - Stress PET
    - Invasive FFR (as part of ICA or PCI)
- Diagnostic tests related to events
    - Brain MRI for stroke/TIA
    - Brain CT for stroke/TIA
- Outpatient days (if not included in DRG rates) for coronary care
- Hospitalizations (if not included in DRG rates and/or charges for excess stays)
    - Any hospitalization on normal ward, IMC, or ICU (days) for coronary care
    - For chest pain (with noninvasive or ICA diagnosis, plus with or without PCI/CABG)
    - For angina pectoris (with noninvasive or ICA diagnosis, plus with or without PCI/CABG)
    - For acute myocardial infarction (with noninvasive or invasive diagnosis, plus with or without PCI/CABG)
    - For stroke
    - For major procedural complications
    - For MICE
    - For congestive heart failure
- Emergency department (EMD) visits
    - For chest pain or angina pectoris
    - For acute myocardial infarction
    - For stroke/TIA
    - For major procedural complications
    - For MICE
    - For congestive heart failure
- Treatment procedures (e.g., using DRG or ICPM)
    - PCI (with or without IVUS and/or OCT)
    - CABG
- Medications (coronary artery disease medications: statins, betablockers, ACE inhibitors or ARB, calcium antagonists, nitrates, antiplatelets, other; if not available per country, one country data will be used)

List 2: Follow-up patient management resources (in- or outpatient) for the primary analysis

- CT (including calcium score scan and CTA)
- ICA (with or without IVUS and/or OCT
- Noninvasive or invasive functional tests
    - Stress ECG
    - Stress echocardiography
    - Stress SPECT
    - Stress MRI
    - Stress PET
    - Invasive FFR (as part of ICA or PCI)
- Diagnostic tests related to events
    - Head MRI for stroke/TIA
    - Head CT for stroke/TIA
- Outpatient days (if not included in DRG rates) for coronary care
- Hospitalizations (if not included in DRG rates and/or charges for excess stays)
    - Any hospitalization on normal ward, IMC, or ICU (days) for coronary care
    - For chest pain (with noninvasive or ICA diagnosis, plus with or without PCI/CABG)
    - For angina pectoris (with noninvasive or ICA diagnosis, plus with or without PCI/CABG)
    - For acute myocardial infarction (with noninvasive or invasive diagnosis, plus with or without PCI/CABG)
    - For stroke
    - For major procedural complications
    - For MICE
    - For congestive heart failure
- Emergency department (EMD) visits
    - For chest pain or angina pectoris
    - For acute myocardial infarction
    - For stroke/TIA
    - For MICE
    - For congestive heart failure
- Treatment procedures (e.g., using DRG or ICPM)
    - PCI (with or without IVUS and/or OCT)
    - CABG
    - Peripheral artery revascularization
- Medications (coronary artery disease medications: statins, betablockers, ACE inhibitors or ARB, calcium antagonists, nitrates, antiplatelets, other; if not available per country, one country data will be used)

List 3: DISCHARGE EXTEND follow-up resources (8.5-year visit) for the 10-year CEA

- EQ-5D-3L questionnaire (quality of life)
- Outpatient cardiologist visits (number since 2nd follow-up)
- Outpatient GP visits (number since 2nd follow-up)
- Hospitalizations for coronary care (since 2nd follow-up)
- Emergency department visits (since 2nd follow-up)
- Treatment procedures: PCI, CABG (since 2nd follow-up)
- Medications (current coronary artery disease medications)
- MACE events (since 2nd follow-up)

4.3 Measurement of resource-use data

Resource-use data will be collected until a median of 3.5 years post randomization from all patients included using trial electronic case report forms (eCRFs), completed by the trial staff at the sites and monitored by the coordinating center. Patient questionnaires at 1 year for the 1st follow-up and after a median of 3.5 years for the 2nd follow-up will be used to collect information on other tests, procedures, outpatient visits, operations, or hospitalizations. For the DISCHARGE EXTEND 8.5-year follow-up visit, additional resource use data will be collected via an adapted questionnaire including EQ-5D-3L, outpatient cardiologist and GP visits, hospitalizations, and medications since the 2nd follow-up (see List 3). These instruments will be prepared in all trial languages and integrated into the EXTEND visit protocol in coordination with 26 clinical centers.

These resource-use data will be captured from two sources: if an enrolled patient seeks care at a DISCHARGE clinical site, then the diagnostic and treatment procedures performed will be captured from the eCRFs maintained by DISCHARGE clinical sites. If a patient instead visits health care providers that are not one of the trial sites, then the number of diagnostic and treatment procedures will be obtained based on self-reporting by patients and review of medical records by the trial sites. Depending on the enrolment date of individual patients, the length of the follow-up time between the initial diagnostic test and the follow-up varies. The follow-up questionnaires also ask patients to report if they had suffered any chest pain or discomfort and whether this led to subsequent seeking of health care within the past year at 1st follow-up and since the 1st follow-up at 2nd follow-up. The questionnaires inquire about health care seeking from a range of health care providers including hospitals, emergency departments, physicians in ambulatory (outpatient) settings, rehabilitation centers, and mobile nursing services. If the same hospital visit is captured in both the eCRFs and the follow-up questionnaires, then the latter will be excluded to avoid double counting. The follow-up questionnaires also ask about current medication.

Finally, the questionnaires incorporate questions on costs borne by patients themselves including out-of-pocket expenditure for paying the health care providers, travelling the distance between patients' homes and health care providers (any transportation costs) and productivity losses. Productivity losses encompass both direct and indirect economic impacts of CAD-related health issues on patients' ability to work or perform daily activities. Specifically, the questionnaire will assess work absenteeism, capturing whether patients had to take time off from work due to CAD symptoms, diagnostic procedures such as coronary computed tomography angiography (CCTA) or invasive coronary angiography (ICA), or subsequent treatments. Additionally, it will evaluate work presenteeism—reduced productivity or efficiency while working due to CAD-related symptoms. For retired patients, homemakers, or those not formally employed, productivity loss will be measured regarding limitations in performing usual activities, such as household tasks, caregiving responsibilities, or other daily routines. These data will provide a comprehensive understanding of the broader economic burden of CAD, extending beyond direct medical costs to include the societal and personal impacts of the disease.

4.4 Monitoring collection of health economic data

Training was provided to individuals responsible for administering the eCRFs. The study health economics expert and his trained team worked closely with the sites to structure data collection with regards to the aims of the health economics analyses (e.g. resource and unit cost collection). Data collection forms were assessed throughout the trial period by the coordinator team and on-site as well as remote monitoring teams to increase quality and consistency of the data (see Study Protocol Section 10.2).

4.5 Database management

Economic data will be securely stored on the trial database hosted at KKS at Charité.

4.6 Data entry

All baseline data will be entered into the electronic case report form (eCRF) by the trial staff at the 26 sites. Follow-up data collected from postal questionnaires or phone contact with patients, relatives, referring physicians, or other health care providers for individual patients and will be entered by site staff. Data entered was verified for consistency with original source data by on-site monitoring teams as well as remote monitoring teams coordinated by KKS and ECRIN. The eCRF database used controls to limit data entry to plausible values and the coordinator team double-checked data entries for within-patient and between-patient plausibility.

4.7 Valuation of resource-use data

Valuation of the resources identified and measured (see Section 4.2 and Lists 1, 2 and 3) will be done using country-specific diagnosis-related group (DRG) tariffs or equivalent. All costs at an individual patient level in participating countries will be converted into Euros using gross domestic product (GDP), data on inflation between 2015 and 2021 for all participating countries and health purchasing power parities (health PPPs) for 2018. Annual costs at an individual patient level will initially be calculated using country level prices and local currencies. All resources will be valued at the 2018 price level regardless of the point in time resources are utilized; for example, the 2018 DRG tariff for a CT will be used as unit cost irrespective of the year a CT scan was performed. All costs at the individual patient level in participating countries will be converted into Euros using the health purchasing power parities (PPPs) for 2018 (Lorenzoni & Koechlin, 2017). Conversion of patient costs using PPPs will ensure that these costs are measured in the same currency at the 2018 price level and that differences in price levels between countries are eliminated (European Union, 2012). For the 10-year CEA using DISCHARGE EXTEND data, resources consumed between the 2nd follow-up and the EXTEND visit will be valued using updated country-specific DRG tariffs for 2022–2029, collected in collaboration with the Mercator Fellow (Prof. Brodszky, PECUNIA network).

4.8 Identification of outcomes

There will be two co-primary outcomes for the health economic analysis plan.

Since the primary outcome of the DISCHARGE trial will be MACE, the health economic analyses plan foresees **to use MACE as the first co-primary outcome for its primary objective**, which is defined as a composite endpoint of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event model (see the SAP for details). The **secondary co-primary outcome** for the primary objective will be Quality-Adjusted Life Years (QALYs) derived from utility scores, obtained using the EQ-5D-3L quality of life instrument as described in section 4.10. Secondary outcomes of the primary analysis include subgroup analyses (see section 5.13) and per-country and 6 healthcare system group analyses (as defined in Section 3.4).

The first and second co-primary outcome of the **secondary objective** of the cost-effectiveness will also be MACE and QALYs similarly to the primary objective but for a lifetime horizon using decision analytical modeling (Section 6). The primary outcome for the **tertiary objective** of the cost-

effectiveness analysis will be relief of angina at 1st follow-up (at 1 year, measured as not having patient-reported angina in the last 4 weeks) from the perspective of the health care provider.

4.9 Measurement of outcomes

The primary clinical outcome of the DISCHARGE trial (MACE) will be assessed at the 1st and 2nd follow-up and will be defined as described below (from Table 3 of SAP).

MACE is defined as the first occurrence of

- Cardiovascular death†
- Nonfatal myocardial infarction ††
- Nonfatal stroke†††

†According to Definitions for Cardiovascular Endpoint Events in Clinical Trials by (Hicks et al., 2015)

††According to the Third Universal Definition of Myocardial Infarction by (Thygesen et al., 2012)

†††According to Updated Definition of Stroke for the 21st Century by (Sacco et al., 2013)

Missing data of the primary clinical outcome MACE will be censored and not be imputed.

The secondary co-primary outcome for the cost-effectiveness analysis will be QALYs which will be captured in two steps. The EQ-5D-3L provides a description of health status, and utility weights developed at the country level will be obtained from EuroQoL. For countries without national utility weights, European harmonized weights currently under development will be considered (https://www.pecunia-project.eu/). Trial patients completed the EQ-5D-3L questions at baseline (time of randomization) and at the 1st and 2nd follow-up. The associated utility weights obtained at these discrete time points will be utilized to estimate QALYs for each patient by applying an area-under-the-curve method. For patients who died before the follow-ups, a utility weight of 0 is imputed from the date of death until the end of the observation period. For patients who are lost to follow up, or for quality of life data that is partially missing from the questionnaires which is often the case in trials (Noble et al., 2012), multiple imputation methods will be utilized as described in the SAP and section 5.10. For the 10-year CEA, MACE and EQ-5D-3L will additionally be assessed at the DISCHARGE EXTEND 8.5-year follow-up visit across all 16 countries, providing a fourth measurement time point for QALY estimation.

4.10 Valuation of outcomes

MACE will be derived from a time-to-event model as described in the SAP. Utility scores will be derived from responses to the EQ-5D-3L. The EQ-5D-3L health-related quality of life instrument is a questionnaire incorporating five health domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Richardson & Manca, 2004). For each domain, patients are asked to indicate whether they have no problems, some problems or severe problems. The EQ-5D-3L provides a description of health status for economic models (Wolowacz et al., 2016), but it does not convey information regarding the relative severity of one health state compared to another. The second step therefore attaches a relative weight reflecting the severity of each possible health state defined by the EQ-5D-3L classification. Relative weights, often referred to as 'utility weights' developed at country level (Dolan, 1997; Golicki et al., 2019; Golicki et al., 2010; Scalone et al., 2013; Wittrup-Jensen et al., 2009) are available from the EuroQoL webpage (https://euroqol.org). For countries without national utility weights, we will seek to use European harmonized weights currently under development in the

PECUNIA project in which Professor William Hollingworth is involved as a PI (https://www.pecunia-project.eu/) or a value set previously developed for the European region (Greiner et al., 2003). Trial patients complete the EQ-5D-3L questions at baseline (time of randomization), one year later as part of the 1st follow-up questionnaire and again after a median of 3.5 years after randomization as part of the 2nd follow-up questionnaire. The associated utility weights obtained at these three discrete time points will be utilized to estimate QALYs for each patient by applying an area-under-the-curve method (Manca, Hawkins, et al., 2005; Matthews et al., 1990). For patients who die before the end of the trial, a utility weight of 0 is imputed from the date of death until the end of the observation period (2nd follow-up) (Ratcliffe et al., 2005).

5. Economic data analysis

5.1 Analysis population

The full analysis set will include all randomized participants as described in the SAP section 8.1 for the definition of the "intention to treat" (ITT) population analysis set. All analyses will be harmonized with the clinical main analysis and the same populations and consistent MACE and QALY data will be used.

5.2 Timing of analyses

The primary health economics analysis will be conducted after 2nd follow-up and unblinding of the data for the primary clinical outcome analysis. There will be no CEA or CUA based on interim data. The 10-year CEA and prospective validation analyses will be conducted upon availability of DISCHARGE EXTEND data (available at the end of 2028).

5.3 Discount rates for costs and benefits

Costs and effects not occurring in the same year will be discounted using a discount rate of 3% corresponding to the low end of social discount rates estimated for individual European countries (Evans & Sezer, 2005; Garcia-Mochon et al., 2021).

5.4 Cost-effectiveness thresholds

While there is no official EU threshold for willingness to pay for a QALY, a subset of EU countries has national thresholds (Cameron et al., 2018) that can be compared to the incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) found in the DISCHARGE project.

5.5 Statistical decision rules

The prime statistic of interest will be ICER comparing CT to ICA. The point estimate of ICER is uncertain due to sampling variation in costs and effects (including benefits and harms) and the level of uncertainty will be estimated. The methods for analyzing and quantifying the ICER depend on the nature of the variation of incremental costs and effects and are described in Section 5.12. In particular, the choice of methods depends on where the point estimate of the ICER is placed in the cost-effectiveness plane (**Figure 1** in Section 5.12) and which quadrants the variation of incremental costs and effects span [32, 33]. For example, if costs (C) are significantly lower and the effects (E) are

significantly better in the CT arm compared to the ICA arm (South-Eastern Quadrant in **Figure 1**), then the decision is certain: the CT intervention is cost-effective compared to the ICA intervention and is 'dominant'. In the North-Eastern Quadrant, the decision between CT and ICA may be more uncertain since the size of the ICER may range from high to low depending on the sampling variation in the costs and effects. In case CT is less costly and shows similar effects as ICA, i.e. the ICER being at the border between South East and South West Quadrant, then CT will be deemed cost-effective depending on the cost-effectiveness threshold (see **Figures 1** and **2**).

Uncertainty surrounding the ICER point estimate will be estimated using the bootstrap procedure. Current guidelines on health economic evaluation recommends the use of bootstrap procedures to quantify the uncertainty when employing patient level data in economic evaluations as opposed to hypothesis testing and p-values (Drummond & McGuire, 2001; Drummond et al., 2015). For the secondary grouping analysis, uncertainty is quantified through the hierarchical Bayesian MCMC framework (10,000 iterations) producing full posterior distributions for group-level ICERs and NMBs. This Bayesian approach is superior to bootstrapping for hierarchical grouped data as it appropriately propagates uncertainty across all model levels (Manca, Rice, et al., 2005; Nixon & Thompson, 2005). Uncertainty measured as 95% confidence intervals will be based on the results from the bootstrap procedure for the ICER (Section 5.12). The resulting pairs of effects and costs from the bootstrap procedure will also be illustrated in the CE plane and the probability of cost-effectiveness for the CT will be illustrated in the CEAC. In secondary outcome publications, p values will reported according to journal policies.

5.6 Analysis of resource use

Differences in the use of services and resources listed above in Section 4.2 between randomized groups will be described but not compared statistically.

5.7 Analysis of costs

A detailed description on the calculation of incremental costs and effects based on individual patient data is available in **Appendix B**.

5.8 Analysis of outcomes

The primary outcome for the health-economic analysis will consist of reported MACE and cost during the clinical trial. MACE will be calculated as the average number of MACE per trial arm during the observation period. MACE will also be analyzed as a time-to-event endpoint. The difference between the two groups will be calculated as the differences in either the mean MACE-free survival time (Zhao & Tian, 2001) or the restricted mean survival time (rmstD) (Royston & Parmar, 2013) (as a sensitivity analysis). The secondary outcome will be QALYs. Average QALYs between the two arms will be calculated using the Area Under Curve (AUC) method. We will adjust QALY calculations for any differences in baseline utility scores as is this is good practice even in large RCTs (Manca, Hawkins, et al., 2005).

Hierarchical Bayesian survival models (12 candidate models across three tiers; see Section 6.1) estimate group-level and country-level hazard functions with partial pooling

5.9 Data cleaning for analysis

MACE and QALY were checked for consistency as part of the main clinical publication. Extreme values of resource use data will be checked against the source documents. Entry errors resulting in extreme unit cost for resources will be clarified with sites and country representatives.

5.10 Missing data and imputation

Missing data for the primary clinical outcome MACE will be treated as censored observations.
Missing values for quality of life and angina in the last four weeks will be treated with imputation methods as described in full detail in Section 9 of the SAP.
In regard to missing costs data, it is possible that either

a) resource use data will be missing for individual patients (e.g. in patients it is known if a MACE occurred or not until follow-up but it is not clear how many and which tests or procedures were done until follow-up) or

b) the unit costs for individual tests or procedures will be missing for some sites and/or some settings (e.g. costs of a functional tests is not known for an individual site at all or is not known either for the inpatient or outpatient setting).

These two situations for missing data on a) the resource utilization level of individual patients or b) unit cost level for certain sites will be treated with the following imputation methods. In both case a) and case b) the level of missing data will be analyzed and if the magnitude of missing data is negligible, the issue will be ignored (Ramsey et al., 2005; Ramsey et al., 2015). In the case that the analyses of missing data show that the issue cannot be neglected, multiple imputation of cost data per country will be employed within the Bayesian framework, providing coherent uncertainty propagation (Faria et al., 2014; Leurent et al., 2018; Ramsey et al., 2015).

5.11 Analysis of cost-effectiveness

Costs measured in Euros at 2018 price level and effects will be available on the patient level. MACE and QALY data will be combined to calculate trial-wide ICERs, while both ICERs and NMBs will be calculated in the case of QALY in the country-specific analysis as follows:

$$ICER = \frac{\overline{C^{ct}} - \overline{C^{ica}}}{\overline{E^{ica}} - \overline{E^{ct}}}$$

$$NMB = \lambda * (\overline{E^{ct}} - \overline{E^{ica}}) - (\overline{C^{ct}} - \overline{C^{ica}})$$

where $\overline{C^{ct}}$ and $\overline{C^{ica}}$ are the arithmetic mean costs among patients in the CT and ICA randomization groups while $\overline{E^{ct}}$ and $\overline{E^{ica}}$ are the arithmetic mean effects (measured as MACE or QALY) and λ is the WTP per QALY. Since the follow-up time differs among patients, mean costs in the two patient groups will express the costs for the average follow-up time in a patient. Similarly, the mean number of MACE in the two patient groups expresses the effect over the average follow-up time in the patient groups. Depending on the effect measure chosen, the ICER expresses the additional costs per MACE averted or per QALY gained from the health care sector or societal perspective if ICA is replaced by CT. The NMB, in contrast, represents the net economic value of the intervention by combining its cost and health benefits into a single monetary figure, providing a direct measure at a given WTP per QALY. A detailed description on the calculation of incremental costs and effects based on individual patient data is available in **Appendix B**.

5.12 Sampling uncertainty

Investigations of the uncertainty of the ICER will be performed by developing a cost-effectiveness plane (CE-plane) and a cost-effectiveness acceptability curve (CEAC).

Following a bootstrapping procedure in which at least 5000 resamples of the original data with replacement followed by calculation of incremental costs, incremental effects and the ICER in each resample, the share of resamples supporting a hypothesis that CT is cost-effective compared to ICA can be calculated given a specific willingness to pay threshold for improved health (Briggs et al., 1997; Chernick, 2008). The CEAC displays the estimated probability that the CT intervention will be deemed cost-effective compared to ICA at any given willingness to pay threshold level for the ICER (Fenwick et al., 2004; Lothgren & Zethraeus, 2000). In order to illustrate the uncertainty or variance of the cost-effectiveness ratio, all incremental cost-effectiveness ratios attained from the bootstrapping procedure are plotted in the cost-effectiveness plane. The bootstrap method is a non-parametric technique, which draws random samples repeatedly, with replacement, from the trial data. This method produces an estimate of the distribution of the ICER. We will, based on the results from the bootstrap procedure, present 95% confidence intervals for the ICER to demonstrate the uncertainty surrounding the estimates of costs and effects. The results from the probabilistic sensitivity analysis will then, as mentioned, be presented in a cost-effectiveness acceptability curve (CEAC) and a cost-effectiveness (CE) plane. The CE plane will give the readers a sense of how much uncertainty there is about incremental costs and effects. See below for an illustration of a CE plane (**Figure 1**) and two examples of a CEAC (**Figure 2**).

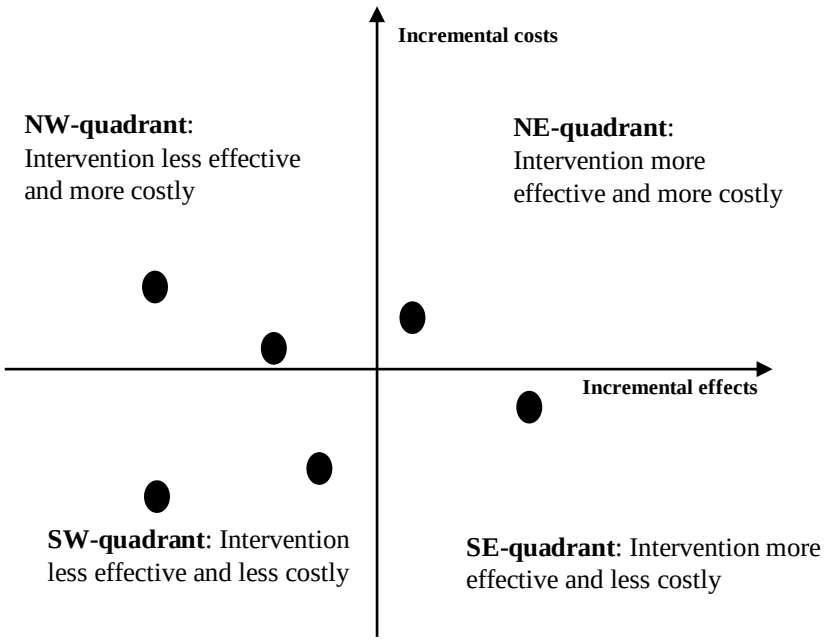
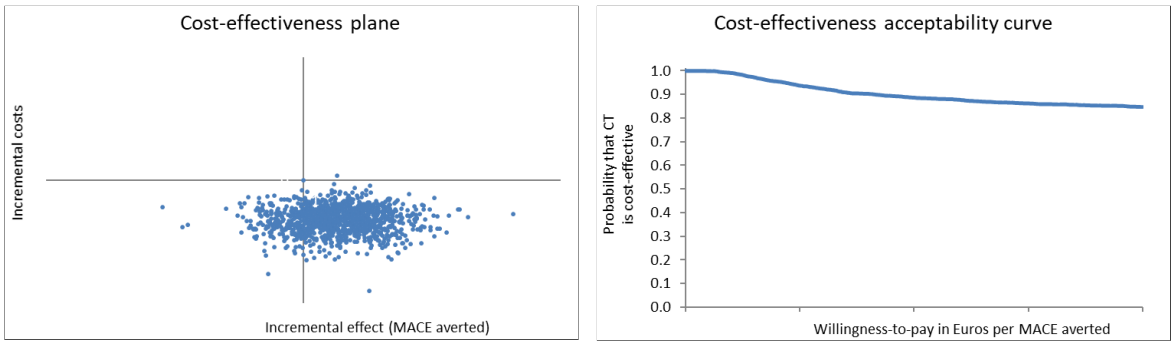


Figure 1: Illustration of a cost-effectiveness plane.

*NW=North-west; NE=North-east; SW=South-west; SE=South-east

A)



B)

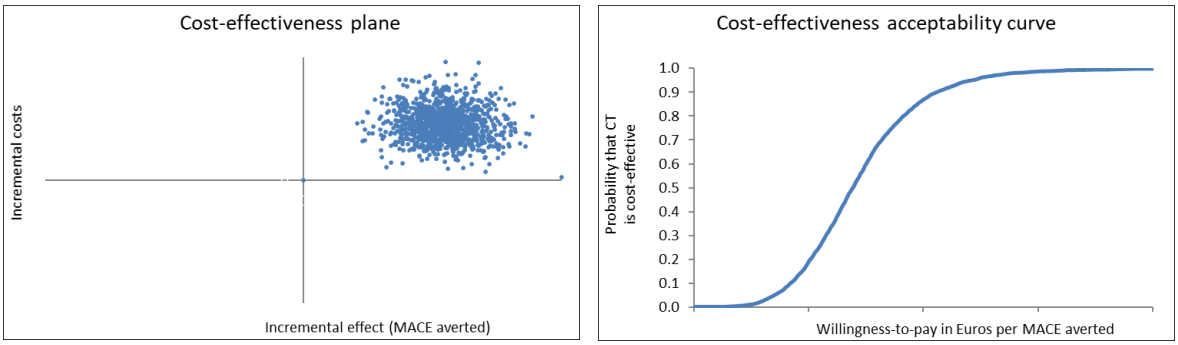


Figure 2: Illustration of two examples of a cost-effectiveness (CE) planes and cost-effectiveness acceptability curves (CEAC).

A) in a situation where CT is less costly and where CT and ICA have almost similar effects (number of MACE not significantly different).

B) in a situation where CT is more costly and more effective (lower number of MACE).

5.13 Subgroup analyses or analysis of heterogeneity

Analyses will also be conducted on the final dataset to investigate how cost-effectiveness varies between different patient subgroups in explorative subgroup analyses as defined below (from the SAP Table 3) for MACE (**List 4**).

List 4: Subgroups for cost-effectiveness analyses

- Gender (male versus female, 116 and 125)
- 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 (Gulati et al., 2021) (< 65, 65-75, > 75)*
- Angina type groups (125)
- Quintiles of pretest probability (ranging from 10-60%; 10-20%, 20-30% etc.)*
- Smoking status (never, former, current)*
- 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 (Montalescot et al., 2013)*
- Personal baseline income categories (measured as quintiles and adjusted using PPP measures) as a proxy of social class**
- Categories of anxiety levels at baseline measured using the HADS (tertiles)**

* Entries identified with asterisk were prespecified in the SAP but not before start of the trial on clinicaltrials.gov. ** Entries identified with two asterisks were prespecified in the HEAP but not before start of the trial on clinicaltrials.gov. 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.

Despite efforts to ensure comparability of cost and effects collected in different participating countries there may still be some degree of between-country variability caused by for example differences in clinical practice patterns and design and organization of health care systems (Drummond et al., 2009; Oppong et al., 2015; Reinhold et al., 2010). The primary country-specific analysis will be supplemented by hierarchical Bayesian multilevel modeling within the 6 healthcare system groups (as defined in Section 3.4) to investigate the clustered nature of the multinational trial data (Manca, Rice, et al., 2005; Nixon & Thompson, 2005). Cost-effectiveness of CT will be analyzed for 7 individual countries with ≥200 patients and for the 6 healthcare system groups as secondary analysis.

Also, different composites of MACE definitions (from SAP Table 3) will be analyzed for cost-effectiveness of CT and ICA as secondary analyses of ICER and CEAC (**List 5**).

List 5: Different composites of MACE for cost-effectiveness analyses

- 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)
- Occurrence of myocardial infarction based on a secondary definition of nonfatal myocardial infarction according to the Fourth Universal Definition of Myocardial Infarction (Thygesen et al., 2018)

* Entries without numbers in parentheses identified with asterisk were not prespecified before start of the trial on clinicaltrials.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.

5.14 Sensitivity analyses

Several sensitivity analyses will be undertaken to explore uncertainties surrounding key parameters in the economic evaluation. One-way sensitivity analyses involving key parameters as well as bootstrapping methods will be performed to assess the certainty of the ICER. The parameters listed in **Table 2** will be included in a univariate and multivariate sensitivity analysis. Moreover, we will also evaluate worst-case scenarios for CT alone and in combination with best-case ICA scenarios to test if the hypothesized superiority of CT over ICA persists. Details are shown in **Table 3** and scenarios will be tested with each parameter changed alone and in combination.

Table 2: Parameters for sensitivity analysis.

Parameter	Baseline estimate	Range
Cost per CT procedure*	Mean cost in € per procedure	Factor: 0.5 - 1.5
Cost per ICA procedure*	Mean cost in € per procedure	Factor: 0.5 - 1.5
Cost per PCI*	Mean cost in € per procedure	Factor: 0.5 - 1.5
Cost per CABG*	Mean cost in € per procedure	Factor: 0.5 - 1.5
Medication cost*	Mean cost in € per patient	Factor: 0.5 - 1.5
Discount rate	3%	0%, 1%, 2%, 3.5%, 5%

* actual results from the DISCHARGE trial will be the base case scenario and in the univariate sensitivity analysis the six parameters above will be tested across the range and in multivariate sensitivity analyses combinations of the six parameters will be tested.

We will also investigate the sensitivity of the ICER to varying follow-up periods, 2 years and 5 years (Kim et al., 2017), as well as two additional methodological choices, as follows. Instead of using country-specific utility weights to value EQ-5D-3L health states for the calculation of QALYs, the ICER will be calculated using a value set from a single country. In a similar vein, rather than using country specific DRG tariffs to represent costs of health care services in each participating country, the ICER will be estimated using DRG tariffs from a single country applied to health care services from all countries. The latter has the potential to be of very practical value to health care authorities in each of the participating countries. Additionally, the sensitivity analysis will include **restricted mean survival time (RMST)** as an alternative to mean MACE-free survival time in assessing survival benefits. RMST

will be calculated for **fixed follow-up periods of 2 and 5 years** to ensure a fair comparison of survival benefits between groups, independent of differences in censoring or extrapolation assumptions.

Treatment effect waning is modeled in five pre-specified scenarios: (1) constant HR (base case), (2) linear decay to null at 10 years, (3) exponential decay with 5-year half-life, (4) crossover scenario (CT benefit reverses after year 7), and (5) a data-driven flexible parametric model with time-varying treatment coefficient estimated from the data itself. All waning scenarios will be reported for both primary and secondary analyses.

5.15 Transferability to LMIC Settings

In addition to the sensitivity analyses described above, we will also employ adaptive techniques to explore how the primary cost-effectiveness and NMB estimates may translate to low- and middle-income country (LMIC) settings. We will utilize a suite of approaches known as "adaptive health technology assessment (HTA)" (Ollendorf et al., 2024). The process will involve identification of one or more LMIC locations that are comparable in terms of setting and process of delivery of CT angiography and ICA. Adjustments to component costs from the DISCHARGE primary analysis will be made, including price and cost benchmarking for the resources consumed between settings, estimation of the full cost of the diagnostic and follow-up pathway, and ascertainment of the system-wide budgetary impact of replacing ICA with CT angiography. Data permitting, adjustments may also be made to the ICER estimates from the primary analysis, including adjusting incremental cost estimates for differences in purchasing power parity and GDP per capita, adjusting incremental MACE and QALY estimates for differences in life expectancy, and adjusting QALY estimates to account for local elicitation of health-state utility data. Regardless of the analyses conducted, a thorough reporting of uncertainties in the adaptation will be provided, including concerns regarding differences in underlying epidemiology, clinical practice and resources available, availability and access to the technologies of interest, and other considerations.

6. Modeling

6.1 Long-Term Projections and Extrapolation Methods

The primary CEA and co-primary CUA will be extrapolated beyond the trial period to a lifetime horizon. The extrapolation framework employs 12 candidate survival models organized in three tiers. The choice of survival extrapolation model is the single largest source of structural uncertainty in health economic evaluation, yet model selection is currently based on within-trial statistical fit (AIC/BIC) and clinical plausibility judgement (NICE TSD 14) (Latimer, 2013). **No prospective validation of extrapolation models against long-term real-world outcomes has ever been conducted.** DISCHARGE + EXTEND enables the first such validation. We propose a three-tier framework comparing 1) standard parametric models (NICE TSD 14) (Latimer, 2013), 2) flexible/advanced methods (NICE TSD 21) (Rutherford et al., 2020), and 3) machine learning survival models (no HTA guidance exists).

This three-tier design directly answers three questions the HTA community cannot currently answer empirically: (1) which standard parametric model extrapolates best? (2) do flexible methods from NICE TSD 21 outperform standard parametrics? (3) should machine learning survival models be considered in HTA submissions? The validation generates evidence for ISPOR, NICE, and CADTH guideline development. CAD-Man and its 10-year follow-up, CAD-Man EXTEND, serve as a pilot for the extrapolation framework.

Implementation: The 12 candidate models are applied across both the primary and secondary analyses tracks, but with different estimation strategies. **Primary analysis (7 countries, ≥200 patients each):** Tier 1 and 2 models are fitted independently per country using country-specific likelihoods with weakly informative priors from literature or CAD-Man trial (no cross-country pooling). Each country produces its own survival curve, ICER, and CEAC. Tier 3 (ML) models are trained on the pooled dataset of all 3,561 patients (Lee et al., 2020; Ryu et al., 2020), then produce country-specific predictions by inputting each country's covariate distribution and unit costs. **Secondary analysis (6 healthcare system groups):** All 12 models use the hierarchical Bayesian framework with three-level partial pooling (patient → country → group), enabling countries with small samples (n<200) to borrow strength from their healthcare system group while preserving country-specific random effects. Tier 3 models are trained on the full pooled dataset with group-level embeddings. In both tracks, country-specific DRG unit costs and EQ-5D-3L value sets are applied to generate locally relevant ICERs.

6.1.1 Phase 1: Decision Tree (0–3.5 Years)

The decision tree models the diagnostic pathway and within-trial events using individual patient data (IPD):

CT-guided arm: CT → [if obstructive CAD or non-diagnostic] → ICA → treatment allocation (PCI / CABG / medical management). If no CAD: medical management only.

ICA-guided arm: Direct ICA → treatment allocation.

All branch probabilities estimated using hierarchical Bayesian logistic regression with country-level random effects:

$$\text{logit}(p_{ij}) = \beta_0 + \beta_1 \times \text{Treatment}_i + \beta_2 \times \text{Age}_i + \beta_3 \times \text{Sex}_i + u_j$$

$$u_j \sim N(0, \tau^2) \quad \text{[country random effect, partial pooling]}$$

Decision tree outputs (3.5 years): Total costs (diagnostic + complications + procedures + MACE hospitalisations + medications), total QALYs (area-under-curve from three EQ-5D-3L measurements), MACE status and type for Markov state allocation.

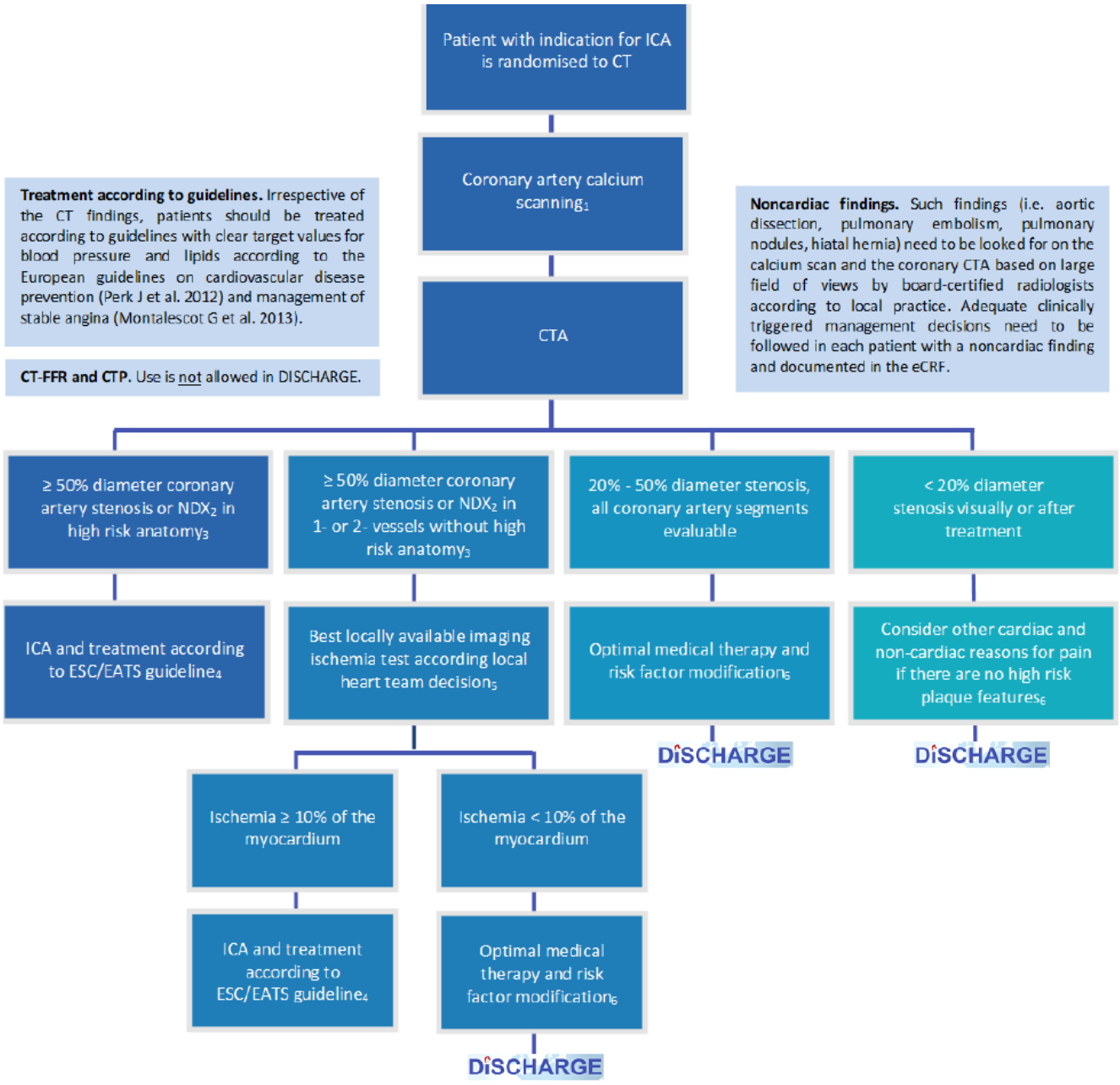


Figure 3: Decision analytic model structure for CT compared to ICA.

6.1.2 Transition to Markov Model

At 3.5 years, patients enter the Markov model based on their trial experience:

- **No MACE during trial** → "Alive without MACE"
- **MI during trial** → "Post-MI" (with tunnel states for time-since-event)
- **Stroke during trial** → "Post-Stroke" (with tunnel states for time-since-event)
- **CV death during trial** → "CV Death" (absorbing)

6.1.3 Phase 2: Markov Cohort Model (3.5 Years → Lifetime):

The decision model for the secondary analyses from the perspective of society will comprise of two arms, with one arm for each intervention group and one arm for the control group. Both arms will be analyzed using a Markov model with health states to which MACE, quality of life, and health care cost collected as part of the trial will be linked together with data from published literature. The model structure will be informed by the patient management flow chart recommendations for CT which is shown in Figure 3 and the actual patient management decisions observed in both arms in the trial will be used to construct the state and transition probabilities, together with published literature, of the model.

Health states (7 in base case): Alive without MACE; Post-MI (Year 1); Post-MI (Year 2+); Post-Stroke (Year 1); Post-Stroke (Year 2+); CV Death (absorbing); Non-CV Death (absorbing). *The tunnel states for Post-MI and Post-Stroke capture the empirically established elevated mortality in the first year after an event, which declines substantially thereafter (Hankey et al., 2000; Jernberg et al., 2015).*

Cycle length: 6 months (consistent with MACE event granularity; half-cycle correction applied).

The model will include transition probabilities (Table 4) for health states similar to (Genders et al., 2015), which will be derived from an updated literature review and probability distributions on MACE and QALY will be taken from the DISCHARGE trial results and other randomized studies on coronary CT (and ICA) as available at the time of model construction. Sick leave and early retirement productivity losses will also be included in the model.

Transition probabilities are derived in seven steps:

Step 1 Baseline hazard functions. Fit the full suite of candidate survival models (Section 3) to DISCHARGE trial KM data within the hierarchical Bayesian framework. The hierarchical Weibull specification, for example:

$h_{ij}(t) = \kappa\lambda_j(\lambda_j \cdot t)^{(\kappa-1)}$

$\log(\lambda_j) = \mu_\lambda + v_j, \quad v_j \sim N(0, \sigma^2_\lambda)$ [country random effect]

$\kappa \sim \text{Gamma}(\alpha, \beta)$ [shape, common across countries]

Step 2 MACE decomposition via competing risks model. Rather than using fixed proportions (which assume the composition of MACE events is constant over time), we model the cause-specific hazards for MI, stroke, and CV death as separate time-varying competing risks. Implementation uses a *cause-specific hazard model* where each event type has its own parametric survival distribution, fitted jointly within the hierarchical framework:

$h_{MI}(t) = \kappa_1\lambda_1(\lambda_1 t)^{(\kappa_1-1)}$ [MI-specific hazard]

$h_{Str}(t) = \kappa_2\lambda_2(\lambda_2 t)^{(\kappa_2-1)}$ [Stroke-specific hazard]

$h_{CVD}(t) = \kappa_3\lambda_3(\lambda_3 t)^{(\kappa_3-1)}$ [CV death-specific hazard]

This allows the relative composition of MACE to change over time (e.g., early events more procedural, late events more atherosclerotic).

Step 3 Cycle probabilities. Convert cause-specific hazards to 6-month transition probabilities: $H_k(t, t+0.5) = \int h_k(u)du$; $p(\text{Alive}\rightarrow\text{Post-MI}) = 1 - \exp[-H_{MI}(t, t+0.5)]$; $p(\text{Alive}\rightarrow\text{Post-Stroke}) = 1 - \exp[-H_{Str}(t, t+0.5)]$; $p(\text{Alive}\rightarrow\text{CV Death}) = 1 - \exp[-H_{CVD}(t, t+0.5)]$. Uncertainty fully propagated via joint posterior sampling (10,000 MCMC iterations).

Step 4 Background mortality. Country-specific Eurostat life tables (age- and sex-specific). $p(\text{Any state} \rightarrow \text{Non-CV Death}) = 1 - \exp[-\lambda_{background} \times 0.5]$. *Crucially, the relative survival / excess hazard models (Tier 2, Section 3) incorporate background mortality directly into the extrapolation, constraining long-term hazard to converge toward population mortality, a biologically necessary constraint that standard parametric models violate.*

Step 5 Post-MACE excess mortality (internally estimated + tunnel states). Estimated internally from DISCHARGE IPD where event counts permit, supplemented by informative Bayesian priors

Post-MI Year 1: HR ~ LogNormal(log(3.5), 0.15^2) [prior from(Jernberg et al., 2015)]

Post-MI Year 2+: HR ~ LogNormal(log(1.8), 0.12^2) [declining excess risk]

Post-Stroke Year 1: HR ~ LogNormal(log(4.0), 0.15^2) [prior from(Hankey et al., 2000)]

Post-Stroke Year 2+: HR ~ LogNormal(log(2.2), 0.12^2) [declining excess risk]

Tunnel states allow time-since-event dependent excess mortality.

Step 6 Treatment effect waning (4 pre-specified scenarios + 1 data-driven).

Scenario 1 (base case): the hazard ratio for MACE and QALY observed during the trial and possible cost differences and trajectories will be assumed to persist after the end of trial follow up. Additionally

Scenario 2: Linear decay to null at 10 years: $HR(t) = 1 + (HR_{trial} - 1) \times \max(0, 1 - t/10)$.

Scenario 3: Exponential decay: 5-year half-life: $HR(t) = 1 + (HR_{trial} - 1) \times \exp(-0.693 \times t/5)$.

Scenario 4: Crossover scenario: CT benefit reverses after year 7 (conservative stress test): $HR(t) = 1 + (HR_{trial} - 1) \times (1 - 2t/14)$ for $t \leq 14$, then $HR = 1/(HR_{trial})$ for $t > 14$.

Scenario 5 (data-driven): Flexible parametric model with time-dependent treatment coefficient using Royston-Parmar splines on the log cumulative hazard scale (Royston & Parmar, 2002). The time-varying HR is estimated from the data itself, with no assumed functional form. (*The only scenario that lets the DISCHARGE EXTEND validation reveal the true waning pattern).*

Step 7 QALY extrapolation (dual approach).

Base case: State-specific EQ-5D-3L utility weights with age-adjustment using country-specific population norms (Ara & Brazier, 2010). Utility decrements: Alive without MACE (baseline EQ-5D), Post-MI (−0.055, Sullivan et al. 2011), Post-Stroke (−0.164, Sullivan et al. 2011), with age-adjustment −0.0003 per year.

Sensitivity analysis: Joint longitudinal-survival model. Fit a shared random effects model linking the longitudinal EQ-5D-3L trajectory (3 measurements per patient) with MACE survival, allowing the utility decline to inform and be informed by the survival process. Implementation: JMbayes2 in R (Brilleman et al., 2019) or Dynamic-DeepHit (Tier 3) (Lee et al., 2020). This captures the possibility that utility decline is not solely state-driven but reflects a continuous deterioration process.

Model outputs: Within-trial costs and QALYs (decision tree) + discounted lifetime Markov costs and QALYs. ICER = ΔCost / ΔQALY. Full posterior distributions via MCMC. CEACs at country-specific WTP thresholds. EVPI at 3.5yr and 10yr.

6.1.4 Structural Sensitivity Analysis: Multi-State Model

As a structural sensitivity analysis, the Markov cohort model is complemented by a **continuous-time multi-state (illness-death) model** estimated directly from individual patient (Putter et al., 2007). This models transitions between Alive → MI, Alive → Stroke, Alive → CV Death, Post-MI → CV Death, Post-Stroke → CV Death, and all states → Non-CV Death as separate intensity functions, without discretising time into cycles. Advantages: (1) naturally handles competing risks without crude MACE decomposition; (2) allows time-varying transition intensities; (3) avoids the Markov assumption that transition probabilities depend only on current state. If the multi-state model produces materially different lifetime ICERs, this is reported as structural uncertainty.

6.2 Three-Tier Candidate Survival Model Portfolio

12 are fitted to the 3.5-year DISCHARGE data, locked on the Open Science Framework (OSF), and prospectively validated against 10-year DISCHARGE EXTEND outcomes. This design directly answers three questions the HTA community cannot currently answer empirically: (1) Which standard parametric model extrapolates best? (2) Do flexible methods from NICE TSD 21 outperform standard parametrics? (3) Should ML survival models be considered in HTA submissions?

6.2.1 Tier 1: Standard Parametric Models (NICE TSD 14, Latimer 2013)

These five distributions form the standard toolkit recommended by NICE TSD 14 (Latimer, 2013) and used in every NICE technology appraisal since 2013:

Model	Hazard Function	Hazard Behavior	Clinical Rationale for CAD
1. Weibull	$h(t) = \kappa\lambda(\lambda t)^{(\kappa-1)}$	Monotonic: increasing ($\kappa>1$) or decreasing ($\kappa<1$)	Most used in CV CEA; flexible monotonic; PH and AFT; cannot capture turning points
2. Gompertz	$h(t) = \lambda \cdot \exp(\gamma t)$	Exponentially increasing ($\gamma>0$) or decreasing ($\gamma<0$)	Biologically plausible: CV risk accelerates with age; natural ageing model
3. Log-logistic	$h(t) = (\alpha/\beta)(t/\beta)^{(\alpha-1)} / [1+(t/\beta)^{\alpha}]$	Non-monotonic: rises then falls ($\alpha>1$)	Captures early procedural risk that diminishes; AFT model; long tails
4. Log-normal	$h(t) = \phi(z)/[\sigma t(1-\Phi(z))]$	Non-monotonic: bell-shaped hazard	Alternative non-monotonic; AFT model; less commonly used in CV
5. Generalized Gamma	3-parameter: (Q, σ, μ)	Nests Weibull, log-normal, Gamma	Diagnostic: parameter values reveal which simpler model is appropriate

6.2.2 Tier 2: Flexible and Advanced Methods (NICE TSD 21, Kearns et al. 2020)

These four models address known limitations of standard parametrics, particularly for complex hazard shapes and long-term extrapolation. *NICE TSD 21(Rutherford et al., 2020) explicitly recommends evaluating these alongside standard models, yet a recent review found only 38% of NICE TAs assess hazard function shape and only 40% attempt external validation (Westerink et al. 2024).*

Model	Specification	Key Advantage	Rationale for DISCHARGE
6. Royston-Parmar Flexible Parametric	Restricted cubic splines on log cumulative hazard: $\ln H(t) = s(\ln t; \gamma, k_0)$	Captures complex, non-monotonic hazard shapes with smooth interpolation	Main TSD 21 innovation; can model turning points in MACE hazard; analytically tractable
7. Mixture Cure Model	$S(t) = \pi + (1-\pi)\cdot S^*(t)$ where π = cure fraction	Models subpopulation that will never experience event	Highly relevant: many DISCHARGE patients have no obstructive CAD; cure fraction = "correctly reassured" proportion
8. Relative Survival / Excess Hazard	$h(t) = h^*(t) + h_{pop}(t, age, sex, country)$ where h^* = excess disease hazard	Constrains long-term hazard to converge to population mortality	Prevents biologically implausible long-term extrapolation; uses Eurostat life tables directly; recommended by TSD 21
9. Bayesian Model Average (BMA)	$h_{BMA}(t) = \Sigma\, w_k \cdot h_k(t)$, weights from posterior model probabilities via stacking (Yao et al. 2018)	Accounts for model uncertainty across all Tier 1 models	NICE TSD 14 recommends presenting results under multiple models; BMA formalises this; Jackson et al. 2017

6.2.3 Tier 3: Machine Learning Survival Models (No HTA Guidance Exists)

Three ML models representing the methodological frontier. NICE, CADTH, and ISPOR have no guidance because no empirical validation against long-term outcomes exists. DISCHARGE + EXTEND provides the first such testbed.

Model	Architecture	Key Advantage	Rationale for DISCHARGE
10. DeepSurv	Deep neural network extending Cox PH; learns non-linear covariate–risk relationships (Katzman et al. 2018)	Maintains PH interpretability; captures non-linear interactions	Can discover complex age×treatment×country interactions invisible to parametric models
11. DeepHit	Deep neural network learning survival distribution directly; natively handles competing risks (Lee et al. 2018, AAAI)	No parametric assumptions; learns joint distribution of MI, stroke, CV death	Directly models competing MACE components without decomposition; tested on SEER (n=68k) and UNOS datasets
12. Random Survival Forest	Ensemble of survival trees; non-parametric; variable importance (Ishwaran et al. 2008)	Robust, interpretable, handles high-dimensional covariates	Standard ML benchmark; interpretable via variable importance; robust to overfitting with n=3,561

Implementation: Tier 1 and 2 models are fitted in Stan via R (brms/rstanarm for standard models; custom Stan code for generalized Gamma, Royston-Parmar, cure models, and BMA). For the primary analysis, models use independent country-specific likelihoods; for the secondary analysis, models use the hierarchical three-level structure. Tier 3 models are fitted in Python using PyCox (PyTorch) for DeepSurv and DeepHit, and scikit-survival for Random Survival Forests. ML models are trained on the pooled DISCHARGE dataset (n=3,561) with treatment arm, country, age, sex, baseline EQ-5D, and comorbidities as features, using 5-fold cross-validation for hyperparameter tuning and early stopping to prevent overfitting. Country-specific survival predictions are generated by inputting each country's covariate profile. All 12 models produce full survival curves, cumulative cost predictions, QALY trajectories, and cause-specific cumulative incidence functions for each treatment arm and country under both analysis tracks.

6.3 Model Selection Protocol

For the 3.5-year base case analysis, a single "primary" model is selected using a structured protocol:

(1) Statistical fit: AIC, BIC (frequentist); DIC, WAIC (Bayesian); concordance index and time-dependent AUC (ML).

(2) Hazard function inspection: Plot predicted vs. observed hazard functions for each model, each treatment arm, stratified by country group. Assess whether the hazard shape is clinically plausible.

(3) Clinical plausibility: Review 10-year and 20-year extrapolated survival with clinical collaborators (Prof. Dewey, Prof. Briggs). Does the model predict biologically reasonable mortality at age 80? 90?

(4) External validation: Compare 10-year projections against CAD-Man EXTEND observed data (pilot).

(5) BMA weights: Report posterior model probabilities across all 12 models; present BMA as primary sensitivity analysis.

All 12 models are retained and pre-registered on OSF. The 3.5-year paper (Paper 1) presents results under the selected primary model and the BMA composite. The validation paper (Paper 3) compares all 12 models against 10-year DISCHARGE EXTEND data, providing the empirical evidence that guidelines currently.

6.4 DISCHARGE EXTEND: 10-Year CEA and Prospective Validation

6.4.1 10-Year Cost-Effectiveness Analysis

Upon availability of DISCHARGE EXTEND data (available at the end of 2028), a 10-year CEA will be performed using observed long-term MACE, resource use, and EQ-5D-3L outcomes — the longest follow-up CEA of CT versus ICA from any randomized trial. DRG tariffs for 2022–2029 will be updated across all 16 countries in collaboration with the Mercator Fellow (Prof. Brodszky, PECUNIA network).

6.4.2 Prospective Validation Protocol

Stage 1: Pre-registration (Month 22–24): Lock all 12 model fits on OSF with time-stamped predictions for five validation targets: (a) MACE cumulative incidence curves (overall and by competing risk), (b) cumulative costs, (c) QALYs (including utility trajectory), (d) ICERs by country/group, (e) CEAC probabilities at €20k/30k/50k thresholds. Submit as Registered Report to Value in Health or Medical Decision Making.

Stage 2: Unblinding (Month 29–34): Compare locked predictions against 10-year observed data. Metrics: mean absolute prediction error, calibration slopes, prediction interval coverage, Kolmogorov-Smirnov test, time-dependent concordance index, integrated Brier score.

Stage 3: Error decomposition: Decompose prediction errors into: (1) survival curve shape, (2) cost trajectory, (3) utility decline, (4) treatment effect waning (which of the 5 scenarios matches?), (5) between-country heterogeneity, (6) competing risk composition.

Stage 4:Tier comparison: Formal comparison of extrapolation accuracy: Tier 1 vs. Tier 2 vs. Tier 3. Report mean and variance of prediction errors within and between tiers. This is the primary output for guideline recommendations.

Stage 5: Policy impact: EVPI at 3.5-year and 10-year time points; ΔEVPI = value of extended follow-up. Policy concordance: did cost-effectiveness recommendations change for each country? NMB comparison at country-specific WTP thresholds.

6.5 Model uncertainty

Parameter uncertainty will be assessed using probabilistic sensitivity analysis (i.e. by fitting a probability distribution to each parameter) and running Monte Carlo simulations. In **Table 4** we provide examples of probability distributions for the parameters included in the model.

Table 4: Transition probabilities (risks), and state-related costs, quality of life weights, MACE and statistical distributions applied in the Monte Carlo simulations.

	ICA	CT	Probabilistic sensitivity analysis – candidate distributions	Source
Risks				
Risk of x	-	-	Beta (α, β)*	Trial
Risk of death	-	-	Beta (α, β)*	Trial
Costs				
Costs in x	-	-	Log-normal (μ, σ^2)**	Trial
Costs in xx	-	-	Log-normal (μ, σ^2)**	Trial
Indirect costs (per month) from sick leave	-	-	Log-normal (μ, σ^2)**	Trial and national statistics
Average gross income per month for country x***	-	-		National statistics from country x
Quality of life weights (QoL)				
QoL weights in state x	-	-	Beta (α, β)*	Trial
QoL weights in state xx	-	-	Beta (α, β)*	Trial
Major Adverse Cardiovascular Event (MACE)				
MACE in state x	-	-	Log-normal (μ, σ^2)**	Trial
MACE in state xx	-	-	Log-normal (μ, σ^2)**	Trial

* The parameters α and β, specifying the distribution are calculated assuming that the deterministic value is the mean of the distribution. The variance was assumed to be 20 % of the mean value $\alpha = \bar{x}\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right)$, $\beta = (1-\bar{x})\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right)$, where $\bar{x}$ is the mean and $\bar{v}$ is the variance, and $\bar{v} < \bar{x}(1-\bar{x})$.

** The parameters of the distribution are calculated assuming that the deterministic value is the mean of the non-logarithmized distribution, and that the variance is 20 % of the mean value $\mu = ln\left[\frac{m}{\sqrt{1+{}^{v}/_{m^2}}}\right]$ and $\sigma^2 = ln\left[1+\frac{v}{m^2}\right]$, where m and v are the mean and variance of the non-logarithmized distribution.

*** The average gross income per month is calculated as the average of gross monthly income for the years x plus labor taxes paid by the employer.

Structural uncertainty is additionally assessed through: (1) multi-state illness-death model vs. Markov cohort (Section 6.1.4), (2) Bayesian Model Average across all 12 candidate models (Section 6.2), (3) five pre-specified treatment effect waning scenarios (Section 6.1.3, Step 6), and (4) joint longitudinal-survival model for QALY extrapolation (Section 6.1.3, Step 7).

6.6 Model validation

The model will be estimated and internally validated using trial data with external validation using (1) CAD-Man EXTEND 10-year follow-up (pilot; Section 6.4), (2) DISCHARGE EXTEND 10-year follow-up (prospective validation; Section 6.4.2), and (2) other randomized controlled trials of CT versus ICA such as CONSERVE (Chang et al., 2019) and CAD-Man (Dewey et al., 2016) as well as randomized trials of CT versus other diagnostic tests in stable chest pain patients such as PROMISE (Douglas et al., 2015; Hoffmann et al., 2017) and SCOT-HEART (Newby et al., 2018; Newby et al., 2015).

6.7 Subgroup analyses/heterogeneity

The subgroups described in section 5.13 will be considered for the decision analytic modeling.

7. Reporting/publishing

7.1 Reporting standards

Publication of the economics analyses of the DISCHARGE trial will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Husereau et al., 2013) and will include the 24-item CHEERS checklist of items to include when reporting economic evaluations of health interventions in cost-effectiveness analyses (CEA).

7.2 Deviations from the HEAP

Any deviation from HEAP will be described and justified in the final published report.

8. Reporting/publishing

8.1 Health economic collection tools

Data collection sheets from the 1st and 2nd follow-up are provided in a **Supplementary Appendix** .

8.2 Deviations from the HEAP

Any deviation from HEAP will be described and justified in the final published report.

9. **Appendix A** Overview of reimbursement to health care providers and the organization of the health care systems in the 16 participating countries

Reimbursement to hospitals and outpatient health care providers differs considerably between countries, as do the ways in which the healthcare system is organized. Below is a brief summary of the organization of healthcare and of hospital and outpatient health care reimbursements in the 16 European countries involved in the DISCHARGE trial.

Austria: The health system is based on social insurance organized on a regional basis, with a coordinating role of the state. The assignment of individuals to the public system of social health insurance is based on profession and with some exceptions, participation is mandatory. There are also private health insurers with mainly supplementary functions. Around 75% of total healthcare expenditure comes from the social insurance contributions, and out-of-pocket expenditure amounts to 18%.

Public and private non-profit hospitals are financed according to the Austrian LKF patient classification system, corresponding loosely to a DRG weight system, with about 1000 groups which may be procedure or diagnosis related. The payment is determined by the LKF weight with mark-ups which may very between regions. The LKF system is currently being extended to cover also outpatient treatments.

Czech Republic: The Czech health system is based on compulsory social insurance based on monthly contribution payments from employers, employees and self-employed. Public sources cover around 85% of total health expenditure, including some 5% from government budgets, and out-of-pocket payments constitutes about 15%.

Hospitals are paid according to a system of DRG weights which are updated annually. The latest version of the DRG system is CZ-DRG 3.0 from 2020. For certain medical services there may be specific rates based on individual contracts. Outpatient services are paid according to a fee-for-service principle.

Denmark: The health system is based on a national health service financed by general taxes and administered by regional health authorities. The public share of total health expenditure is 84%. Out-of-pocket payments amount to 14% of total expenditure.

Hospitals are owned and administered by regions. The use of DRG prices varies between regions, their main function is in determining the annual hospital budgets. There is no patient co-payment for inpatient or outpatient treatments.

Finland: The system is based on municipally governed healthcare financed by state and municipal taxes and covering around 62%, social health insurance covering 13% and private insurance and out-of-pocket payments, covering 5% and 20%, respectively, of total healthcare expenditure.

Hospitals are paid by municipalities using price lists based on NordDRG. User charges are widespread, including daily inpatient hospital charges and outpatient treatments.

Germany: The health system is based on compulsory health insurance, which can take the form of either social insurance administered by a large number of sickness funds, covering around 76% of total healthcare expenditure, and private insurance. The sickness funds collect contributions from employers and employees, and the funds are then redistributed through a central pool. Out-of-pocket payments amount to 12% of total expenditure.

Hospital inpatient services are paid according to a system of DRG, outpatient services are paid according to rates depending on type of insurance and sickness fund.

Hungary: The health system is state administered and the public expenditures are financed through a health insurance fund obtaining its funding from payroll taxes and government transfers. Private spending in the form of out-of-pocket payments amount to 27% of total health expenditure.

Hospitals are paid by the health insurance fund according to DRGs for acute care and bed days for chronic care, but actual payment is restricted by budget constraints. Out-of-pocket payment plays a minor role in inpatient care but matters more for outpatient care.

Ireland: The health system is based on a national health system financed by general taxes supplemented by specific charge on employees and self-employed. Government financing amounts to 73% of total health expenditure. Private out-of-pocket payments constitute 12% and voluntary health insurance, providing easier access, amounts to 13%.

Hospitals are paid using a DRG system for determining budgets. Patient co-payment is large, based on bed-days, both for inpatient and outpatient services.

Italy: The Italian health system is a based on regionally administered national health service with universal coverage. The public system covers 74% of total health, out-of-pocket payments amount to 24%, with privat health insurance covering the remaining 2%.

Payment for inpatient hospital care is based on DRG weights, which are set on national level but can be modified by the regional administration, resulting in rates which can differ considerably from one region to another. Rates for outpatient services are set by the regions. Patient co-payment plays an important role both in inpatient and in outpatient medical care.

Latvia: The healthcare system is of National Health Service (NHS) type with government funding, which however covers only around 55% of total healthcare expenditure. The system of user charges is extensive and regards most aspects of healthcare, with statutory user charges for inpatient care at NHS hospitals and full payment outside the NHS system. State-owned hospitals are supplemented by hospitals with other types of ownership.

Hospitals are reimbursed using several different methods, including fixed payments for treatments, bed-days and system of DRG prices, which is used for negotiating the reimbursement but not as a single reimbursement method.

Lithuania: The system is centered around a national health insurance fund with compulsory membership, the funding of which is composed of membership contributions as well as direct government financing. In 2010, taxes amounted to 40% of total health expenditure, while social insurance contributions and out-of-pocket payments contributed with 32% and 27% respectively.

Hospitals are with few exceptions state-owned. A system of DRG weights for reimbursement of hospital treatments, has been introduced in 2012 replacing a system of case-based payment.

Poland: The health system is based on a mandatory health insurance NFZ with member payments taking the form of a payroll tax. The NFZ covers around 60% of total healthcare expenditure, while out-of-pocket payments of patients amount to about 30%. Hospitals are owned by the state or the regions.

Payment of hospitals is negotiated with NFZ on a regional level, and the agreements of negotiation are influenced by the DRG prices as well as other factors. The actual reimbursements may therefore vary from one hospital to another and with the length of stay of the patient.

Portugal: The Portuguese health system is based on a tax-financed national health service for the general population, supplemented by health insurance schemes for particular professions, known as health subsystems, financed by employer and employee contributions, and voluntary supplementary health insurance. The public healthcare covers around 65% of total healthcare expenditure, and private out-of-pocket payments amount to 27%.

Hospitals are financed through budgets set up using DRGs, and the health subsystems pay for inpatient and outpatient treatments according to DRG prices. There is no patient co-payment for inpatient treatments but there is co-payment for outpatient services.

Romania: The system is based on compulsory health insurance covering 85% of the population, leaving out some people working in agriculture and not employed in the private sector. The health insurance covers around 67% of total health expenditure, while out-ot-pocket payments covers around 19%. Informal payment is believed to be widespread.

Hospitals are paid using a mixture of DRG, case payments, day tariffs and other components. The DRG system in use. There is a co-payment in the form of an admittance fee for hospital treatment.

Ambulatory care has been reimbursed by 25-30% of the DRG for corresponding inpatient treatment but has since 2014 been given specific tariffs.

Serbia: The health system is based on mandatory social insurance, but the health insurance fund has insufficient income for the purpose, so that private sources, of which out-of-pocket expenditure is the most important, cover around 42% of total healthcare expenditure. Informal payments are also of some importance.

Hospitals are state-owned, and reimbursement of hospital services based on a DRG system was introduced in 2019. The DRG-based reimbursement has not yet replaced earlier methods based on budgetary assignments. Patient copayment is widespread.

Spain: The health system in Spain is administrated by regional governments and is financed mainly by taxes, private expenditure amounts to 28.9% of total health expenditure, with 23.9% being out-of-pocket expenditure. Hospital inpatient care constitutes more than half of the public health expenditure.

Hospitals are both publicly and privately owned, the latter contribute about 30% of all discharges. Publicly owned hospitals are funded by regional authorities by a procedure employing regional DRG tariffs, but the payments to hospitals are non directly connected to current provision of services. Private hospitals are paid according to regional agreements based on DRGs. There are no patient co-payments for hospital inpatient or outpatient treatments.

United Kingdom: The health system is based on the National Health Service (NHS) financed by general taxes, and 79% of total health expenditure comes from public sources, while out-of-pocket payments amount to 16%.

A system based on purchaser-provider split was introduced in the 1990s, and a version still remains in force in England, where providers are paid by Health Resource Groups on behalf of the NHS according to a national tariff based on DRGs. Hospitals obtain 60% of their funding from DRG payments. In Scotland, Wales and Northern Ireland, funding of hospitals takes place through block contracts. There is no patient co-payment for hospital services.

For further information on country health systems and hospital reimbursements, the data provided by the European Observatory on Health Systems and Policies will be used

https://eurohealthobservatory.who.int/home

Austria: health system review 2018, *Health Systems in Transition* 20(3).

Czech republic: health system review 2015, *Health Systems in Transition* 17(1).

Denmark: Country health profile 2019, *State of Health in the EU,* European Observatory on Health Systems and Policy. 2019.health system review 2015, *Health Systems in Transition* 17(1),

Finland: health system review 2019, *Health Systems in Transition* 21(2).

Germany: health system review 2014, *Health Systems in Transition* 16(2),

Germany: country health profile 2019, *State of Health in the EU,* European Observatory on Health Systems and Policy. 2019.

Hungary: country health profile 2019, *State of Health in the EU,* European Observatory on Health Systems and Policy. 2019.

Ireland: health system review 2009, *Health Systems in Transition* 11(4),

Ireland: country health profile 2019, *State of Health in the EU,* European Observatory on Health Systems and Policy. 2019.

Italy: health system review 2015, *Health Systems in Transition* 17(1),

Italy: country health profile 2019, *State of Health in the EU,* European Observatory on Health Systems and Policy. 2019.

Latvia: health system review 2019, *Health Systems in Transition* 21(4).

Lithuania: health system review 2013, *Health Systems in Transition* 15(2).

Lithuania: country health profile 2019, *State of Health in the EU,* European Observatory on Health Systems and Policy, 2019.

Poland: health system review 2019, *Health Systems in Transition* 21(1).

Portugal: health system review 2017, *Health Systems in Transition* 19(2),

Romania: health system review 2016, *Health Systems in Transition* 18(4).

Serbia: health system review 2019, *Health Systems in Transition* 21(3).

Spain: health system review 2018, *Health Systems in Transition* 20(2),

United Kingdom: health system review 2015, *Health Systems in Transition* 17(5),

10. **Appendix B** Detailed description on the calculation of incremental costs and effects based on individual patient data

The key measures to estimate from trial data are the costs and effects (MACE and QALYs) in the two study groups from which the incremental cost-effectiveness ratio (ICER) can be calculated. These measures will be estimated taking an aggregate approach where trial-wide data are pooled before analysis. For example, the trial-wide effect of shifting from ICA to CT in terms of MACE and QALYs will be estimated using all patients in the trial irrespective of country of origin. Further, costs will be calculated by applying unit cost estimates from individual countries to the number of resource use events from individual patients. This fully pooled analysis will result in estimates of trial-wide effects and cost-effectiveness rather than estimates for individual countries (which will be included in secondary analyses).

Analyses will be incremental and include all patients according to the group they were randomized to (intention-to-treat-analysis). At the end of the clinical trial, costs measured in Euros at 2018 price level and effects are available for each participating patient. Cost of an individual patient for the period from initial diagnosis until the end of the follow-up will be estimated as follows for the intervention group (the CT group):

$$(1) \qquad hC_i^{ct} = \sum_{t=0}^{4} \sum_{a} (S_{it}^{a} * c^{a} + M_{it}) (1+r)^{-t}$$

where hC_i^{ct} is the total discounted value of the cost from a health care sector perspective in 2018 prices of patient *i* in the intervention group from the time of the initial diagnostic test to the end of follow-up, S_{it}^{a} indicates the number of times patient *i* has consumed a health service of type *a* in period *t* and c^{a} is the unit cost of a health service of type *a*. Further, M_{it} is the cost of medication consumed by patient *i* in period *t*. Time period *t*=0 refers to the period between the point in time a patient is exposed to the initial diagnostic test and first follow-up while *t*=1 refers to the period between first and second follow-up (and similarly for *t*=2 and *t*=3) The discount rate *r* is 3% (0.03) corresponding to the low end of the range of social discount rates estimated for individual European countries using the social time preference rate approach [28]. Similarly, cost of an individual patient from the control group (the ICA group) from a health sector perspective is:

$$(2) \qquad hC_j^{ica} = \sum_{t=0}^{4} \sum_{a} (S_{jt}^{a} * c^{a} + M_{jt}) (1+r)^{-t}$$

with a similar interpretation as above. When the broader societal perspective is taken, costs borne by patients must be incorporated also. Cost of an individual patient for the period from the initial diagnostic test until the end of the follow-up period will be estimated as follows for the intervention group (the CT group):

$$(3) \qquad sC_i^{ct} = \sum_{t=0}^{4} \sum_{a} (S_{it}^{a} * c^{a} + M_{it} + TE_{it} + TL_{it}) (1+r)^{-t}$$

where sC_i^{ct} is the total discounted value of the cost from a societal perspective in 2018 prices of patient *i* in the intervention group from the initial diagnostic test to the end of the follow-up period and where variables S_{it}^{a} , c^{a} and M_{it} have the same interpretations as described above. The variable TE_{it} is the annual cost of travelling for patient *i* in time period *t* whereas TL_{it} indicates the value of time lost from being unable to work by patient *i* in period *t*. Similarly, cost of an individual patient from the control group (the ICA group) from the societal perspective is:

$$(4) \qquad sC_j^{ica} = \sum_{t=0}^{4} \sum_{a} (S_{jt}^{a} * c^{a} + M_{jt} + TE_{jt} + TL_{jt}) (1+r)^{-t}$$

with a similar interpretation as above.

The effect on individual patients will be calculated for the period from the initial diagnostic test and the end of the follow-up period is denoted E_i^{ct} for patient *i* in the intervention group and E_j^{ICA} for patient *j* in the control group. The effect measure to be used for the cost-effectiveness analyses will be the number of MACE and QALYs in the follow-up period.

The point estimate of the incremental cost-effectiveness ratio (*ICER*) from a health sector perspective will be calculated using the variables described above:

$$(5a) \qquad ICER_h = \frac{\overline{hC_{\square}^{ct}} - \overline{hC_{\square}^{ica}}}{\overline{MACE_{\square}^{ica}} - \overline{MACE_{\square}^{ct}}} = \frac{\Delta hC}{\Delta E}$$

and

$$(5b) \qquad ICER_h = \frac{\overline{hC_{\square}^{ct}} - \overline{hC_{\square}^{ica}}}{\overline{QALYs_{\square}^{ct}} - \overline{QALYs_{\square}^{ica}}} = \frac{\Delta hC}{\Delta E}$$

where a bar over a variable indicates the arithmetic mean; for example, $\overline{hC_{\square}^{ct}}$ is the arithmetic mean costs among patients in the intervention arm from the time of the initial diagnostic test and until the end of the follow-up. The measure ΔhC indicates the difference in mean costs between patients in the CT and the ICA arm also referred to as incremental costs while ΔE is the difference in mean effect between the two patient groups, the incremental effect. The point estimate of the incremental cost-effectiveness ratio (*ICER*) from a societal perspective will be calculated as:

$$(6a) \qquad ICER_s = \frac{\overline{sC_{\square}^{ct}} - \overline{sC_{\square}^{ica}}}{\overline{MACE_{\square}^{ica}} - \overline{MACE_{\square}^{ct}}} = \frac{\Delta sC}{\Delta E}$$

and

$$(6b) \qquad ICER_s = \frac{\overline{sC_{\square}^{ct}} - \overline{sC_{\square}^{ica}}}{\overline{QALYs_{\square}^{ct}} - \overline{QALYs_{\square}^{ica}}} = \frac{\Delta sC}{\Delta E}$$

with a similar interpretation as the ICER from a health sector perspective.

To complement the ICER analysis, in the case of country-specific CUA, the Net Monetary Benefit (NMB) will also be calculated to provide a direct monetary representation of cost-effectiveness by integrating costs and effects based on a predefined WTP threshold per QALY. The NMB is expressed from the health sector as well perspective as:

$$(7a) \qquad NMB_h = \lambda * (\overline{QALYs^{ct}} - \overline{QALYs^{ica}}) - (\overline{hC^{ct}} - \overline{hC^{ica}})$$

and from societal prespective as:

$$(7b) \qquad NMB_s = \lambda * (\overline{QALYs^{ct}} - \overline{QALYs^{ica}}) - (\overline{sC^{ct}} - \overline{sC^{ica}})$$

As mentioned, the economic evaluation will be divided into two components depending on the follow-up time of patients. The number of MACE and QALYs will likewise be measured until a median of 3.5 years in the primary cost-effectiveness analysis. Since the follow-up time differs among patients, mean costs in the two patient groups will express the costs for the average follow-up time in a patient group. Similarly, the mean number of MACE and QALYs in the two patient groups expresses the effect over the average follow-up time in the patient groups. If the mean follow-up times in the two patient groups are not significantly different, the ICER can be calculated using equations 5 and 6. Depending on the effect measure chosen, the ICER expresses the additional costs per MACE averted or per QALY gained from the health sector or societal perspective if the ICA diagnostic method is replaced by CT.

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