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Long-term Health Outcomes and Cost-Effectiveness of Coronary CT Angiography in Patients with Suspicion for Acute Coronary Syndrome

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Abstract

Background—Randomized trials have shown favorable clinical outcomes for coronary CT angiography (CTA) in patients with suspected acute coronary syndrome (ACS). Our goal was to estimate the cost-effectiveness of coronary CTA as compared to alternative management strategies for ACP patients over lifetime.

Methods—Markov microsimulation model was developed to compare cost-effectiveness of competitive strategies for ACP patients: 1) coronary CTA, 2) standard of care (SOC), 3) AHA/ACC Guidelines, and 4) expedited emergency department (ED) discharge protocol with outpatient testing. ROMICAT-II trial was used to populate the model with low to intermediate risk of ACS patient data, whereas diagnostic test-, treatment effect-, morbidity/mortality-, quality of life- and cost data were obtained from the literature. We predicted test utilization, costs, 1-, 3-, 10-year and over lifetime cardiovascular morbidity/mortality for each strategy. We determined quality adjusted life years (QALY) and incremental cost-effectiveness ratio. Observed outcomes in ROMICAT-II were used to validate the short-term model.

Results—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).

Conclusion—Coronary CTA in patients with suspected ACS renders affordable long-term health benefits as compared to alternative strategies.

Keywords

Coronary CTA; Acute Chest Pain; Acute Coronary Syndrome; Cost-Effectiveness Analysis; Markov Microsimulation Model

1. INTRODUCTION

Several randomized comparative effectiveness trials have demonstrated that early coronary computed tomographic angiography (CTA) improves the efficiency of emergency department (ED) triage in acute chest pain (ACP) patients with suspected acute coronary syndrome (ACS) by significantly reducing hospital admissions and decreasing length of hospital stay as compared to standard of care.^{1–3} This improvement is driven by an increased diagnostic certainty rendered through CTA by establishing the absence of coronary artery disease (CAD). Absence of CAD, which is the most important finding in 50% of patients, carries a very high negative predictive value for major adverse cardiac events (MACE) during index hospitalization and moreover, a warranty period for at least two more years.⁴ On the other hand, the detection of obstructive CAD by coronary CTA in 10% of patients leads to increased rates of invasive coronary angiography (ICA) and percutaneous coronary

intervention (PCI) and – at least in systems without gate keeper or closed referral system –⁵ subsequently higher cost of care in coronary CTA-based strategies.¹ Not surprisingly, studies of short follow-up from 30 days to one year were not able to demonstrate improvement in health outcomes.⁶ Thus, concerns have been voiced as to whether coronary CTA is indeed beneficial to these patients, especially considering national efforts such as the “less is more” initiative and evidence from non-US studies showing that expedited ED protocols without inpatient diagnostic testing may lower costs while remaining equally safe in the short-term.^{7,8} Besides absence of CAD or obstructive CAD, coronary CTA detects non-obstructive CAD in about 40% of patients, a finding that has significant prognostic implications, with some studies suggesting that aggressive lipid lowering therapy based on obstructive and non-obstructive CAD, independent of statin eligibility based on ASCVD score, results in improved outcomes.⁹

Strategies that are alternatives to early coronary CTA include functional testing, expedited ED protocols with the intent to perform diagnostic testing in an outpatient setting^{6, 8}, and a strategy based on the American Heart Association/ American College of Cardiology (AHA)/ ACC guidelines.¹⁰ Despite the fact that ROMICAT-II has been conducted several years ago and there have been several other more recent publications in ACP population, there are still no long-term data on resource utilization and outcomes available with the longest reported follow-up of 19 months.¹¹ 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 in the long term, we developed a Markov microsimulation model to determine lifetime health outcomes and cost-effectiveness of available ED management strategies for patients with suspected ACS.

2. METHODS

2.1. Simulation Model Overview

We developed a Markov microsimulation model 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.^{2,8,10,12}

2.2. Patient Population

The Markov model was populated using individual data on demographics and cardiovascular risk factors from the 1,000 patients enrolled in the “Rule Out Myocardial Infarction/ Ischemia Using Computer Assisted Tomography” (ROMICAT) II trial (Table 1).² In brief, the ROMICAT-II trial randomized 1000 patients at low-intermediate risk of ACS who presented to the ED with suspicion of ACS and in whom ED caregivers ordered diagnostic testing to rule out ACS between April 2010 and January 2012 at nine US hospitals to either an early coronary CTA strategy or standard of care (SOC). Model input parameters beyond the 28-day follow up were estimated using published sources (Appendix, Supplemental Tables 3–5). Thus, the simulation model had two distinctive components: a short-term model

(ED presentation and the first month afterwards) and a long-term Markov microsimulation model (second month until end of life) (Fig. 1).

2.3. Short-term model

In the short-term model, 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. The management strategies are outlined in detail in Figures 2a–d. Briefly, the early coronary CTA and SOC strategy reflect the actual patient management as observed in ROMICAT-II.² The hallmark of the early coronary CTA strategy was the early discharge of more than 50% of patients after a single troponin test, while the SOC performed functional testing (75% myocardial perfusion imaging) in nearly 80% of patients after serial troponin testing (Figures 2a and 2b). The expert consensus strategies were based on an abstraction of the current ACC/AHA guidelines for patients with ACP (Figure 2c).¹⁰ In this strategy, patients in whom ACS was ruled out were managed based on their cardiovascular risk profile and diagnostic test results. The strategy of expedited ED discharge is based on the study by Than et al.⁸ (Figure 2d) and assumes that advanced diagnostic testing is performed on an outpatient basis. An important limitation of this strategy is the reportedly limited compliance with recommendations for outpatient testing.^{13, 14} Based on available data, we assumed in this strategy that 12% of patients with negative troponin results will follow-up with a cardiologist and 50% with a primary care physician (of which 50% will be referred to a cardiologist), leaving 38% of patients discharged without any physician follow-up.

Some aspects of management were similar for all strategies. For example, patients with a positive troponin were always referred to ICA. While the diagnostic testing sequence varied between the strategies, the model assumes conditional independence and uses the same accuracies for individual tests regarding the detection of CAD and ACS across all strategies based on the most recent literature (Appendix, Supplemental Table 1). Guideline-recommended treatment (Appendix, Supplemental Table 2) was based on the estimated CAD and ACS status.

2.4. Long-term model

The long-term model was used to estimate quality adjusted life years (QALYs) and lifetime costs of care. As a basis we estimated the probability of future coronary revascularization procedures including PCI and CABG, adverse cardiovascular events, including myocardial infarctions and CV death, as well as overall mortality rates at 1, 3, and 10 years and over a lifetime.

Progression of CAD, an important determinant for future coronary revascularization procedures including PCI and CABG, and adverse cardiovascular events, including myocardial infarctions and CV death, was modeled as a function of age, gender, disease status and National Cholesterol Education Program (NCEP) risk score from a cohort of stable chest pain patients using a simulated annealing approach.^{15,16} Cardiovascular mortality and morbidity rates were modeled based on the presence and extent of CAD in the CONFIRM registry.^{17,18} Mortality rates for non-ST segment elevation myocardial infarction

(NSTEMI) and unstable angina (UA) depended on the underlying CAD status, and mortality due to causes other than CAD was based on US life tables (Appendix, Supplemental Table 3).^{19–22} We assumed that patients newly diagnosed with significant CAD were started on medical therapy per AHA/ACC guidelines (Appendix, Supplemental Table 2). We assumed that appropriate treatment reduced CAD mortality (proportionally) by 23% (Preventive fraction: one minus odds ratio of 0.77).²³ A second assumption was that missed ACS increased 30 day mortality by 70–90% (hazard ratios between 1.70–1.90).²⁴

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 myocardial infarctions and die from either cardiovascular disease or other causes (Figure 1).

2.5. Health-related quality of life, healthcare costs data, and incremental cost-effectiveness ratio

Quality of life was determined by the presence and extent of CAD, the treatment method (medical treatment or intervention), and whether obstructive CAD was treated or not. In our approach we follow Ladapo et al..²⁵ As such, we estimated the probability of having typical angina versus nonspecific or atypical chest pain based on the underlying CAD status according to the CASS registry, and whether a patient was treated for CAD. We used utility values for various chest discomfort classifications that were derived from Lalonde et al. (Appendix, Supplemental Table 4).^{26, 27} We combined the data to calculate the impact of CABG and PCI on chest pain. Quality adjusted life years (QALYs) were calculated by weighting life years with quality of life values.

Costs were derived from three different sources: 1) The costs of diagnostic tests, initial and recurrent cardiac interventions, and hospitalizations were directly derived from the micro-costing at each ROMICAT-II clinical site. Thus, actual health care costs such as cost for diagnostic testing (CTA, ETT, SPECT, Stress Echo, ICA) and interventions (PCI, CABG) during the index care episode were assessed from reports from hospital cost-accounting systems and physician billing records;^{2, 12} 2) costs of outpatient office visits were based on Medicare reimbursements, and 3) costs of long-term medical therapy were derived from the RedBook (Appendix, Supplemental Table 5).

The incremental cost-effectiveness ratio (ICER) expresses the costs per additional QALY, i.e. the costs to live an additional year in perfect health. The ICER was calculated as the difference in costs between two strategies and divided by the difference in quality adjusted life years. To estimate the ICER, costs and QALYs were discounted at 3% annually.

2.6. Sensitivity analyses

2.6.1. Risk of ACS—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 characteristics reflected the CT-STAT study population.²⁸ Although we did not have access to patient level data for this trial, we were able to simulate a cohort that met its described characteristics well (Appendix, Supplemental Table 6).

2.6.2. Diagnostic Accuracy of coronary CTA to detect obstructive CAD—As diagnostic accuracy for obstructive CAD may determine rates of referral to invasive coronary angiography and may vary between CT scanners and readers, we conducted a bivariate sensitivity analysis to determine the ICER across a range of sensitivities (85% to 100%) and specificities (50% to 100%).

2.6.3. Treatment effect of aggressive medical therapy for obstructive CAD—In our main analysis we assume that life time statin therapy reduces CAD mortality by 23% assuming full compliance.²³ In order to address uncertainty regarding the treatment effect, we conducted a sensitivity analysis using the upper and lower bounds of the confidence interval, i.e. 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.

2.7. Statistical analyses and computer software

All 1,000 ROMICAT-II patients ran through each of the four strategies 1000 times. We first validated the short-term model by comparing model-predicted short-term outcomes in the coronary CTA and SOC strategy with the observed short-term outcomes (e.g. length of stay, number of interventions, cost of care) in ROMICAT-II.

All comparisons are reported without p values because all analyses were run with sample sizes (1,000,000, i.e., each of the 1,000 patients 1000 times) large enough to generate stable estimates of the effect sizes of interest, ensuring that the difference in QALYs and costs between the interventions was >2 times the (larger) standard error of the mean.²⁹ The model was programmed in TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, MA, USA). All data and statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX, USA).

3. RESULTS

3.1. Population Characteristics

The ROMICAT-II population (n=1000) was defined as middle aged (54.2 ± 8.1 years), equally representing gender (53.2% male), and by a substantial cardiovascular risk factor (RF) burden (52.8%: 2 – 3 RF; 9.9%: >3 RF). Overall, 50.7% of patients had no CAD, 43% non-obstructive CAD and 6.3% obstructive CAD. The incident of ACS during index hospitalization was 7.5% (NSTEMI: 2.3%; UA: 5.2% (Table 1).

3.2. 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 2). This data validates the accuracy of the short-term model.

As in ROMICAT-II, early coronary CTA was most accurate in identifying patients with obstructive CAD (98%), followed by Expert Consensus (75%), and SOC (69%). In contrast,

the predicted accuracy of the expedited ED discharge strategy to identify patients with obstructive CAD was very low (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. For example, 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 higher revascularization rate with early coronary CTA resulted in significantly higher total costs as compared to expedited ED discharge (\$4,490 vs. \$2,513), while difference to SOC (\$4,144) and expert consensus (\$4,064) was relatively small (Table 3).

Among all strategies, patients without CAD had the lowest rate of invasive angiographies after early coronary CTA (1.4%) followed by expedited ED discharge (3.8%), SOC (7.1%), and Expert consensus (9.4%). This is accompanied by 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). In contrast, patients without CAD in the SOC or Expert consensus strategy had a length of stay that was twice as long (27.6 hours and 26.9 hours) and costs that were 50% higher (\$3,482 and \$3,289).

3.3. Long-term health and economic outcomes (Figure 1)

The major health and economic outcomes one, three, and 10 years after ED presentation and over a lifetime are shown in Table 4. 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 versus 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. For example, while the PCI rate for early coronary CTA was 1.9 times higher than the rate for expedited ED discharge after 3 years (4.4% versus 2.3%), this decreased to 1.3 times higher over a lifetime (7.0% vs. 5.4%) (Table 4). Additional costs over a lifetime were highest for coronary CTA and approximately \$2,000 higher as compared to expedited ED discharge, \$370 higher as compared to SOC and \$460 higher as compared to Expert Consensus.

3.4. Incremental Cost Effectiveness Ratio

In a comparison of all four strategies, performing an early coronary CTA in the ED resulted in a gain of 25 quality adjusted life days (QALD) when compared to expedited ED discharge (QALYs: 23.09 vs. 23.02), 17 QALD compared to SOC (QALYs: 23.09 vs. 23.05) and 12 QALD compared to expert consensus (QALYs: 23.09 vs. 23.06) (Table 5). The coronary CTA strategy extendedly dominated the SOC and the expert consensus strategies, i.e. the ICER of the coronary CTA strategy was lower than the ICER of the SOC strategy and the ICER of the expert consensus strategy (Central Figure 1). Thus, 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 rendered a cost per QALY of \$ 49,428. In a head to head comparison of coronary CTA to SOC the ICER decreased to \$ 13,961.

3.5. Sensitivity Analyses

Treatment effect of aggressive medical therapy for obstructive CAD (Figure 3)

—Assuming a relative risk decrease of only 0.18 representing the lower bound of the 95% CI, the ICER increased from \$ 49,000 to \$ 60,000.²³ 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.

Diagnostic Accuracy of coronary CTA to detect obstructive CAD—

We determined the ICER across a range of sensitivities (85% to 100%) and specificities (50% to 100%) of coronary CTA to detect obstructive CAD as compared to invasive angiography. Overall, the ICER of coronary CTA versus expedited 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 CABG (Appendix, Supplemental Table 7).

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 (Appendix, Supplemental Table 8).²⁸

4. DISCUSSION

This cost-effectiveness analysis based on a Markov microsimulation model compared the lifetime health and economic outcomes of four contemporary management strategies for patients with suspected ACS. The major result is that the data suggest that an early coronary CTA strategy is cost-effective over a lifetime as compared to competing strategies, including early ED discharge. This is due to an early detection of true CAD status by early coronary CTA that despite an initial increase in testing, interventions, and costs results in a reduction in cardiovascular mortality starting to emerge 3 years after the initial ED presentation,

primarily through appropriate medical therapy. This effect was not only sustained but expanded throughout life. 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 to 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 sensitivity analysis, assuming a 50% cardiologist follow-up rate, ICER decreased to ~\$34,000 per QALY, however, coronary CTA remained more cost effective. In a head-to-head comparison of the two most common strategies of coronary CTA and SOC (functional testing), the ICER was much lower with \$14,000 per QALY.

In addition, we show that the benefits of coronary CTA vary with adherence to aggressive lipid lowering therapy, although coronary CTA remained cost-effective at higher costs per QALY (up to \$90,000). 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. While there are no long-term studies in patients with suspected ACS who underwent coronary CTA, the recent results from the SCOT-HEART trial in a stable chest pain population validate the assumptions and results of our modeling in that they demonstrate a lower incidence of death from coronary heart disease or myocardial infarction after coronary CTA as compared to stress testing strategy. In addition, the results confirmed our assumptions that an initial increase in testing and revascularization after coronary CTA is followed by less testing over mid-term follow-up, while patients who underwent stress testing experienced an increase in testing and revascularization over time.³⁰

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.³¹ An often-cited value for approval or payment of medical interventions is US \$100 000 per QALY.^{32–34} 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 intermediate value (70–90K per QALY). It is interesting to note that both scenarios compare favorably with established strategies such as lung cancer screening (130K per QALY³⁵), and screening for CAD in patients with type 2 diabetes mellitus or HIV.^{36,37} Even though an addition of 12–25 quality adjusted days on an individual's lifespan may appear underwhelming to some, from a societal point of view this translates to an additional 0.4 Million QALYs on the life span of the 6 million patients presenting annually to the ED in the US each year. Thus, early coronary CTA in patients with suspected ACS could have a significant public health and economic impact.

It is perhaps not surprising that an expedited ED discharge strategy appears beneficial in the short-term but is inferior in the long-term when compared to a strategy that delivers powerful prognostic information in every patient at the beginning. A major factor driving this difference is that 50% of patients who have obstructive CAD would not be detected with this strategy. We have not considered the cost of repeated ED visits in the expedited

discharge strategy, nor the litigation costs for missed detection of CAD. Our model confirms the low risk for major adverse cardiovascular event (MACE) after ED discharge^{38,39} in this population consistent with findings of short-term follow-up studies that did not detect any differences in health outcomes between a coronary CTA strategy and SOC.^{2,40} Moreover, our model highlights that such studies need a minimum follow-up of 3 years in order to detect emerging differences between the strategies. Though there is no such data from randomized trials, several observational studies have uniformly demonstrated that patients with non-obstructive and obstructive CAD detected on coronary CTA are at significantly higher long-term risk for developing MACE compared to those without the disease, even after adjustment for traditional risk factors (HR non-obstructive: 2.5; HR obstructive: 11.2).⁴¹ Moreover, the prognostic accuracy of coronary CTA is significantly higher as compared to functional testing.

While the careful use of diagnostic testing is extremely important, our data suggests that a change in how to perceive an ED visit, from a point of care to rule out MI at the lowest costs possible to a unique opportunity to lay the ground work for an optimized medical prevention using coronary CTA to accurately establish CAD status would be cost effective. Moreover, in the future, availability of CT FFR may lead to a lower rate of ICAs and perhaps even subsequent PCI in patients who are positive for anatomic but not for hemodynamic significant stenosis.

The strengths of our analysis are (1) the use of patient level data for the demographics, clinical presentation, traditional CVD risk factors, and CAD status as observed in the ROMICAT-II trial to populate the baseline model (2) the ability to use real per patient data from ROMICAT-II on testing, interventions, health outcomes and cost during the index hospitalization and over the following 28 days to calibrate and validate the short-term model and (3) the robustness of the model to simulate the natural history of CAD, its associated morbidity and mortality, and the effects of treatment over different time horizons.

It is important to emphasize that our modeling while based on ROMICAT-II includes several important sensitivity analyses; thereby, accommodating difference in populations and outcomes presented in subsequent publications.¹¹ In these, changes in the treatment effect and adherence to aggressive lipid lowering therapy for obstructive CAD resulted in a moderate increase of the ICER between \$60,000/QALY and \$90,000/QALY which is still below \$100,000 per QALY. In addition, we showed that although the strength of coronary CTA is a very high negative predictive value in the absence of CAD, the benefits of coronary CTA are diminished if the incidence of ACS is too low rendering coronary CTA 50% less cost-effective (ICER: 73,200/QALY for ACS incidence of 1.8% as seen in CT-STAT). This increase in costs was primarily related to the lower underlying prevalence of CAD and thus fewer treatments. Similarly, we show that a lower specificity of early coronary CTA for the detection of obstructive CAD leads to an increased ICER (about \$10,000 for a decrease in specificity from 90% to 70%), emphasizing the importance of acquiring coronary CTA data sets with diagnostic image quality and having them interpreted by highly skilled readers.

4.1. Limitations

Inherent in this type of 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, as discussed, the main outcomes of our analyses benefitted from the availability of individual patient data from randomized clinical trials. Some of the data we used was derived from studies performed a long time ago, e.g. data regarding the quality of life. It is reassuring, though, that the life expectancy for different trial populations approximates those observed in the CDC vital statistics when accounting for higher disease burden in the trial population compared to the overall population (RII: model: 24.7 years, CDC: 27.0 years, CT-STAT: model 29.0 years, CDC: 31.4 years).⁴² Moreover, the 2 year outcomes of our model were comparable to the observed 2 year outcomes in clinical trials, i.e. ROMICAT I trial.⁴

5. CONCLUSION

Considering long-term health outcomes and costs of care, early coronary CTA appears to be the most cost-effective strategy in patients with suspected ACS as compared to alternative strategies including expedited ED discharge. Benefits of early coronary CTA are expected to be seen three years after ED presentation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ACP	Acute chest pain
ACS	Acute coronary syndrome

AHA/ACC	American Heart Association/American College of Cardiology
ASCVD	Atherosclerotic cardiovascular disease
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CTA	Computed tomography angiography
ED	Emergency department
ICA	Invasive coronary angiography
ICER	Incremental cost-effectiveness ratio
MACE	Major adverse cardiovascular event
NSTEMI	Non-ST segment elevation myocardial infarction
PCI	Percutan coronary intervention
QALY	Quality adjusted life years
RF	Risk Factor
ROMICAT-II	Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography
SOC	Standard of care
UA	Unstable angina

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Fig. 1.

Markov microsimulation model with data sources for short and long term health and economic outcomes of four competing ED management strategies. Baseline population characteristics as observed in the ROMICAT-II Trial. Short term model validation based on 28 day management and outcomes observed in the ROMICAT-II. MACE (dark grey bars) includes myocardial infarction and cardiovascular death, whereas Coronary Revascularization (light grey bars) represents PCI and CABG. Major model inputs for long term simulation: ROMICAT-II, Ottawa cohort of stable chest pain and literature. CABG = Coronary artery bypass graft; CAD = Coronary artery disease; CTA = Computed tomography angiography; ED = Emergency Department; MACE = Major adverse cardiovascular events; PCI = Percutaneous coronary intervention.

Fig. 2.

A. Diagnostic Pathways in coronary CTA Strategy.

a: Functional tests: 0.23 SPECT, 0.06 stress ECHO, 0.06 ETT.

b: Average pathway probabilities; Patients undergo pathways according to a split based on risk factors.

ACS = Acute coronary syndrome; CABG = Coronary artery bypass graft; Cath = Coronary catheterization (++ = significant stenosis (> 70%), + = mild stenosis); CCTA=Coronary computed tomographic angiography (++ = significant stenosis, + = mild stenosis) f/u = follow up; ECHO = Echocardiography; ETT = Exercise tolerance test; LM = Left-main disease; PCI = Percutaneous coronary intervention; SPECT = Single-photon emission computed tomography; Trop = Troponin test; VD=Vessel disease. PP Meds = Primary prevention medication: Aspirin and Statin (for patients with hypertension, diabetes, or dyslipidemia), SP Meds = Secondary prevention medication: Aspirin and Statin, TP Meds = Tertiary prevention medication: Aspirin, Statin, and Betablocker (non-diabetic patient) or ACE (diabetic patient), ACS Meds = ACS medication: Aspirin, high-dose Statin, Clopidogrel (one year only), Beta blocker and ACE.

B. Diagnostic Pathways in the Standard of Care Strategy.

a: Average pathway probabilities; Patients undergo pathways according to their propensity score.

ACS = Acute coronary syndrome; CABG = Coronary artery bypass graft; Cath = Coronary catheterization (++ = significant stenosis (> 50%), + = mild stenosis); CP = Chest pain; ECG = Electrocardiogram; ETT = Exercise tolerance test; LM = Left-main disease; PCI = Percutaneous coronary intervention; SPECT = Singlephoton emission computed tomography; STECHO = Stress echocardiography; Trop = Troponin test; VD = Vessel disease. PP Meds = Primary prevention medication: Aspirin and Statin (for patients with hypertension, diabetes, or dyslipidemia), SP Meds = Secondary prevention medication: Aspirin and Statin, TP Meds = Tertiary prevention medication: Aspirin, Statin, and

Betablocker (non-diabetic patient) or ACE (diabetic patient), ACS Meds = ACS medication: Aspirin, high-dose Statin, Clopidogrel (one year only), Beta blocker, and ACE.

C. Diagnostic Pathways per AHA/ACC Guidelines.

Per AHA/ACC guidelines patient management after stress testing is guided by the presence of traditional risk factors and diabetes. The table at the bottom of the figure demonstrates the probabilities to receive type of functional testing.

ACS = Acute coronary syndrome; CABG = Coronary artery bypass graft; Cath = Coronary catheterization (++ = significant stenosis (> 50%), + = mild stenosis); CP = Chest pain; ECG = Electrocardiogram; ECHO = Echocardiography; ETT = Exercise tolerance test; LM = Left-main disease; PCI = Percutaneous coronary intervention; SPECT = Single-photon emission computed tomography; Trop = Troponin test; Txt = Treatment; VD = Vessel disease. PP Meds = Primary prevention medication: Aspirin and Statin (for patients with hypertension, diabetes, or dyslipidemia), SP Meds = Secondary prevention medication: Aspirin and Statin, TP Meds = Tertiary prevention medication: Aspirin, Statin, and Betablocker (non-diabetic patient) or ACE (diabetic patient), ACS Meds = ACS medication: Aspirin, high-dose Statin, Clopidogrel (one year only), Beta blocker, and ACE.

D2. Diagnostic Pathways in the Standard of Care Expedited ED Protocol Strategy.

ACS=Acute coronary syndrome; CABG=Coronary artery bypass graft; Cath=Coronary catheterization (++ = significant stenosis (> 50%), + = mild stenosis); CP=Chest pain; ECG=Electrocardiogram; LM=Left-main disease; PCI=Percutaneous coronary intervention; Trop=Troponin test; VD=Vessel disease.

PP Meds=Primary prevention medication: Aspirin and Statin (for patients with hypertension, diabetes, or dyslipidemia), SP Meds=Secondary prevention medication: Aspirin and Statin, ACS Meds=ACS medication: Aspirin, high-dose Statin, Clopidogrel (one year only), Beta blocker, and ACE.

Fig. 3.

Treatment effect of aggressive medical therapy for obstructive CAD. Left side: Treatment effect of aggressive medical therapy for obstructive CAD (> 50%): light grey column: baseline case assuming that life time statin therapy reduces CAD mortality by 23% (22); mild and dark grey column: sensitivity analysis using the upper (30%) and lower (18%) bounds of the confidence interval of relative risk reduction. Right side: Sensitivity analyses for validations in treatment compliance: light grey column: baseline case assuming that life time statin therapy reduces CAD mortality by 23% (22); mild grey column: 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); dark grey: full compliance for 5 years and no treatment effect afterwards. CAD = Coronary artery disease, RR = Risk reduction.

Table 1.

Baseline Population characteristics for the Markov Model.

	Population [#] (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.

Table 2.

Model validation.

Variables	ROMICAT II Early CCTA		ROMICAT II Standard of Care	
	Trial	Simulation	Trial	Simulation
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.

Table 3.

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

	ROMICAT II CCTA *	ROMICAT II 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

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

* 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

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

Table 5.

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

Coronary CTA = Coronary computed tomographic angiography; ICER = Incremental cost-effectiveness ratio; QALY = Quality-adjusted life year

* 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. The Table shows that an early CCTA strategy cost 49,428 per additional QALY compared to expedited ED protocol.