PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Combination of Anatomical and Functional Evaluations Improves the Prediction of Cardiac Event in Coronary Artery Bypass Patients
AUTHORS	Kawai, Hideki; Sarai, Masayoshi; Motoyama, Sadako; Ito, Hajime; Takada, Kayoko; Harigaya, Hiroto; Takahashi, Hiroshi; Hashimoto, Shuji; Takagi, Yasushi; Ando, Motomi; Anno, Hirofumi; Ishii, Junichi; Murohara, Toyoaki; Ozaki, Yukio

VERSION 1 - REVIEW

REVIEWER	Benjamin Chow, MD Associate Professor of Medicine and Radiology Univeristy of Ottawa Heart Institute Canada
REVIEW RETURNED	20-Jul-2013

THE STUDY	The authors study 204 patients who underwent both CT coronary angiography and myocardial perfusion imaging in patients with coronary artery bypass grafts. They determine that both UCT and SSS scores are independent and incremental measures of patient outcome. Comments: The authors use a composite endpoint comprising of cardiac death, non-fatal MI, unstable angina requiring revascularization, and heart failure hospitalization. Many would consider unstable angina requiring revascularization or heart failure hospitalization as softer endpoints. As an example, when a patient has been told there have CAD, they are more likely to subsequent present with symptoms potentially necessitating admission and revascularization. The authors should consider redoing their entire analysis using cardiac death and non-fatal MI. Or at least as a subanalysis. Can he authors also explain why heart failure requiring admission is an important endpoint? In the methods section, they define unstable angina described as acute chest pain with or without ECG changes negative cardiac enzymes. Can they please further define whether or not these are in-patients or out-patients? For example, a patient presenting to an out-patient clinic with new chest pain and subsequently undergoes revascularization one month after clinic visit could fall under unstable angina? Patient population. Please confirm that this is a retrospective analysis. I am concerned that since that this is a retrospective analysis, that patients undergoing SPECT or CTA had the second test for clinical reasons. For example, why did some SPECT patients have a CT angiogram after the SPECT and vice

	versa? Could this bias the results? Is the population biased? It would be important to disclose the percentage or proportion of individuals who underwent SPECT first versus CTA first. The description of the Stress/Rest Myocardial Perfusion image acquisition is inadequate and requires more detail. Please proof read the entire manuscript for both spelling and English style. The authors both have references regarding the prognostic value of CT Angio. I notice that reference #5 does not use contemporary CT scan technology. I suggest that they reference other prognostic studies such as Min et al JACC 2011 (CONFIRM Registry), Chow et al. JACC 2010 (Large single centre 64-slice CT). Page 8 line 42, the authors should review the technical wording such as “retrospective triggering”. It should be “retrospective gating”. The entire manuscript should be re-read for style and grammar.

REVIEWER	Todd C. Villines, MD, FACC, FSCCT, FACP Walter Reed National Military Medical Center Co-Director, Cardiac CT Program Director, Cardiovascular Research Program Director, Cardiology Fellowship Program Associate Professor of Medicine, USUHS
REVIEW RETURNED	31-Jul-2013

THE STUDY	The authors should more fully describe the patients included in this analysis (e.g., % with heart failure and scan/study indications), as stated in my response to the authors.
GENERAL COMMENTS	Dr. Kawai and colleagues have conducted a very interesting analysis reporting the incremental prognostic usefulness of coronary CTA and myocardial perfusion imaging (MPI) in patients with prior coronary artery bypass graft (CABG) surgery. Specifically, the authors demonstrate that the severity of residual coronary artery disease, measured as unprotected coronary territories (UCT) based on native and graft stenosis severity on CTA, and perfusion abnormality severity as measured by SSS, each had independent prognostic value beyond standard clinical risk variables. Interestingly, but perhaps not surprisingly, the combination of anatomic (CTA) and functional information from MPS had the best prognostic value. The paper is interesting as there is little data integrating anatomic and functional non-invasive testing results for prognosis in patients who are post-CABG. The limitations, however, are the relatively small number of patients studied (204) resulting in a small number of events (27), of which nearly half (12 events) were composed of admission for heart failure, a “soft” endpoint, particularly considering the significantly lower LV ejection fraction among patients with subsequent events. Further, the patients do not directly measure the degree of infarct on MPS. In addition, use of appropriate medical treatment was not ascertained. I have the following questions/comments for the authors:

	1. Abstract a. The stenosis severity cut-off to define a UCT should be stated in the abstract. b. It is unfortunate that the authors included hospitalization for heart failure. I would be more favorable to this endpoint if it were incident heart failure and not an admission in a patient with known recurrent episodes of heart failure. 2. Methods a. The authors should explain the use of the EuroSCORE II as their measure of clinical risk in these patients, particularly as this is not a preoperative cohort. If patients were being evaluated for pending surgery, this should be documented and considered when assessing subsequent events (? Perioperative events). b. Recommend using the term “retrospective gating”; reserve “triggering” for prospectively triggered acquisitions. c. The term “segmented reconstruction” should be clarified. Do the authors mean multi-segmented reconstruction (using data from multiple cardiac cycles to improve temporal resolution)? d. The dose of nitroglycerin should be stated. e. The precise definition of a UCT should be stated more clearly in the methods. f. Did the authors report on MPS areas of fixed perfusion defects (presumed scar or hibernating myocardium)? g. I recommend that the authors state, briefly, the rationale for excluding patients undergoing early revascularization. 3. Results a. The number of non-evaluable segments should be delineated for the reader, particularly since the expected number of non-evaluable segments is suspected to be relatively high in this population using CTA AND given that such segments were considered severely diseased. b. I am curious as to the “correspondence rate” of abnormal perfusion in the distribution of UCT. c. Table 1: recommend avoiding the abbreviation “OMI” as this is not a standard abbreviation. d. The authors should also report in Table 1 the proportion of patients with prior diagnosis of heart failure, particularly as this is a part of the composite endpoint. e. The mean SSS, any further MPS details (% w/scar/fixed defects), % uninterpretable segments on CTA, % with left main, 3v CAD, graft stenosis should be reported, as should be the general indications for the scans (summary) given the retrospective nature of the study.

	f. I recommend reporting the individual components of the primary outcome within Table 2a. g. Recommend listing the numbers at risk below the Kaplan-Meier figures. 4. Discussion a. I recommend adding the following points to the limitations section: small number of “hard” events during follow-up (inclusion of heart failure), lack of data regarding appropriateness of medical therapy which may have influenced results.

VERSION 1 – AUTHOR RESPONSE

In Response to Reviewer: Dr. Benjamin Chow, MD
Associate Professor of Medicine and Radiology
Univeristy of Ottawa Heart Institute
Canada

>The authors should consider redoing their entire analysis using cardiac death and non-fatal MI. Or at least as a subanalysis. Can he authors also explain why heart failure requiring admission is an important endpoint?

We analysed again using cardiac death and non-fatal MI as hard event. At follow-up, hard events were observed in 10 patients. In the univariate Cox analysis, UCT and SSS were the only two predictors for hard events (HR: 2.58; 95% CI: 1.27 to 5.21; p=0.0099 and HR: 1.09; 95% CI: 1.03 to 1.16; p=0.0032, respectively), though LVEF, time since CABG, and EuroSCORE Ⅱ were not significant predictors of hard events. Using ROC analysis, the cut-off levels were determined as 1 for UCT [area under curve (AUC) = 0.72] and 4 for SSS (AUC = 0.72), respectively. We divided all patients into 4 groups. Cox hazard analysis showed that patients in Group D (UCT; ≥1, SSS ≥4) were at higher risk than patients Group A (log rank p=0.0313), but we did not show the additive value of each examination statistically, perhaps due to the sample size. In summary, to predict hard events (cardiac death and non-fatal MI), the combination of each examination is useful. To predict cardiac events, the advantages of each imaging examination complement the limitations of the other.
We think that heart failure admission is one of important endpoints and some studies regarded it as main endpoint1). Among the patients with low ejection fraction (EF), heart failure admission is one of the problems to solve. Significantly, we demonstrated that the combination of CTA and MPI improved the cardiac events prediction of the clinical model including EF.

1) Abel E. Moreyra, et al. Incidence and trends of heart failure admissions after coronary artery bypass grafting surgery. European Journal of Heart Failure (2013) 15, 46–53

>In the methods section, they define unstable angina described as acute chest pain with or without ECG changes negative cardiac enzymes. Can they please further define whether or not these are in-patients or out-patients? For example, a patient presenting to an out-patient clinic with new chest pain and subsequently undergoes revascularization one month after clinic visit could fall under unstable angina?

We defined unstable angina according to the European Society of Cardiology guidelines as acute chest pain with or without the presence of ECG abnormalities 1). We always use the same definition2). Similarly on the latest guidelines, non-ST-elevation ACS is qualified to as NSTEMI or

unstable angina based on the measurement of troponins3).

1) Bassamd JP, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007; 28: 1598 – 1660.
2) Motoyama S, Kawai H, et al. Morphologic and functional assessment of coronary artery disease--potential application of computed tomography angiography and myocardial perfusion imaging. Circ J. 2013; 77(2):411-7.
3) Christian W. Hamm, et al. Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2011; 32: 2999 – 3054.

>Patient population. Please confirm that this is a retrospective analysis. I am concerned that since that this is a retrospective analysis, that patients undergoing SPECT or CTA had the second test for clinical reasons. For example, why did some SPECT patients have a CT angiogram after the SPECT and vice versa? Could this bias the results? Is the population biased? It would be important to disclose the percentage or proportion of individuals who underwent SPECT first versus CTA first.

This was a retrospective study. Previously, Takagi Y, et al. (my colleague) reported the assessment of internal thoracic artery using CT and MPI4). In our hospital, for the purpose of research using non-invasive imaging, we perform CTA and MPI routinely. So we do not afraid of the population bias. Actually, 92 patients underwent CTA first, 110 patients underwent SPECT first, and 2 patients underwent on the same day.

4) Takagi Y, et al. Non-invasive Evaluation of Internal Thoracic Artery Anastomosed to the Left Anterior Descending Artery with 320-Detector Row Computed Tomography and Adenosine Thallium-201 Myocardial Perfusion Scintigraphy. Ann Thorac Cardiovasc Surg. 2012; 18(1):24-30.

>The description of the Stress/Rest Myocardial Perfusion image acquisition is inadequate and requires more detail.

In line with your suggestion, I revised.
“Early single photon emission tomography (SPECT) was performed 10 min after the adenosine stress test; late SPECT was performed 4 h thereafter. SPECT images were acquired using a dual-headed SPECT gamma camera (ADAC VERTEX-plus; EPIC, USA). Tomographic reconstruction was performed using a standard filtered back-projection technique with a ramp filter to produce a transaxial tomogram. No scatter or attenuation correction was applied. From these transaxial tomograms, the long axis of the left ventricle was identified, and oblique-angled tomograms were generated (i.e., vertical long-axis, short-axis, and horizontal long-axis tomograms).”

>The authors both have references regarding the prognostic value of CT Angio. I notice that reference #5 does not use contemporary CT scan technology. I suggest that they reference other prognostic studies such as Min et al JACC 2011 (CONFIRM Registry), Chow et al. JACC 2010 (Large single centre 64-slice CT).

In line with your suggestion, I changed the #5 reference to “Chow et al. JACC 2010”.

>Page 8 line 42, the authors should review the technical wording such as “retrospective triggering”. It should be “retrospective gating”.

In line with your suggestion, I changed the word.

In Response to Reviewer: Todd C. Villines, MD, FACC, FSCCT, FACP
Walter Reed National Military Medical Center
Co-Director, Cardiac CT Program
Director, Cardiovascular Research
Program Director, Cardiology Fellowship Program

Associate Professor of Medicine, USUHS

>1. Abstract

>a. >The stenosis severity cut-off to define a UCT should be stated in the abstract.

In line with your suggestion, I added it.
“CTA defined unprotected coronary territories (UCT) (0, 1, 2, or 3) by evaluating the number of significant stenoses which were defined as left main trunk ≥50% diameter stenosis, other native vessel stenosis ≥70%, or graft stenosis ≥70%.”

>b. >It is unfortunate that the authors included hospitalization for heart failure. I would be more favorable to this endpoint if it were incident heart failure and not an admission in a patient with known recurrent episodes of heart failure.

Of 204 patients, 17 patients had a history of heart failure before CTA and MPI exams. Of the 17 patients, only 3 patients had recurrent heart failure. Of the 12 patients occurring heart failure after both examinations, new onset heart failure occurred in 9 patients.

>2. Methods

>a. >The authors should explain the use of the EuroSCORE II as their measure of clinical risk in these patients, particularly as this is not a preoperative cohort. If patients were being evaluated for pending surgery, this should be documented and considered when assessing subsequent events (? Perioperative events).

Before we discuss the future cardiac event risk of CABG patients by imaging modalities, we determined the preoperative risk assessment of these patients. Previous MI, single or multi-vessel disease, combined heart disease, CKD, DM, age, gender are determined critical factor to calculate EuroSCORE II which could assess the risk of cardiac surgery. If there might be some differences of EuroSCORE II, the result and prognosis would be different from masked postoperative assessment for these patients. Actually EuroSCORE II was one of the predictive factors in univariate analysis, so we used it as one of predictors in multivariate analysis.

>b. >Recommend using the term “retrospective gating”; reserve “triggering” for prospectively triggered acquisitions.

In line with your suggestion, I changed the word.

>c. >The term “segmented reconstruction” should be clarified. Do the authors mean multi-segmented reconstruction (using data from multiple cardiac cycles to improve temporal resolution)?

Yes, we do.

>d. The dose of nitroglycerin should be stated.

I added the next sentence.
“Isosorbide dinitrate spray 1.25mg was provided immediately before CCTA.”

>e. >The precise definition of a UCT should be stated more clearly in the methods.

Patients were categorized according to the number (0, 1, 2, or 3) of unprotected coronary territories (UCTs). Each patient had 3 coronary territories, corresponding to each major epicardial artery (left anterior descending artery, circumflex artery or artery supplying the posterior descending artery [right coronary artery or circumflex artery]) and their corresponding branches (diagonal and marginal arteries). A coronary territory was deemed unprotected if: 1) an ungrafted native coronary artery had a significant stenosis; 2) a significant stenosis in the native artery was distal to the graft insertion; or 3) a native artery and its graft both had significant stenoses.

>f. >Did the authors report on MPS areas of fixed perfusion defects (presumed scar or hibernating myocardium)?

Yes, we report on the SSS, including ischemia, scar, and hibernating area.

>g. >I recommend that the authors state, briefly, the rationale for excluding pat>ients undergoing early revascularization.

I added next phrase in the result. “Four patients undergoing early revascularization were excluded because we could not study their natural histories after examination.”

>3. Results

>a. >The number of non-evaluable segments should be delineated for the reader, particularly since the expected number of non-evaluable segments is suspected to be relatively high in this population using CTA AND given that such segments were considered severely diseased.

Twenty-six native coronary artery segments (10 RCA, 7 LMT, 4 LAD, 5 Cx) were non-evaluable due to severe calcification or implanted stents. Two coronary artery segments (1 RCA, 1 Cx) and 2 grafts (1 SVG to RCA, 1 LITA-LAD) were non-evaluable due to artifact.

>b. I am curious as to the “correspondence rate” of abnormal perfusion in the distribution of UCT.

Of 99 patients with abnormal perfusion, 51 patients had abnormal but 48 patients had normal UCT.

>c. Table 1: recommend avoiding the abbreviation “OMI” as this is not a standard abbreviation.

I changed old myocardial infarction (OMI) to prior myocardial infarction (PMI).

>d. The authors should also report in Table 1 the proportion of patients with prior diagnosis of heart failure, particularly as this is a part of the composite endpoint.

In line with your suggestion, I added “prior heart failure” in Table 1.

>e. The mean SSS, any further MPS details (% w/scar/fixed defects), % uninterpretable segments on CTA, % with left main, 3v CAD, graft stenosis should be reported, as should be the general indications for the scans (summary) given the retrospective nature of the study.

I described about not only “SSS”, but also “SRS” and “SDS” in the result.
Mean SSS, SRS, and SDS were 7.03±8.65, 5.21±7.70, and 1.82±3.23, respectively.
Mean % fixed defects was 10.3% (7/68).

Mean UCT was 0.51±0.72, and % uninterpretable segments on CTA were 0.4% (2/507), 7.37% (7/95), 3.61% (21/582) in grafts, LMT, and other coronary artery segment, respectively.

>f. I recommend reporting the individual components of the primary outcome within Table 2a.

I added next data in Table 2a.
UCT=0 n=8 MI 3, HF 5
UCT≥1 n=19 cardiac death 3, MI 6, late revascularization 3, HF 7
SSS<4 n=4 MI 3, late revascularization 1
SSS≥4 n=23 cardiac death 3, MI 6, late revascularization 2, HF 12

>g. Recommend listing the numbers at risk below the Kaplan-Meier figures.

I modified figures.

>4. Discussion

>a. >I recommend adding the following points to the limitations section: small number of “hard” events during follow-up (inclusion of heart failure), lack of data regarding appropriateness of medical therapy which may have influenced results.

I commented about small number of hard events and lack of the data about medical therapy in the follow-up.

VERSION 2 – REVIEW

REVIEWER	Benjamin Chow University of Ottawa Heart Institute Canada No competing interests
REVIEW RETURNED	15-Aug-2013

THE STUDY	I am still concerned that they used U/A as an outcome measure. This can be an extremely subjective criteria and is the main limitation of the manuscript.
RESULTS & CONCLUSIONS	The reserach answers their 'research question', but the outcome measures used to answer the question are on the 'soft' side.