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Computed Tomography Coronary Angiography Added to Standard Care with High-Sensitivity Cardiac Troponin for Acute Chest Pain

Jae Gyung Kim[1], Eun Ho Choo[2]*, Dongjae Lee[2], Chan JK[2], Hyo SA[2], Jong Min Lee[2] and Hui-Kyoung J[2]

[1]Branch of Cardiology, Department of Internal Medicine, National Cancer Center, Goyang, Korea
[2]Division of Cardiology, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea

Abstract

European Society of Cardiology (ESC) 0/3-h algorithm using high sensitivity cardiac troponin (hs-troponin) is recommended to detect acute myocardial infarction (MI) for patients with acute chest pain. As hs-troponin may be less specific, we assessed the usefulness of coronary computed tomography angiography (CCTA) in addition to standard care for patients with acute chest pain. We investigated 695 patients who visited the emergency department for acute chest pain and performed serial hs-troponin T and CCTA. Obstructive coronary artery disease (CAD) on CCTA was defined as >=50% stenosis. The primary outcome was the occurrence of MI within 30 days. According to ESC 0/3-h algorithm, patients were categorized into rule-out (425, 61.2%), rule-in (155, 22.3%), and observe group (115, 16.5%). Eighty-one patients (11.7%) were diagnosed with MI. Two hundred ten patients had obstructive CAD on CCTA. The addition of obstructive CAD on CCTA to ESC 0/3-h algorithm improved the diagnostic accuracy for MI (area under the curve: from 0.85 to 0.911, p=0.003). Even for the rule-in and rule-out patients, the specificity (from 78.9% to 94.5%) and positive predictive value (from 32.1% to 62.8%) were significantly improved after the addition of CCTA to ESC 0/3-h algorithm. Half of the patients in the rule-in group did not undergo invasive coronary angiography based on CCTA findings without further MI events. CCTA added to the serial hs-troponin may improve the prediction of MI in patients with acute chest pain.

Keywords: Computed Tomography Angiography • Troponin • Chest pain • Emergency Department • Myocardial infarction

Introduction

For the differential diagnosis of patients with acute chest pain and inconclusive electrocardiogram, serial test of high sensitivity cardiac troponin (hs-troponin) are currently used to rule-out myocardial infarction (MI) in emergency department(ED) [1]. However, hs-troponin can rise in the all event of cardiac damage in various situations, so even if hs-troponin rises, up to one-third do not have obstructive coronary artery disease (CAD) in invasive coronary angiography (ICA) [2,3]. Conversely, patients with acute chest pain and normal hs-troponin may have significant coronary artery disease at risk of future MI unless evaluated and treated [4,5].

Coronary CT angiography (CCTA) is a useful diagnostic modality in patients with chest pain, though it has controversial issues about radiation exposure, contrast media, and financial and technical feasibility [6,7]. CCTA is considered to be a consumptive test for low-risk patients with acute chest pain in some reports [8,9], while the other study reported that CCTA can reduce unnecessary ICA and diagnostic cost in patients suspected of CAD or MI [10,11]. Thus, we investigated whether the presence of obstructive coronary artery disease (CAD) on CCTA has additional efficacy to diagnose MI over a scenario of an European Society of Cardiology (ESC) 0/3-h algorithm [12] using the serial hs-troponin T. Moreover, we investigated whether CCTA can identify more patients with significant CAD requiring coronary revascularization in the era of hs-troponin.

***Address for Correspondence:** Choo Eun Ho, MD, Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-Daero, Seocho-Gu, Seoul, 06591, Republic of Korea, Tel:+82-31-820-3203, Fax: +82-31-847-0461, E-mail: cmcchu@catholic.ac.kr*

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Research Methodology

Design and population

Among patients who visited the emergency department of an academic university hospital due to acute chest pain, we consecutively enrolled the patients who were prescribed and implemented CCTA simultaneously with the second hs-troponin T assay after initial hs-troponin T assay. We initially collected 742 patients who underwent CCTA in the ED from February 2014 to August 2018 (Figure 1). We excluded those who never had any chest discomfort (n=44) and who presented with ST-segment depression of > 1 mm on the initial ECG (n=3). A total of 695 patients have finally included in this analysis, and none of the participants had any severe renal dysfunction (estimated glomerular filtration rate < 30 min/ml/1.73 m^2) or any history of life-threatening contrast allergies. The study protocol was approved by the institutional review board of our hospital, and no informed consent was required.

Clinical risk assessment

For the risk stratification, we collected traditional risk factors such as age, sex, hypertension, diabetes, and current smoking for all patients. Moreover, we collected every parameter of the TIMI risk score, GRACE score for non-ST elevation-ACS, HEART score and Emergency Department Assessment of Chest pain Score (EDACS) including the pain characteristics, hemodynamic status, ECG findings, the positivity of cardiac markers, and other associated conditions for atherosclerosis. We defined typical chest pain as radiating pain to the arms, shoulders, neck, and jaw or exertional chest pain, dyspnea, or that associated with diaphoresis [13,14].

Measurement of high sensitivity troponin T and application of ESC 0/3-h algorithm

The hs-troponin T (Roche Elecsys®) was tested when patients presented

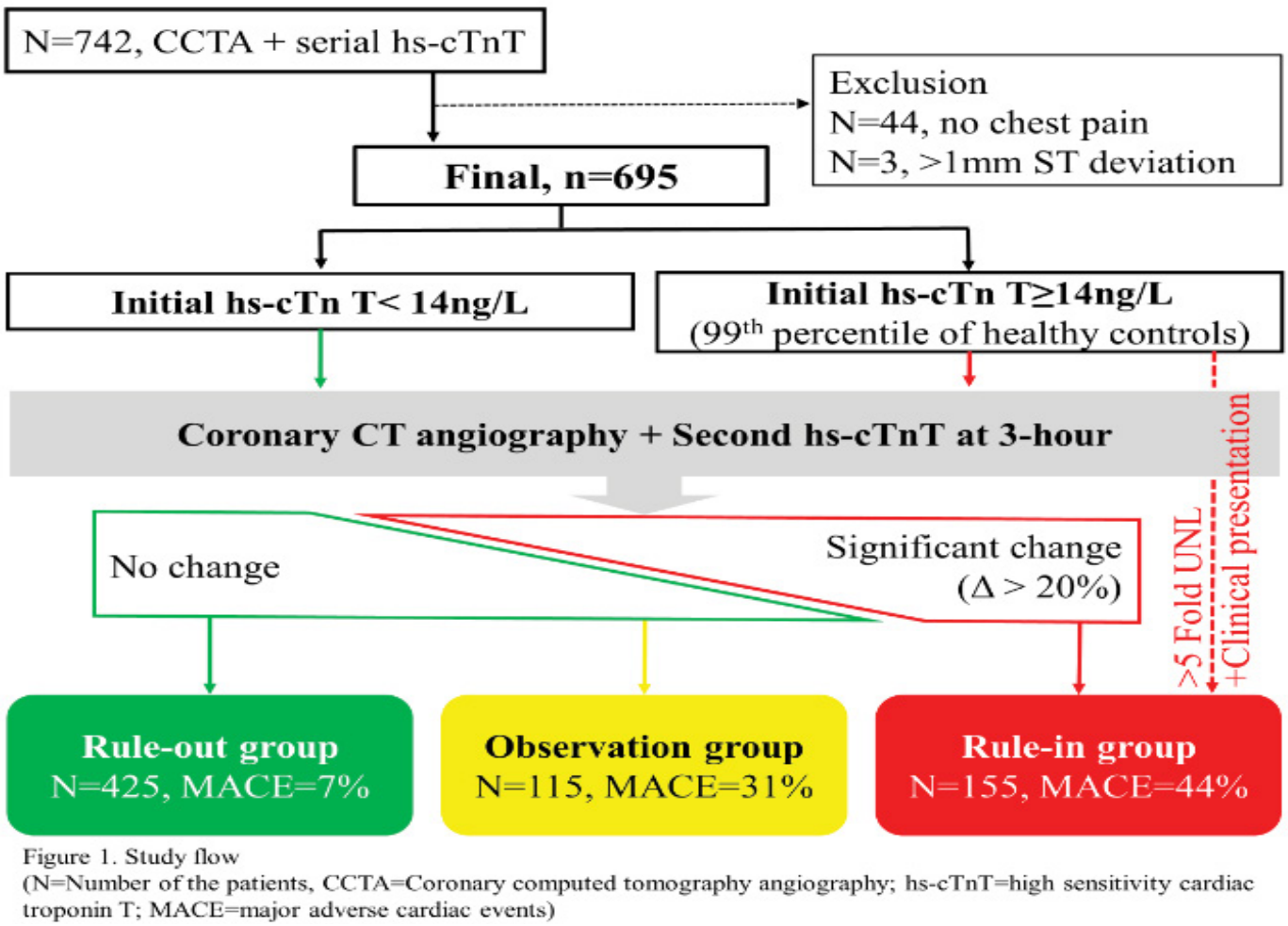

Figure 1. Study flow
(N=Number of the patients, CCTA=Coronary computed tomography angiography; hs-cTnT=high sensitivity cardiac troponin T; MACE=major adverse cardiac events)

Figure 1. Study flow chart (N: Number of Patients; CCTA: Coronary Computed Tomography Angiography; Hs-Troponin T: High Sensitivity Cardiac Troponin T; ESC: European Society of Cardiology; NSTE-ACS: Non-ST Elevation Acute Coronary Syndrome; UNL: Upper Normal Limit Same As 99th Percentile of Healthy Controls; MACE: Major Cardiac Adverse Event).

at the ED and was repeated 3 hours later during the stay in the ED. The first and second results of the hs-troponin T assays in the ED were collected, and the differences, percentage of change, and time interval were evaluated. We classified the patients into three groups according to the ESC 0/3-h rule-out algorithm of the NSTE-ACS using hs-troponin (Figure 1). According to the fourth universal definition of myocardial infarction, the 99Th percentile of a healthy population on the hs-troponin T assay (0.014 ng/ml) was used as the cut-off value. A significant change in the serial troponin assays was defined as > 20% of the baseline value [12,15]. There were 27 patients with the first hs-troponin T exceeding five times of cut-off value which would determine early to receive ICA. For them, CCTA was implemented because they had inappropriate conditions for ICA immediately, such as high bleeding tendency or suspicion of active infection, and they classified as the same way. The laboratory data known to be associated with hs-troponin, such as the creatinine kinase-myocardial band (CK-MB), creatinine, hemoglobin, and high sensitivity C reactive protein (hsCRP) were also collected.

Image acquisition and data interpretation of the CCTA

CCTA was performed with a modern CT scanner (SOMATOM Definition, Siemens Healthcare Forchheim, Germany) located in the ED. A beta-blocker (propranolol 40 - 80mg) was administrated to achieve heart rates of < 70 beats/min, and sublingual nitro-glycerine was administered before the CCTA scan. All CCTA data were interpreted by three radiologists with at least four years of CCTA experience according to the guideline recommendation [16]. The coronary calcium score was calculated according to the Agatston's scoring method. Major vessels were included in the reporting, and the lesions were classified into 5 categories for the stenosis severity (no visible stenosis - 0%, minimal stenosis – 1 ~ 49%, moderate stenosis – 50 ~ 69%, severe stenosis-70 ~ 99%, occluded - 100%). Then the reports were reviewed by cardiologists and the positive result of obstructive CAD on the CCTA was defined as a ≥ 50% stenosis of the coronary arteries with a diameter of > 2.0 mm [17].

Study endpoint

The primary outcome was occurrence of MI within 30 days. The secondary outcomes included the rates of ICA and major adverse cardiac events (MACE) defined as the composite outcome of cardiac mortality, MI, and coronary revascularization within 30 days. The medical records, as well as the qualification of the national health insurance service for mortality, were thoroughly reviewed by two certified cardiologists and a dedicated research nurse. The diagnosis of myocardial infarction was based on the Fourth Universal Definition of myocardial infarction and was confirmed by source documents and adjudicated by two cardiologists independently [18]. Coronary revascularization included PCI and coronary artery bypass graft surgery, and coronary disease burden was quantified from the review of individual coronary angiograms. Patients who survived but did not return to our hospital system were assumed to be free of MI or coronary revascularization within 30 days [19] because most of them (94 of 100) were belong to the rule-out or negative CCTA group.

Statistical analysis

The baseline and biochemical characteristics were compared and summarized. A comparison of the categorical variables was performed using a chi-squared or Fisher's exact test and the Kruskal-Wallis test for continuous variables. We underwent the same analysis mentioned above for each triage group according to the ESC 0/3-h rule-out algorithm. We measured sensitivity, specificity, negative predictive value, and positive predictive value of the ESC 0/3-h algorithm among patients of rule-out and rule-in group and compared to CCTA. We measured the model discrimination by obtaining the Harrell's

C-statistics for each model and comparing the difference between them. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Baseline characteristics

The baseline characteristics of the study population stratified by the 0/3-h ESC rule-out algorithm using the serial hs-troponin T assay. The mean age in the 695 patients was 58 years old, and 60% of the patients were male. The patients in the observation group were more likely to have diabetes mellitus, hyperlipidemia, a family history of CAD, a previous history of CAD, and a prior stroke. Also, the patients in the observation group had a higher baseline value of serum creatinine, hsCRP, CK-MB, hs-troponin T, and clinical risk scores than the other two groups. The prevalence of obstructive CAD on CCTA exhibited was higher in patients with the rule-in group (47.7%) and observation (48.7%) group than in those with the rule-out group (18.8%)($P < 0.001$). There were no differences among the groups in the interval length of the serial hs-troponin T (mean 2.7 ± 2.3 hours).

The 30-day clinical outcomes according to the ESC 0/3-h algorithm and CCTA

Within 30 days, MI occurred in 81 patients (11.7%) consisting of 0% of patients in the rule-out group, 29% of patients in the rule-in group, and 31% of patients observe group. MACE occurred in 120 patients (17.3%) within 30 days. The prevalence of MACE was highest in the rule-in group (31.9%) and lowest in the rule-out group (6.8%). Among patients with obstructive CAD in CCTA, 35% were diagnosed with MI, and more than half developed MACE, whereas only 1.4% and 1.9% of patients with negative CCTA results had MI and MACE within 30 days.

Comparative predictive value of the CCTA beyond the ESC 0/3-h algorithm

We compared diagnostic performance for MI between the ESC 0/3-h algorithm and ESC 0/3-h algorithm plus CCTA. Addition of obstructive CAD in CCTA to ESC 0/3-h algorithm improved the C-index for the prediction of MI (from 0.850 to 0.911, p=0.003) (Figure 2). Even excluding patients in observe group who are supposed to undergo additional tests, the addition of obstructive CAD in CCTA significantly improved the specificity (from 79.9% to 94.5%) and the positive predictive value (from 30.9% to 60.8%). CCTA had better performance for the prediction of MACE than ESC 0/3-h algorithm after excluding the observation group. (C-index 0.882 vs. 0.719, 95% CI of difference 0.112 – 0.215, $p < 0.001$). CCTA showed higher sensitivity, negative predictive value, and positive predictive value for the prediction of MACE than ESC 0/3-h algorithm after excluding the observation group.

Deferring invasive coronary angiography

Even in the rule-in group, less than half of the patients (74 of 155, 45.7%) had obstructive CAD on the CCTA. On the discretion of the cardiologist in charge, only 75 of 155 patients in rule-in group underwent ICA. MI or MACE within 30 days did not occur in any patients in the rule-in group who had no obstructive CAD on the CCTA and deferred the ICA.

Discussion

We demonstrated the additional CCTA to the ESC 0/3-h algorithm using hs-troponin significantly improved the prediction of a 30-day MI or MACE in the patients with acute chest pain visiting ED. Diagnostic strategies supplemented by early CCTA may not only increase the specificity and positive predictive value for the prediction of MI by reduction of unnecessary ICA but also identify more patients with significant CAD in these patients.

CCTA is considered as an excellent gatekeeper to rule-out acute coronary syndrome with a high negative predictive value [6,7]. CCTA was associated with better prediction power for MACE than various clinical risk scores alone

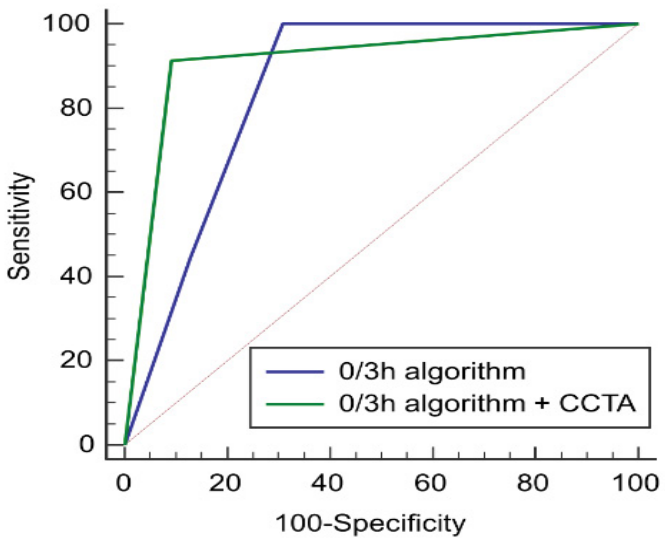

Figure 2. Improvement in the prediction accuracy of myocardial infarction adding coronary computed tomography angiography. Area under curve increased from 0.850 to 0.911 with 95% confidence interval of difference of 0.02 - 0.10 and p value of 0.003.

[20]. CCTA showed a better diagnostic accuracy for MACE than the initial hs-troponin [21] and coronary calcium score [22]. In our study, the accuracy of diagnosis of MI could be further improved by in addition to ECG and hs-troponin in the ED. The reduction of unnecessary ICA by additional CCTA was consistent with previous study [10]. BEACON study found the CCTA is safe, requires less outpatient testing, and has a lower cost, but failed to prove the usefulness of CCTA to identify more patients with significant CAD requiring revascularization [8]. In our study, CCTA could find patients with significant stenosis and a low hs-troponin level, even though the incidence of MACE was similar and the proportion of high-risk patients is lower in our study than that in BEACON study. It may be because other non-invasive tests were allowed for the control group in the BEACON study. Besides, compared to another previous study [21], the incidence of obstructive CAD was higher in the negative hs-troponin group (19.3% vs. 8.9%) but was lower in the rule-in and observation groups (46.3% vs. 61.9%) in this study. The different characteristics of our study population may explain our results different from other studies (Figure 2).

A recent study suggested the diagnostic threshold of the hs-troponin based on the 99th centile derived from a healthy reference population may be too sensitive to increase the incidence of an MI without increasing adverse events [23]. The patients with initial hs-troponin T above the 99 percentiles could be considered at high risk for CAD, but only 30% had signs of CAD in a previous report [24], which is consistent to our results. We can also question whether we should perform ICA in all patients in the rule-in group where showed low diagnostic yield [25]. CCTA can be used as a guide in a practical strategy to avoid any unnecessary ICA and in an on-site ad-hoc PCI in clinical practice. The trade-off of the cost between the CCTA and a reduction in the ICA is already validated in two prospective randomized trials [26].

The rule-out group of ESC 0/3-h algorithm could be discharged and go for stress testing following the guidelines. However, in the current practice setting, not all patients are amenable to the stress testing and the patients' adherence to non-invasive testing after discharge from the ED is low [27]. CCTA could find the patients with significant CAD in rule-out group of our study, which suggests that the evaluation for patients in the rule-out group is necessary. CCTA might allow them to be discharged safely with confidence as in the previous reports [6,7]. Even for those with non-obstructive CAD, a single CCTA test in the ED can provide information and be a guide for long-term medical therapy for a better outcome [28].

Limitations

This study is a single-centre observational study without comparing MACE with patients who did not undergo CCTA. The overall profile of the risk factors

and incidence of obstructive CAD in our cohorts (30.2%) was much higher compared to the other CCTA trial for acute chest pain in low to intermediate-risk patients [9]. We enrolled consecutive patients who presented with acute chest pain visiting ED without unequivocally positive results for ischemia after initial ECG and biomarker analysis.

Conclusion

Performing CCTA as an add-on test to ESC 03-h algorithm using the serial hs-troponin T may improve the prediction of MI and MACE in patients with acute chest pain in the ED. CCTA testing in patients with acute chest pain would reclassify low to intermediate risk patients and defer unnecessary ICA, thereby improving the utilization of hospital resources to focus on the patients with the highest risk.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Twerenbold, Raphael, Jasper Boeddinghaus, Thomas Nestelberger and Karin Wildi, et al. "Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction." *J Am Coll Cardiol* 70(2017): 996-1012.
2. Melki, Dina, Johan Lugnegård, Joakim Alfredsson and Suzanne Lind, et al. "Implications of introducing high-sensitivity cardiac troponin T into clinical practice: data from the SWEDEHEART registry." *J Am Coll Cardiol* 65(2015): 1655-1664.
3. Odqvist, Maria, Per-Ola Andersson, Hans Tygesen and Kai M. Eggers, et al. "High-sensitivity troponins and outcomes after myocardial infarction." *J Am Coll Cardiol* 71(2018): 2616-2624.
4. Smulders, MW, Sebastiaan CAM Bekkers, Yvonne JM van Cauteren and Anna Liefhebber, et al. "Risk stratification and role for additional diagnostic testing in patients with acute chest pain and normal high-sensitivity cardiac troponin levels." *Plos One* 13(2018): e0203506.
5. Adamson, Philip D., Michelle CW, Marc RD and Nicholas L. Mills et al. "Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain." *J Am Coll Cardiol* 74(2019): 2058-2070.
6. Raff, Gilbert L., Udo Hoffmann, and James E. Udelson. "Trials of imaging use in the emergency department for acute chest pain." *JACC Cardiovascular Imaging* 10(2017): 338-349.
7. Nieman K and Hoffmann U Cardiac computed tomography in patients with acute chest pain. *Eur Heart J* 36(2015): 906–914.
8. Dedic, Admir, Marisa ML, Jeroen Schaap and Jeronymus Lammers, et al. "Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study." *J Am Coll Cardiol* 67(2016): 16-26.
9. Reinhardt SW., Chien-Jung Lin, Eric Novak, and David L. Brown, et al. "Noninvasive cardiac testing vs. clinical evaluation alone in acute chest pain: a secondary analysis of the ROMICAT-II randomized clinical trial." *JAMA Intern Med* 178(2018): 212-219.
10. Smulders MW, Bas LJH Kietselaer, Joachim EW and Pieter C. Dagnelie, et al. "Initial imaging-guided strategy versus routine care in patients with non–ST-segment elevation myocardial infarction." *J Am Coll Cardiol* 74(2019): 2466-2477.
11. Chang Ha JJ, Lin FY, Gebow D, An HY, Andreini D and Bathina R, et al. Selective Referral Using CCTA Versus Direct Referral for Individuals Referred to Invasive Coronary Angiography for Suspected CAD: A Randomized, Controlled, Open-Label Trial. *JACC Cardiovasc Imaging* 12(2019):1303–1312.
12. Roffi, Marco, Carlo Patrono, Jean-Philippe Collet and Christian Mueller, et al. "2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology." *Eur Heart J* 37(2016): 267-315.
13. Mark, Dustin G., Jie Huang, Uli Chettipally and Mamata V. Kene, et al. "Performance of coronary risk scores among patients with chest pain in the emergency department." *J Am Coll Cardiol* 71(2018): 606-616.
14. Poldervaart JM., M Langedijk, B. E. Backus and I. M. C. Dekker, et al. "Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department." *Int J Cardiol* 227(2017): 656-661.
15. Ferencik, Maros, Thomas Mayrhofer, Michael T Lu and Pamela K. Woodard, et al. "High-sensitivity cardiac troponin I as a gatekeeper for coronary computed tomography angiography and stress testing in patients with acute chest pain." *Clin Chem* 63(2017): 1724-1733.
16. Leipsic, Jonathon, Suhny Abbara, Stephan Achenbach and Ricardo Cury, et al. "SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee." *J Cardiovasc Comput Tomogr* 8(2014): 342-358.
17. Poon, Michael, Michael Cortegiano, Alexander J. Abramowicz and Margaret Hines, et al. "Associations between routine coronary computed tomographic angiography and reduced unnecessary hospital admissions, length of stay, recidivism rates, and invasive coronary angiography in the emergency department triage of chest pain." *J Am Coll Cardiol* 62(2013): 543-552.
18. Thygesen, Kristian, Joseph S. Alpert, Allan S. Jaffe and Bernard R. Chaitman, et al. "Fourth universal definition of myocardial infarction (2018)." *Eur Heart J* 40(2019): 237-269.
19. Teressa, Getu, Mengru Zhang, Philip Lavenburg and Gregg Cantor, et al. "Validity of coronary artery disease consortium models for predicting obstructive coronary artery disease & cardiovascular events in patients with acute chest pain considered for coronary computed tomographic angiography." *Am J Cardiol* 122(2018): 1310-1321.
20. Korley FK., Constantine Gatsonis, Bradley S. Snyder and Richard T. George, et al. "Clinical risk factors alone are inadequate for predicting significant coronary artery disease." *J Cardiovasc Comput Tomogr* 11(2017): 309-316.
21. Liu, Ting, Guan Wang, Peiling Li, and Xu Dai. "Risk classification of highly sensitive troponin I predict presence of vulnerable plaque assessed by dual source coronary computed tomography angiography." *Int J Cardiol Imaging* 33(2017): 1831-1839.
22. Bittner, Daniel O., Thomas Mayrhofer, Fabian Bamberg, Travis R. Hallett, Sumbal Janjua, Daniel Addison, John T. Nagurney et al. "Impact of coronary calcification on clinical management in patients with acute chest pain." *Circ Cardiovasc Imaging* 10(2017): e005893.
23. Shah, Anoop SV, Atul Anand, Fiona E. Strachan and Amy V. Ferry, et al. "High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial." *Lancet* 392(2018): 919-928.
24. Árnadóttir, Ásthildur, Kirstine Roll Vestergaard, György Sölétormos, and Rolf Steffensen, et al. "Prediction of coronary heart disease or heart failure using high-sensitivity cardiac troponin T: A pilot study." *Eur J Clin Investig* 48(2018): e13009.
25. Patel, Manesh R, Eric D. Peterson, David Dai and J. Matthew Brennan, et

al. "Low diagnostic yield of elective coronary angiography." *N Engl J Med* 362(2010): 886-895.

26. Rudziński, Piotr Nikodem, Mariusz Kruk, Cezary Kępka and U. Joseph Schoepf, et al. "The value of coronary artery computed tomography as the first-line anatomical test for stable patients with indications for invasive angiography due to suspected coronary artery disease: CAT-CAD randomized trial." *J Cardiovasc Comput Tomogr* 12(2018): 472-479.
27. Paoloni, Richard, and Razaq Ibuowo. "A cohort study of chest pain patients discharged from the emergency department for early outpatient treadmill exercise stress testing." *Emerg Med Australas* 25(2013): 416-421.
28. Williams, Michelle C, Philip DA, and David E. Newby. "Coronary CT angiography and subsequent risk of myocardial infarction." *N Engl J Med* 380 (2019): 300-301.

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