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Utility of non-invasive diagnostic testing alternatives among patients with chest pain

PhD thesis

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List of Abbreviations

ACS	Acute coronary syndrome
AHA/ACC	American Heart Association/American College of Cardiology
ASCVD	Atherosclerotic cardiovascular disease
CAD	Coronary artery disease
CTA	Computed tomography angiography
ECG	Electrocardiogram
ECHO	Echocardiography
ED	Emergency department
ESC	European Society of Cardiology
FFR-CT	Fractional flow reserve based on CT
Hs-cTn	High-sensitivity troponin
ICA	Invasive coronary angiography
ICER	Incremental cost-effectiveness ratio
LOD	Level of detection
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
NSTEMI	Non-ST segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PROMISE	PROspective Multicenter Imaging Study for Evaluation of chest pain
QALY	Quality adjusted life years
ROMICAT	Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography
SCOT-HEART	Scottish Computed Tomography of the Heart
SOC	Standard of care
SPECT	Single photon emission computed tomography
UAP	Unstable angina pectoris

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1 Introduction

Chest pain is one of the most common presenting complaints at the emergency department (ED) in developed countries posing tremendous burden on the healthcare systems.(1, 2) In the United States alone, annually more than 6.5 million patient present with chest pain in an emergency setting and further 4 million as outpatients resulting in 8.7 subsequent non-invasive diagnostic testing for suspected coronary artery disease (CAD) at the expense of $15 billion.(3, 4)

Patients with chest pain further constitute diagnostic and logistic hurdles in the ED and in outpatient setting. Most of the times symptoms are associated with non-cardiac and non-life-threatening disparities not requiring emergency treatment and hospitalization as only approximately one-third of patients are eventually diagnosed with an acute coronary syndrome (ACS) or stable CAD. However, CAD affects >18 million adults in the US and CAD associated heart disease remains the leading cause of death worldwide.(5) Hence diagnostic testing alternatives enabling quick and efficient diagnosis of acute myocardial injury or chronic coronary syndrome are being developed.

In acute setting, the introduction of high-sensitivity cardiac troponin (hs-cTn) assays, permitting the quantification of small degrees of myocardial injury, enable rapid rule-in and rule-out of ACS. Further, in acute and in chronic setting, coronary computed tomography angiography (CTA) has emerged to be a non-invasive diagnostic tool to examine the coronary arteries among patients with symptoms of chest pain. However, to optimize the triaging of patients with chest pain, assessment of the clinical utility of diagnostic testing alternatives is warranted.

1.1 Troponin-based acute chest pain management

For patients presenting with acute chest pain the key elements of the diagnostic algorithm for evaluation of ACS are clinical assessment, ECG, and measurement of cardiac troponin.(6, 7) Advancements in troponin assay technology have led to the development of hs-cTn assays, that allow the detection of very low levels of and small changes in troponin levels, already within one hour.(8-11) Even in the absence of ACS most patients have measurable troponin concentrations, therefore the binary nature of information derived by

conventional troponin assays (i.e. acute myocardial infarction [AMI] present or absent), has evolved more into a continuous measure, requiring more nuanced interpretation.(12) This led to the development of new diagnostic algorithms for several commercially available hs-cTn assays for the diagnosis of ACS. These hs-cTn -based decision algorithms seek to speed up the triage of patients presenting with acute chest pain in the ED and to avoid unnecessary hospitalizations. These algorithms either use analytic benchmarks as for example suggested by the US Food and Drug Administration or assay specific triaging thresholds.

1.1.1 Analytic benchmark as thresholds for acute chest pain management

Traditional analytic characteristics of troponin assays include the level of detection (LOD), which is the lowest concentration an assay can detect, and 99th percentile upper reference limit, which is the troponin concentration determined to indicate the presence of myocardial injury. Early diagnostic algorithms may set the threshold for early rule-out after a single blood testing to the limit of detection (LOD) and use the 99th percentile cut point to define abnormal troponin values (as defined by the Fourth Universal Definition of Myocardial Infarction [MI] (6)). Further in some instances it is recommended to perform serial testing at one-, two- or three hours for patients with measurable troponin below the 99th percentile and recommend management based on the change in troponin concentration.(13, 14) However, the known differences in the assays' analytic characteristics e.g. their analytic sensitivities (as per the LOD) and the use of different reference populations to derive each assay's 99th percentile (15) raises the question whether the use of analytic benchmarks would render similar risk assessment across assays.

1.1.2 Assay specific thresholds for acute chest pain management

The purpose for assay-specific thresholds is to eliminate those differences between assays emerging from their distinct analytic attributes and thus to establish common cut-points based on the results of large clinical trials that allow for rendering similar management recommendations across different platforms. The European Guidelines for the management of ACS in patients presenting without persistent ST-segment elevation published in 2020(6) and in 2023(16) (ESC Guidelines) recommend serial blood testing for troponin measurement at either zero and one or at zero and two hours after presentation. Further, the Guidelines endorse assay-specific fixed thresholds for several commercially available hs-cTn platforms

to achieve standardized care across different assays used for triaging patients with suspected ACS.

1.2 Knowledge gap in troponin-based acute chest pain management

While many published studies, including those based on analytic benchmarks or assay specific diagnostic algorithms, have reported excellent negative predictive values (99.5 to 99.8%) to rule-out-, and high specificities (95.0 to 99.0%) to rule-in AMI for the individual assays(17-20); it remains unknown whether differences in analytic sensitivity (LOD) and derivation of the 99th percentile affect classification of blood samples into analytic categories, or render different management recommendations to rule-out/observe/rule-in patients with suspected ACS. Further, whether there is an agreement among hs-cTn assays when applying the ESC Guidelines-recommended assay-specific thresholds is yet to be determined. Finally, the influence of potential discordance across assays on clinical utility, thus whether non-invasive diagnostic testing results, clinical-, and predicted quality-of-care outcomes of patients are consistent across assays is unknown and whether they these outcomes are improved when compared to a conventional troponin-based strategy.

1.3 Non-invasive diagnostic testing-based chest pain management

1.3.1 Acute chest pain management with coronary CT imaging

Among patients, who are at low to intermediate risk for ACS, initial work up with biomarkers and electrocardiographic (ECG) testing is often inconclusive and therefore this patient population is particularly challenging to diagnose. Further, neither clinical presentation, nor traditional risk factors and risk scores allow for a safe initial triage, as the adverse event rate even in patients with the lowest scores is still around 2%, which is over the generally accepted 1% error rate.(21)

Several randomized comparative effectiveness trials have demonstrated that early coronary CT imaging improves the efficiency of ED triage of patients at low- to intermediate risk for ACS.(22-24) Improvement in hospital admission and length of hospital stay effectiveness endpoints were improved, achieved by the ability of coronary CT to rule-out the presence of any coronary plaques. No CAD at index hospitalization, occurring in approximately 50% of the patients, has a very high negative predictive value for major

adverse cardiovascular events (MACE). Further, coronary CTA identifies non-obstructive CAD in about 40% of patients which carries significant prognostic information: improved outcomes were reported when lipid lowering therapy was initiated based on the presence of underlying CAD independent of ASCVD risk recommended statin eligibility.(25) However, obstructive CAD, detected in around 10% of patients, results in increased invasive coronary angiography (ICA) and percutaneous coronary intervention (PCI) rates associated with to higher costs of care. Coronary CTA is able to detect the presence of CAD, including those with obstructive and non-obstructive presentation. Data suggest, that aggressive lipid lowering therapy based on the presence of obstructive and non-obstructive CAD (and not based on the atherosclerotic cardiovascular disease [ASCVD] risk score suggested statin eligibility) results in improved outcomes.(25) Yet, studies with short follow up period, i.e. 30 days to one year, fail to demonstrate improvement in clinical utility of coronary CT in acute chest pain management. Therefore, it is questioned whether coronary CTA is indeed beneficial.

1.3.2 Stable chest pain management with non-invasive diagnostic testing

Of the 8.7 million non-invasive testing performed in the US for the evaluation of patients with chest pain around two-thirds are carried out with nuclear imaging with single photon emission computed tomography (SPECT), one-third is stress echocardiography.(4, 26, 27) However, the positive predictive value of these tests for anatomically obstructive CAD in patients referred to invasive coronary angiography (ICA) remains low (38%).(28) Meanwhile, coronary CT imaging, the only test that allows for the non-invasive visualization of prevalent CAD, is currently performed in less than 5% of chest pain evaluations. Randomized comparisons between functional and anatomic index testing in low-risk stable chest pain, the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) and Scottish Computed Tomography of the Heart (SCOT-HEART), have rendered mixed results. The PROMISE trial reported no differences between anatomic and functional evaluation strategies in stable chest pain for incident MACE after two years while the SCOT-HEART study showed a 41% reduction of non-fatal MI for patients randomized to coronary CTA compared to functional testing after 5 years.(29, 30) In addition to that, both trials reported higher referral rates to ICA and subsequent revascularization after 2 years,

with SCOT HEART reporting similar ICA and revascularizations rates between the two strategies after 5 years.(30, 31) Recent data support to add hemodynamic assessment of coronary lesions with fractional flow reserve based on standard resting coronary CTA (FFR-CT) in patients with intermediate stenosis as it leads to a two-fold increase in specificity over anatomic assessment with coronary CTA alone (74% vs 34%), compared to gold standard invasive FFR.(32)

1.3.3 Knowledge gap in the non-invasive testing-based management of chest pain

First, no data has been generated that assesses the long-term impact of using coronary CTA as an index test for patients with acute chest pain in relation to alternative diagnostic strategies, including functional testing, expedited ED protocols with the intent to perform diagnostic testing in an outpatient setting(33, 34) and a strategy based on the American Heart Association/American College of Cardiology (AHA)/ACC) guidelines.(35)

Second, due to the ambiguous results on the clinical utility of coronary CTA for stable chest pain assessment generated by large clinical trials (i.e. PROMISE and SCOT HEART) with intermediate length follow up (i.e. 2- and 5 years), long-term results are warranted to determine whether anatomical assessment of stable CAD is superior compared to standard of care functional testing. Further, no data yet exists on the clinical utility of the addition of FFR-CT and whether it would improve clinical work up of patients with suspected stable coronary atherosclerosis by optimizing patient selection for ICA.

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2 Objectives

The goal of this thesis was to ascertain the following aims:

2.1 To assess the agreement between state-of-the-art hs-cTn assays.

Aim 1: To determine whether differences in assay sensitivity and derivation of the 99th percentile affect classification of blood samples into analytic categories (<LOD/LOD-99th percentile/>99th percentile) when measuring troponin by using 3 hs-cTn assays in patients with suspected ACS.

Aim 2: To determine the agreement among four hs-cTn assays when applying the ESC Guidelines-recommended assay-specific thresholds and to assess whether non-invasive diagnostic testing results-, clinical-, and predicted quality-of-care outcomes of patients are consistent across assays and whether quality-of-care outcomes are improved when compared to a conventional troponin-based strategy.

2.2 To assess the clinical utility of coronary CTA vs standard of care in chest pain.

Aim 3: To determine whether the availability of information on the presence and extent of CAD by coronary CTA will offset higher initial costs by a significant improvement in health outcomes long-term, and to determine lifetime health outcomes and cost-effectiveness of available ED management strategies for patients with low- to intermediate risk for ACS.

Aim 4: To determine the long-term health outcomes and cost-effectiveness of initial anatomic (CT) vs functional diagnostic approaches to patients with low-risk stable chest pain.

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3 Methods

3.1 Patient populations

3.1.1 ROMICAT I and II trials

To assess *Aims 1, 2* and *3*, we included patients with suspected ACS enrolled in the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) I and II trials (NCT00990262 and NCT01084239) who were referred for further noninvasive diagnostic testing after inconclusive initial ED triage, defined as negative conventional troponin measurement and non-ischemic ECG.(36, 37) Briefly, ROMICAT I was an observational cohort study in which individuals with suspected ACS were managed according to standard care and also underwent coronary CTA with results blinded to health care providers. ROMICAT II trial was a multicenter, randomized controlled trial in which the enrolled subjects were randomized to undergo standard of care vs coronary CTA, where the result of coronary CTA was part of the decision making. All included patients provided written informed consent, and the studies were approved by the local institutional review board. In both studies, ACS was defined as either MI or UAP and adjudicated by an independent events committee.

To assess *Aims 1* and *2* we included patients who consented to blood draw (38, 39) and whose blood samples were analyzed with three and four state-of-the-art hs-cTn assays, respectively.(40-42) To assess *Aim 1*, data was utilized from the ROMICAT I and II trials, and to ascertain *Aims 2* and *3*, we restricted our analysis to the ROMICAT II study.

3.1.2 PROMISE trial

To assess *Aim 4*, we studied patients included in the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial (ClinicalTrials.gov identifier: NCT01174550), which is a multicenter, randomized, pragmatic trial designed to compare non-invasive cardiovascular testing alternatives, e.g. functional and anatomical testing, in to determine the presence of prevalent obstructive CAD.(30, 43) The PROMISE trial recruited altogether 10,003 symptomatic outpatients presenting with stable chest pain whose referring physician requested non-urgent, non-invasive cardiovascular testing to exclude the presence

of obstructive CAD. The included patients were randomized either to functional (SPECT, stress echocardiography or exercise tolerance test) or to anatomical testing (cardiac CT) arm. Patients with acute or unstable presentation, known history of CAD or with any contraindication for contrast enhanced coronary CTA were excluded from the trail. All included patients provided written informed consent. Local or central institutional review board approved the study protocol at each coordinating center and enrolling sites.

3.2 The assessment of the agreement between state-of-the-art hs-cTn assays

3.2.1 High sensitivity cardiac troponin measurements

3.2.1.1 Blood samples

In the ROMICAT I trial(38) a single blood draw was performed, while in ROMICAT II(39) sequential blood testing was performed at the time of ED presentation and at two hours and four hours thereafter. Blood was collected into tubes containing EDTA and immediately centrifuged and stored in microcentrifuge tubes at -80°C until sample assessment. All samples were tested with three state-of-the-art high sensitivity assays for the purpose of *Aim 1* (Roche Elecsys Gen 5 [Roche Diagnostics, Penzberg, Germany], Abbott ARCHITECT [Abbott Laboratories, Irving, TX], Siemens Vista [Siemens Diagnostics, Newark, DE]) (*figure 3*).(40-42), and blood samples were tested on serum with four hs-cTn assays for to investigate *Aim 2* (Roche Elecsys Cobas Gen 5 assays [e411; Roche Diagnostics, Penzberg, Germany], Abbott ARCHITECT [Abbott Laboratories, Irving, TX], a pre-commercial version of the Siemens Vista [Siemens Diagnostics, Newark, DE], and the Beckman ACCESS [Beckman Coulter, Brea, CA]). The analytic properties of assays, as limit of detection (LOD), 99th percentile, and 10% coefficient of variation are summarized in ***Table 1***.(40-42) All blood samples were analyzed in a blinded fashion for clinical information.

Table 1. *Analytic characteristics of high-sensitivity troponin assays.(44)*

	LOD	LOQ	Overall 99th %tile	Sex specific 99th %tile, female / male
Roche Elecsys, TnT, ng/L	5	6	19	14 / 22
Abbott Architect, TnI, ng/L	1.7	2.3	28	17 / 35
Siemens Vista, TnI, ng/L	2	3	58.9	53.7 / 78.5
Beckmann Access, TnI, ng/L	1-2	0.9-2.3	18.2	11.8 / 19.7

AMI=acute myocardial infarction; TnI=Troponon I; TnT=Troponin T. LOD=limit of detection; LOQ=limit of quantification; CV=coefficient of variance; %tile=percentile.

3.2.1.2 Analytic benchmarks

We defined analytic benchmarks along assay specific analytic characteristics frequently used as the generally applicable thresholds in diagnostic algorithms of ACS. The analytic benchmarks were the followings: below LOD, LOD to 99th percentile and above the 99th percentile. In a per sample analysis, we determined the agreement across assays to classify blood samples obtained in the ROMICAT I and ROMICAT II trials, independent of the timing of blood drawn (treated as independent blood samples), according to analytic benchmarks (***Figure 1***).

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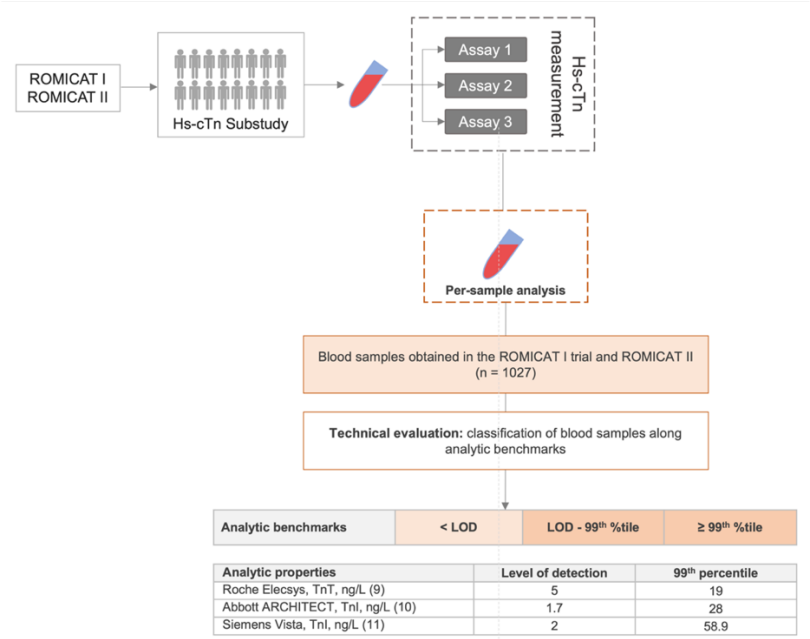


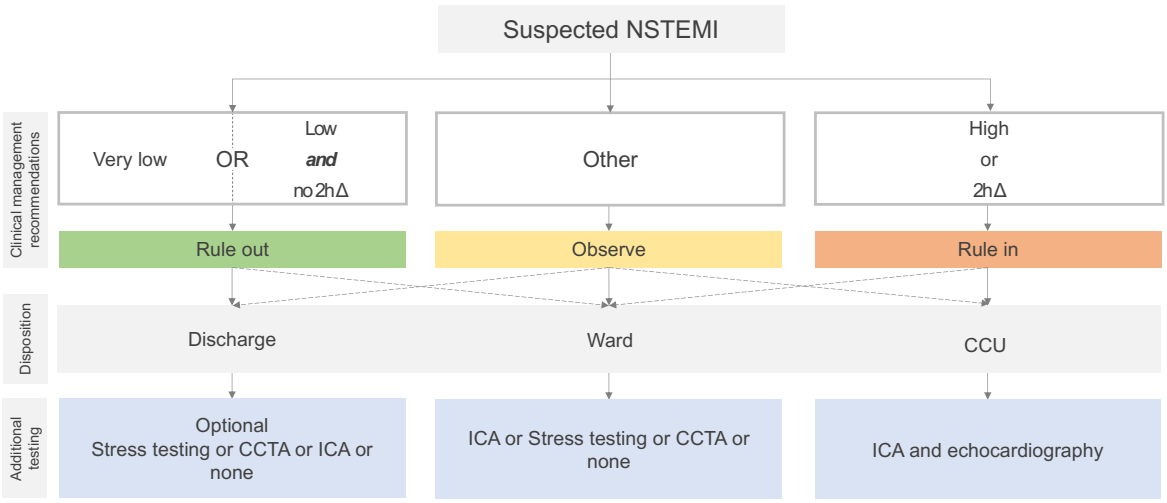
Figure 1. *Outline of the per sample analysis and the used thresholds to assess the concordance between three hs-cTn assays.*

ACS=Acute Coronary Syndrome; ESC=European Society of Cardiology; Hs-cTn=High Sensitivity Cardiac Troponin; LOD=Limit of Detection; ROMICAT=Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography; 1st=1st blood drawn for the measurement of hs-cTn; 2nd=2nd blood drawn for the measurement of Hs-cTn; %tile=Percentile.

3.2.1.3 Patient management recommendations

The 0/2 hour rule-out and rule-in algorithm recommended by the ESC Guidelines was used to define the management recommendations of ACS in hemodynamically stable patients presenting with acute chest complaints. As defined by the ESC Guidelines, '*rule-out*' management recommendation was defined as low likelihood for non-ST segment myocardial infarction (NSTEMI) with very low hs-cTn measurement at presentation or with low baseline levels and lack of a relevant increase after serial hs-cTn testing. '*Rule-in*' management recommendation was defined as high likelihood for NSTEMI with at least moderately elevated hs-cTn concentration at presentation or with a clear rise in hs-cTn concentrations. Any patient who did not meet the criteria for rule-out or rule-in were stratified into '*observe*'.

Agreement across assays to stratify patients according to ESC Guidelines-defined assay-specific thresholds at 0 and at 2 hours was determined (***Figure 2***).



ESC 2020 Guidelines 0/2 hour algorithm	Very low	Low	No 2hΔ	High	1hΔ
Roche Elecsys , ng/L	<5	<14	<4	≥52	≥10
Abbott ARCHITECT, ng/L	<4	<6	<2	≥64	≥15
Siemens Vista, ng/L	<3	<8	<7	≥120	≥20
Beckman Access, ng/L	<4	<5	<5	≥50	≥20

Figure 2. *0/2 hour rule-out and rule-in algorithm recommended by the ESC Guidelines to define the management recommendations for patients with suspected ACS based on fixed thresholds for the assessed 4 hs-cTn assays.*

ACS=acute coronary syndrome; CCTA=coronary computed tomography angiography; CCU=coronary care unit; ICA=invasive coronary angiography; hs-cTn=high-sensitivity cardiac troponin; NSTEMI=non-ST-segment elevation myocardial infarction; ROMICAT=Rule Out Myocardial Infarction/ Ischemia Using Computer Assisted Tomography.

3.2.2 Non-invasive diagnostic testing

Association of management recommendations with noninvasive diagnostic test findings and the agreement across the studied assays among patients who underwent either coronary CTA or nuclear myocardial stress perfusion imaging (single-photon emission computed tomography, [SPECT]) was assessed. A positive result of coronary CTA was

defined as the presence of obstructive coronary artery disease (CAD, defined as a luminal narrowing ≥50%. A positive result of SPECT was defined as the presence of any stress-induced ischemia (reversible myocardial perfusion defect).

3.2.3 Clinical outcomes

Clinical outcomes of patients and their hs-cTn based management recommendations as per the ESC Guidelines were assessed. At the time of the conduction of this current analysis the ESC 2020(6) Guidelines were the most recent, however during the review process of our work the ESC 2023 Guidelines(16) were released. These two documents contain the exact same information regarding the hs-cTn assay thresholds. However, given that our work was based on the 2020 Guidelines we used that as a basis of this research. The outcome of the ROMICAT II trial was clinically adjudicated ACS, which was defined as either MI or unstable angina pectoris (UAP) as adjudicated by an independent events committee.(37) MI was defined clinically, utilizing history, results from ECG and development of an abnormal troponin measurement as determined with a conventional troponin assay run at the time of the ROMICAT II trial at 6 or 9 hours after ED presentation. UAP was defined as clinical symptoms suggestive of ACS with objective evidence of obstructive CAD and myocardial ischemia, such as a positive stress test.

3.2.4 Observed and predicted quality-of-care outcomes

We compared quality-of-care outcomes across the four assays to evaluate the agreement between the platforms. Further, quality-of-care outcomes were compared between the hs-cTn-based vs conventional troponin-based strategies.

We evaluated whether ESC Guidelines-compliant risk stratification rendered different quality-of-care outcomes versus those observed in ROMICAT II. Quality-of-care outcomes included utilization of advanced cardiac testing including coronary CTA, exercise treadmill testing, stress echocardiography, nuclear myocardial perfusion imaging, or ICA. Consistent with ESC Guidelines, it was assumed that patients stratified as ruled-out based on the first hs-cTn measurement (i.e. very low risk) would be diagnosed after 1 hour of waiting time and could be discharged from the ED without further testing after 2 hours. Patients that

could be ruled-out after the second hs-cTn measurement, and thus were diagnosed after 3 hours (blood drawn at 2 hours plus 1 hour waiting time), could be discharged from the ED without further testing 4 hours after ED presentation. All remaining patients were assumed to be managed as in the ROMICAT II trial.

Diagnostic yield was calculated as number of patients in whom diagnostic testing was abnormal divided by the number of patients who underwent, i.e. as observed, or would undergo, i.e. as predicted, cardiac testing. Cumulative radiation exposure (which included exposure from coronary CTA, nuclear myocardial perfusion imaging, and ICA) was calculated. Disposition of patients, length of stay, time to diagnosis, and need for non-invasive cardiac testing were also evaluated.

Healthcare costs during the index care episode were assessed using reports from hospital cost-accounting systems and physician billing records. Cost data were available in 649 out of 1,000 ROMICAT II patients using 2012 US dollars.(23, 37) To predict the costs when applying the ESC Guidelines-derived management recommendations regression coefficients were generated based on a multivariate linear regression model (using information from the 649 patients, the regression model explained 86% of the variability in costs with R^2=0.856) that included total cost as dependent variable and length of stay of more than 8 hours (binary), number of non-invasive cardiac tests, ICA (binary), in-patient hospitalization (binary), PCI (binary), and coronary artery bypass graft surgery (binary) as independent variables. The total health care costs were then calculated by multiplying the predicted cost coefficients by their corresponding parameters for each patient included in our study, i.e. original input parameters for as observed analysis and modified parameters for as predicted analysis. Further details on the methodical description can be found in the published manuscripts.(45, 46)

3.3 The assessment of clinical utility of coronary CTA delivered anatomical imaging vs alternative strategies

3.3.1 Acute chest pain setting

We developed a Markov microsimulation model which was populated using individual data on demographics and cardiovascular risk factors from the 1,000 patients enrolled in the ROMICAT II trial to simulate four management strategies for individual patients who present to the ED with suspected ACS. These strategies are: 1) early coronary CTA as observed in ROMICAT II, 2) standard of care (functional testing) as observed in ROMICAT II, 3) Expert Consensus strategy based on current ACC/AHA guidelines and 4) an expedited ED protocol strategy with early discharge and the intent to perform diagnostic testing in an outpatient setting.

We developed a short-term model, in which we estimated the probability of each strategy to accurately detect underlying CAD and ACS, as well as test and treatment utilization and costs within the first month after ED presentation. Further, we developed a long-term model, which was used to estimate quality adjusted life years (QALYs) and lifetime costs of care for the studied pathways. As a basis, we estimated the probability of future coronary revascularization procedures including PCI and CABG, adverse cardiovascular events, including MI and cardiovascular death, as well as overall mortality rates at 1, 3, and 10 years and over a lifetime. Across a lifetime, transition to different health states is modeled in monthly cycles at which time the CAD status of each patient is determined. The CAD status could remain the same or progress, and patients could suffer from Mis and die from either cardiovascular disease or other causes (***Figure 3***).

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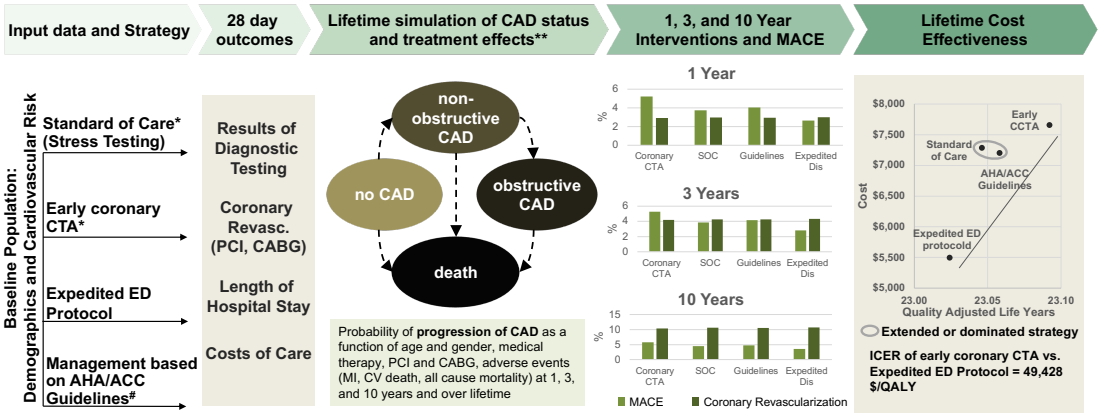

Figure 3. *Markov microsimulation model with short- and long-term health and economic outcomes of 4 competing management strategies. The model was populated with baseline population characteristics as observed in the ROMICAT II Trial. Short-term model validation was based on 28-day management and outcomes as observed in the ROMICAT II. 1-, 3- and 10-year MACE outcomes include non-fatal myocardial infarction and cardiovascular death, and coronary revascularization outcomes include PCI and CABG. CABG=Coronary artery bypass graft; CAD=Coronary artery disease; CTA=Computed tomography angiography; ED=Emergency Department; ICER=Incremental cost-effectiveness ratio; MACE=Major adverse cardiovascular events; PCI=Percutaneous coronary intervention.*

3.3.1.1 Study endpoints

The short-term model predicted length of stay-, testing-, and interventions for both the coronary CTA and SOC strategy, which results were used for the model validation.

The long-term model predicted health- and economic outcomes, including cardiovascular events and mortality rates at 2-, 3-,10 years and over lifetime, quality of life, quality adjusted life years (QALYs), lifetime costs of care and incremental cost-effectiveness ratio (ICER), that expresses the costs per additional QALY i.e. the costs to live an additional year in perfect health. To estimate the ICER, costs and QALYs were discounted at 3% annually.

3.3.1.2 Sensitivity analyses

We conducted 3 sensitivity analyses: (1) to assess the impact of the risk profile of the incoming cohort, we performed a sensitivity analysis in which we replaced the ROMICAT-II cohort with a cohort whose demographic and clinical characteristic profile similar to the CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) study (24) population, which we were able to simulate without a patient-level data by modeling a cohort that met its described characteristics well; (2) we conducted a bivariate sensitivity analysis to determine the ICER by modifying the diagnostic accuracy of coronary CTA across a range of sensitivities (85%–100%) and specificities (50%–100%) as the diagnostic accuracy for obstructive CAD may vary between CT scanners and readers that influences ICA/revascularization referrals; (3) in order to address uncertainties around the medical treatment effect, we conducted a sensitivity analysis using the upper and lower bounds of the confidence interval of the 23% relative risk reduction of statin therapy on lifetime mortality as described in the literature, i.e. assuming a 18% and 30% relative risk reduction. In addition, we performed sensitivity analyses for variations in compliance, including a scenario with 5 years of full compliance followed by 5 years of declining compliance (in monthly steps with none of the patients on statins after 10 years), and full compliance for 5 years and no treatment effect afterwards. Further details on the methodical description can be found in the published manuscript.(47)

3.3.2 Stable chest pain setting

We developed a Markov microsimulation model using individual patient-level data (i.e. demographic characteristics and risk factors) from 10,003 real-life US patients from the PROMISE trial presenting with suspicion of obstructive CAD. We compared the following strategies: 1) coronary CTA, 2) coronary CTA with FFR-CT, and 3) functional testing. Each patient entered the model 100 times with a health state defined by their underlying CAD status (ie, no CAD, nonobstructive CAD, or obstructive CAD) and underwent different life cycles and disease progression based on probabilities. The likelihood of positive test results, referral to downstream ICA and subsequent revascularization, statin therapy, and related benefits that translated into different risk of MACE were simulated based on the initial correct

diagnosis of CAD and CAD progression. The model was validated by comparing model outcomes with outcomes observed in PROMISE. The validated model was used to simulate short-term (60 days), mid-term (2- and 5 years), and long-term (over lifetime) health and economic outcomes, as well as cost-effectiveness over a lifetime (***Figure 4***). Further details on the methodical description can be found in the published manuscript.(48)

3.3.2.1 Study endpoints

This study had 4 end points, which included 1) rates of diagnostic ICA and revascularization-to-ICA ratio at 60 days; 2) rate of coronary revascularization (PCI or CABG) at 60 days, 2 years, 5 years, and over lifetime; 3) MACE (MI, CV mortality), all-cause mortality, and the composite endpoint at 2 years, 5 years, and lifetime; and 4) cost-effectiveness, defined as cost and QALYs at 2 years, 5 years, and over a lifetime, and ICER and life-years gained over lifetime.

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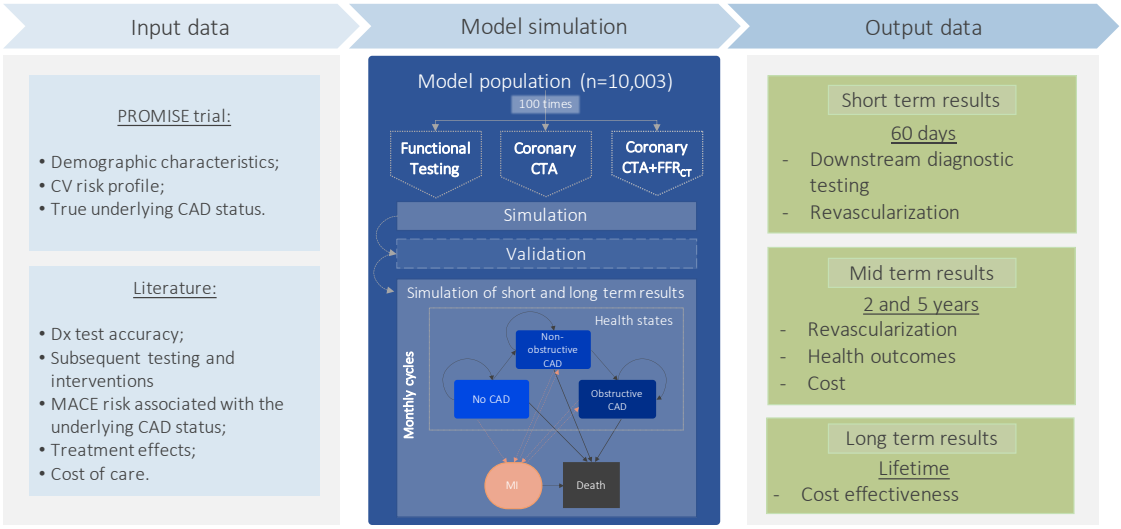

Figure 4. *Overview of the Markov microsimulation-model utilizing individual patient-level data. We populated the model with baseline population characteristics, risk factors and underlying true CAD status as observed in PROMISE, and diagnostic test accuracy, baseline rules for further testing and interventions, MACE risk associated with the underlying CAD status, treatment effects and cost of care as reported in the literature. After simulation of the 60-day and 2-year functional testing and coronary CTA results, the model accuracy was validated by comparing model simulated with observed patient management, health outcomes and costs in PROMISE for coronary CTA and functional testing. Next, simulation of short-term and long-term outcomes of the model population after undergoing the index testing with coronary CTA, functional testing, CTA+FFR-CT, by modeling health states (no CAD, non-obstructive CAD, obstructive CAD) and transitions within, in monthly cycles until end of life. Model outcomes were downstream diagnostic testing and revascularization rate in short-term and revascularization, health outcomes and cost over 2 and 5 years, finally cost-effectiveness over lifetime.*

CAD=Coronary artery disease; CTA=Computed tomography angiography; CV=Cardiovascular; Dx=Diagnostic; FFR-CT=Non-invasive fractional flow reserve derived from computed tomography; MACE=Major adverse cardiovascular event; MI=Myocardial infarction; PCI=Percutaneous coronary intervention.

3.3.2.2 Subgroup and sensitivity analyses

To assess the robustness of ICER analyses, we conducted subgroup analyses stratified by (1) sex and (2) median age (<60 years or ≥60 years).

We also conducted 2 sensitivity analyses: (1) adherence to medical therapy, a scenario of 5 years of full adherence followed by 5 years of declining adherence (in monthly steps with no patients receiving statins after 10 years) and another scenario with full adherence for 5 years and no medical treatment effect afterwards; (2) to assess whether adding functional information to anatomical stenosis would substantially affect the rate of invasive testing among those with luminal narrowing greater than 70%, we expanded the indication of FFR-CT to include such patients.

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4 Results

4.1 Agreement between high-sensitivity troponin assays in patients with suspected acute coronary syndromes

4.1.1 Classification of blood samples into analytic categories (*Aim 1*)

4.1.1.1 Patient population

We evaluated 322/368 study subjects enrolled to the ROMICAT I trial and 302/1,000 ROMICAT II patients of whom 1,027 individual blood samples were obtained (n=608 obtained at arrival, n=251 at 2 hours, and n=168 at 4 hours), (***Figure 5***).

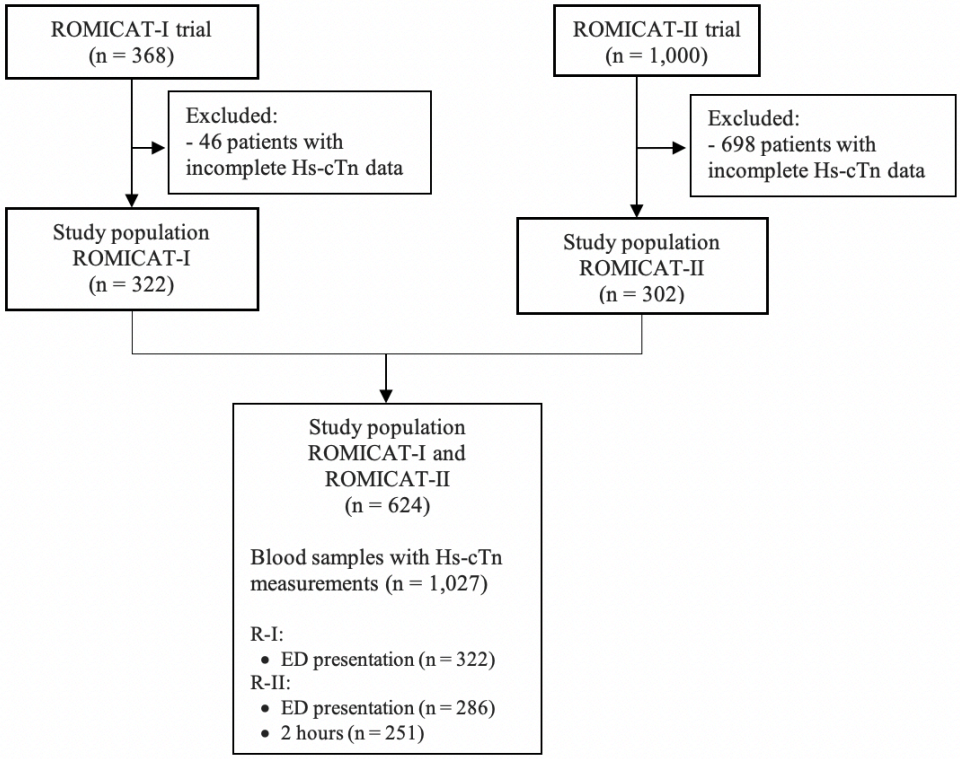

Figure 5. *Consort diagram of the patient population assessed to determine whether differences in assay sensitivity and derivation of the 99th percentile affect classification of blood samples into analytic categories when measuring troponin by using 3 hs-cTn assays in patients with suspected ACS.*

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The average age of the patients was 52.8±10.0 years, 39.4% were women, most had a low Thrombolysis in Myocardial Infarction (TIMI) risk score (TIMI score 0 or 1: 84.8%; 529/624), and 7.9% (49/624) had an adjudicated diagnosis of ACS. Among patients referred to noninvasive testing, 20.5% 98/479) had obstructive coronary artery disease (CAD) on coronary CTA and 24.3% (46/189) had inducible myocardial ischemia on SPECT (***Table 2***).

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Table 2. *Baseline demographic characteristics of the ROMICAT I and II subjects assessed in the per-sample analysis.*

	Total (n=624)	**ROMICAT I (n=322)**	**ROMICAT II (n=302)**	**P value**
Age, years	52.8 ± 10.0	52.6 ± 11.7	52.9 ± 7.8	0.70
Female sex, n (%)	246 (39.4)	121 (37.6)	125 (41.4)	0.37
BMI, kg/m^2	28.9 ± 5.4	28.9 ± 5.9	28.9 ± 4.7	0.91
Cardiovascular risk factors				
Hypertension, n (%)	286 (45.8)	128 (39.8)	158 (52.3)	**0.002**
Diabetes mellitus, n (%)	82 (13.1)	37 (11.5)	45 (14.9)	0.24
Dyslipidemia, n (%)	249 (39.9)	121 (37.6)	128 (42.4)	0.25
Former/current smoker, n (%)	303 (48.6)	155 (48.1)	148 (49.0)	0.87
Family hx of premature CAD, n (%)	193 (30.9)	80 (24.8)	113 (37.4)	**0.001**
Number of CV risk factors, n (%)				**0.003**
0-1	268 (43.0)	159 (49.4)	109 (36.1)	
2-3	307 (49.2)	142 (44.1)	165 (54.6)	
≥4	49 (7.9)	21 (6.5)	28 (9.3)	
TIMI score, n (%)				**<0.001**
0	342 (54.8)	154 (47.8)	188 (62.3)	
1	187 (30.0)	101 (31.4)	86 (28.5)	
2	75 (12.0)	50 (15.5)	25 (8.3)	
≥3	20 (3.2)	17 (5.3)	3 (1.0)	
Prior medication				
Aspirin, n (%)	171 (27.4)	103 (32.0)	68 (22.5)	**0.009**
Beta-blocker, n (%)	127 (20.4)	75 (23.3)	52 (17.2)	0.07
Statin, n (%)	174 (27.9)	91 (28.3)	83 (27.5)	0.86
Non-invasive diagnostic testing				
Positive test, n (%)	125/517 (24.2)	80/322 (24.8)	45/195 (23.1)	0.67
Positive coronary CTA*, n (%)	98/479 (20.5)	58/322 (18.0)	40/157 (25.5)	0.07
Positive SPECT**, n (%)	46/189 (24.3)	38/132 (28.8)	8/57 (14.0)	**0.041**
Clinical events				
ACS, n (%)	49 (7.9)	24 (7.5)	25 (8.3)	0.77
AMI, n (%)	11 (1.8)	5 (1.6)	6 (2.0)	0.77
UAP, n (%)	38 (6.1)	19 (5.9)	19 (6.3)	0.87

*Positive coronary CTA: >50% luminal narrowing; **Positive SPECT: evidence of stress induced ischemia defined as reversible myocardial perfusion defect.
ACS=Acute coronary syndrome; BMI=Body mass index; CAD=Coronary artery disease; CV=Cardiovascular; MI=Myocardial infarction; UAP=Unstable angina pectoris.

4.1.1.2 Agreement between hs-cTn assays in classifying blood samples according to analytic benchmarks

The proportion of samples <LOD and between LOD to 99th percentile was significantly different between all assays (<LOD: 56.3% [578/1,027] vs 10.4% [107/1,027] vs 41.2% [423/1,027]; LOD to 99th percentile: 36.5% [375/1,027] vs 83.5% 858/1,027] vs 52.6% [540/1,027] for Roche Elecsys, Abbott Architect and Siemens Vista, respectively, p<0.001). The proportion of samples classified >99th percentile on the other hand did not differ significantly (7.2% [74/1,027] vs 6.0% [62/1,027] vs 6.2% [64/1,027], p=0.114), (***Table 3***).

Table 3. *Agreement between assays in classifying blood samples according to analytic benchmarks.*

Analytic benchmarks	**Roche Elecsys n (%)**	**Abbott Architect n (%)**	**Siemens Vista n (%)**	**P values***			
				Roche vs. Abbott	Roche vs. Siemens	Abbott vs. Siemens	Overall Comparison
< LOD	578 (56.3)	107 (10.4)	423 (41.2)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
LOD - 99th %tile	375 (36.5)	858 (83.5)	540 (52.6)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
> 99th %tile	74 (7.2)	62 (6.0)	64 (6.2)	0.064	0.157	0.670	0.114
Total	1,027 (100.0)	1,027 (100.0)	1,027 (100.0)	N/A	N/A	N/A	N/A

*Indicating the differences between the assays.
LOD=Limit of detection; %tile=Percentile.

The proportion of samples concordantly classified into the same analytic benchmarks was low with 37.4% (384/1,027; Kappa: 0.22). The highest concordance occurred for classification of samples >99th percentile (43.6%, 44/101; Kappa: 0.70); however, among the 57 discordant blood samples, 9 were classified simultaneously as <LOD by at least one assay.

Concordance was lower for LOD to 99th percentile (29.3%, n=266/908; Kappa: 0.15), where 56 discordant cases classified >99th percentile in parallel, while the rest was overlapping with the benchmark of <LOD resulting in a very low concordance for <LOD (11.1%, 74/669; Kappa: 0.16), (***Figure 6***).

When using the 99th percentile as a binary threshold, the proportion of blood samples above the99th percentile was similar for all assays when non–sex-specific 99th percentiles were applied (7.2%,6.0%, and 6.2% per Roche, Abbott, and Siemens, respectively).

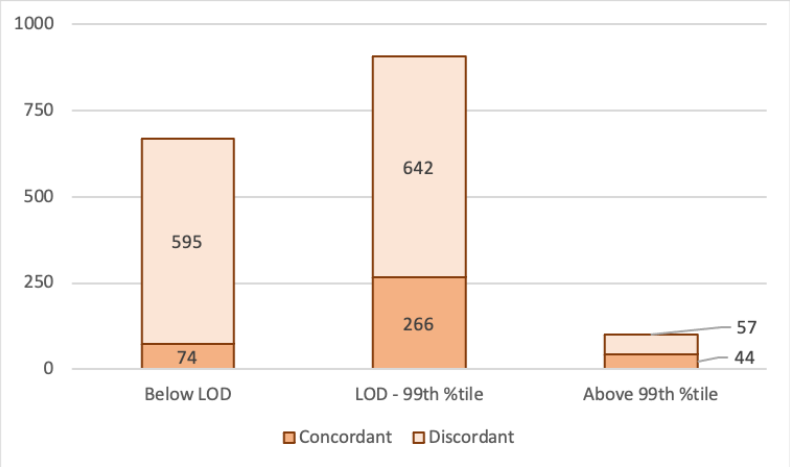

Figure 6. *Agreement between assays in classifying blood samples along analytic benchmarks using non-sex specific 99th percentile.*

Concordant is defined as agreement between all three assays, anything else is considered as discordant, where we define discordant as cases which are classified to more than one analytic benchmark, therefore the overall sum of the columns is not equal to the overall sum of studied blood samples (n=1,027), but it is higher because of the redundancy. LOD=Limit of detection; 99th%tile=99th percentile.

In pairwise comparison, Roche vs Abbott agreed in 47.8% (overall: 491/1027; Kappa=0.17; <LOD: 15.9%, 94/591; Kappa=0.12; LOD to 99th percentile: 39.6%, 350/883; Kappa=0.12; >99th percentile: 52.8%, 47/89; Kappa=0.67), Roche vs Siemens in 64.0% (overall: 657/1027; Kappa=0.37; <LOD: 50.8%, 337/664; Kappa=0.38; LOD to 99th percentile: 43.2%, n=276/639; Kappa=0.30; >99th percentile: 46.8%, 44/94; Kappa=0.61)

and Abbott vs Siemens in 62.2% (overall: 639/1,027; Kappa=0.27; <LOD: 18.3%, 82/448; Kappa=0.17; LOD to 99th percentile: 56.6%, 505/893; Kappa=0.22; >99th percentile: 70.3%, 52/74; Kappa=0.81), respectively.

4.1.2 Agreement between hs-cTn assays to stratify patients into rule-out/observe/rule-in per the ESC Guidelines (*Aim 2*)

4.1.2.1 Patient population

Of 1,000 randomized subjects of the ROMICAT II trial 238 (23.8%) had blood samples analyzed with all four assays (***Figure 7***).

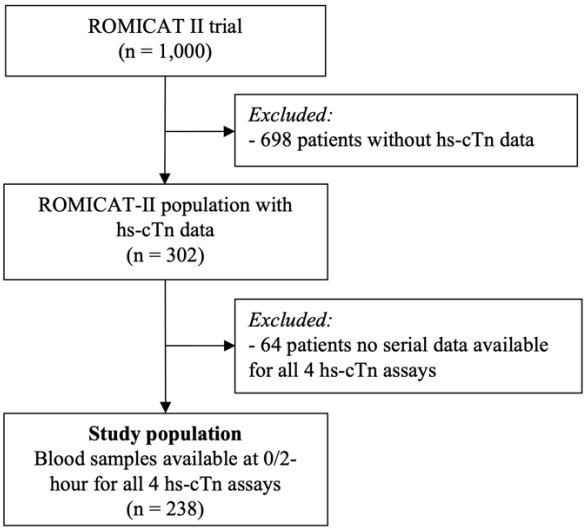

Figure 7. *Consort diagram of the patient population assessed to determine the agreement among four hs-cTn assays when applying the ESC Guidelines-recommended assay-specific thresholds and to assess whether non-invasive diagnostic testing results, clinical, and predicted quality-of-care outcomes of patients are consistent across assays and whether quality-of-care outcomes are improved when compared to a conventional troponin-based strategy.*

Baseline characteristics of the patients are summarized in ***Table 5***. Patients were on average 52.7±8.0 years old, 40.3% (96/238) were female, and most had 0-3 cardiovascular risk factors (90.7%, 216/238). Of those who underwent anatomical testing with coronary CTA 25.6% (30/117) had obstructive CAD and of those who were tested with SPECT, 16.3%

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(n=7/43) had inducible myocardial ischemia. Most, 91.2% (217/238), of patients had low (<2) TIMI risk score, and adjudicated ACS was diagnosed in 7.6% (18/238).

Table 5. Demographic characteristics of patients with biomarkers in the ROMICAT II trail.

	ROMICAT-II (n=238)
Age, years	52.7 ± 8.0
Female sex, n (%)	96 (40.3)
BMI, kg/m^2	29.1 ± 4.7
Cardiovascular risk factors	
Hypertension, n (%)	124 (52.1)
Diabetes mellitus, n (%)	40 (16.8)
Dyslipidemia, n (%)	105 (44.1)
Former/current smoker, n (%)	118 (49.6)
Family history of premature CAD, n (%)	87 (36.6)
Number of cardiovascular risk factors, n (%)	
0-1	81 (34.0)
2-3	135 (56.7)
≥4	22 (9.2)
TIMI score, n (%)	
0	145 (60.9)
1	72 (30.3)
2	19 (8.0)
≥3	2 (0.8)
Prior medication	
Aspirin, n (%)	55 (23.1)
Beta-blocker, n (%)	42 (17.7)
Statin, n (%)	65 (27.3)
Non-invasive diagnostic testing	
Positive test, n (%)	34/145 (23.5)
Positive CCTA*, n (%)	30/117 (25.6)
Positive SPECT**, n (%)	7/43 (16.3)
Clinical events	
ACS, n (%)	18 (7.6)
AMI, n (%)	5 (2.1)
UAP, n (%)	13 (5.5)

**Positive coronary CTA: >50% luminal narrowing; **Positive SPECT: evidence of stress induced ischemia defined as reversible myocardial perfusion defect. ACS=acute coronary*

syndrome; AMI=acute myocardial infarction; BMI=body mass index; CAD=coronary artery disease; CCTA=coronary computed tomography angiography; SPECT=single-photon emission computed tomography; TIMI=thrombolysis in myocardial infarction; UAP=unstable angina pectoris.

4.1.2.2 Agreement between hs-cTn assays to stratify patients into rule-out/observe/rule-in per the ESC Guidelines

After the arrival troponin measurement, the assays differed in stratifying patients into rule-out (Roche 60.9% vs Abbott 63.5% vs Siemens 55.0% vs Beckman 86.6%, p<0.001) and observe (Roche 37.0% vs Abbott 33.6% vs Siemens 42.0% vs Beckman 10.5%, p<0.001), but did not differ for rule-in (Roche 2.1% vs Abbott 2.9% vs Siemens 2.9% vs Beckman 2.9%, p=0.57), (***Table 6***). Kappa values for rule-out, observe and rule-in were 0.40, 0.35 and 0.76, respectively. The overall concordance across the assays was 49.6% (118/238; Kappa: 0.40), and all four assays agreed to stratify patients to rule-out, observe and rule-in in 46.3%, 11.1% and 40.0%, respectively (***Figure 8a***).

After the second hs-cTn measurement, disagreement among the assays remained for rule-out (Roche 89.9% vs Abbott 76.5% vs Siemens 78.6% vs Beckman 86.6%, p<0.001) and observe (Roche 6.7% vs Abbott 20.6% vs Siemens 17.7% vs Beckman 9.2%, p<0.001), while for rule-in the assays remained similar (Roche 3.4% vs Abbott 2.9% vs Siemens 3.8% vs Beckman 4.2%, p=0.62), (***Table 6***). Kappa values for rule-out, observe and rule-in were 0.53, 0.42 and 0.65, respectively. The overall concordance across the assays was 74.0% (176/238; Kappa: 0.50), and assays agreed in 74.3% 9.4% and 31.3% for rule-out, observe and rule-in strata, respectively (***Figure 8b***).

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***Table 6**. Agreement between assays in stratifying patients based on baseline (0 hour) and serial (0/2 hour) hs-cTn measurements.*

	Management recommendation	Roche Elecsys n (%)	Abbott Architect n (%)	Siemens Vista n (%)	Beckman Coulter	P values*						
						Roche vs. Abbott	Roche vs. Siemens	Abbott vs. Siemens	Roche vs. Beckman	Siemens vs. Beckman	Abbott vs. Beckman	Overall
0 hour	Rule-out	145 (60.9)	151 (63.5)	131 (55.0)	206 (86.6)	0.431	0.080	**0.002**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Observe	88 (37.0)	80 (33.6)	100 (42.0)	25 (10.5)	0.310	0.146	**0.003**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Rule-in	5 (2.1)	7 (2.9)	7 (2.9)	7 (2.9)	0.317	0.317	1.000	0.317	1.000	1.000	0.572
	Total	238 (100.0)	238 (100.0)	238 (100.0)	238 (100.0)	-	-	-	-	-	-	-
0/2 hours	Rule-out	214 (89.9)	182 (76.5)	187 (78.6)	206 (86.6)	**<0.001**	**<0.001**	0.251	0.103	**<0.001**	**<0.001**	**<0.001**
	Observe	16 (6.7)	49 (20.6)	42 (17.7)	22 (9.2)	**<0.001**	**<0.001**	0.144	0.221	**<0.001**	**<0.001**	**<0.001**
	Rule-in	8 (3.4)	7 (2.9)	9 (3.8)	10 (4.2)	0.655	0.706	0.317	0.480	0.655	0.180	0.623
	Total	238 (100.0)	238 (100.0)	238 (100.0)	238 (100.0)	-	-	-	-	-	-	-

*Indicating the differences between the assays.

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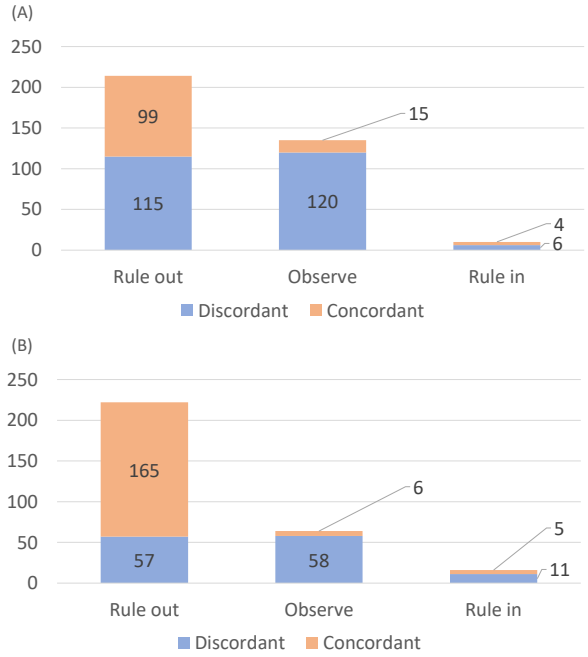

Figure 8. *Agreement between assays in patient management recommendations based on the ESC Guidelines provided 0/2 hour algorithm.* ***A.*** *1st hs-cTn measurement.* ***B.*** *1st and the 2nd hs-cTn measurements.*

4.1.2.3 Non-invasive diagnostic testing results and clinical outcomes

60.9% (145/238) of the patients underwent non-invasive testing (102/145 CTA, 28/145 SPECT, 15/145 CTA and SPECT), (***Table 7***). Among those stratified to rule-out, 21.6% (29/134) vs 20.0% (23/115) vs 21.4% (25/117) vs 19.1% (24/126) per Roche, Abbott, Siemens and Beckman, respectively, were identified to have obstructive CAD or inducible myocardial ischemia, and of them 21/29 (72.4%) were risk-stratified as rule-out by all 4 assays. Among patients who were stratified as rule-out by at least one of the four assays, 4.2 (9/214) vs 3.3% (6/182) vs 3.7% (7/187) vs 3.4% (7/206) for Roche, Abbott, Siemens and Beckman, respectively, were diagnosed with ACS (2.8-3.7% UAP and 0.0-0.6% MI).

Table 7. *Patient management recommendations per the 0/2 hour algorithm and clinical findings.*

		Rule out				Observe				Rule in			
		Roche Elecsys n=214	**Abbott Architect n=182**	**Siemens Vista n=187**	**Beckman Coulter n=206**	**Roche Elecsys n=16**	**Abbott Architect n=49**	**Siemens Vista n=42**	**Beckman Coulter n=22**	**Roche Elecsys n=8**	**Abbott Architect n=7**	**Siemens Vista n=9**	**Beckman Coulter n=10**
Any dx test received, n (%)	145	134/214 (62.6)	115/18 2 (63.2)	117/187 (62.6)	126/20 6 (61.1)	9/16 (56.3)	26/49 (53.1)	22/42 (52.4)	14/22 (63.6)	2/8 (25.0)	4/7 (57.1)	6/9 (66.7)	5/10 (50.0)
Pos. test, n (%)	34	29/134 (21.6)	23/115 (20.0)	25/117 (21.4)	24/126 (19.1)	4/9 (44.4)	9/26 (34.6)	5/22 (22.7)	6/14 (42.9)	1/2 (50.0)	2/4 (50.0)	4/6 (66.7)	4/5 (80.0)
Pos. CCTA, n (%)	30	25/108 (23.2)	19/92 (20.7)	21/96 (22.3)	21/99 (21.2)	4/8 (50.0)	9/22 (40.9)	5/18 (27.8)	6/14 (42.9)	1/1 (100.0)	2/3 (66.7)	4/5 (80.0)	3/4 (75.0)
Pos. SPECT, n (%)	7	6/39 (15.4)	5/34 (14.7)	5/34 (14.7)	3/36 (8.3)	1/3 (33.3)	2/8 (25.0)	1/7 (14.3)	3/5 (60.0)	0/1 (0.0)	0/1 (0.0)	1/2 (50.0)	1/2 (50.0)
ACS, n (%)	18	9/214 (4.2)	6/182 (3.3)	7/187 (3.7)	7/206 (3.4)	5/16 (31.3)	7/49 (14.3)	4/42 (9.5)	4/22 (18.2)	4/8 (50.0)	5/7 (71.4)	7/9 (77.8)	7/10 (70.0)
AMI, n (%)	5	1/214 (0.5)	1/182 (0.6)	0/187 (0.0)	1/206 (0.5)	1/16 (6.3)	0/49 (0.0)	1/42 (2.4)	0/22 (0.0)	3/8 (37.5)	4/7 (57.1)	4/9 (44.4)	4/10 (40.0)
UAP, n (%)	13	8/214 (3.7)	5/182 (2.8)	7/187 (3.7)	6/206 (2.9)	4/16 (25.0)	7/49 (14.3)	3/42 (7.1)	4/22 (18.2)	1/8 (12.5)	1/7 (14.3)	3/9 (33.3)	3/10 (30.0)

ACS=acute coronary syndrome; AMI=acute myocardial infarction; CCTA=coronary computed tomography angiography; Pos.=Positive; SPECT=single-photon emission computed tomography; UAP=unstable angina pectoris.

4.1.2.4 Quality-of-care outcomes

Agreement between the four assays

Predicted rate of non-invasive testing differed modestly between the four assays, i.e. the rate of no testing was 92.0% (219/238) vs 80.7% (238/192) vs 82.8% (197/238) vs 88.7% (211/238) for Roche, Abbott, Siemens and Beckman, respectively (***Table 8***). However, rates of invasive testing and interventions and radiation exposure were similar across the hs-cTn assays (all $p>0.05$). Rates of patient disposition and treatment times differed moderately across assays, with ED discharge rates of 80.3% to 90.8% ($p<0.001$), and the mean length-of-stay (6.7±15.8 to 10.1±26.1 hours, $p<0.001$) and mean time-to-diagnosis (2.6±6.2 to 4.3±7.5 hours, $p<0.001$). Mean healthcare costs differed slightly between the assays with $2,571±2,897 vs $2,784±3,234 vs $2,894±4,371 vs $2,651±3,138

per patient (p<0.001), and $1,988±702 vs $2,070±729 vs $2,051±704 vs $1,973±681 when excluding ACS patients (p<0.001) for Roche, Abbott, Siemens and Beckman, respectively.

Predicted, hs-cTn-based strategies vs observed, conventional troponin-based strategy

Predicted rates of any testing (8.0-19.3% vs 91.2%, p<0.001) and radiation exposure (1.7±7.9-2.7±8.9 mSv/patient vs 9.1±11.8 mSv/patient, p<0.001) for all hs-cTn assay were markedly lower compared to observed, conventional troponin-based measurements (***Table 8***). The diagnostic yield of testing (26.8-37.0% vs 14.8%, p>0.05), the invasive testing rates (3.4-4.2% vs 8.0%, p>0.05) and intervention rates (2.9-3.8% vs 5.4%, p>0.05) were similar compared to the observed, conventional troponin assay-based data. Hs-cTn-based, predicted patient pathways resulted in a higher discharge rate compared to the observed, conventional troponin-based strategy (80.3-90.8% vs 21.0%). Consequently, length-of-stay (6.7±15.8-10.1±26.1 hours vs 25.1±28.5 hours, p<0.001) was substantially shorter with the hs-cTn-based strategies, with also a faster time-to-diagnosis compared to observed data (2.6±6.2-4.3±7.5 hours vs 14.5±12.9 hours, p<0.001). Ultimately, predicted hs-cTn-based strategies improved utility-of-care with lower costs compared to observed data ($2,571±2,896-2,894±4,371 vs $3,889±4,833, p<0.001).

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Table 8. *Advanced cardiac testing, radiation exposure, disposition, length of hospital stay, time-to-diagnosis and healthcare costs as observed in the ROMICAT II trial vs as predicted using decision rules based on highly sensitive troponin and cardiovascular risk factors.*

	As Observed (n=238)	**As predicted**			
		***Roche Elecsys* (n=238)**	***Abbott Architect* (n=238)**	***Siemens Vista* (n=238)**	***Beckman Coulter* (n=238)**
Non-invasive diagnostic testing, n (%)*					
No testing	21 (8.8)	219 (92.0)	192 (80.7)	197 (82.8)	211 (88.7)
1 test	171 (71.9)	9 (3.8)	29 (12.2)	26 (10.9)	12 (5.0)
≥ 2 tests	46 (19.3)	10 (4.2)	17 (7.1)	15 (6.3)	15 (6.3)
Diagnostic yield, n (%)**	14.8	31.6	28.3	26.8	37.0
Invasive coronary angiography, n (%)	19 (8.0)	8 (3.4)	10 (4.2)	10 (4.2)	10 (4.2)
Intervention, n (%)					
PCI	12 (5.0)	7 (2.9)	9 (3.8)	8 (3.4)	8 (3.4)
CABG	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Cumulative radiation exposure (mSv/patient)***	9.1±11.8	1.7±7.9	2.7±8.9	2.7±8.7	2.4±9.0
Disposition					
ED discharge	50 (21.0)	216 (90.8)	191 (80.3)	197 (82.8)	212 (89.1)
Observational unit admission	147 (61.8)	8 (3.4)	31 (13.0)	26 (10.9)	13 (5.5)
Hospital admission	38 (16.0)	13 (5.5)	15 (6.3)	14 (5.9)	12 (5.0)
Left against medical advice	3 (1.3)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Length of hospital stay, hours					
Median (IQR)	23.3 (8.4–28.7)	2.0 (2.0–4.0)	2.0 (2.0–4.0)	2.0 (2.0–4.0)	2.0 (2.0–2.0)
Mean ± SD	25.1±28.5	6.7±15.8	9.2±17.6	10.1±26.1	6.9±17.2
Time-to-diagnosis, hours					
Median (IQR)	8.2 (6.0–22.3)	1.0 (1.0–3.0)	1.0 (1.0–3.0)	1.0 (1.0–3.0)	1.0 (1.0–1.0)
Mean ± SD	14.5±12.9	2.8±5.4	4.3±7.5	4.2±7.2	2.6±6.2
Healthcare cost per patient in US $					
Median (IQR)	2,698 (1,837-2,698)	1,837 (1,837-1,837)	1,837 (1,837-2,698)	1,837 (1,837-2,698)	1,837 (1,837-1,837)
Mean ± SD	3,889 ± 4,833	2,571 ± 2,896	2,784 ± 3,234	2,894 ± 4,371	2,651 ± 3,138
Non-ACS patients only					
Median (IQR)	2,698 (1,837-2,698)	1,837 (1,837-1,837)	1,837 (1,837-1,837)	1,837 (1,837-1,837)	1,837 (1,837-1,837)
Mean ± SD	2,784 ± 1,341	1,980 ± 696	2,070 ± 729	2,051 ± 704	1,965 ± 670

**Cardiac testing included coronary computed tomography angiography, exercise treadmill test, stress echocardiography, nuclear myocardial perfusion imaging, and invasive coronary angiography.*

***Diagnostic yield calculated as number of patients in whom diagnostic test was abnormal (stress test positive for ischemia, coronary CTA or invasive coronary angiography with*

>50% stenosis) divided by the number of patients who underwent (as observed) or could undergo (as predicted) cardiac testing

****Radiation exposure included exposure from coronary computed tomography, nuclear myocardial perfusion imaging, and invasive coronary angiography.*

CABG=coronary artery bypass graft; ED=emergency department; PCI=percutaneous coronary intervention.

4.2 Clinical utility of coronary CTA delivered anatomical imaging vs standard of care among patients with chest pain

4.2.1 Long-term health outcomes and cost-effectiveness of coronary CTA in patients with suspicion for acute coronary syndrome (*Aim 3*)

4.2.1.1 Patient population

The ROMICAT II population (n=1,000, mean age: 54.2 ± 8.1 years) represented genders equally (53.2% male), and is characterized by a substantial cardiovascular risk factor burden (2 - 3 risk factor: 52.8%; >3 risk factor: 9.9%). Overall, 50.7% of patients had no CAD, 43% non-obstructive CAD and 6.3% obstructive CAD. Incident ACS during index hospitalization occurred in 7.5% (2.3% NSTEMI and 5.2% unstable angina), (***Table 9***).

Table 9. *Baseline Population characteristics for the Markov Model.*

	ROMICAT II (n=1,000)
Age (years)	54.2 ± 8.1
Men, n (%)	532 (53.2)
Cardiovascular risk factors, n (%)	
Hypertension	541 (54.1)
Diabetes mellitus	173 (17.3)
Dyslipidemia	454 (45.4)
Former or current smoker	492 (49.2)
Family history of premature CAD	271 (27.1)
Number of cardiovascular risk factors, n (%)	
0 or 1	373 (37.3)
2 or 3	528 (52.8)
≥ 4	99 (9.9)
TIMI score, n (%)	
0	614 (61.4)
1	288 (28.8)
2	85 (8.5)
3	13 (1.3)
Acute coronary syndrome	
Myocardial Infarction	23 (2.3)
Unstable Angina	52 (5.2)
Coronary artery disease (CAD)*	
No CAD	507 (50.7)
Non-obstructive CAD (<50% stenosis)	430 (43.0)
Obstructive CAD (>/=50% stenosis)	63 (6.3)

*ROMICAT II patient level data; *CAD status was determined using invasive cardiac catheterization, coronary CTA, and functional test results.*

4.2.1.2 Short-term outcomes – index hospitalization and 28-day outcomes

Overall, the short-term model predicted length of stay, testing, and interventions for both the coronary CTA and SOC strategy very accurately predicted the observations made during the ROMICAT-II trial (***Table 10***). This data validates the accuracy of the model.

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Table 10. Model validation.

Variables	Observed ROMICA II trial Coronary CTA	Model simulation Coronary CTA	Observed ROMICAT II Trial Standard of Care	Model simulation Standard of Care
Length of Stay (hours)	*23.2*	24.7	*30.8*	30.1
Functional Testing				
SPECT (%)	*12*	9.6	*27*	29.4
Stress ECHO (%)	*4*	1.3	*20*	20.2
ETT (%)	*4*	1.1	*32*	32.5
Cath (%)	*12*	17.5	*8*	11.2
Intervention				
PCI (%)	*5*	5.0	*3*	2.7
CABG (%)	*1*	1.2	*1*	0.6
Radiation exposure - mSv	*14.3*	13.5	*5.3*	5,1
Cost of Care – U.S. $ *				
Emergency Department	*2,101*	2,246	*2,566*	2,558
Hospital	*1,925*	2,377	*1,308*	1,340
Total (with F/U)	*4,289*	4,623	*4,060*	3,899

CABG=Coronary artery bypass graft; Cath=Coronary catheterization; ECHO=Echocardiography; ETT=Exercise tolerance test; PCI=Percutaneous coronary intervention; SPECT=Single-photon emission computed tomography.

As in ROMICAT II, early coronary CTA was the most accurate in identifying patients with obstructive CAD (98%), followed by Expert Consensus (75%), and SOC (69%). The predicted accuracy of the expedited ED discharge strategy to identify patients with obstructive CAD was lower than the other alternatives (46%), while CAD status remained unknown to patients and providers in more than 50% of patients with underlying CAD. The higher yield in diagnosis of obstructive CAD correlated with the frequency of subsequent revascularizations, as such twice as many patients underwent PCI after early coronary CTA as compared to expedited ED discharge (5.2% vs. 2.6%). In contrast, the predicted length-of-stay was shortest for expedited ED discharge (12.3 hours) followed by early coronary CTA (23.4 hours), SOC (30.6 hours) and Expert Consensus (30.9 hours). The diagnostic costs during index hospitalization were highest for coronary CTA ($2,692) followed by Expert Consensus ($2,535), SOC ($2,501), and only $1,891 for expedited ED

discharge. The significantly higher total cost associated with coronary CTA was due to the higher revascularization rate compared to the other strategies (***Table 11***).

Table 11. Short-term outcomes – Comparison between four competing management strategies.

	ROMICAT II CCTA*	ROMICAT SOC*	Expert Consensus*	Expedited ED Protocol*
Length of Hospital Stay (hours)	23.4	30.6	30.9	12.3
Noninvasive Diagnostic testing				
CCTA (%)	100.0	0.0	0.0	0.0
SPECT (%)	8.8	29.8	22.1	8.2
Stress ECHO (%)	1.3	20.6	28.4	10.5
ETT (%)	1.2	32.5	29.0	10.8
Invasive Coronary Angiography (%)	16.1	11.3	14.1	6.6
Accuracy to detect obstructive CAD#				
True positive (%)	98.6	68.9	75.0	45.5
False positive (%)	3.7	1.4	1.3	0.5
Coronary Revascularization				
PCI (%)	4.3	3.0	3.3	2.1
CABG (%)	0.9	0.7	0.7	0.5
Cost of Care ($)				
Diagnostic costs (incl. angiography)	2,692	2,501	2,535	1,891
Treatment costs	1,798	1,643	1,529	622
Total	4,490	4,144	4,064	2,513

**The outcomes were based on a simulation of each strategy in 1000 patients from ROMICAT II trial, #estimated based on published diagnostic accuracy data for each test.*

CCTA=Coronary Computed Tomographic Angiography; ECHO=Echocardiography; ET=Exercise Tolerance Test; PCI=Percutaneous Coronary Intervention; SPECT=Single-Photon Emission Computed Tomography.

Among patients without CAD, those who received early coronary CTA had the lowest rate of ICA (1.4%), followed by expedited ED discharge (3.8%), SOC (7.1%), and Expert consensus (9.4%). This was associated with a reduction in length-of-stay and cost for the early coronary CTA strategy, which was similar to the expedited ED discharge (13.2 hours vs. 9.9 hours and $2,262 vs. $2,035). Patients without CAD in the SOC or Expert consensus strategy had a doubled length-of-stay (27.6 hours and 26.9 hours) and 50% higher costs ($3,482 and $3,289).

4.2.1.3 Long-term health and economic outcomes

The major health and economic outcomes 1, 3, and 10 years after ED presentation and over a lifetime are shown in ***Table 12***. Overall, the differences in rates of MI were relatively small between the strategies, albeit slightly higher rates were observed in the SOC and the expedited ED discharge strategies. MI rates increased from around 2.6% after a year to around 12.2% over a lifetime. However, the relative differences in cardiovascular mortality for early coronary CTA vs expedited ED discharge were noticeable after 10 years (5.06% vs 5.36%) and further increased over a lifetime (45.64% versus 46.10%). In contrast, the cardiovascular mortality benefit of early coronary CTA was smaller when compared to the other two strategies.

Coronary revascularization rates remained high over the lifetime in the early coronary CTA strategy, but the difference in revascularization rate between coronary CTA and the other strategies decreased over time i.e. PCI rate for early coronary CTA was higher than the rate for expedited ED discharge after 3 years (4.4% versus 2.3%), which relative difference decreased over a lifetime (7.0% vs. 5.4%). Lifetime costs were highest for coronary CTA; approximately $2,000 higher as compared to expedited ED discharge, $370 higher as compared to SOC and $460 higher as compared to Expert Consensus.

Table 12. *Simulated long-term health and economic outcomes – one, three, and ten years after ED presentation and over lifetime.*

	1 Year				3 Years				10 Years				Lifetime			
	RII CCTA	RII SOC	Exp Con	Exp D/C	RII CCTA	RII SOC	Exp Con	Exp D/C	RII CCTA	RII SOC	Exp Con	Exp D/C	RII CCTA	RII SOC	Exp Con	Exp D/C
MI (%)	2.57	2.59	2.57	2.58	3.15	3.17	3.15	3.16	5.33	5.37	5.34	5.38	12.17	12.29	12.22	12.26
PCI (%)	4.34	3.03	3.30	2.18	4.39	3.11	3.39	2.30	4.75	3.59	3.84	2.85	7.00	6.03	6.23	5.37
CABG (%)	0.88	0.71	0.75	0.47	0.89	0.74	0.77	0.50	1.05	0.91	0.94	0.68	2.04	1.93	1.94	1.72
CV death (%)	0.35	0.38	0.38	0.42	1.04	1.11	1.10	1.17	5.06	5.23	5.21	5.36	45.64	45.91	45.89	46.10
Overall mortality (%)	1.05	1.07	1.07	1.08	3.11	3.16	3.16	3.21	13.46	13.52	13.55	13.64	100.00	100.00	100.00	100.00
Cost total ($)	4,580	4,230	4,149	2,590	4,756	4,397	4,320	2,741	5,417	5,037	4,965	3,333	7,662	7,288	7,205	5,498

CABG=Coronary artery bypass graft; CCTA=Coronary Computed Tomographic Angiography; CV=Cardiovascular; Exp. Con=Expert Consensus; Exp. D/C=Expedited Discharge (Expedited ED Protocol); MI=Myocardial Infarction; PCI=Percutaneous coronary intervention; SOC=Standard of Care.

4.2.1.4 Incremental Cost Effectiveness Ratio

In a comparison of the assessed strategies, performing an early coronary CTA in a gain of 25 additional days in perfect health when compared to expedited ED discharge (QALYs: 23.09 vs. 23.02), 17 compared to SOC (QALYs: 23.09 vs. 23.05) and 12 compared to expert consensus (QALYs: 23.09 vs. 23.06) (***Table 13***). The coronary CTA strategy extendedly dominated the SOC and the expert consensus strategies, i.e. the SOC as well as the expert consensus strategy were inferior to early coronary CTA because they were more expensive for an equal gain in QALYs. Compared to the second most efficient strategy (expedited ED protocol), the coronary CTA strategy was cost effective by rendering an ICER of $49,428/QALY, which is under the universally accepted cost-effectiveness threshold of $100,000/QALY. In a head-to-head comparison of coronary CTA to SOC the ICER decreased to $13,961/QALY.

Table 13. *Incremental Cost-effectiveness ratio of different strategies to manage patients with acute chest pain.*

	Cost ($)	Cost difference	QALYs	QALYs difference	ICER ($/QALY)
Expedited ED discharge protocol	5,498		23.024		
Guidelines	7,205	1,707	23.058	0.034	Dominated
Standard of Care as in ROMICAT II	7,288	83	23.046	-0.012	Dominated
Early coronary CTA as in ROMICAT II	7,662	374	23.092	0.046	**49,428**

Cost and QALYs are reported as undiscounted values; ICER is estimated based on discounted values (3% annual). The ICER shows the costs per additional QALY, i.e. the costs per additional year in perfect health. Coronary CTA=Coronary computed tomographic angiography; ICER=Incremental cost-effectiveness ratio; QALY=Quality-adjusted life year.

4.2.1.5 Sensitivity analyses

ED Population and Risk of ACS: In populations with a lower prevalence of ACS (i.e.: CT-STAT: 1.8% ACS vs. ROMICAT-II: 7.5% ACS) ICER for coronary CTA increased to 73,192$/QALY, thus remained cost-effective.

Diagnostic Accuracy of coronary CTA to detect obstructive CAD: We determined the ICER across a range of sensitivities (85%–100%) and specificities (50%–100%) of coronary CTA to detect obstructive CAD as compared to invasive angiography. Overall, coronary CTA strategy remained cost-effective, as the ICER of coronary CTA vs expedited ED discharge ranged from $46,000 for a near perfect diagnostic accuracy to $70,000/QALY for a specificity of 50% and a sensitivity of 85%. Notably, changes in specificity resulted in larger changes of ICER (between $17,000 and $20,000/QALY) than changes in sensitivity (between $2,500 and $5,000/QALY), possibly as a result of unnecessary and ineffective ICA and downstream revascularization.

Treatment effect of aggressive medical therapy for obstructive CAD: Assuming a relative risk decrease of only 0.18 representing the lower bound of the 95% CI, the ICER increased

from $ 49,000 to $ 60,000. Assuming a variation of adherence to medical therapy, we studied two scenarios: 1) 5 years of full compliance followed by 5 years of declining compliance resulted in an increase of the ICER from $ 49,000 to $ 78,500; 2) 5 years of full compliance followed by a complete lack of adherence and no treatment effect resulted in nearly a doubling of the ICER from $ 49,000 to $ 90,000. Therefore, variation of the treatment effect and compliance still resulted in coronary CTA to be cost-effective over early ED discharge.

4.2.2 Cost-effectiveness Analysis of Anatomic vs Functional Index Testing in Patients with Low-Risk Stable Chest Pain

4.2.2.1 Patient population

The model cohort had identical individual patient demographics, including age, sex, race and cardiovascular risk factors as the 10,003 individual patients of the PROMISE trial(30) (***Table 14***). The median age was 60.0 (IQR: 54.4-65.9) years, 52.7% were women, and 22.6% belonged to a racial or ethnic minority. The population had a substantial cardiovascular risk factor burden: 25.3% had a CAD risk equivalent and two-thirds (67.6%) had a ten-year risk of events of ≥7.5%. The mean pretest likelihood of obstructive CAD according to a combined Diamond and Forrester and Coronary Artery Surgery Study model was 53.3±21.4%.

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Table 14. *Demographics and cardiovascular risk and two-year MACE in patients with stable chest in the Markov-model.*

Variables	PROMISE trial (n=1,000,300)
Mean age (years), median (IQR)	60.0 (54.4-65.9)
Female sex, n (%)	5,270 (52.7)
Race, n (%)	
White	7,693 (77.7)
Black	1,071 (10.8)
Other	1,239 (12.4)
CV risk factors	
Body-mass index (kg/m^2), mean ± SD	30.5 ± 6.1
Hypertension, n (%)	6,501 (65.0)
Diabetes, n (%)	2,144 (21.4)
Dyslipidemia, n (%)	6,767 (67.7)
Family history of premature CAD, n (%)	3,202 (32.1)
PAD or cerebrovascular disease, n (%)	552 (5.5)
CAD risk equivalent, n (%)	2,531 (25.3)
Metabolic syndrome, n (%)	3,772 (37.7)
Current or past tobacco use, n (%)	5,104 (51.0)
Sedentary lifestyle, n (%)	4,866 (48.8)
History of depression, n (%)	2,058 (20.6)
Risk burden	
No risk factors, n (%)	263 (2.6)
Mean number of risk factors per patient	2.4 ± 1.1
Mean combined Diamond and Forrester and Coronary Artery Surgery Study risk score	53.3 ± 21.4
Framingham Risk Score Categories, n (%)	
Low-risk (<6%)	686 (6.9)
Intermediate-risk (6-20%)	5,114 (51.2)
High-risk (>20%)	4,188 (41.9)
Framingham Risk Score, median (IQR)	17.1 (10.6-28.6)
ASCVD Risk, n/total n (%)	

Low-risk (<7.5%)	3,204 (32.4)
Elevated-risk (≥7.5%)	6,697 (67.6)
ASCVD Risk, median (IQR)	11.3 (6.1-19.8)
Chest pain type, n (%)	
Typical angina	1,166 (11.7)
Atypical angina	7,773 (77.7)
Non-anginal pain	1,064 (10.6)
MACE over a medina follow-up of 2.4 years, n (%)	
CV Death or MI	157 (1.6)
MI	70 (0.7)
CV Death	35 (0.4)
Death from any cause	149 (1.5)
Death or MI	216 (2.2)

Patient characteristics of the 1,000,300 modeled individuals were simulated based on individual patient data from the PROMISE trial, therefore are identical to the original PROMISE cohort. ASCVD=Atherosclerotic cardiovascular disease; CAD=Coronary artery disease; CV=Cardiovascular; IQR=Interquartile range; MACE=Major adverse cardiovascular event; MI=Myocardial infarction; PAD=Peripheral artery disease; SD=Standard deviation.

4.2.2.2 Model Validation

We modeled the assignment of the different functional testing alternatives utilized in PROMISE and observed accurate predictions, i.e. for stress SPECT: 67.5% vs 67.2%; stress echocardiography: 22.4% vs 22.5%; and exercise treadmill testing: 10.2% vs 10.4%, as modeled vs observed in PROMISE, respectively. Similarly, the model accurately simulated the diagnostic test results, i.e.: rate of coronary CTA finding of 30-69% stenosis: 31.6% vs 31.4%; rate of functional testing findings of inducible myocardial ischemia: 8.8% vs 7.9%; respectively (***Figure 9.A and B***); rates of ICA and revascularization compared to observed clinical management (coronary CTA strategy: ICA 12.2% vs 12.3%; revascularization 6.2%

vs 6.4%; functional strategy: ICA 8.1% vs 8.2%; revascularization 3.2% vs 3.3% for observed vs simulated, respectively). Lastly, the model accurately predicted costs as compared to observed costs (coronary CTA strategy: $2,494 vs $2,546; functional strategy: $2,240 vs $2,189) and two-year MACE (coronary CTA strategy: 2.1% vs 2.3%; functional strategy: 2.2% vs 2.4%; respectively).

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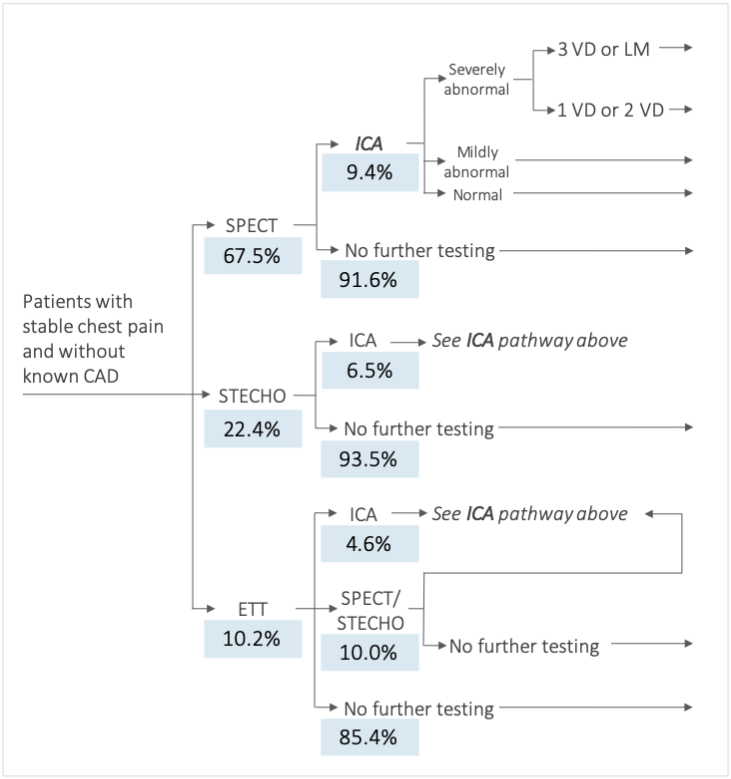

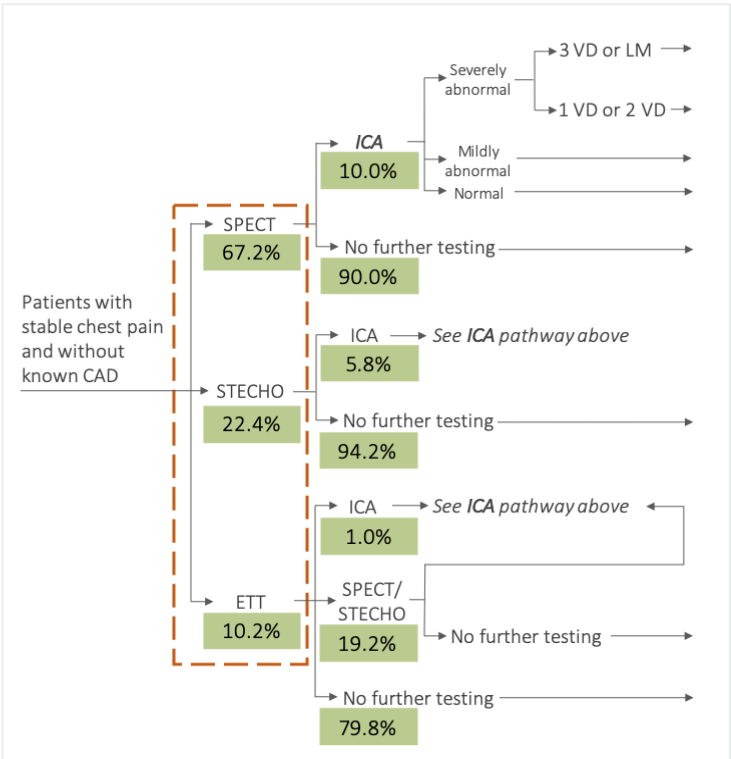

Figure 9.A. *Comparison of observed vs simulated rate of testing and test findings for CTA strategy. Data based on site and core laboratory reads. ICA findings: Severely abnormal: CAD ≥70% stenosis; Mildly abnormal: non-obstructive CAD 1-70% stenosis; Normal: no stenosis. CTA and SPECT findings: as defined in supplemental table 2.(25)CAD=Coronary artery disease; CTA=Computed tomography angiography; ICA=Invasive coronary angiography; LM=Left Main disease; PROMISE=PROspective Multicenter Imaging Study for Evaluation of chest pain; SPECT=Single photon emission computed tomography; VD=Vessel disease.*

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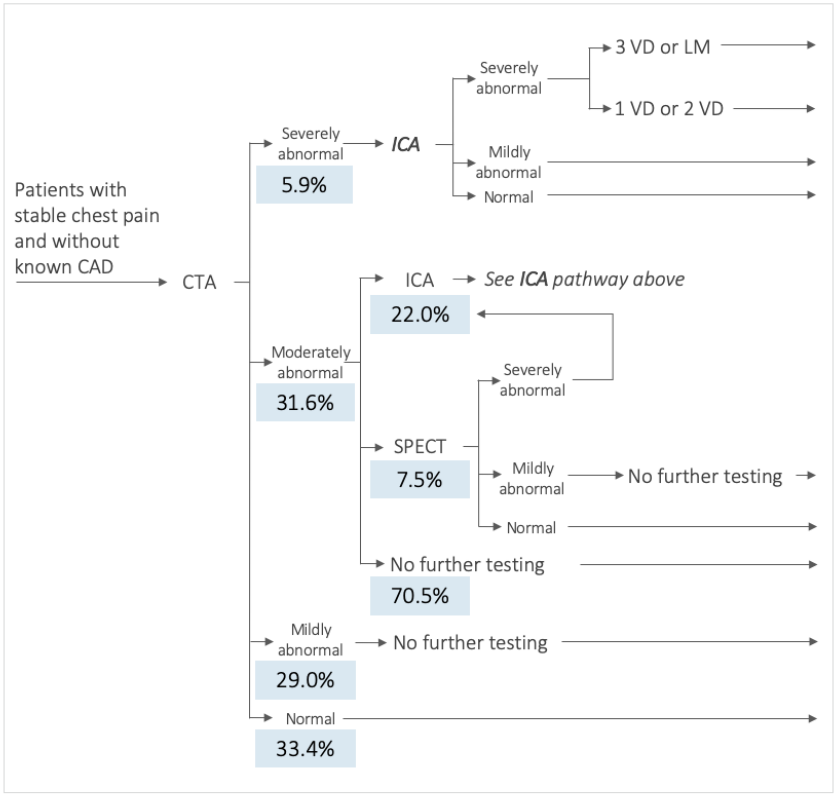

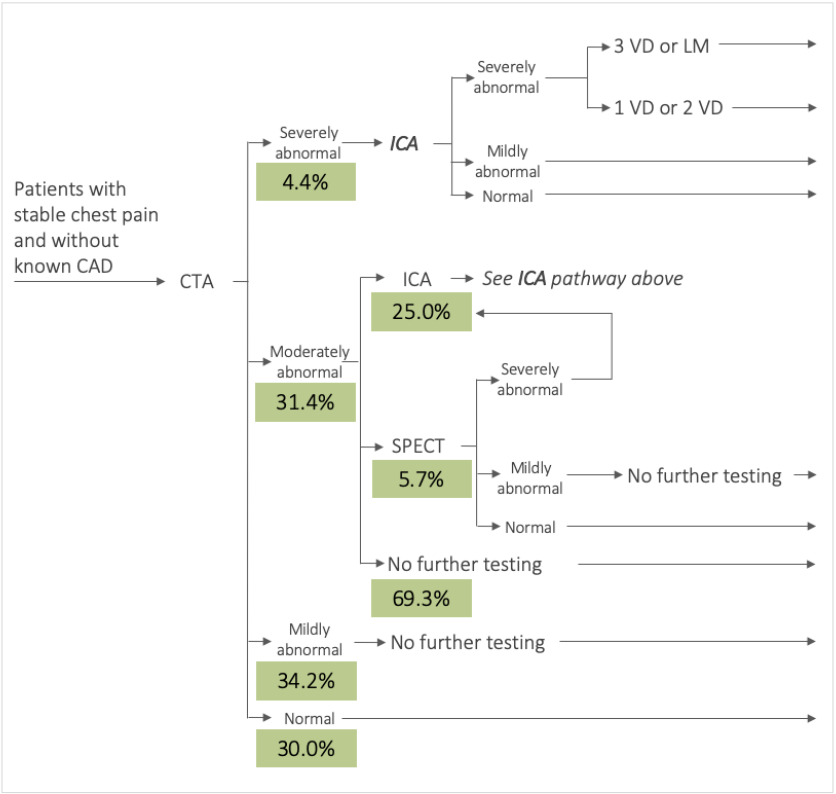

Figure 9.B. *Comparison of observed vs simulated rate of test distribution and findings for functional strategy. Average pathway probabilities as observed in PROMISE versus as model simulated, where patients underwent pathways according to their risk score. E.g.: if patient is at lower risk than there is a higher probability that the given patient will be tested with ETT. ICA findings: Severely abnormal: CAD ≥70% stenosis; Mildly abnormal: non-obstructive CAD 1-70% stenosis; Normal: no stenosis. SPECT, STECHO, ETT findings: as defined in supplemental table 2.(25) CAD=Coronary artery disease; ETT=Exercise Treadmill Test; ICA=Invasive coronary angiography; LM=Left Main disease; PROMISE=PROspective Multicenter Imaging Study for Evaluation of chest pain; STECHO=Stress echocardiography; SPECT=Single photon emission computed tomography; VD=Vessel disease.*

4.2.2.3 Comparison of coronary CTA, CTA+FFR-CT and functional testing strategies

Short-term outcomes

Overall, 31.4% of patients had a 30-69% stenosis on coronary CTA and underwent CTA+FFR-CT. Based on ASCVD risk score and diagnostic test results patients were eligible for statin therapy in 67% per functional strategy, 85.4% per coronary CTA and 85.5% per coronary CTA+FFR-CT, respectively. Because of the higher sensitivity of coronary CTA to detect CAD, the frequency of ICA and coronary revascularization was higher for coronary CTA and CTA+FFR-CT compared to functional testing (ICA: 12.3% and 10.5% vs 8.1%; revascularization: 6.6% and 6.3% vs 3.3%; respectively), (***Figure 10***). The revascularization-to-ICA ratio for anatomic approaches was higher compared to functional testing, indicating a more effective patient selection for ICA (revascularization-to-ICA ratio: 59.5%, 53.7% and 40.7%, for CTA+FFR-CT, coronary CTA and functional strategy; respectively), (***Figure 10***).

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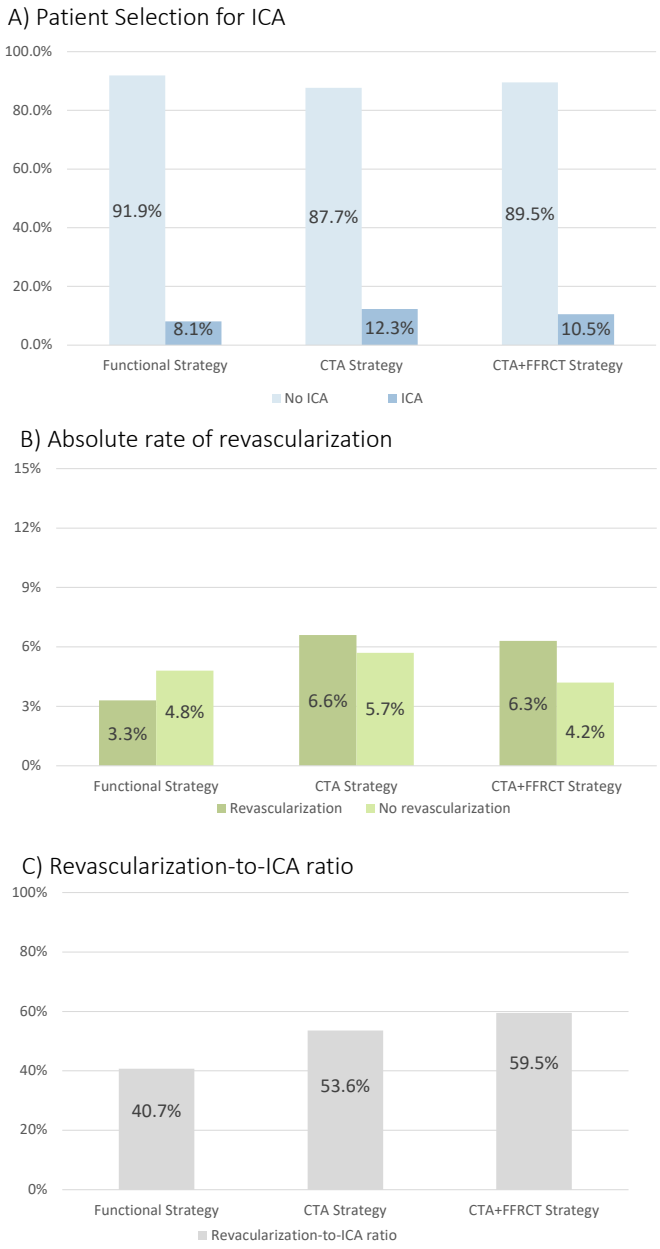

Figure 10. *Rate of ICA, revascularization and revascularization-to-ICA ratio based on functional strategy, coronary CTA strategy and CTA+FFR-CT strategy. Panel A: Rate of ICA based on coronary functional strategy, CTA strategy, and CTA+FFR-CT strategy. Panel B: Rate of revascularization when ICA was performed based on the three strategies. Panel C: the yield of ICA per the three strategies. CTA=CT angiography; ICA=Invasive coronary angiography; FFR-CT=Non-invasive fractional flow reserve derived from computed tomography; ICA=Invasive coronary angiography.*

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Mid-term and long-term (lifetime) outcomes

The 2-year revascularization rates of anatomic approaches were nearly twice as high as functional testing (6.6% and 6.3% for coronary CTA alone and CTA+FFR-CT vs 3.7% for functional testing) and remained higher after 5 years - although functional strategy saw the highest relative increase (15.9% vs 2.9% and 3.1%, for functional testing, coronary CTA and coronary CTA+FFR-CT; respectively), (***Table 15***). MACE rate in this low-risk stable chest pain population was low across all strategies, not exceeding 1.5% after two- and 3.9% after 5 years. Higher costs of anatomic approaches after 2- and 5 years were mainly driven by the higher ICA and revascularization rates. Additional cost of FFR-CT ($1,450 per assessment) was offset by fewer ICAs and revascularizations after 5 years compared to coronary CTA alone. Anatomic approaches had higher QALYs at both 2- and 5 years: QALY gain for CTA+FFR-CT and for CTA alone: 0.12 and 0.13 or 1.5 months of longer life in perfect health, respectively (***Table 15***).

Table 15. Model-derived coronary revascularization and MACE at two and five years and over lifetime by index test strategy.

Index test	2 years			5 years			Lifetime		
	Coronary CTA	CTA+ FFR-CT[a]	Functional testing	Coronary CTA	CTA+ FFR-CT[a]	Functional testing	Coronary CTA	CTA+ FFR-CT[a]	Functional testing
Revascularization, %	6.59	6.33	3.62	6.78	6.53	4.38	12.59	12.44	13.33
PCI	4.59	4.33	2.95	4.71	4.45	3.59	8.41	8.24	10.40
CABG	2.00	2.00	0.67	2.07	2.08	0.79	4.18	4.20	2.93
MACE, %									
CV Death or MI	1.11	1.10	1.44	3.05	3.05	3.89	48.61	48.82	51.83
MI	0.75	0.73	0.90	1.92	1.92	2.29	14.34	14.41	15.11
CV Death	0.37	0.39	0.55	1.19	1.20	1.68	42.13	42.30	44.89
Death from any cause	1.42	1.42	1.61	4.12	4.11	4.61	100.00	100.00	100.00
Death or MI	2.16	2.13	2.49	5.95	5.93	6.78	100.00	100.00	100.00
Cost per patient (US$)	$ 2,808	$ 2,998	$ 2,404	$ 3,276	$ 3,251	$ 2,759	$ 7,989	$ 7,222	$ 8,683
QALYs per patient	1.869	1.870	1.867	4.610	4.611	4.598	25.162	25.143	24.680

[a]*FFR-CT performed in patients with 30 to 69% stenosis as detected by coronary CTA.*

Abbreviations: CABG, Coronary artery bypass grafting; CTA=Computed tomography angiography; CV=Cardiovascular; FFR-CT=Non-invasive fractional flow reserve derived from computed tomography; MACE=Major adverse cardiovascular event; MI=Myocardial infarction; PCI=Percutaneous coronary intervention; QALY=Quality adjusted life years.

Long-term, there was a significant dynamic in coronary revascularizations, costs and QALYs. Over lifetime, the model predicted similar frequency of coronary revascularizations across all strategies (***Table 15.***) As a result, differences in costs between the anatomic and functional approaches decreased. Over lifetime, anatomic approaches had significantly higher QALYs compared to functional testing (QALY gain for CTA+FFR-CT and for CTA alone: 0.46 and 0.48 that equals to 6 months longer life in perfect health). Over lifetime, coronary CTA strategy was cost-effective compared to functional testing (ICER: $2,743/QALY), and coronary CTA+FFR-CT strategy was less costly and more effective and thus dominated functional testing (***Table 16***). Modeling different accuracies for CTA and FFR-CT by assuming worse performance due to the outdated CT technology used in the PROMISE trial did not alter the results of the main analysis.

Table 16. *Cost, QALYs, incremental cost-effectiveness ratio and life years gained of coronary CTA and coronary CTA+FFR-CT compared to functional testing.*

	Undiscounted cost	Cost difference*	Undiscounted QALYs	QALY difference*	Discounted ICER ($/QALY)**	Life years gained (years)
Coronary CTA vs Functional testing						
Functional strategy	$ 7,989		24.68			26.51
Coronary CTA strategy	$ 8,683	$694	25.16	0.48	$ 2,743 / QALY ***	27.03
Coronary CTA+FFR-CT vs Functional testing						
Functional strategy	$ 7,989		24.68			26.51
CTA+FFR-CT strategy	$ 7,222	-$767	25.14	0.46	CTA+FFR-CT dominates **** Functional testing	27.01

**Cost and QALY differences are expressed in reference to functional strategy.*

***Discounted at 3% annually as recommended by the US Panel on Cost-Effectiveness in Health and Medicine.(49, 50)*

****A strategy is considered cost-effective when ICER is below $100,000/QALY.(51)*

*****A strategy dominated the other, if it has lower cost and higher QALY compared to the comparator strategy.*

CTA=Computed tomography angiography; FFR-CT=Non-invasive fractional flow reserve derived from computed tomography; ICER=Incremental cost-effectiveness ratio; ICA=Invasive coronary angiography; MI=Myocardial infarction; QALY=Quality adjusted life years.

4.2.2.4 Sensitivity Analyses and Subgroup Analyses

Subgroup analyses: Compared with functional strategy, coronary CTA remained cost-effective in women and men (ICER range, $1912/QALY for women to $3559/QALY for men) as well as in individuals older than and younger than the median age of 60 years (ICER $2616/QALY and $2842/QALY, respectively). CTA with FFR-CT was cost-effective in men (ICER, $192/QALY) but dominated the functional strategy across other subgroups.

Adherence to Medical Therapy: Modeling a continuous decline in statin therapy adherence after 5 years, the lifetime cost of coronary CTA strategy decreased to $6,438 (95% CI, $6,413-$6,464) but also resulted in the loss of health benefits and thus yielded lower QALY (QALY difference, 0.12; 95% CI, 0.10-0.14). However, coronary CTA remained cost effective compared with functional strategy (ICER, $2927/QALY). Similar results were seen for a CTA with FFR-CT strategy. Modeling complete nonadherence to statin therapy for anatomical strategies after 5 years resulted in the loss of some of the observed health benefits compared with functional testing but still lower MACE rates for anatomic strategies compared with functional testing. However, anatomic approaches were still cost-effective compared with functional testing (CTA alone, $2291/QALY; CTA with FFR-CT, $2723/QALY), mostly because of the decreased costs of care.

Expanding the Indication of FFR-CT to Patients with Greater Than 70% Luminal Narrowing: Expanding the use of FFR-CT to the 4.4% of patients who had greater than 70% stenosis resulted in a downward reclassification and avoidance of ICA in 17.8% of these patients. At 60 days, this would lead to an overall decrease of ICA by 0.8% (from 10.5% to 9.7%) and coronary revascularizations (from 6.3% to 5.5%) in the overall population and a 4.4% increase of the size of the FFR-CT group. Over a lifetime, results are very similar compared with the main analysis, resulting in lower cost and higher QALYs for coronary CTA and FFR-CT strategy compared with the functional testing strategy.

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5 Discussion

5.1 Agreement between high-sensitivity troponin assays

In a head-to-head comparison of hs-cTn assays we assessed differences between clinically used platforms. On a per sample level analysis, we found that 3 hs-cTn assays cleared by the FDA, agreed to stratify blood samples similarly in 37.4%. This extends our knowledge on the differences in analytic performance, predominantly at the level of sensitivity, by quantifying these discordances and suggesting an around 2-fold difference between assays in the proportion with samples with troponin values over the LOD (43.7%, 89.6%, and 58.8% samples with measurable troponin for Roche, Abbott, and Siemens, respectively, $p < 0.001$). In terms of the 99th percentile, that is the recommended threshold for myocardial injury by the Fourth Universal Definition of MI(52), when used as a binary threshold to rule-in or rule-out blood samples, we found no differences. However, there are some limitations when using the 99th percentile as a threshold. Noteworthy limitation for example is that the 99th percentile thresholds have been generated based on different reference cohorts for each assay. To overcome such limitations assay-specific fixed thresholds have been generated, as made available in the ESC 2020 Guidelines, for example.

Therefore, in a subsequent analysis we assessed the agreement across four hs-cTn assays to stratify patients with suspected ACS to rule-out/observe/rule-in strata based on the ESC 2020 Guidelines. We reported significant differences between 4 hs-cTn assays to stratify patients to rule-out and observe clinical management recommendations but not for rule-in. This finding can be explained in part by the fact that the suggested cut-points were derived by using different reference populations.(20, 53) Another potential reason for the observed discordances is that different assays measure different troponin isotypes (i.e. troponin I: Abbott, Siemens, and Beckmann and troponin T: Roche), which behave differently to some extent.(54, 55) However, given that the thresholds in the ESC Guidelines recommended 0/2 h are assay specific, the differences between the isotypes are anticipated to have no impact on the assay performances as all were calibrated to detect troponin changes/dynamics along the same clinical outcomes. Further, the agreement between troponin-I assays was not higher compared with troponin-I vs. troponin-T assays (Abbott vs. Siemens: 90.3%; Abbott vs.

Beckmann: 82.8%; Abbott vs. Roche: 82.4%; Siemens vs. Roche: 82.8%, Siemens vs. Beckmann: 85.3%; Beckmann vs. Roche: 88.2%); thus, we speculate that the observed differences are mainly occurring in the rule-out strata, more likely to be associated with threshold-related discordance vs. being the result of differences in troponin release dynamics between isotypes. Thresholds for rule-in strata rendered similar results across the assays with substantial agreement at 0 and 2 h (kappa 0.76 and 0.65, respectively); thus, thresholds for the identification of patients with myocardial ischemia seem to be universally more fine-tuned – with the caveat of having a few observations for the rule-in strata and thus the lack of discordance could be the result of type 2 statistical error.

We further interrogated clinical and quality-of-care outcomes, to better understand the potential impact of the observed disagreement between the assays. According to the non-invasive diagnostic testing results, despite the observed disagreement across the assays in the number of patients who were stratified to rule-out clinical management recommendation (76.5–89.9%, $P < 0.001$), ∼20% of patients had obstructive CAD or inducible myocardial ischemia for all assays. When assessing the overlap of these patients among assays, we found that 72% ($n = 21/29$) were stratified as rule-out by all four assays. An important consideration is that the ESC 2020 Guideline management recommendations are not constrained to triaging of patients based on troponin but suggest further non-invasive or invasive testing options for each risk stratum (rule-out/observe/rule-in). Among patients who were stratified to rule-out, further diagnostic testing may be triggered and lead to the recognition of undetected disease. While the lack of detectable troponin is a good predictor of major adverse cardiovascular events-free survival in the short term and not the lack of significant ischemia or CAD, this is especially important because of the prognostic value of inducible myocardial ischemia/obstructive CAD. However, the ESC hs-cTn algorithms are designed to identify ACS and not to determine underlying CAD.

In terms of the assessed quality-of-care outcomes, the observed differences across the assays affected predicted quality-of-care outcomes in the proportion as patients were stratified as rule-out and observe and consequently resulted in similar discrepancies. For example, diagnostic yield, disposition of patients, length of stay, and time-to-diagnosis endpoints were significantly different based on the hs-cTn assay used to place individuals in the rule-out

category. On the other hand, endpoints mainly determined by the rule-in management strata were similar across hs-cTn methods; thus, quality-of-care outcomes, such as the rate of invasive testing, rate of interventions, and radiation exposure, were also similar across groups. However, even if the care of those who were recommended to be in ruled-in strata entails greater healthcare costs, the differences among the assays in the proportion of patients who were stratified to rule-out still affected the overall healthcare costs and thus cost-of-care was modestly but significantly different across the assays.

We assessed a population with low-to-intermediate risk for ACS, the use of hs-cTn assay-based alternatives markedly decreased the admission rate, suggesting the ESC 2020 Guidelines perform well compared with a conventional troponin-based alternative. The nearly four-fold difference in discharge rate between conventional troponin-based vs. hs-cTn–based strategies potentially further explains the substantial improvement observed for other subsequent predicted quality-of-care outcomes, such as length of hospital stay, time-to-diagnosis, and cost-of-care.

5.2 Cost-effectiveness of anatomic testing in patients with chest pain

We demonstrated that coronary CT as an index testing in patients with acute chest pain in the ED environment, and among patients with stable chest pain in an outpatient setting is cost effective over lifetime compared to other alternative pathways/strategies.

In an acute chest pain setting, the higher costs of an initial CT-based strategy associated with increase in testing and interventions, are offset by a reduction in cardiovascular mortality starting to emerge 3 years after the initial ED presentation, primarily through appropriate medical therapy, which effect was not only sustained but expanded over lifetime. To the contrary, the initially cost savings through fewer tests resulted in a lack of correct classification of CAD status of many patients. On average, coronary CTA added 12–25 days of quality-adjusted life per patient, which is achieved at the cost of ~$50,000 per QALY when compared to a strategy of expedited ED discharge. This was based on the assumption that only 37% of patients expeditiously discharged would have an outpatient cardiologist follow-up, which is consistent with published data. In a head-to-head comparison of the two most common strategies of coronary CTA and SOC (i.e. functional testing), the

ICER was much lower with $14,000 per QALY. A similar increase in ICER was seen for lower diagnostic accuracy for the detection of stenosis, i.e. using older CT technology and for the assumptions that patients at much lower risk for ACS would undergo early CTA. To put these results in perspective, the ACC/AHA Guideline statement on cost and value methodology classifies interventions resulting in gains per QALY costing < 50K as a high value, 50–100K as an intermediate value, and > 100K as a low value.(56) As per the cost-effectiveness guidelines, a strategy is considered cost-effective under an ICER of $100,000/QALY.(57) Hence, our base case scenario suggests that coronary CTA is highly cost-effective ($49,428 per QALY) in patients with suspicion for ACS while sensitivity analyses assuming limitations suggest an inter-mediate value (70–90K per QALY) – still under the accepted cost-effectiveness threshold and comparing favorably to established strategies of i.e. lung cancer screening (130K/QALY)(58) and screening for CAD among diabetic or HIV patients.(59, 60)

An expedited ED discharge strategy appears beneficial in the short-term but is inferior in the long-term, which is predominantly driven by the fact that 50% of patients who have obstructive CAD would not be detected with this strategy when compared to a strategy (i.e. coronary CTA) that delivers powerful prognostic information in every patient at the beginning. The increasing utility of coronary CTA use in the acute chest pain setting is further underscored by the In the VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography in Patients with Acute Coronary Syndromes) that showed the benefit of CTA imaging in patients with NSTEMI.(61, 62)

The cost-effectiveness analysis of coronary CTA among patients with stable chest pain rendered similar results, as using a Markov model incorporating individual patient level data from PROMISE, suggest that anatomic approaches are cost-effective compared with functional testing across a wide range of assumptions in clinical care and patient characteristics, mostly because of a higher sensitivity to detect nonobstructive and obstructive CAD and the ability to tailor statin therapy accordingly. The addition of FFR-CT to coronary CTA resulted in further but modest improvement by allowing a more targeted patient revascularization associated with higher initial costs which were offset on the long term. Our model, similar to PROMISE and SCOT-HEART, showed overall low rates of ICA

and coronary revascularization within 2- and 5 years for all strategies but with higher rates for anatomic approaches compared with functional testing (12.3% and 10.5% vs 8.1% for ICA, respectively, and 6.6% and 6.3% vs 3.3% for revascularization, respectively). This observation, in line with widely published data,(63-66) appeared to be driven by the higher sensitivity of anatomic testing to detect any form of CAD. Furthermore, optimized patient selection for ICA and subsequent coronary revascularization was shown for FFR-CT, which reclassified intermediate lesions with a luminal narrowing of 30% to 69%9,16,17 (revascularization-to-ICA ratio: CTA with FFR-CT, 59.5%; CTA strategy, 53.7%; functional testing, 40.7%), consistent with previous observational studies (revascularization-to-ICA ratio for FFR-CT in the ADVANCE registry,(64) 59.5%; PLATFORM study,51 58.3%(63)). The observed modest improvement of the addition of FFR-CT to coronary CTA alone can be explained by the fact that only 31% of patients qualified to receive FFR-CT with a low positivity rate. Our results reflect the impact of statin therapy, given the assumption of getting similar optimal medical treatments except for statins and as we assessed what differences would it lead to if on the ground of the same CAD severity one receives vs does not receive treatment with statin. Our model estimated 23% and 22% higher MACE rate for the functional testing at years 2 and 5 respectively (close to the 41% reduction in MACE as observed in the SCOT-HEART trial) driven by the differences in diagnostic accuracy to detect CAD and initiation of statin treatment between the strategies (i.e. 67% for functional testing vs 85% for anatomic approaches). We speculate that our estimates of statin effect are probably conservative given our baseline assumption of full-adherence in the functional arm, which puts around 2/3 of the population on statin treatment (compared with the observed 57% in SCOT-HEART and 50% in PROMISE). Over a lifetime, the model estimated similar frequencies of revascularizations across strategies. Consequently, differences in costs decreased, and anatomic approaches had significantly higher QALYs compared with functional testing (0.46 and 0.48 additional QALY gain for CTA with FFR-CT and CTA alone, respectively) and thus were cost-effective compared with functional testing. This principal finding was consistent across subgroups and sensitivity analyses. In all comparisons, anatomic approaches either dominated functional testing and/or were cost-effective, with cost per QALY below $50 000, making it high value according to the

ACC/AHA.(56) Moreover, assuming a willingness-to-pay threshold of $100 000/QALY, the probabilities that coronary CTA strategy and CTA with FFR-CT were cost-effective compared with functional testing is 69.4% and 65.4%, respectively. Additionally, our results are consistent with prior cost-effectiveness analysis publications, in which anatomical testing was shown to be cost-effective compared with functional assessment among those with low to intermediate pretest probability, thus, among patients with identical risk profiles as the PROMISE population.(67, 68)

This thesis has several limitations. First, the ROMICAT patient cohort does not reflect the entire spectrum of patients presenting with suspicion for ACS to EDs in the United States. The ROMICAT trials included patients at intermediate likelihood of ACS, who were referred to further noninvasive diagnostic testing after inconclusive initial triage (normal conventional troponin-T and non-ischemic ECG). This group represents approximately 20% of all-comer patients with suspicion of ACS presenting to U.S. EDs and moreover, poses the highest diagnostic challenge for safe and efficient triage. Further limitation is that the 0/2-h algorithm was developed for the Siemens Centaur platform, but not for the Siemens Dimension Vista. Moreover, the assay we used was a pre-commercial assay and is likely different from the platform that has been commercially implemented. Given that the differences between the 2 assays are relatively small, with the Centaur being a slightly more sensitive assay(69), a small proportion of samples and patients may be reclassified; however, it is unlikely that this would have altered our results substantially in terms of agreement among the 3 assays. Our data on them, Siemens assay, however, warrant replication with the commercially available platform. An additional limitation is that the chest pain onset in the ROMICAT II trial was not recorded, and the ESC Guideline 0/2 h algorithm was designed for patients with chest pain onset >3 h. We anticipate that the majority of our patients was fulfilling this criterion by the design of the trial and potential delays in patient evaluation. Another limitation of our analysis is that at it used as a bases the ESC 2020 Guidleines, whereas the ESC released a newer iteration on their acute chest pain management recommendations in 2023(16). However, given that the two documents recommend the same troponin-based triaging algorithms and the assay-specific thresholds for the hs-cTn assay are identical, this seem to minimally impact the overall significance of our research.

Additionally, the costs of care were based on the US healthcare system. Because the demonstrated differences in quality-of-care outcomes reflect patient management and are independent of financing, they are not affected by differences in financing between countries; therefore, the conclusion that hs-cTn–based approaches are cost saving compared with conventional troponin-based strategies can be universally drawn.

Inherent limitation in cost effectiveness research is that the results are based on data simulations and thus represent estimates, which applies to all strategies. As such the model is highly dependent on the quality of the input data. However, the main outcomes of our analyses benefitted from the availability of individual patient data from randomized clinical trials (i.e. ROMICAT II and PROMISE). Moreover, outcomes of our model were comparable and thus validated with observed outcomes of clinical trials.(30, 70) Further, inherent limitations of diagnostic accuracy values are based on core laboratory test readings, which were the same for all tests and strategies and were similar to published data. Additionally, the generalizability of our results to countries other than the United States is limited, given the differences in the health care systems in general and the differences in management of patients with chest pain, including costs and type of diagnostic testing.

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6 Conclusions

We conclude that this analysis focusing on emerging new technologies to optimize chest pain diagnostics revealed substantial differences between hs-cTn platforms when classifying blood samples along analytic benchmarks and stratifying patients to rule-out/observe/rule-in management recommendations based on the ESC 2020 Guidelines recommended assay specific thresholds. We conclude that caregivers should be aware of the substantial discordance between commercially available hs-cTn assays in stratifying patients with intermediate likelihood of ACS according to standard analytical benchmarks that may result in different management recommendations. These observed discordances have significant impact on quality-of-care outcomes.

We further conclude that early coronary CTA is the most cost-effective strategy in patients with suspected ACS when compared to alternative strategies, including expedited ED discharge. Further, among patients with low-risk stable chest pain, anatomic assessment with coronary CTA presents a more favorable initial diagnostic option compared with functional testing.

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7 Summary

Diagnosis and management of patients with chest pain, a leading presenting complaint to the ED/outpatient clinics, constitute a tremendous healthcare burden. Diagnostic tests for quick and efficient diagnosis therefore are developed. In patients with acute chest pain high-sensitivity cardiac troponin (hs-cTn) assays enable a rapid rule-in/rule-out of acute coronary syndrome. Further, in chest pain, coronary CTA has emerged to be a non-invasive testing alternative. However, to optimize triaging patients with chest pain, assessment of the clinical utility of diagnostic testing alternatives is warranted. My PhD research focused on the assessment of the concordance of hs-cTn assays utilized in the diagnostic assessment of patients with acute chest pain and assessed its impact on clinical utility. Further, I focused on the investigation of the cost-effectiveness of coronary CTA- vs testing alternatives for patients with chest pain.

On a per-sample level, the agreement between 3 FDA-approved hs-cTn assays to classify blood samples along analytic benchmarks was low (37%). Further, based on the ESC Guidelines recommended assay specific thresholds the agreement between 4 hs-cTn assays was low (49.6%), which impacted the predicted quality-of-care outcomes.

In a Markov-microsimulation model-based cost-effectiveness analysis based on the ROMICAT II trial, early coronary CTA is a cost-effective strategy in patients with suspected ACS as compared to alternative strategies. We further developed a Markov microsimulation model based on the PROMISE trial and demonstrated that coronary CTA is cost-effective in the evaluation of low-risk stable chest pain compared with functional testing.

This analysis of emerging new technologies to optimize chest pain diagnostics suggest that clinicians should be aware of the substantial discordance between commercially available hs-cTn assays in stratifying patients with suspected ACS according to standard analytical benchmarks and ESC Guidelines suggested assay-based fixed thresholds, which may impact quality-of-care outcomes proportionally. Additionally, the results of this thesis suggest that anatomic strategies may present a more favorable initial diagnostic option in the evaluation of patients presenting with chest pain compared with alternative testing strategies.

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8 Összefoglalás

Mellkasi fájdalom, amely az egyik vezető panasz sürgősségi és ambuláns betege ellátásban, hatalmas egészségügyi terhet jelent. Ennek megoldása gyors és hatékony diagnosztikai módszereket igényel. Akut mellkasi fájdalom diagnosztikájában magas érzékenységű szív-troponin (hs-cTn) mérése lehetővé teszik az akut koszorúér-szindróma gyors kizárását, megerősítését. Ezen felül, mellkasi fájdalom esetén a koszorúér-CT egy nem-invazív tesztelési alternatíva. A mellkasi fájdalommal érkező betegek triázsát optimalizálása céljából szükséges a diagnosztikai tesztelés alternatíváinak klinikai hasznosságának értékelése. A PhD kutatásom célja ezért a hs-cTn esszék közötti megegyezés vizsgálata, és annak hatásának elemzése a klinikai hasznosságra. Továbbá célom, hogy megvizsgáljam a koszorúér-CT és egyéb tesztelési alternatívák költséghatékonyságát mellkasi fájdalommal érkező betegeknél.

3, FDA által jóváhagyott hs-cTn platform között az egyezés az analitikai referenciapontokon való besorolásban alacsony volt (37%). Továbbá, az ESC Irányelvek által ajánlott platform-specifikus küszöbértékek alapján az egyezés 4 hs-cTn esszé között alacsony volt (49,6%), ami befolyásolta a klinikai ellátás hatékonyságát.

Egy Markov-mikroszimulációs modell alapú költséghatékonysági elemzés alapján a korai koszorúér-CT egy költséghatékony stratégia akut mellkasi fájdalommal vizsgált betegeknél, más alternatív stratégiákhoz képest. Továbbá, a koszorúér-CT alapú anatómiai stratégiák kedvezőbb kezdeti diagnosztikai lehetőséget jelentenek az alacsony kockázatú stabil mellkasi fájdalom értékelésében funkcionális teszteléshez képest.

PhD-m eredményei alapján tehát, a kezelő orvosoknak szükséges tisztában lenniük a kereskedelmi forgalomban lévő hs-cTn esszék közötti jelentős eltérésekkel az akut koronáira szindróma gyanújával vizsgált betegek rizikóelemzésekor az ESC Irányelvek által javasolt vizsgálati alapú fix küszöbértékek szerint, amelyek arányosan befolyásolhatják a klinikai ellátás hatékonyságát. Ezen felül, a disszertáció eredményei szerint az anatómiai stratégiák kedvezőbb kezdeti diagnosztikai lehetőséget jelenthetnek azon betegek értékelésében, akik mellkasi fájdalommal jelentkeznek, más tesztelési stratégiákkal összehasonlítva.

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10 Bibliography of the publications (Total IF: 439.384)

10.1 Publications related to the dissertation (IF: 40.642)

1. Goehler A, Mayrhofer T, Pursnani A, Ferencik M, Lumish HS, Barth C, **Karády J**, Chow B, Truong QA, Udelson JE, Fleg JL, Nagurney JT, Gazelle GS, Hoffmann U. Long-term health outcomes and cost-effectiveness of coronary CT angiography in patients with suspicion for acute coronary syndrome. J Cardiovasc Comput Tomogr. 2020 Jan-Feb;14(1):44-54. doi: 10.1016/j.jcct.2019.06.008. Epub 2019 Jun 25. PMID: 31303580; PMCID: PMC6930365.
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