



# SEALONE (Safety and Efficacy of Coronary Computed Tomography Angiography with Low Dose in Patients Visiting Emergency Room) trial: study protocol for a randomized controlled trial

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## Capsule Summary

### What is already known

*It is unknown whether a low-dose cardiac computed tomography angiography strategy using prospective gating and limited scan range can provide clinically sufficient diagnostic safety in emergency department patients with acute chest pain.*

### What is new in the current study

*We present a study protocol to test a hypothesis that a low-dose cardiac computed tomography angiography protocol using prospective electrocardiogram-triggering and limited-scan range can provide sufficient diagnostic safety for early triage of patients with acute chest pain.*

**Objective** Chest pain is one of the most common complaints in the emergency department (ED). Cardiac computed tomography angiography (CCTA) is a frequently used tool for the early triage of patients with low- to intermediate-risk acute chest pain. We present a study protocol for a multicenter prospective randomized controlled clinical trial testing the hypothesis that a low-dose CCTA protocol using prospective electrocardiogram (ECG)-triggering and limited-scan range can provide sufficient diagnostic safety for early triage of patients with acute chest pain.

**Methods** The trial will include 681 younger adult (aged 20 to 55) patients visiting EDs of three academic hospitals for acute chest pain or equivalent symptoms who require further evaluation to rule out acute coronary syndrome. Participants will be randomly allocated to either low-dose or conventional CCTA protocol at a 2:1 ratio. The low-dose group will undergo CCTA with prospective ECG-triggering and restricted scan range from sub-carina to heart base. The conventional protocol group will undergo CCTA with retrospective ECG-gating covering the entire chest. Patient disposition is determined based on computed tomography findings and clinical progression and all patients are followed for a month. The primary objective is to prove that the chance of experiencing any hard event within 30 days after a negative low-dose CCTA is less than 1%. The secondary objectives are comparisons of the amount of radiation exposure, ED length of stay and overall cost.

**Results and Conclusion** Our low-dose protocol is readily applicable to current multi-detector computed tomography devices. If this study proves its safety and efficacy, dose-reduction without purchasing of expensive newer devices would be possible.

**Keywords** Computed tomography; Coronary angiography; Chest pain; Radiation

## INTRODUCTION

Chest pain is one of the most common complaints in the emergency department (ED) with an annual visit of eight to ten million patients in United States.<sup>1</sup> Cardiac computed tomography angiography (CCTA) is a valuable imaging tool for the early triage of patients with low to intermediate risk acute chest pain.<sup>2</sup> The test is quick and simple and can reliably rule out acute coronary syndrome (ACS) as well as other critical conditions such as pulmonary embolism and aortic dissection.<sup>3,4</sup> Therefore, rapid discharge protocols utilizing the test are gaining popularity in many EDs.

However, such practice has been criticized for causing unnecessary radiation exposure.<sup>5</sup> The prevalence of ACS in patients with acute chest pain visiting EDs is about 10% to 20% and the chance of missing ACS is about 2% when traditional approaches were adopted.<sup>3,6,7</sup> Therefore, if a systematic implementation of a CCTA-based early triage protocol is supposed to be justified, the radiation exposure from the test should be minimized. However, despite the presence of dose-reduction techniques that are readily applicable to most multi-detector computed tomography (CT) imagers, the amount of radiation exposure from CCTA imaging has been unacceptably high.<sup>8,9</sup>

We believe this is due to the lack of prospective clinical trials that have proven the diagnostic safety of a low-dose CCTA pro-

tol, especially in a real ED situation. We hypothesized that a low-dose CCTA protocol with prospective ECG-triggering and limited-scan range, which are readily applicable to most 64 or higher channel multi-detector CT imagers, can provide sufficient diagnostic safety for early triage of patients with acute chest pain. We initiated a multicenter prospective randomized controlled clinical trial assessing its diagnostic safety and other important aspects (radiation dose, ED length of stay, and cost). This report provides a comprehensive summary of our study design and several practical issues raised so far.

## METHODS

### Trial design and setting

The study is a prospective, randomized, controlled, multi-center trial comparing a low-dose CCTA protocol using prospective electrocardiogram (ECG)-triggering and limited scan range with a conventional imaging protocol for early triage of low-to-intermediate-risk patients presenting to the ED with acute chest pain. The primary objective is to prove that the chance of experiencing any hard event (cardiac death or myocardial infarction) within 30 days after a negative low-dose CCTA test is less than 1%.<sup>4</sup> The secondary objectives are direct comparisons of the amount of radiation exposure, ED length of stay and overall cost between low-dose

and conventional CCTA protocol.

Three academic hospitals in South Korea are participating in this trial. Sites 1 and 3 are located in Seoul metropolitan city with annual ED visit of over 100,000 and 45,000, respectively. Site 2 is located in Seongnam city with over 80,000 annual ED visits. All the three hospitals are capable of emergency percutaneous coronary intervention on a full-time basis.

This study was reviewed and approved by the institutional review boards of all participating hospitals (SNUBH IRB no. B-1211/177-005). Informed consent is absolutely required for study participation. This study was registered on December 20 2012 under ClinicalTrials.gov number NCT 01770444 and patient enrollment was first started in June 21 2013.

### Participants

Adult patients aged 20 to 55 with acute chest pain or equivalent symptoms requiring further evaluation to rule out ACS are eligible to participate in this trial. The decision for enrollment is made by treating physicians after an initial evaluation that includes ECG, chest PA and cardiac bio-marker and D-dimer tests. Older (aged > 55) patients are excluded because the harmful cumulative effect of radiation exposure from a CCTA test would relatively be small in this population.<sup>5</sup> Patients clinically suspected of having acute pulmonary embolism or aortic dissection are also excluded because our low-dose protocol employs limited scan range from sub-carina to base of heart. Specifically, the former condition is excluded using modified Wells criteria,<sup>10</sup> while the later is excluded using clinical criteria suggested by von Kodolitsch et al.<sup>11</sup> In addition, patients with increased D-dimer are also excluded because of its association with both of the conditions.<sup>12-14</sup> The followings are the complete list of the exclusion criteria: 1) known coronary artery disease and/or any related intervention (e.g., percutaneous coronary intervention, coronary artery bypass graft surgery); 2) elevated cardiac biomarkers (creatinine kinase-MB and troponin I); 3) ischemic ECG changes; 4) documented evidence of low left ventricular systolic function (ejection fraction  $\leq$  45%); 5) thrombolysis in myocardial infarction risk score > 4; 6) unstable vital sign (e.g., hypoxemia, shock); 7) underlying conditions in which the administration of iodinated contrast and/or beta blockers are contraindicated (e.g., renal failure, heart failure, reactive airway diseases); 8) atrial fibrillation on initial ECG; 9) active renal disease or serum creatinine  $\geq$  1.5 mg/dL; 10) negative coronary angiography or CCTA within 6 months; 11) modified Wells criteria > 4; 12) any of the following symptoms or signs suggestive of aortic dissection<sup>11</sup> (i) chest pain with immediate onset, a tearing or ripping character, or both; ii) mediastinal widening, aortic widening, or both on chest radiography; iii) pulse

**Table 1.** HR control protocols

Facility	Oral beta-blockers dosing regimen	Intravenous beta-blockers dosing regimen
Site 1	Bisoprolol tablet HR > 90 bpm: 2.5 mg <sup>a)</sup>	Esmolol bolus over 1 minute HR 65–80 bpm: 1 mg/kg HR > 80 bpm: 2 mg/kg (up to 3 times or 3 mg/kg)
Site 2	Oral metoprolol tablet HR 65–70 bpm: 50 mg HR > 70 bpm: 100 mg HR > 90 bpm or body weight > 90 kg: consider 150 mg	Esmolol bolus over 1 minute HR 65–70 bpm: 0.5 mg/kg $\times$ 0.7 HR 70–90 bpm: 0.5 mg/kg HR > 90 bpm: 0.5 mg/kg $\times$ 1.3 (up to 3 times or 2 mg/kg)
Site 3	Same as site 2	Same as site 2

HR, heart rate.

<sup>a)</sup>Patients with heart rate > 65 and  $\leq$  90 bpm are administered with intravenous esmolol in computed tomography room if required.

differentials, blood pressure differentials, or both); 13) D-dimer > 0.5  $\mu$ g/mL.

### Interventions

#### *Patient preparation*

Eligible patients signing informed consent are provided with a colored wrist band for better recognition by researchers and ED/radiology staff. As prospective ECG triggering requires rather strict control of heart rate (HR),<sup>15,16</sup> patients with a HR greater than 65 beats per minute measured at the time of enrollment undergo HR control using beta blockers. These protocols are described in Table 1 in detail. The researchers can use either oral beta antagonist (bisoprolol at site 1, metoprolol at sites 2 and 3) or intravenous (IV) bolus esmolol injection. Oral beta-antagonists are administered just after enrollment while IV esmolol bolus is administered right before CT imaging. If IV beta-antagonist administration does not reach the target HR (< 65), additional boluses can be administered at the discretion of treating physicians. Study participants are assigned to either low-dose or conventional CCTA protocol in the CT room by opening the next sealed, opaque envelope containing the assignment of a patient.

#### *CT protocols and image interpretation*

The detailed description of the imaging protocol is in Table 2. Basically, the patients assigned to low-dose CCTA undergo prospective ECG triggering cardiac CT with limited scan range from sub-carina to the heart base. The patients assigned to conventional CCTA undergo retrospective ECG-gating cardiac CT with tubecurrent modulation covering the entire chest.

Image interpretation is provided by cardiac imaging specialists. The distribution, severity and characteristics of observed coronary lesions and other clinically relevant non-coronary abnormalities are reported if there are any.

**Table 2.** Cardiac computed tomography angiography protocols

Protocol	Gating	Scan range	Heart motion assessment	Estimated radiation dose
Conventional CCTA	Retrospective <sup>a)</sup>	Clavicle to heart base	Available	10 mSv
Low-dose CCTA	Prospective	Sub-carina to heart base	Not available	4.5 mSv

CCTA, cardiac computed tomography angiography.

<sup>a)</sup>With tube current modulation.

**Table 3.** High-risk image and clinical findings

High-risk image finding	High-risk clinical finding
Significant coronary artery stenosis ( $\geq 50\%$ )	Dynamic ST-T change
Regional wall motion abnormality <sup>a)</sup>	Increasing biomarkers
Perfusion defect	Ongoing chest pain or dyspnea
Non-coronary high-risk findings (e.g., pulmonary embolism, aortic dissection, pneumothorax, severe pneumonia)	Other high-risk findings (e.g., ventricular arrhythmia, high-degree block, syncope, desaturation or shock)

<sup>a)</sup>Regional wall motion assessment is only available in conventional protocol group.

### Disposition after the test

Patient ED disposition is determined by both CT findings and clinical progression in ED. Basically, patients with no high-risk findings in their CCTA images as defined in Table 3 are discharged with short-term (1-week) cardiology out-patient department follow-up visit. However, if a false negative result is suspected because of the presence of any high risk clinical features such as dynamic ECG changes, increasing biomarkers, ongoing chest pain/dyspnea or other clinically worrisome findings, the treating physician can delay or hold discharge for further evaluation. Disposition of patients with positive or equivocal CCTA test result is determined by the treating emergency physicians and/or cardiology consultant.

### Data collection

Baseline characteristics including demographic information, thrombolysis in myocardial infarction risk score, Canadian Cardiovascular Society angina grading scale and Killip class are collected at the time of enrollment. Similarly, the results of serial ECGs and cardiac biomarker tests (creatinine kinase-MB and troponin I) as well as CCTA imaging are also collected as soon as their results are reported. The clinical course during the first month after discharge is assessed from the patients or their surrogates via a telephone interview. They are asked about whether there were additional functional or imaging tests (e.g., treadmill test, myocardial perfusion imaging, cardiac positron emission tomography, invasive coronary angiography), unstable angina, myocardial infarction, cardiac arrest, hospital admission or revascularization. If there were any, detailed descriptions of the event(s) are obtained from the contacted person and the hospital(s) involved. If the patients or their surrogates could not be contacted, hospitals located nearby the house of the patient are asked whether the patient visited them for any related problems. In cases where all the above mea-

asures fail, the Korean National Statistical Office is contacted whether the patient was reported to be deceased.

### Outcomes

The primary objective of this trial is to determine whether the chance of having a hard event (myocardial infarction or death) within the first month after negative low-dose CCTA result is less than 1%. The secondary objectives are to compare the diagnostic accuracy, incidence of major adverse cardiac events within one month after discharge, overall radiation exposure, ED length of stay and overall cost between the two groups.

### Sample size

The primary endpoint of this study is to test the hypothesis that the chance of having a hard event within one month after negative CCTA is less than 1%. Based on the pooled results of previous studies, we assumed that the chance of having a hard event in patients without significant ( $\geq 50\%$ ) coronary stenosis is about 0.576<sup>4,17,18</sup> per one thousand and therefore we estimated that at least 387 patients with negative test results are required for a statistical power of 0.80 to prove the hypothesis with a one-sided test at a 0.05 significance level. If a 10% prevalence of patients with significant stenosis on the test<sup>7</sup> and a 5% attrition rate, 454 patients are required in the low-dose CCTA arm. An additional 227 patients (2:1 allocation) for the conventional CT group make the total size of the study population 681 patients.

### Randomization

Participants will be randomly allocated to either low-dose or conventional CCTA protocol in a 2:1 ratio. The randomization procedure is confidential. Each study participant is allocated to either low-dose or conventional CCTA protocol in the CT room by open-

ing the next sequential sealed opaque envelope containing the next assignment. The randomization process and the preparation and distribution of the sealed envelopes were done at site 2. This is a single blind study in which only participating patients are blinded to their assigned protocol. This is because of the obvious difference in scan range which makes it impossible to blind the treating physicians and radiologists to the allocation.

### Statistical methods

The primary hypothesis will be accepted if the upper bound of the one-sided 95% confidence interval of false negative rate lies below the predetermined safety margin of 1% missing rate. For secondary outcomes, both intention-to-treat analysis and additional per-protocol analysis will be carried out. Student's t-test, Mann-Whitney U-test, chi-square test, and Fisher's exact test will be performed for comparisons as appropriate for the nature of the variables being compared. P-values < 0.05 will be considered significant. All analyses will be performed using STATA ver. 12 (Stata Corp., College Station, TX, USA).

## DISCUSSION

Radiation exposure from CCTA can be reduced by altering one of three elements; exposure duration, scan range and radiation density. Our low-dose protocol using prospective gating and limited scan range can minimize the exposure duration and scan range. However, these modifications have their own requirements or shortcomings which might impede their nationwide implementation. To facilitate the process, the following interventions can be applied.

### Development of a dedicated heart rate control protocol

Prospective gating requires strict control of heart rate and its variability.<sup>15</sup> Therefore a quick and simple but effective heart rate control protocol that can be readily adopted in chaotic ED is essential. We reviewed previous studies<sup>19-25</sup> and prepared heart rate control protocols based on both oral beta-antagonist and IV esmolol bolus administration at the beginning of the study. If a patient has sufficient physiologic reserve to compensate for the prolonged beta-blocking effect, oral beta-antagonist (with additional IV esmolol bolus if required) is a great option because of its simplicity. However, if a patient has limited physiologic reserve and prolonged beta-blockade needs to be avoided, IV esmolol which has ultra-short acting properties should be used instead with proper monitoring. In this study, the researchers can choose either of the approaches as most of the patients eligible for this study would have preserved cardiac function.

### Clinical exclusion of pulmonary embolism and aortic dissection

ACS is not the only source of acute chest pain which can lead to serious consequences. One of the great advantages of CCTA is its ability to rule out dangerous non-coronary etiologies of chest pain such as aortic dissection and pulmonary embolism. Though low-dose CCTA protocol does cover the thorax under carina, there is a possibility of missed aortic dissection or pulmonary embolism. Therefore, patients with an unlikely clinical probability of pulmonary embolism and a normal D-dimer level are included in this study.<sup>10</sup> As for aortic dissection, though helpful, both low clinical probability and normal D-dimer level cannot reliably rule out the condition.<sup>11,14</sup> Our rationale was that though the low-dose CCTA is not perfect, the chance of having a false negative result would be minuscule as the prevalence of aortic dissection confined to the aortic arch should be very low.<sup>26</sup>

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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## REFERENCES

1. Owens PL, Barrett ML, Gibson TB, Andrews RM, Weinick RM, Mutter RL. Emergency department care in the United States: a profile of national data sources. *Ann Emerg Med* 2010;56: 150-65.
2. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Cardiovasc Comput Tomogr* 2010;4:407.e1-33.
3. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT

- (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol* 2011;58:1414-22.
4. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med* 2012;366:1393-403.
  5. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA* 2007;298:317-23.
  6. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000;342:1163-70.
  7. Hoffmann U, Bamberg F, Chae CU, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol* 2009;53:1642-50.
  8. Hausleiter J, Meyer T, Hermann F, et al. Estimated radiation dose associated with cardiac CT angiography. *JAMA* 2009;301:500-7.
  9. Takakuwa KM, Halpern EJ, Gingold EL, Levin DC, Shofer FS. Radiation dose in a "triple rule-out" coronary CT angiography protocol of emergency department patients using 64-MDCT: the impact of ECG-based tube current modulation on age, sex, and body mass index. *AJR Am J Roentgenol* 2009;192:866-72.
  10. van Belle A, Buller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006;295:172-9.
  11. von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. *Arch Intern Med* 2000;160:2977-82.
  12. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med* 2004;140:589-602.
  13. Brown MD, Newman DH. Evidence-based emergency medicine. Can a negative D-dimer result rule out acute aortic dissection? *Ann Emerg Med* 2011;58:375-6.
  14. Shimony A, Filion KB, Mottillo S, Dourian T, Eisenberg MJ. Meta-analysis of usefulness of d-dimer to diagnose acute aortic dissection. *Am J Cardiol* 2011;107:1227-34.
  15. Earls JP, Schrack EC. Prospectively gated low-dose CCTA: 24 months experience in more than 2,000 clinical cases. *Int J Cardiovasc Imaging* 2009;25(Suppl 2):177.
  16. Sun Z, Choo GH, Ng KH. Coronary CT angiography: current status and continuing challenges. *Br J Radiol* 2012;85:495-510.
  17. Hollander JE, Chang AM, Shofer FS, McCusker CM, Baxt WG, Litt HI. Coronary computed tomographic angiography for rapid discharge of low-risk patients with potential acute coronary syndromes. *Ann Emerg Med* 2009;53:295-304.
  18. Hollander JE, Chang AM, Shofer FS, et al. One-year outcomes following coronary computerized tomographic angiography for evaluation of emergency department patients with potential acute coronary syndrome. *Acad Emerg Med* 2009;16:693-8.
  19. Jimenez-Juan L, Nguyen ET, Wintersperger BJ, et al. Failed heart rate control with oral metoprolol prior to coronary CT angiography: effect of additional intravenous metoprolol on heart rate, image quality and radiation dose. *Int J Cardiovasc Imaging* 2013;29:199-206.
  20. Mahabadi AA, Achenbach S, Burgstahler C, et al. Safety, efficacy, and indications of beta-adrenergic receptor blockade to reduce heart rate prior to coronary CT angiography. *Radiology* 2010;257:614-23.
  21. Maffei E, Palumbo AA, Martini C, et al. "In-house" pharmacological management for computed tomography coronary angiography: heart rate reduction, timing and safety of different drugs used during patient preparation. *Eur Radiol* 2009;19:2931-40.
  22. Roberts WT, Wright AR, Timmis JB, Timmis AD. Safety and efficacy of a rate control protocol for cardiac CT. *Br J Radiol* 2009;82:267-71.
  23. Shapiro MD, Pena AJ, Nichols JH, et al. Efficacy of pre-scan beta-blockade and impact of heart rate on image quality in patients undergoing coronary multidetector computed tomography angiography. *Eur J Radiol* 2008;66:37-41.
  24. Pannu HK, Sullivan C, Lai S, Fishman EK. Evaluation of the effectiveness of oral beta-blockade in patients for coronary computed tomographic angiography. *J Comput Assist Tomogr* 2008;32:247-51.
  25. Degertekin M, Gemici G, Kaya Z, et al. Safety and efficacy of patient preparation with intravenous esmolol before 64-slice computed tomography coronary angiography. *Coron Artery Dis* 2008;19:33-6.
  26. Tsai TT, Isselbacher EM, Trimarchi S, et al. Acute type B aortic dissection: does aortic arch involvement affect management and outcomes? Insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 2007;116(11 Suppl):I150-6.