Long-term prognostic value of coronary computed tomography angiography in chest pain patients

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LONG-TERM PROGNOSTIC VALUE OF CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY IN CHEST PAIN PATIENTS

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**Ethics**

This study was conducted according to the principles set forward in the declaration of Helsinki and according to Good Clinical Practice. Permission was obtained from the regional ethical review board in Linköping (independent government authority), Dnr M6-09 with amendments Dnr 2013/278-32 and 2015/112-32.
Long-term prognostic value of coronary computed tomography angiography in chest pain patients.
Abstract:

Background

Coronary computed tomography angiography (CCTA) is increasingly used to detect coronary artery disease (CAD), but long term follow-up studies are still scarce.

Purpose

To evaluate the prognostic value of CCTA in patients with suspected CAD.

Material and Methods

A total of 1205 consecutive CCTA patients with chest pain were classified as normal coronary arteries, non-obstructive CAD or obstructive CAD. The primary outcome was major adverse cardiac event (MACE), defined as a composite outcome including cardiac death, myocardial infarction, unstable angina pectoris or late revascularization (after > 90 days).

Results

Over 7.5 years (median 3.1 years) follow-up, Kaplan Meier estimates demonstrated a MACE in 1.0%, 4.6% and 20.7% in normal coronary arteries, non-obstructive CAD and obstructive CAD, respectively. Log rank test for pairwise comparisons showed significant differences between non-obstructive CAD and normal coronary arteries (p = 0.023) and between obstructive CAD and normal coronary arteries (p <0.001). In a multivariable analysis, adjusting for classical risk factors, non-obstructive CAD and obstructive CAD were
independent predictors of MACE, with hazard ratios of (HR) 3.22 (p=0.041) and HR 25.18 (p<0.001), respectively.

**Conclusion**

Patients with normal coronary arteries have excellent long-term prognosis, but the risk for MACE increases with non-obstructive and obstructive CAD. Both non-obstructive and obstructive CAD are independently associated with future ischemic events.

**Key words**

Cardiac, Computed tomography angiography, CT, ischemia/infarction, epidemiology
Introduction

Cardiovascular disease (CVD) in general and coronary artery disease (CAD) in particular is the most common cause of death in the world (1). CVD is also the most expensive disease group in the European Union (2), and in the United States of America (3).

Diagnosis of suspected stable CAD involves clinical evaluation, cardiac stress testing and coronary imaging. Modalities for stress testing and coronary imaging are described in the current European Society of Cardiology (ESC) (4), and American College of Cardiology (ACC) (5) guidelines, among them coronary computed tomography angiography (CCTA). Recommended equipment to perform CCTA is a 64-slice scanner or better (6). Current ESC guidelines recommend CCTA primarily in patients with low pretest probability (PTP) and in the lower range (PTP <50%) of intermediate risk (4,7). ACC guidelines recommend CCTA primarily when a patient is unable to perform a stress test, with discrepancy between clinical suspicion and stress test, or when the ECG is uninterpretable. CCTA has been shown to have a high sensitivity and high negative predictive value (8,9). While short- and medium term outcomes after CCTA have been previously described (10-15), very few studies have described long-term outcome (16,17).

The aim of this study was to evaluate long-term prognostic value of CCTA in consecutive chest pain patients with no history of CAD.

Material and methods

The Swedish Web-based system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART), a nationwide quality registry collecting data on CAD care and interventions, was used to
identify patients (18). For this analysis we used a local part of the registry where CCTA examinations were collected.

**Study population**

Between 1 July 2007 and 31 December 2014, all consecutive patients (n=1370) at our center undergoing CCTA due to suspected CAD, without previous CAD, were included. A total of 144 examinations (10.5%) were excluded due to inadequate image quality; 48 with extensive calcifications (3.3%), 53 with motion artefacts (3.8%), 19 with poor contrast timing (1.4%) and 24 patients (1.7%) due to miscellaneous reasons, the majority with a combination of motion artefacts and extensive calcifications/poor contrast timing. Only the first CCTA for an individual patient was included, in order to avoid double counting. Finally, three examinations (0.2%) were excluded because the patients were foreign citizens and therefore not available for long-term follow-up, leaving a final study population of 1205 patients, 693 women (57.5%) and 512 men (42.5%). (Fig.1).

All patients were referred by a specialist in cardiology. Patients that were clinically classified with a PTP in the low and lower intermediate ranges were eligible for CCTA, according to clinical routine at our center. All patients were regarded as stable chest pain, a total of 1133 (94.0%) being outpatients and 72 (6.0%) inpatients. No patient was referred from the emergency room.

Medical history was recorded within the framework of the SWEDEHEART protocol and basic biometrical data and routine laboratory tests were collected.

**Image acquisition**

All CCTA examinations were performed according to current guideline recommendations (6), with four dual source CT scanners: Siemens Somatom Definition (2007-2009), Siemens
Somatom Definition Flash (2009-2012), Siemens Somatom Definition Flash with Stellar detector (2012-2014) and Siemens Somatom Force (2014). All examinations were obtained by three radiographers with special training in CCTA.

For Somatom Definition, a retrospectively gated spiral protocol was used. For Somatom Definition Flash and Somatom Definition Flash with stellar detector three prospectively ECG-gated protocols and a retrospectively ECG-gated spiral protocol were used.

For Somatom Force one prospectively ECG-gated high-pitch protocol and one retrospectively gated spiral protocol were used. Nitroglycerin (up to 1.2 mg sublingual) and beta blocker (up to 10 mg metoprolol i.v.) were administered if heart rate > 65 bpm.

Data reporting

Of the originally included 1396 CCTA, 1178 (84.4%) were interpreted by three interventional thoracic radiologists, with four years CCTA experience when the study commenced in 2007. Of the remaining examinations 218 (15.6%) CCTA were interpreted by one cardiologist and one thoracic radiologist who started clinical CCTA training in 2011, initially under supervision. When data was reported to the SWEDEHEART registry, examinations were classified as either normal coronary arteries/non-obstructive CAD or obstructive CAD. For the purpose of this study, all examinations with normal coronary arteries/non-obstructive CAD were further classified (blinded to clinical outcomes) as either normal coronary arteries or non-obstructive CAD.

Non–obstructive CAD was defined as atheromatosis with a narrowing of the luminal diameter of < 50%, and obstructive CAD as a narrowing of the luminal diameter of ≥50%, (Fig. 2). Atheromatosis was defined as presence of structures >1mm² within and/or adjacent to artery lumen, clearly distinguishable from vessel lumen, and surrounding pericardial tissue, according to the method described by Min et al. (19).
Outcomes

Data from the SWEDHEART registry was merged with the National Board of Health and Welfare Patient Registry, which contains data on all hospitalizations in Swedish hospitals, and the National Board of Health and Welfare National Cause-of-death Registry. The primary outcome, major cardiac adverse event (MACE,) was a composite of cardiac death, myocardial infarction, unstable angina pectoris and late revascularization (>90 days after CCTA).

Cardiovascular death was defined as described in the recent ACC /American Heart Association consensus paper (20). Myocardial infarction diagnosis was made according to the “Universal definition of myocardial infarction” (21). Unstable angina pectoris was defined according to clinical guidelines. Revascularization was performed as either percutaneous coronary intervention (PCI) or coronary by-pass surgery. In order not to include revascularizations performed as a direct consequence of CCTA findings, only those performed later than 90 days after CCTA were counted. Stable angina and non-specific chest pain diagnoses were made at the discretion of the treating cardiologist.

Finally, we performed a comparison of investigation costs for a CCTA strategy as compared to a strategy with invasive coronary angiography (ICA), using unit costs at our institution in 2016. The CCTA strategy obviously includes costs for two investigations (CCTA and ICA) for patients with an inconclusive CCTA and those with an ICA during follow-up.

Statistics

Continuous variables are presented as median and inter-quartile range (IQR), and categorical variables as numbers and percentages. Differences between normal coronary arteries, non-obstructive CAD and obstructive CAD were evaluated with Kruskal-Wallis or one-way
ANOVA as appropriate for continuous variables, and $\chi^2$-test for categorical variables. Fischer´s exact test was used in analyses with few (n < 5) outcomes.

Time-to-event curves were drawn using the Kaplan-Meier method, and differences between the groups assessed with the log rank test. A Cox proportional regression analysis assessed the importance of CCTA findings after adjustment for differences in age, gender and cardiovascular risk factors. Diabetes, smoking, hypertension, hyperlipidemia, gender and age were considered as potential confounding factors and inserted one at a time in the model. If the potential confounder was significant or if the hazard ratios for CCTA findings changed more than 10%, the variable was retained in the final model. Hence, the final model included CCTA findings, age and gender, but only CCTA findings remained statistically significant. Hazard ratios (HR) with 95% confidence intervals (CI) are presented.

The three-year incidence for MACE and readmission due to stable angina pectoris or chest pain was calculated for patients with a follow-up period of ≥ three years (n=655). Difference between groups was calculated using $\chi^2$-test or Fischer´s exact test. A p-value <0.05 was considered significant. Statistical analysis was performed using IBM SPSS version 23.0 (IBM, Armonk, NY, USA).

**Ethics**

This study was conducted according to the principles set forward in the declaration of Helsinki and according to Good Clinical Practice. Permission was obtained from the regional ethical review board. In accordance with the ethical regulations for Swedish registries and Swedish legislation, patients were informed about their participation in the registry and the right to deny participation or have data removed, which waives any requirement for written consent.
Results

Maximum follow-up was 2724 days/7.5 years, with a median follow-up of 1121 (IQR 415-1793) days/3.1 years. Normal coronary arteries were found in 668 patients (55.4%), non-obstructive CAD in 360 patients (29.9%) and obstructive CAD in 177 patients (14.7%). Median age was 56 years, 7% had diabetes, 47% hypertension, 37% hyperlipidemia, 50% were smokers or ex-smokers and 41% were overweight or obese with Body Mass Index > 25 kg/m². We found significant differences in several baseline characteristics according to observed CAD on CCTA. (Table 1)

In total, 218 patients had a subsequent ICA. Of those, 20 patients had normal findings, 49 patients had non-obstructive stenosis and 149 patients had obstructive stenosis on the index CCTA. Only one of the 20 patients with normal coronary arteries on CCTA underwent an ICA within 90 days as compared to 49% and 88% for patients with non-obstructive CAD and obstructive CAD respectively.

Kaplan Meier estimates over 7.5 years demonstrated a MACE in five (1.0 %) patients with normal coronary arteries, nine (4.6%) patients with non-obstructive CAD and 34 (20.7%) of patients with obstructive CAD. Log rank test with pairwise comparisons showed significant differences for both obstructive CAD (p <0.001) and non-obstructive CAD vs. normal coronary arteries (p = 0.023) (Fig. 3).

Cox regression multivariate analysis with adjustment for clinical characteristics and CVD risk factors, identified non-obstructive CAD and obstructive CAD as the only independent predictors of MACE with a HR of 3.48, 95% CI; 1.13-10.67, (p=0.029) and a HR of 29.26, 95% CI; 10.86-78.83, (p<0.001), respectively, with normal coronary arteries as reference.
A total of 655 patients had a follow-up time of three years. The incidence of MACE during three years of follow-up was 1.1% with normal coronary arteries, 2.5% with non-obstructive CAD (p=0.289 compared with normal coronary arteries) and 20.7% with obstructive CAD (p<0.001 compared with normal coronary arteries), (Table 2).

The three-year incidence of readmissions for stable angina pectoris were 0.8%, 2.5% and 9.8 % and readmissions for chest pain were 6.7%, 7.0% and 14.6% in patients with normal coronary arteries, non-obstructive CAD and obstructive CAD respectively, (Table 2).

Twelve patients died during long-term follow-up (1.0%): five (0.7%) with normal coronary arteries, five (1.4%) with non-obstructive CAD and two (1.1%) with obstructive CAD (p = 0.558). One death was cardiac-related (non-obstructive CAD), eight deaths were due to malignancy (five with normal coronary arteries, two with non-obstructive CAD, one with obstructive CAD), one due to amyloidosis (non-obstructive CAD), one to motor neuron disease (obstructive CAD) and one to trauma (non-obstructive CAD).

Investigation cost per patient was estimated to € 778 with a CCTA strategy and € 1.458 with a routine ICA strategy.

**Discussion**

In this study of 1205 consecutive chest pain patients with low to intermediate risk of CAD and up to 7.5 years of follow-up, normal CCTA findings was associated with excellent long-term prognosis, while outcome was progressively worse in non-obstructive and obstructive CAD, also after adjustment for age and conventional risk factors.
CCTA has been described as a useful tool for risk stratification in patients with suspected CAD (10-17). However, studies describing long-term prognosis are scarce. In this real world study, we consecutively included chest pain patients, reflecting everyday clinical practice. We achieved almost complete follow-up, with only three patients (0.2%) lost to follow-up, (foreign citizens without Swedish personal identity number), as compared to approximately 5-15% reported in earlier studies (11,14,16). Also, all examinations were performed according to current guidelines, using a 2 x 64 slice DSCT or better. In comparison, Dougoud et al. (16) reported longer median follow-up of 6.9 years, but the study group was considerably smaller (n = 218). Hadamitzky et al. (13) studied a larger population (n=1584) and a median follow-up of 5.6 years, but CCTA examinations were partly performed on older, 16-slice scanners.

In our study, more women than men were referred for CCTA (57.5% vs 42.5%), with a higher rate of normal coronary arteries (62.1% vs 37.9%), a finding that probably reflects the gender specific challenges in clinical assessment of suspected CAD. The result, indicating higher rate of normal coronary arteries in women, is in accordance with earlier findings among patients referred for ICA (22). Similar to earlier studies, 85.3% (n=1028) of the patients had normal coronary arteries or non-obstructive CAD. The proportion of normal coronary arteries (55.4%) was higher compared to most previous studies (10,13,15-17), indicating a somewhat different population, at low risk.

Even so, the prognostic value of non-obstructive CAD, as compared to normal coronary arteries, was similar to earlier trials, supporting the use of CCTA in low and intermediate risk patients. We observed a significantly higher rate of MACE in patients with non-obstructive CAD (4.6% vs. 1.0%, p= 0.023) or obstructive CAD (20.7% vs. 1.0%, p<0.001) compared with normal coronary arteries. A progressively worse prognosis in non-obstructive CAD and obstructive CAD is coherent with other studies using a similar definition of MACE (11-17), In addition, a multivariable analysis showed that non-obstructive and obstructive CCTA
findings were independently associated with MACE after adjusting for classical cardiovascular risk factors, age and gender, with normal coronary arteries as reference. A recently published paper reported a similar independent association between MACE and non-obstructive CAD + Leamna score >5 (23). This association may not be surprising since classical risk factors are risk factors for atherosclerosis while the findings on CCTA are evidence of established atherosclerosis. While patients with obstructive CAD are usually further evaluated and treated, our result indicate that also patients with non-obstructive CAD may benefit from a more preventive treatment strategy. No randomized trials have evaluated benefit from statin treatment based on CCTA findings. However, in an observational study lowered risk of cardiovascular events with statin treatment was observed among patients with extensive, but non-obstructive CAD (24). The role of CCTA in the work-up of chest pain patients is yet to be defined, but a recent trial from Scotland, where patients were randomized to standard care or standard care plus CCTA, indicated that the additional information from the CCTA may inform decision making to improve clinical outcome. Addition of CCTA resulted in higher diagnostic certainty and a borderline significant reduction in death/myocardial infarction without an increase in ICA (25).

In addition to evaluation of ischemic events and deaths, we present data on readmissions due to stable angina pectoris or unspecific chest pain, which, to our knowledge, has not been studied in this context before. We found a relatively high rate of readmissions regardless of findings on CCTA, which may raise questions about alternative pathology causing the symptoms. Even though earlier trials have indicated high rates of readmission (26), and accordingly extensive health care costs in chest pain patients, this has not been shown in a CCTA population before. In fact, it has been shown that the use of CCTA may actually reduce readmissions (27-28). Our results may indicate the need for a different follow-up, after
a reassuring CCTA, including information and work-up, to further decrease readmissions in
chest pain patients without obstructive CAD.

One of the cost drivers for this population is the investigation costs. Using the unit costs at our
institution in 2016, the investigation cost per patient with our CCTA strategy was € 778. If all
patients in the study had been managed with ICA, the per patient cost would have been €
1,458. Thus, the CCTA strategy used in this study showed a 46.6 % reduction in
investigation costs compared to an ICA approach.

There are important limitations to this study. First, considering the low number of events, the
study population is small. However, several prior studies have had smaller populations, and
this analysis adds important information with long follow-up. Second, the reporting to the
SWEDEHEART register is largely based on a single-reader clinical evaluation. However, this
is usually clinical routine, and for evaluation of a method in clinical routine it may also be
considered a strength. Third, we report a relatively high number of exclusions due to
inadequate image quality (10.5%), in comparison, others report 1.6-9.0 % (11-13, 15-17).
This may partly be due to the strict frames of inclusion; if any arterial segment was
considered uninterpretable, the whole examination was determined as unreadable. Thus, our
data do not contain any unreadable segments, which could also be considered a strength.
Fourth, external validity may be limited due to being a single center study. In addition,
calcium scoring is not routinely performed at our center, which may have led to a comparably
large number of uninterpretable examinations due to extensive calcifications.

In conclusion, chest pain patients with low to intermediate risk for CAD demonstrating
normal coronary arteries on CCTA have a very favorable prognosis over long-term follow-up,
while outcome is progressively worse in non-obstructive and obstructive CAD, even after
adjustment for age and conventional risk factors for CVD. In addition, chest pain patients undergoing CCTA are, regardless of findings, frequently readmitted for chest pain or angina.
References


<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Normal coronary arteries</th>
<th>Non-obstructive CAD</th>
<th>Obstructive CAD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1205)</td>
<td>(n=668)</td>
<td>(n=360)</td>
<td>(n=177)</td>
<td></td>
</tr>
<tr>
<td>Men n (%)</td>
<td>512 (42.5%)</td>
<td>253 (37.9%)</td>
<td>150 (41.7%)</td>
<td>109 (61.6%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Women n (%)</td>
<td>693 (57.5%)</td>
<td>415 (62.1%)</td>
<td>210 (58.3%)</td>
<td>68 (38.4%)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>56 (48-64)</td>
<td>52 (44-60)</td>
<td>60 (53-66)</td>
<td>62 (54-66)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>26.0 (23.7-29.0)</td>
<td>25.7 (23.5-28.3)</td>
<td>26.3 (23.5-30.1)</td>
<td>26.6 (24.5-29.1)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>S-creatinine (µmole/L)</td>
<td>72 (63-83)</td>
<td>71 (62-80)</td>
<td>74 (63-85)</td>
<td>78 (66-87)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>605 (50.0%)</td>
<td>300 (44.9%)</td>
<td>199 (55.2%)</td>
<td>106 (59.9%)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Current smokers</td>
<td>151 (12.5%)</td>
<td>79 (11.8%)</td>
<td>48 (13.3%)</td>
<td>24 (13.6%)</td>
<td></td>
</tr>
<tr>
<td>Ex-smokers (&gt;1 month)</td>
<td>454 (37.7%)</td>
<td>221 (33.1%)</td>
<td>151 (41.9%)</td>
<td>82 (46.3%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>84 (7.0%)</td>
<td>32 (4.8%)</td>
<td>35 (9.7%)</td>
<td>17 (9.6%)</td>
<td>p=0.005</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>561 (46.6%)</td>
<td>250 (37%)</td>
<td>193 (53.6%)</td>
<td>118 (66.7%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia n (%)</td>
<td>440 (36.5%)</td>
<td>208 (31.1%)</td>
<td>157 (43.6%)</td>
<td>75 (42.4%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Overweight/obesity (BMI≥25)</td>
<td>734 (60.9%)</td>
<td>394 (59.0%)</td>
<td>216 (60.1%)</td>
<td>124 (70.1%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Overweight (BMI ≤25)</td>
<td>492 (40.8%)</td>
<td>287 (43.0%)</td>
<td>121 (33.6%)</td>
<td>84 (47.5%)</td>
<td></td>
</tr>
<tr>
<td>30), n (%)</td>
<td>242 (20.1%)</td>
<td>107 (16.0%)</td>
<td>95 (26.4%)</td>
<td>40 (22.6%)</td>
<td>p&lt;0.05</td>
</tr>
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<tr>
<td>Obesity(BMI&gt;30), n (%)</td>
<td>201 (92-347.5)</td>
<td>180 (90-329)</td>
<td>216 (94-391)</td>
<td>220 (98-345)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>DLP CCTA (mGycm)</td>
<td>80 (73-80)</td>
<td>80 (71-80)</td>
<td>80 (74-80)</td>
<td>80 (78-80)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Iodinated contrast agent (ml)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations:
CAD; Coronary Artery Disease
SD; Standard Deviation
IQR; Inter-Quartile Range
BMI; Body Mass Index
DLP; Dose-Length Product.

Continuous variables are presented as median values with inter-quartile range. The null hypothesis was tested with Kruskal-Wallis for continuous variables, and the $\chi^2$-test for nominal variables.
Table 2: 3-year outcome with normal, non-obstructive and obstructive coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=655)</th>
<th>Normal Coronary Arteries (n=372)</th>
<th>Non-obstructive CAD (n=201)</th>
<th>Obstructive CAD (n=82)</th>
<th>p-value Non-obstructive vs. Normal</th>
<th>p-value Obstructive vs. Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (n (%))</td>
<td>26 (4.0)</td>
<td>4 (1.1)</td>
<td>5 (2.5)</td>
<td>17 (20.7)</td>
<td>0.289</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac death (n (%))</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>MI (n (%))</td>
<td>7 (1.1)</td>
<td>2 (0.5)</td>
<td>2 (1.0)</td>
<td>3 (3.7)</td>
<td>0.615</td>
<td>0.043</td>
</tr>
<tr>
<td>UAP (n (%))</td>
<td>15 (2.3)</td>
<td>2 (0.5)</td>
<td>2 (1.0)</td>
<td>11 (13.4)</td>
<td>0.615</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late revascularization (n (%))</td>
<td>6 (0.9)</td>
<td>1 (0.3)</td>
<td>2 (1.0)</td>
<td>3 (3.7)</td>
<td>0.282</td>
<td>0.020</td>
</tr>
<tr>
<td>Other Readmissions (n (%))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable AP (n (%))</td>
<td>16 (2.4)</td>
<td>3 (0.8%)</td>
<td>5 (2.5)</td>
<td>8 (9.8)</td>
<td>0.136</td>
<td>&lt;0.001</td>
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<tr>
<td>Chest pain (n (%))</td>
<td>51 (7.8)</td>
<td>25 (6.7)</td>
<td>14 (7.0)</td>
<td>12 (14.6)</td>
<td>0.912</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Abbreviations:
CCTA; Coronary Computed Tomography Angiography
MACE; major adverse cardiovascular event
MI; Myocardial infarction
UAP; Unstable angina pectoris
AP; Angina pectoris
CAD; Coronary artery disease.
Differences between normal coronary arteries vs. non-obstructive CAD and obstructive CAD were calculated using Pearson’s Chi-Square or Fischer’s exact test as appropriate.

**Figure legends**

**Fig.1:**
Flow chart. Inclusions and exclusions.

**Fig.2:**
Multiplanar reconstruction (MPR) of the left anterior descending coronary artery in three different patients. Left: Normal artery. Mid: Non-obstructive, calcified CAD. Right: Obstructive coronary CAD.

**Fig.3:**
Kaplan Meier estimates over 7.5 years: 1.0% experienced MACE in the group with normal coronary arteries, 4.6% in the group with non-obstructive CAD and 20.7% in the group with obstructive CAD. Log rank test with pairwise comparisons showed significant differences for both obstructive CAD vs. normal coronary arteries (p <0.001) and non-obstructive CAD vs. normal coronary arteries (p = 0.023).
The graph shows the Kaplan-Meier survival curve for patients with different types of coronary artery disease (CAD) from 0 to 8 years. The patients are grouped into three categories:

- **Normal coronary arteries**: Represented by a red dashed line with markers. The number of patients at risk for each year is as follows:
  - Year 0: 668
  - Year 1: 544
  - Year 2: 446
  - Year 3: 368
  - Year 4: 265
  - Year 5: 169
  - Year 6: 99
  - Year 7: 26

- **Non-obstructive CAD**: Represented by a green line with markers. The number of patients at risk for each year is as follows:
  - Year 0: 360
  - Year 1: 295
  - Year 2: 246
  - Year 3: 196
  - Year 4: 137
  - Year 5: 98
  - Year 6: 61
  - Year 7: 23

- **Obstructive CAD**: Represented by a blue line with markers. The number of patients at risk for each year is as follows:
  - Year 0: 177
  - Year 1: 110
  - Year 2: 86
  - Year 3: 65
  - Year 4: 42
  - Year 5: 31
  - Year 6: 15
  - Year 7: 5

The graph indicates a higher risk of events for patients with obstructive CAD compared to those with normal coronary arteries or non-obstructive CAD.