Predictive Value of Coronary CT Angiography and Calcium Scoring for Coronary Artery Problems and Adverse Cardiac Events in Low-risk Chest Pain Patients

Aref Albakri, Giso Frhr.von der Recke, Heyder Omran

ABSTRACT

Background: Current evidence supporting the predictive value of coronary artery calcium scores (CACs) and coronary computed tomography angiography (CCTA) for adverse cardiac events in low-risk CAD patients is based on short follow-up periods. However, a long latency between the onset of coronary artery disease (CAD) and the occurrence of adverse events warrants longer follow-up periods. **Methods:** We reported our experience on the predictive power of CACs and CCTA for cardiac deaths and hospitalization in low risk chest pain patients followed for five years. In total, we enrolled 346 patients (mean age=62.07: male=53%) presenting with chest pain, no prior CAD on CCTA and negative to low CACs. The primary endpoint was cardiac death and hospitalization for cardiac causes. **Results:** During follow-up, six patients died due to non-cardiac causes (old age, cancer or stroke) and excluded from analysis (person-time follow-up rate=99.13%). In the remaining 340, none achieved the primary endpoint. There were no reported cases of cardiac deaths or hospitalization for cardiac causes (event rate = 0%). All patients were free of coronary artery problems. **Conclusion:** In low-risk chest patients, CACs and CCTA is an excellent predictor for up to five year event-free CAD, cardiac death and hospitalization for cardiac causes.

Key Words: Coronary Computed Tomography Angiography (CCTA), Coronary artery calcium scores (CACs), coronary artery disease (CAD)

Aref Albakri, Giso Frhr.von der Recke, Heyder Omran

St-Marien hospital Bonn Venusberg, department of internal medicine, Bonn, Germany

Correspondence

Aref Albakri

St-Marien hospital Bonn Venusberg, department of internal medicine, Bonn, Germany

E-mail: arefalbakri@yahoo.com

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INTRODUCTION

Chest pain is a frequent complaint of patients presenting to the emergency department usually suggesting an underlying acute coronary syndrome (requiring prompt intervention and treatment), coronary artery disease (CAD) or other non-life threatening conditions **(Sharp, Broder & Sun 2018)**. In these patients, the challenge has been to identify those at low-risk of adverse cardiac events to institute appropriate prophylactic therapy. The Framingham risk score (a population-based risk factor model) is a widely used tool for coronary risk stratification on individual patients but it has limited ability in discriminating those who will or will not experience CAD **(DPCG 2002)**. To improve risk prediction, one of the recommended approach is non-invasive imaging using coronary computed tomography angiography (CCTA), which directly visualizes and quantifies atherosclerotic plaque burden providing a more individualized risk assessment compared to population-based risk factor models **(Budoff et al. 2008; Staniak et al. 2014)**.

Coronary CTA without contrast agent allows calculation of coronary artery calcium scores (CACs) to quantify the presence and extent of calcified plaque while CCTA with contrast agent allows discrimination between calcified and non-calcified plaque as well as detection of the presence, extent and severity of coronary stenosis **(Abdulla et al. 2007; Arbab-Zadeh & Hoe 2011; Kolossvary et al. 2017).** However, the predictive value of CACs and CCTA have been limited to short-to-intermediate term studies with a mean follow-up of two years **(Gruettner et al. 2013; Hadamitzky et al. 2013).** This period is too short to evaluate atherosclerotic disease progression due to a long latency between the onset of CAD and the occurrence of cardiac events **(Hadamitzky et al. 2013)**. The objective of this study is to evaluate the predictive value of CACs and CCTA for adverse cardiac events defined as the presence of CAD, cardiac deaths or hospitalization for cardiac causes in low-risk chest pain patients followed-up for an extended follow-up period of five years.

MATERIALS AND METHODS

Patient Selection

This single-center prospective study enrolled consecutive patients with typical and atypical chest pains who underwent non-emergent CCTA as part of their diagnostic workup at our hospital between October 2009 and December 2011. CCTA was performed to exclude patients with CAD. Patients were eligible if they were in stable sinus rhythm and had no contra-indication for iodinated contrast agents. Patients with intermediate CACs defined as Agatston Score 101-400 Hounsfield Units (HU) or high CACs (> 400 HU), with previous myocardial infarction (MI), a history of coronary

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revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]) were excluded. The local institutional review board approved the study protocol and written informed consent was obtained from all subjects prior to enrolment.

CCTA Procedure

All scans were performed using a 64-slice scanner (Lightspeed VR 64-MSCT, General Electrics, Milwaukee, WI, USA). Patients with a pre-scan heart rate greater than 65 beats per minute (bpm) received intravenous β-blocker therapy (metoprolol 5 mg incrementally up to 20 mg) to achieve a resting heart rate of less than 65 bpm. Whether or not a resting heart rate was achieved, all patients underwent scanning. After positioning patients on the scanner table, those with systolic blood pressure of at least 100 mmHg received sublingual nitroglycerin 0.8 mg to achieve coronary vasodilation. Initially, patients underwent non-enhanced electrocardiography (ECG)-gated scan to obtain CACs. Then, contrast timing was tested using a bolus of 10-20 ml contrast agent and 50 ml saline flush. Contrast enhanced scan was then obtained using 80-140 ml contrast agent and a scan range of 4-6 ml/s followed by 50 ml saline flush. Important scan parameters included rotation time 350 msec, collimation 64 x 0.625 mm, tube voltage 120 kV, and tube current 600 mA.

Image Interpretation

After image acquisition, a technician anonymized all patients' information on the image datasets. All scans were analyzed on a remote workstation (Vitrea 2, Vital images, USA, or Advantage, GE Healthcare, USA). Total calcium burden on the coronary vessel wall was quantified based on a standard built-in algorithm using an equivalent of the Agatston score adopted for the multi-slice CT scanner. The predefined CACs categories were (a) 0: negative; (b) 1-100: low; (c) 101-400: intermediate; and (d) > 400: high, as defined in the Heinz Nixdorf Recall study [10]. Two experienced readers evaluated each vessel segment and resolved any discrepancy by consensus. The degree of stenosis was visually classified as no relevant stenosis (< 25%), mild stenosis (25%-49%), moderate stenosis (50%-74%), and severe stenosis (≥ 75%).

Follow-up Data

The follow-up period was five years, up to April 2016. The follow-up rate was determined based on the Person-Time Follow-up Rate (PTFR) method developed by Xue et al. **(2017)** in which follow-up rate is calculated as observed person-time divided by total person-time assuming no dropouts. The clinical endpoint was adverse cardiac events, defined as cardiac death or hospitalization for cardiac causes. Cardiac death was defined as death due to MI, heart failure or cardiac arrhythmia. We collected data for adverse cardiac events through telephone interviews with patients or the next-of-kin for patients with out-of-hospital cardiac deaths, interviews with patient's physician, and hospital records. A standard questionnaire was administered in all patient interviews.

Statistical Analysis

We used the IBM SPSS software version 22 to analyze study data. Categorical data was expressed as numbers or percentage while continuous data as mean and standard deviation. Statistical evaluations were based on the number of events of primary endpoint and event-free survival for primary endpoint.

RESULTS

Study Population

In total, from October 2009 to December 2011, 1038 patients who presented with chest pains at our hospital gave written informed consent to the study protocol. At presentation, no patient had CAD (significant stenosis) on CCTA. Six hundred and ninety two (692) patients who had intermediate CACs (101-400 HU) to high CACs (> 400 HU) were excluded. The remaining 346 patients were finally enrolled in the study constituting 150 patients with negative CACs (0.00 HU) and 196 with low CACs (1-100 HU). Six patients were lost to follow-up (Figure 1), three in the second year and three in the third year. They were older (age range 86-93 years) and succumbed to cancer, stroke or old age. The follow-up rate based on the PTFR is 99.13%. The 340 patients whose results were analysed were older (mean age = 62.07 years) with

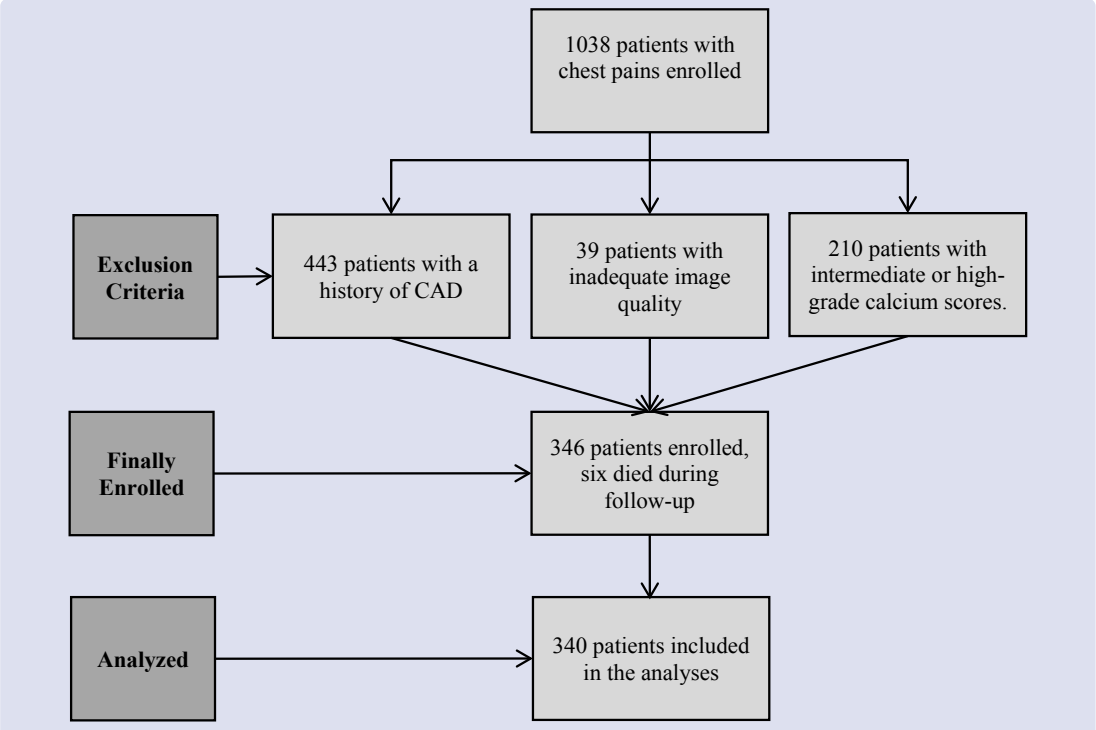

Figure 1: Flow Chart of Patient Selection

Table 1: Baseline Patient Characteristics

Patient Characteristics	Patient Population n=340 (%)
Mean Age	62.07
Male Sex	182 (53)
Smoking	111(32)
Diabetes	45(13)
Hypertension	169(49)
Family History of CAD	83(24)
Chest Pain: Typical Angina	141(41)
Atypical Angina	119(35)
Non-Anginal	80(24)

an almost proportional gender representation (male = 53%). Table 1 provides summary of baseline characteristics of the 340 patients.

Adverse Cardiac Events

In patients with chest pains with no known but suspected CAD, and negative to low CACs did not experience any case of cardiac deaths, hospitalization for cardiac causes and were free or coronary artery problems with an event rate of 0%. When the patients were assessed using the Framingham risk score, men had 10-14% and women 2-4% indicating a very low 10-year risk of developing coronary complications.

DISCUSSION

We undertook this study to describe our experience in the utility of CACs and CCTA for predicting cardiac death and hospitalization in low risk chest-pain patients. Our findings indicate patients with no CAD on CCTA assessment, and with negative to low CACs predict free of cardiac death and event free survival of hospitalization for cardiac causes for up to five years. Although six patients died due to non-cardiac causes (old age, stroke or cancer) during the follow-up period, none of the remaining 340 patients died due to cardiac causes or hospitalized for adverse cardiac events. The findings strongly indicate that negative to low CACs and absence of significant stenosis on CCTA offer an excellent negative predictive value for CAD and adverse cardiac events for an extended period of five years.

The value of CCA and/or CCTA in predicting cardiac events in patients with known or suspected CAD has been supported in previous studies. In the longest follow-up study, Gruettner et al. **(2013)** reports a 10-year event-free survival against cardiac death and nonfatal myocardial infarction on patients with normal coronary artery on baseline CCTA. The association between CACs and CCTA has been supported by reports of CACs having a statistically significant correlation with major adverse cardiac events **(Greenland et al. 2004; Plank et al. 2014; Shemesh et al. 2010)**. Negative CACs is associated with 1.2% cardiac deaths increasing to 5.0% and 5.3% for intermediate (101-400) and high (>400) CACs **(Greenland et al. 2004)**. CCTA also has an excellent negative predictive value (99.4%) of CCTA for composite end-points ST-elevation MI, non-ST-elevation MI and cardiac death **(Chang et al. 2011)**. However, while Chang et al. **(2011)** and Kwon et al. **(2011)** reported CACs has no incremental value compared with CCTA, the two studies had a shorter follow-up (30 –days) and included patients with CAD respectively.

Several other studies have reported incremental predictive value of CACs and CCTA to traditional population-based risk factor models. The use of CACs and CCTA has been demonstrated to provide additional prognostic information to that provided by population-based risk factors in asymptomatic patients without known or suspected CAD **(Shaw et al. 2003)**. In particular, direct quantification of the presence and extent of calcified plaque by CACs improves the predictive power of clinical risk factors from 0.71 to 0.82 and to 0.93 after adding CCTA **(Hou et al. 2012)** . CACs also refines risk stratification based on traditional risk factors by reclassifying 23% of individuals in the intermediate risk group to high risk and 13% to low risk **(Polonsky et al. 2010).** The Nuclear Cardiology and Cardiac CT of the European Society of Cardiology explains that CACs and CCTA improve risk stratification of CAD and adverse cardiac events by quantifying total atherosclerotic burden and discriminating between calcified and non-calcified plaque **(Perrone-Filardi et al. 2010).**

The negative predictive value of CACs and CCTA for MACE in chest-pain patients at low risk of CAD has important clinical implications. Chest pain is a frequent complaint in patients presenting to emergency department. The challenge is discriminating between at low- and at high-risk patients **(Lee & Goldman 2000; Perrone-Filardi et al. 2010**). The present findings shows that combined use of CACs and CCTA can provide an excellent negative predictive value for CAD and adverse cardiac events in low-risk chest pains for up to five years. Inclusion of CACs and CCTA can thus improve risk stratification and inform appropriate therapy. However, concurrent utility of CACs and CCTA in low-risk chest pain patients raises concerns of increased radiation exposure and cost of care. This creates the need to select patients who will benefit from assessment using both CACs and CCTA or either test alone to reduce the risk of radiation-induced cancer at an additional cost.

Study Limitations

This single center study enrolled patients with low-risk chest pains (no CAD on CCTA, and negative to low CACs). This inclusion criterion excludes patients with known CAD or patients with intermediate to high CACs and thus limits the applicability of the findings to these populations and to the general public. The second important limitation can be the use of patient interviews to gather follow-up data on cardiac death and hospitalization. Patient re-call limits the accuracy or completeness of data collected because of the inherent risk of recall bias (**Hadamitzky et al. 2013**) To validate the current findings or to generalize them to patients with known CAD or with intermediate to high CAD, a large multi-center study is warranted.

CONCLUSION

Non-invasive cardiac imaging using CACs and CCTA enables direct visualization and quantification of coronary atherosclerotic plaque. In patients with chest pains and no prior CAD, CCTA and negative to low CACs is an excellent predictor of five-year event-free survival for CAD and adverse cardiac events (cardiac death and hospitalization for cardiac causes). The inclusion of CACs and CCTA to the traditional population-based risk factors can potentially improve risk stratification of low-risk chest pain patients.

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