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

Ph.D. thesis

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1. Introduction

Chest pain is among the commonest presenting complaints to the emergency departments (ED) and outpatient clinics. 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. Most of the times, however, chest pain symptoms are 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. 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.

2. Objectives

The goal of this thesis was to ascertain the agreement between hs-cTn assays to classify blood samples into analytic categories (<LOD/LOD-99th percentile/>99th percentile) when

using the Food and Drug Administration (FDA) recommended analytic benchmarks and to stratify patients into clinical management recommendations (rule-out/observe/rule-in) when applying the ESC Guidelines-recommended assay-specific thresholds and associated quality-of-care outcomes (*Aims 1 and 2*).

Further, my thesis aimed to assess the clinical utility of coronary CTA vs standard of care in chest pain with a Markov-microsimulation model (*Aims 3 and 4*).

3. Methods

3.1. Patient population

To assess *Aims 1, 2* and *3*, we assessed 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 electrocardiogram (ECG). 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.

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. 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 to receive functional or to anatomical testing.

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

In the ROMICAT I trial a single blood draw was performed, while in ROMICAT II sequential blood testing was performed at the time of ED presentation and at two hours and four hours thereafter. All samples were tested with three state-of-the-art high sensitivity assays for the purpose of *Aim 1* and blood samples were tested with four hs-cTn assays for to investigate *Aim 2*. All blood samples were analyzed in a blinded fashion for clinical information.

We determined the agreement between the assays along analytic benchmarks and the ESC Guidelines recommended management recommendations. We further compared quality-of-care outcomes across the assays when using the ESC Guidelines recommended management recommendations.

Analytic benchmarks were defined along assay specific analytic characteristics (i.e. <LOD, LOD to 99th percentile and >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.

The ESC Guidelines recommended 0/2 hour rule-out and rule-in algorithm was used to define the management recommendations (i.e. rule-out, observe and rule-in).

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

3.2.1. Acute chest pain setting

We developed a Markov microsimulation model which was populated using individual data 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 assessed short-term the predicted length of stay-, testing-, and interventions for both the coronary CTA and SOC strategy, which results were used for the model validation. Long-term we determined 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.

3.2.2. Stable chest pain setting

We developed a Markov microsimulation model using individual patient-level data from 10,003 real-life US patients from the PROMISE trial presenting with suspicion of obstructive CAD. We compared strategies of 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 assess 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.

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)

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. 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 1,027 samples, 56.3% vs 10.4% vs 41.2% classified as <LOD ($p<0.001$), 36.5% vs 83.5% vs 52.6 as between LOD to 99th percentile ($p<0.001$) and 7.2% vs 6.0% vs 6.2% as >99th percentile (p=NS) by Roche, Abbott, and Siemens, respectively. 37.4% (n=384/1,027) of blood samples were classified into the same analytic benchmark category, with low concordance across benchmarks (<LOD 11.1%; LOD-99th percentile 29.3%; >99th percentile 43.6%). 19.6–21.1% of patients who were recommended to discharge

had positive diagnostic test findings and 2.8-4.3% had ACS at presentation.

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

Of 1,000 randomized subjects of the ROMICAT II trial 238 (23.8%) had blood samples analyzed with all four assays. 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). Among the 238 patients, the overall concordance across assays to classify patients into rule-out/observe/rule-in strata was 74.0% (176/238). Platforms significantly differed for rule-out (89.9% vs 76.5% vs 78.6% vs 86.6%, $p<0.001$) and observe strata (6.7% vs 20.6% vs 17.7% vs 9.2%, $p<0.001$), but not for rule-in (3.4% vs 2.9% vs 3.8% vs 4.2%, $p=0.62$). Among patients stratified as "rule-out" 19.1-21.6% had obstructive CAD and 3.3-4.2% had adjudicated ACS. Predicted disposition of patients and cost-of-care differed across the hs-cTn assays (all $p<0.001$). When compared to observed, conventional troponin-based management, predicted quality-of-care outcomes significantly improved with hs-cTn-based strategies (direct discharge: 21.0% vs 80.3-90.8%, cost-of-care: \$3,889±4,833 vs \$2,578±2,896-2,894±4,371, all $p<0.001$).

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)

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%. Estimated short-term outcomes accurately reflected observed outcomes in ROMICAT-II as coronary CTA was associated with higher costs ($4,490 vs. $2,513-$4,144) and revascularization rates (5.2% vs. 2.6%-3.7%) compared to alternative strategies. Over lifetime, coronary CTA dominated SOC and ACC/AHA Guidelines and was cost-effective compared to expedited ED protocol ($49,428/QALY). This was driven by lower CV mortality (coronary CTA vs. expedited discharge: 3-year: 1.04% vs. 1.10-1.17; 10-year: 5.06% vs. 5.21-5.36%; respectively).

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

The model cohort was based on the 10,003 individual patients enrolled in the PROMISE trial. The median age of the n=1,000,300 modeled population 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%. The Markov-model accurately predicted the test assignment, results of anatomic and functional index testing, referral to ICA, revascularization, MACE, and costs at 60-days and two years when compared to observed data in PROMISE. Anatomic approaches lead to higher ICA and revascularization rates at 60-days, 2- and 5 years as compared to functional testing, but were more effective in patient selection for ICA (60-day revascularization-to-ICA ratio: 53.7% of CTA, 59.6% of CTA+FFRCT and 40.7% of functional testing). Over lifetime, anatomic approaches gained additional 6 months in perfect health compared to functional testing (QALYs of CTA: 25.16 and CTA+FFRCT: 25.14 vs functional: 24.68), driven by the assumption of that identification of any atherosclerotic

disease would lead to tailored statin therapy. Anatomic strategies were less costly and more effective, thus CTA+FFRCT dominated and CTA alone was cost-effective (ICERs: $1,912-3,559/QALY) compared to functional testing.

5. Conclusions

Caregivers should be aware that there are significant differences between hs-cTn assays in stratifying individual samples according to analytical benchmarks and that patient management may differ when using the rule-out/observe/rule-in management recommendations based on the ESC Guidelines depending on which hs-cTn assay is utilized. Further, our data suggest that these observed differences have substantial 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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