Coronary computed tomography angiography without significant stenosis predicts favourable three-year prognosis

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ORIGINAL ARTICLE

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ABSTRACT

INTRODUCTION: The objective of this study was to evaluate the incidence of death, cardiovascular events and the use of later non-scheduled imaging for coronary artery disease (CAD) in patients suspected for CAD and discharged without a need for further examination or treatment from an outpatient clinic following coronary computed tomography angiography (CCTA).

MATERIAL AND METHODS: This was a retrospective cohort study among patients discharged from an outpatient clinic after CCTA at our institution during 2009 and 2010. Follow-up was performed using nationwide Danish registers.

RESULTS: A total of 683 (68.2%) out of 1001 patients were discharged from the outpatient clinic after CCTA with no need for further examination. These patients were included in our study. After a median follow-up of 37 months, a low all-cause mortality of 3.7 per 1,000 person-years was found. There was only one case of acute myocardial infarction and no cases of death related to cardiovascular disease. A total of 5.0% of the patients later underwent non-scheduled imaging, predominantly invasive coronary angiography. No patients had revascularisation performed during the study period.

CONCLUSION: Patients with suspected CAD discharged after CCTA with no need for further examination have a favourable cardiovascular prognosis.

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Since its introduction, coronary computed tomography angiography (CCTA) has evolved to become a large-volume imaging modality in patients with suspected coronary artery disease (CAD). Consistently, CCTA has been shown to have a high sensitivity and a high negative predictive value compared with invasive coronary angiography (ICA) [1]. CCTA is often used in patients with a low to intermediate pretest probability of significant CAD. However, the specificity of CCTA is reported to be sub-optimal, and diagnostic performance is decreased if non-evaluable CCTAs are included in the analysis of diagnostic performance [2]. The diagnostic performance during implementation of this imaging modality at our institution has previously been validated with ICA as a reference [3]. Evidence on the prognostic value of CCTA is increasing [4]. Most importantly, the international CONFIRM registry has reported an annualised death rate of 0.28% among patients with normal CCTA findings [5]. The results from this registry also indicate that CCTA may predict future myocardial infarction and cardiovascular death. This is observed across ethnicities [6] and for patients without the chest pain syndrome [7]. Moreover, mortality may also be predicted by CCTA in diabetics [8]. The low incidence of cardiovascular events, including a low incidence of revascularisation after a normal CCTA, was confirmed in a study in a Danish hospital where revascularisation treatment was not an option and where the follow-up period was relatively short [9].

In the present study, we aimed to evaluate the consequences and prognosis in patients who were discharged from a university hospital following a normal CCTA and with no need for further examination, a situation most common encountered in daily clinical practice. The main objectives were to evaluate the incidence of cardiovascular events and the incidence of later non-scheduled imaging in these patients.

MATERIAL AND METHODS

The present study was a retrospective cohort study.

Patients

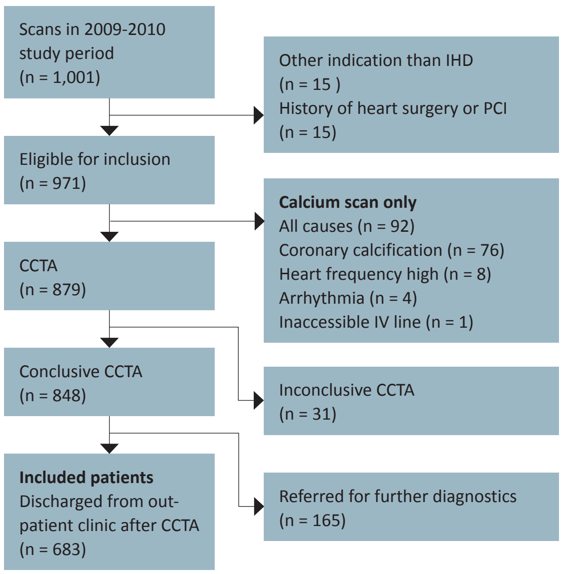
Patients who had a CCTA performed due to suspected CAD in the period from 1 January 2009 to 31 December 2010 were eligible for inclusion. In general, the subjects were not evaluated with exercise electrocardiography (ECG) or other stress modality before CCTA. Patients with a history of heart surgery, percutaneous coronary intervention (PCI) or acute myocardial infarction (MI) were excluded. Only patients who were discharged from the cardiology outpatient clinic following a full contrast enhanced scan were included in the present study.

Coronary computed tomography angiography and interpretation

CCTA was performed using a 64-slice dual source computed tomography scanner (GE Healthcare Lightspeed VCT, Milwaukee, USA). First, a calcium scan was ac-

FIGURE 1

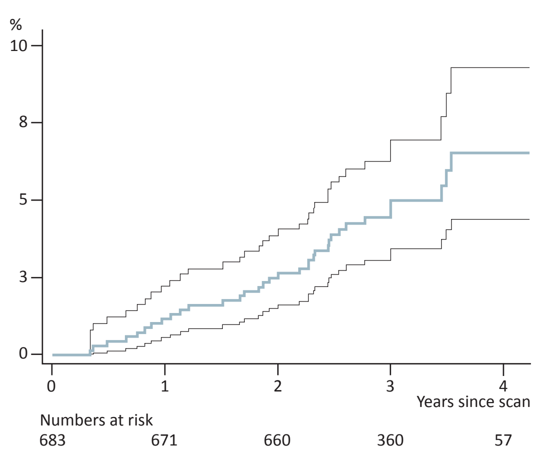
Patient selection flow chart.



CCTA = coronary computed tomography angiography; IHD = ischaemic heart disease; IV = intravenous; PCI = percutaneous coronary intervention.

FIGURE 2

Cumulative percentage incidence of first re-imaging for patients initially discharged from coronary computed tomography angiography. The cumulative incidence curve accounts for the competing risk of death and censoring caused by different follow-up times. 95% confidence interval has been added to the cumulative incidence curve.



quired and the Agatston score (coronary artery calcium score (CACS)) was calculated with the "SmartScore" software (GE Healthcare, Milwaukee, USA) [10]. The cardiologist could choose to stop the scan protocol after the initial calcium scan on the basis of an Agatston score > 400, as these patients were most likely referred for ICA because of their increased likelihood of significant coronary stenosis. The CCTAs were evaluated by one of three experienced senior cardiologists. The referral for further diagnostic imaging was done by the interpreting cardiologist on the basis of the patient's history and symptoms and the result of the CCTA.

Variables and outcomes

The following events were recorded as prognostic outcomes: Hospitalisation for acute myocardial infarction, all-cause mortality, cardiovascular-related death and revascularisation by PCI or coronary artery bypass grafting. Also additional non-scheduled diagnostic imaging such as ICA, exercise testing, perfusion imaging and re-CCTA were recorded.

Follow-up

All subjects were followed from the time of CCTA until 1 April 2013. Follow-up data regarding downstream testing, revascularisation therapy and hospitalisation for acute MI were obtained from the Danish National Patient Registry. Data regarding death and causes of death were obtained from the Civil Registration System and the Danish Cause of Death Register and from patient health records. The cause of death was determined independently and blinded by two experienced cardiologists on the basis of the above documentation. Referral and indication for re-imaging were clarified through patient files.

Statistics

Continuous data regarding body mass index (BMI), age and creatinine are presented as means ± standard deviations (SD). Comparisons were made using two-sided t-tests. Categorical data are presented as numbers (proportions) and analysed using Fisher's exact test. Rates are presented as events per 1,000 person-years and 95% confidence intervals were calculated.

Trial registration: not relevant.

RESULTS

CCTA was done in a total of 1,001 patients (**Figure 1**). A total of 683 (68.2%) patients were discharged from the outpatient clinic after CCTA without further examination and were included in the data analysis. Patient demographics and risk factors recorded on the day of CCTA are reported in **Table 1**. Data completeness after review in the individual patient health records for missing values were 99.5% for all variables except for creatinine (96%). In general, the subjects studied were middle-aged, more women than men, and with a moderate prevalence of hypertension, hypercholesterolaemia and positive familial histories of ischaemic heart disease

(Table 1). The total average estimated scan radiation exposure was 6.89 mSv (SD 4.2 mSv). A total of 435 subjects (64%) had an Agatston score of zero.

The patients were followed for a median period of 37 months (interquartile ranges 32-42 months). One case of non-fatal acute myocardial infarction (MI) was observed. A total of eight deaths were recorded during the follow-up period resulting in an all-cause mortality rate of 3.7 per 1,000 person years (95% confidence interval (CI) 1.6; 7.4 per 1,000 person years). Six deaths were due to cancer and one death was due to severe chronic obstructive pulmonary disease (COPD). One death could not be classified and therefore cardiovascular death cannot be ruled out.

During the follow-up, 22 patients (3.2%) underwent an ICA, five patients (0.7%) had a myocardial perfusion imaging and 11 patients (1.6%) had a new CCTA. Only one patient had an exercise ECG testing performed and this was as part of the myocardial perfusion imaging protocol. Four patients had more than one of these additional non-scheduled diagnostic imaging tests performed. Thus, a total of 34 patients (5.0%) underwent a new examination due to suspected CAD (**Figure 2**). This corresponds to an incidence rate of the first re-examination of 16.4 per 1,000 person-years (95% CI 11.6; 22.7 per 1,000 person-years). Of these, 15 patients were referred for re-imaging from their general practitioner, five from a specialized private cardiology clinic, three from regional hospitals and in one case no information on referral was available. A total of eight patients were referred from our own cardiology department, and of these five had a preceding acute admission with chest pain or dyspnoea. Another two cases of re-imaging were done pre-operatively. A total of 32 patients presented with suspected angina pectoris as the indication for the renewed examination. No patients had a revascularisation performed in the follow-up period.

Patients receiving re-imaging were older (59.0 versus 54.8 years; p = 0.0037) and had a higher BMI (28.1 versus 26.0 kg/m^2; p = 0.003). Other cardiovascular risk factors were quite equally distributed among the two groups (**Table 2**). The average CACS was higher among the patients receiving re-imaging with Agatston score (35.6 versus 22.5). The degree of coronary calcification, and consequently the Agatston score, is affected by age, sex and race. A high Agatston score at the index CCTA could be a possible predictor for repeated imaging. We therefore evaluated if the patient had a higher than median Agatston score for his or her age and sex. To do this, we used reference values for median coronary artery calcium scores from a large scale population-based unselected European cohort [11]. Patients younger than 45 years and older than 74 years were not included in the analysis because there was no reference value for the Agatston score for these age groups. This post-hoc analysis was done for 581 (83%) of the patients in the present study. Only two patients receiving re-imaging were not included in the analysis, both of whom were younger than 45 years and both had Agatston scores of zero. Only six out of 32 patients (19%) receiving re-imaging had an Agatston score higher than the median for their age and gender. This was not significantly different (p = 0.67) from the group that did not receive re-imaging in which 150 out of 549 (27%) patients had an Agatston score above the median for their age and gender.

DISCUSSION

In this cohort study of 683 patients discharged from the outpatient clinic after CCTA without a need for further examination, we found that patients had a good cardiovascular prognosis. During the median follow-up period of 37 months, these subjects had an overall mortality rate of 3.7 per 1,000 person-years. A total of 5.0% of the patients underwent re-evaluation with the use of imaging for suspected CAD, which again did not result in any revascularisation therapy.

In the 2013 European ESC guidelines, CCTA is recommended for ruling out coronary artery stenosis in patients with a low to intermediate pretest probability of CAD [12]. In the present observational study, CCTA was used as a frontline diagnostic tool for suspected CAD. The 683 patients who were discharged from the outpatient clinic experienced no revascularisation therapy and there was only one case of non-fatal MI.

For one case, the cause of death could not be clarified and, unfortunately, the patient was lost to follow-up.

TABLE 1

Patient baseline characteristics (N = 683).

Men, n (%)	226 (33)
Age, mean (± SD), yrs	54.8 (± 9.7)
Body mass index, mean (± SD), kg/m^2	26.2 (± 4.2)
Familial history of IHD, n (%)	327 (48)
Current smoker, n (%)	158 (23)
Diabetes[a], n (%)	24 (4)
Hypertension[b], n (%)	257 (38)
Hypercholesterolaemia[b], n (%)	197 (29)
Creatinine, mean (± SD), mmol/l	71.8 (± 15)
Coronary artery calcium score (Agatston score), n (%)	
0	435 (64)
1-100	204 (30)
101-400	41 (6)
> 400	3 (0.4)

IHD = ischaemic heart disease; SD = standard deviation.
a) Disease requiring oral treatment or insulin injection.
b) Current intake of lipid-lowering or blood pressure-lowering drugs.

TABLE 2

Comparison of the patients by re-imaging after coronary computed tomography angiography.

	Receiving re-imaging (N = 34)	Other (N = 649)	p-value
Men, n (%)	11 (32)	215 (33)	> 0.99
Age, mean (± SD), yrs	59.0 (± 9)	54.8 (± 10)	0.0037
Body mass index, mean (± SD), kg/m^2	28.1 (± 4)	26 (± 3.9)	0.0030
Familial history of IHD, n (%)	17 (50)	310 (48)	0.86
Current smoker, n (%)	7 (21)	151 (23)	0.84
Diabetes[a], n (%)	1 (3)	23 (4)	>0.99
Hypertension[b], n (%)	11 (32)	247 (38)	0.59
Hypercholesterolaemia[b], n (%)	11 (32)	186 (29)	0.70
Creatinine, mean (± SD), mmol/l	73.7 (± 16)	70.5 (± 15)	0.23
Coronary artery calcium score (Agatston score), n (%)			
0	17 (50)	418 (64)	–
1-100	14 (41)	190 (29)	–
101-400	3 (9)	38 (6)	–
> 400	0	3 (5)	–

IHD = ischaemic heart disease; SD = standard deviation.
a) Disease requiring oral treatment or insulin injection.
b) Current intake of lipid-lowering or blood pressure-lowering drugs.

The case of non-fatal MI was a 63-year-old female with known COPD and use of oxygen at home. At the index CCTA, she had an Agatston score of 30 without any significant coronary artery stenosis. Fifteen months after the CCTA, she was admitted with intermittent chest pain and suspected COPD exacerbation. Coronary biomarkers were elevated and ECG showed ST-depressions in leads V4-V6. Echocardiography showed septal hypokinesia. No ICA was performed due to the patient's wish. Based on the patient's history, this MI is considered a type 2 MI.

There is a large body of evidence on the favourable prognosis for patients with normal CCTA findings [4, 13]. Most recent studies use a 16-segment coronary artery scoring model for interpretation of a CCTA and divide patients into groups with normal, non-obstructive CAD or obstructive CAD based on CCTA [5]. In our study, we focused on consequence-related results after CCTA. This yields a division of patients into two groups: Referral for further diagnostic testing or discharge from cardiology outpatient clinic because of no signs of significant CAD. The present observations from a single centre confirm the favourable prognosis in subjects discharged after CCTA. In recent studies, a high proportion of patients was found to have non-obstructive CAD, most frequently defined as coronary stenosis < 50% [5]. These patients are shown to have a slightly, but significantly less favourable prognosis than patients with a completely normal CCTA. Such patients, considered to have non-obstructive CAD on CCTA, were discharged without further testing, and were thus included in our study. Despite this, we still found a low three-year incidence rate.

We found that 5.0% of the patients were re-evaluated with an imaging modality, predominantly ICA. In all cases, this re-imaging was due to new referral after the initial CCTA-reader had discharged the patient. In the present study, it was not possible to identify predictors for patients being re-evaluated. Numerous factors might influence the extent of this re-evaluation: the organisation of the health-care system, the prevalence and treatment of non-cardiac chest pain and awareness of cardiovascular disease in the general population are potential factors. If the favourable prognosis after CCTA is not known to the physician, this might lead to continued suspicion of CAD. We therefore propose that improving the referring physician's knowledge of the excellent prognostic power of CCTA results may be of great impact.

The subsequent non-scheduled imaging after discharge from an outpatient clinic following a normal CCTA highlights a potential problem concerning the credibility of CCTA. This adds to the problem of the low specificity of CCTA, which results in false positives and a suboptimal diagnostic performance [2]. The finding that re-evaluation had no consequences adds to the evidence of the prognostic power of CCTA for predicting the need for revascularisation therapy. There are currently no guidelines on re-evaluation of patients who are discharged from CCTA, and there is no well-established "warranty period" in which a normal CCTA predicts a good prognosis and no need for revascularisation. With an expansive growth in the population of patients who have undergone CCTA, research and clarification of predictors and reasons for re-evaluation and the "warranty period" of a CCTA is needed.

Limitations

In our study, the classification of deaths was done by review of patient health records and information from the Danish Cause of Death Registry. Both sources might potentially contain misclassifications of causes of death. One case of death could not be classified and is therefore potentially a cardiovascular death. The finding of no cardiovascular death in this study should therefore be interpreted with caution.

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LITERATURE

1. Abdulla J, Abildstrom SZ, Gotzsche O et al. 64-multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: a systematic review and meta-analysis. Eur Heart J 2007:3042-50.
2. Schuetz GM, Schlattmann P, Dewey M. Use of 3 × 2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of coronary CT angiography studies. BMJ 2012;345:e6717.
3. Rasmussen K, Tilsted HH, Aarøe J et al. Detection of stenoses in the

coronary arteries using 64-slice computed tomography. Ugeskr Læger 2010:2839-44.

4. Hulten EA, Carbonaro S, Petrillo SP et al. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. J Am Coll Cardiol 2011;57:1237-47.
5. Min JK, Dunning A, Lin FY et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol 2011;58:849-60.
6. Hulten E, Villines TC, Cheezum MK et al. Usefulness of coronary computed tomography angiography to predict mortality and myocardial infarction among Caucasian, African and East Asian ethnicities (from the CONFIRM [Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter] Registry). Am J Cardiol 2013;111:479-85.
7. Cho I, Chang H-J, Sung JM et al. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). Circulation 2012;126:304-13.
8. Rana JS, Dunning A, Achenbach S et al. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes): an InteRnational Multicenter Registry. Diabetes Care 2012;35:1787-94.
9. Ovrehus KA, Bøtker HE, Jensen JM et al. Influence of coronary computed tomographic angiography on patient treatment and prognosis in patients with suspected stable angina pectoris. Am J Cardiol 2011;107:1473-9.
10. Ghadri JR, Goetti R, Fiechter M et al. Inter-scan variability of coronary artery calcium scoring assessed on 64-multidetector computed tomography vs. dual-source computed tomography: a head-to-head comparison. Eur Heart J 2011;32:1865-74.
11. Schmermund A, Möhlenkamp S, Berenbein S et al. Population-based assessment of subclinical coronary atherosclerosis using electron-beam computed tomography. Atherosclerosis 2006;185:177-82.
12. Montalescot G, Sechtem U, Achenbach S et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013:2949-3003.
13. Habib PJ, Green J, Butterfield RC et al. Association of cardiac events with coronary artery disease detected by 64-slice or greater coronary CT angiography: a systematic review and meta-analysis. Int J Cardiol 2013;169:112-20.