# Cardiovascular computed tomography for diagnosis and risk stratification of coronary artery disease

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# Chapter 16

# Influence of smoking on the prognostic value of cardiovascular computed tomography coronary angiography

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# Abstract

Computed tomography coronary angiography (CTA) is an important non-invasive imaging modality increasingly used for the diagnosis and prognosis of coronary artery disease (CAD). The purpose of the current study was to determine the influence of smoking status on the prognostic value of CTA in patients with suspected or known CAD. In 1207 patients (57% male, age 57±12 years) referred for CTA, the presence of significant CAD (≥50% stenosis) was determined. During follow-up the following events were recorded: all cause mortality, and non-fatal infarction. The prognostic value of CTA in smokers and non-smokers was compared using an interaction term in the Cox proportional hazard regression analysis. Significant CAD was observed in 327 patients (27%), and 273 patients (23%) were smokers. During a median follow-up time of 2.2 years, an event occurred in 50 patients. After correction for baseline characteristics including smoking in a multivariate model, significant CAD remained an independent predictor of events. Furthermore, a significant interaction ($p<0.05$) was observed between significant CAD and smoking. The annualized event rate in smokers with significant CAD was 8.78% compared to 0.99% in smokers without significant CAD ($p<0.001$). In non-smokers with significant CAD the annualized event rate was 2.07% compared to 1.01% in non-smokers without significant CAD ($p=0.058$). In conclusion, the prognostic value of CTA was significantly influenced by smoking status. The event rates in patients with significant CAD were approximately 4-fold higher in smokers compared to non-smokers. These findings suggest that smoking cessation needs to be aggressively pursued, especially in smokers with significant CAD.

# Introduction

The introduction of multi-slice computed tomography coronary angiography (CTA) has changed the field of non-invasive imaging. In contrast to functional imaging techniques assessing myocardial perfusion and wall motion, CTA can provide direct non-invasive anatomic assessment of the coronary arteries. Because of the high negative predictive value for detection of significant CAD (defined as ≥50% stenosis), [1] the technique is increasingly used as a gatekeeper for further diagnostic testing. In the last 3-4 years, several single and multicenter studies have suggested that CTA may also provide important prognostic information. These studies have shown that patients with significant CAD detected on CTA are associated with worse outcome compared to patients without significant CAD.[2-7]

Although the prognostic value of CTA and its incremental value over baseline clinical variables have thus been previously described, no reports have specifically focused on the prognostic value of CTA in smokers. This may be of interest, as smoking is an important but also modifiable risk factor resulting in an approximately 2 to 4 times increased risk of coronary heart disease compared to non-smokers.[8, 9] Furthermore, smoking has recently been shown to significantly increase the risk of events in asymptomatic individuals with evidence of atherosclerosis according to the coronary calcium score (CS), when compared to non-smokers with a similar calcium burden.[10] It is conceivable that smoking has a similar effect on risk stratification with CTA. The purpose of the current study was therefore to determine the influence of smoking status on the prognostic value of CTA in patients with suspected or known CAD.

# Methods

The study population consisted of patients who were clinically referred for CTA because of chest pain symptoms or a high risk profile for cardiovascular disease. Patients were enrolled at the University Hospital in Zurich, Switzerland, and at the Leiden University Medical Center, The Netherlands. Results from this prospective registry have been previously published.[5] Exclusion criteria were: cardiac arrhythmias, renal insufficiency (defined as a glomerular filtration rate <30 ml/min), known hypersensitivity to iodine contrast media, and pregnancy. In addition, patients with an uninterpretable CTA examination or coronary artery bypass grafts were excluded. Clinical patient characteristics were collected by the referring physician. Patients provided informed consent and the study was approved by the local ethics committees in both participating centers.

### CTA acquisition and data analysis

Patients were scanned using a 64-row CT scanner (Aquilion64, Toshiba Medical Systems, Otawara, Japan; and General Electrics LightSpeed VCT, Milwaukee, WI, US) or with a 320-row CT scanner (Toshiba Multi-slice Aquilion ONE system, Toshiba Medical Systems, Otawara, Japan). Before the examination, the patient's heart rate and blood pressure were monitored. In the absence of contraindications, patients with a heart rate exceeding 65 beats per minute were administered beta-blocking medication (50-100 mg metoprolol, oral or 5-10 mg metoprolol, intravenous). All scan parameters have been previously published.[11-13]

Post-processing of the CTA examinations was performed on dedicated workstations (Vitrea2 and VitreaFx, Vital Images, USA; and Advantage GE Healthcare, USA). CTA examinations were read by two experienced readers at both participating centers, blinded to follow-up results. Coronary anatomy was assessed using a 17 segment model according to a modified American Heart Association classification.[14] Normal CTA was defined as completely normal anatomy or minimal wall irregularities <30%, non-significant CAD was defined as the presence of luminal narrowing with a maximal luminal diameter stenosis <50%, and significant CAD was defined as the presence of a lesion exceeding ≥50% maximal luminal diameter stenosis.

### Follow-up results

Patient follow-up data were gathered using clinical visits or standardized telephone interviews. A composite endpoint was constructed using all cause mortality, and non-fatal myocardial infarction. Non-fatal infarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the ECG.[15] Patients with stable complaints undergoing an early elective revascularization within 60 days after CTA were excluded from the survival analysis.

### Statistical analysis

Normally distributed continuous variables were expressed as mean values (± standard deviation). Non-normally distributed continuous variables were expressed as median values with a 25th-75th percentile. Categorical baseline data were expressed in numbers and percentages. Differences between smokers and non-smokers were compared using the Student t and chi-square tests. Cox regression analysis was used to determine the prognostic value of significant (≥50% luminal narrowing) CAD on CTA. First univariate analysis of baseline clinical variables, and CTA was performed using a composite endpoint of all cause mortality, and non-fatal infarction. For each variable a hazard ratio with a 95%-confidence interval (95%-CI) was calculated. A multivariate model was created to assess the independent prognostic value of CTA. To compare the prognostic value of CTA in smokers and non-smokers a final multivariate model was constructed to test for interaction between smoking

and CTA. Multivariate models were created using stepwise backward elimination; first all baseline clinical variables were included in the model, subsequently the least significant variable was excluded one at a time until all variables in the model reached a p-value <0.5. Annualized event rates were calculated based on the number of events per 100 patient years follow-up (FU). Survival curves were estimated with the Kaplan-Meier method, and curves were compared using the log-rank test. Statistical analyses were performed using SPSS software (version 16.0, SPSS Inc, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

# Results

The study population consisted of 1467 patients presenting at the University Hospital Zurich (n=468), and at the Leiden University Medical Center (n=999). In 44 (3%) patients the CTA examination was uninterpretable due to the presence of motion artifacts, increased noise due to a high body mass index, and breathing. In addition, 117 patients (8%) were lost to follow-up. Finally 99 patients (7%) were excluded due to early revascularization. After exclusion, a total of 1207 remained for analysis. The majority of patients were symptomatic (67%), the remaining 33% of patients were referred because of a high risk profile with or without an abnormal exercise ECG. An overview of the baseline characteristics of the study population is presented in Table 1.

**Table 1.** Patient characteristics

| | Total (n = 1207) | Non-smokers (n=934) | Smokers (n=273) | P-value |
|---|---|---|---|---|
| Age (years) | 56.8±11.9 | 57.4±12.2 | 54.8±10.9 | 0.002 |
| Gender (male) | 690 (57%) | 514 (55%) | 176 (64%) | 0.006 |
| Risk Factors | | | | |
| Diabetes | 299 (25%) | 226 (24%) | 73 (27%) | 0.39 |
| Hypertension | 587 (49%) | 455 (49%) | 132 (49%) | 0.92 |
| Hypercholesterolemia | 461 (38%) | 341 (37%) | 120 (44%) | 0.03 |
| Family history of CAD | 475 (39%) | 342 (37%) | 133 (49%) | <0.001 |
| Obesity (BMI ≥ 30 kg/m2) | 220 (18%) | 176 (19%) | 44 (16%) | 0.26 |
| History | | | | |
| Previous MI | 96 (8%) | 68 (7%) | 28 (10%) | 0.11 |
| Previous PCI | 116 (10%) | 82 (9%) | 34 (13%) | 0.07 |
| Known CAD | 135 (11%) | 96 (10%) | 39 (14%) | 0.07 |

## CTA results

Significant CAD was observed on CTA in 327 patients (27%). In the remaining 880 patients (73%) non-significant CAD was observed in 425 patients (35%) and 455 patients (38%) were

classified as normal. Figure 1 illustrates the prevalence of significant CAD on CTA according to smoking status. In non-smokers (n=934), significant stenosis was observed on CTA in 229 patients (25%), compared to 98 (36%) of the 273 patients who smoked (p<0.001).

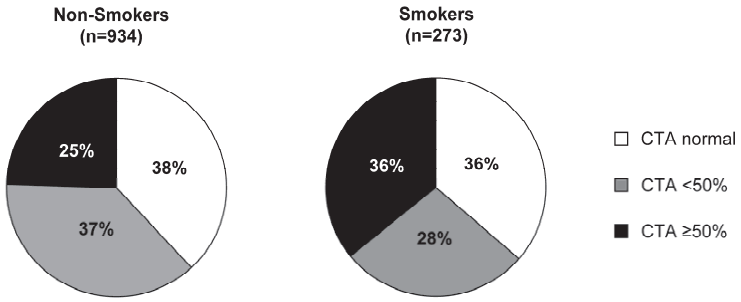


**Figure 1.** Relationship between CTA findings and Smoking.

## Follow-up results

The median FU time was 2.2 years (25-75th percentile: 1.3-3.2 years). During the FU period a myocardial infarction occurred in 12 patients and all cause mortality was registered in 40 patients. The composite endpoint of all cause mortality and myocardial infarction occurred in 50 patients. This resulted in an event rate of 1.8 per 100 patient years FU.

## Survival analysis

The presence of significant CAD on CTA was a significant univariate predictor of events (Table 2). After correction for baseline clinical variables including smoking status, significant CAD remained an independent predictor of events (Table 2). An event rate of 4.01 events per 100 patient years FU was observed in patients with significant CAD compared to 1.0 event per 100 patient years FU in patients without significant CAD.

To assess the prognostic value of significant CAD on CTA in smokers and non-smokers, a second multivariate model was constructed to test for interaction (Table 3). The prognostic value of CTA was significantly higher in smokers compared to the prognostic value of CTA in non-smokers (interaction p = 0.031, and p = 0.045 adjusted for age, diabetes, hypercholesterolemia, obesity, and known CAD). The event rate in smokers with significant CAD was 8.78 events per 100 patient years FU compared to 0.99 events per 100 patient years FU in smokers without significant CAD (p<0.001). In non-smokers with significant CAD the event rate was 2.07 events per 100 patient years FU compared to 1.01 events per 100 patient years FU in non-smokers without significant CAD (p=0.058). The survival rate following CTA according to smoking status is illustrated in Figure 2.

**Table 2.** Univariate and Multivariate predictors of events

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95%-CI) | p-value | HR (95%-CI) | p-value |
| Age (years) | 1.1 (1.0-1.1) | <0.001 | 1.1 (1.0-1.1) | <0.001 |
| Gender (male) | 1.1 (0.6-1.9) | 0.68 | | |
| Diabetes | 1.6 (0.9-2.9) | 0.11 | 1.8 (1.0-3.5) | 0.07 |
| Hypertension | 1.2 (0.7-2.2) | 0.46 | | |
| Hypercholesterolemia | 1.1 (0.6-1.9) | 0.67 | | |
| Family history CAD | 0.9 (0.5-1.6) | 0.68 | | |
| Obesity (BMI ≥ 30 kg/m2) | 0.49 (0.2-1.2) | 0.13 | 0.5 (0.2-1.3) | 0.2 |
| Known CAD | 2.3 (1.2-4.3) | 0.01 | 1.8 (0.9-3.5) | 0.1 |
| Current Smoking | 2.9 (1.6-4.9) | <0.001 | 2.6 (1.4-4.7) | <0.05 |
| Significant CAD | 4.1 (2.3-7.2) | <0.001 | 2.4 (1.3-4.4) | <0.05 |

**Table 3.** Interaction between Smoking and significant CAD on CTA

| Exposure | Patients | Event | HR (95%-CI) | p-value |
|---|---|---|---|---|
| No Smoking | | | | |
| CTA <50% | 705 | 16 | 1.0 (reference) | |
| CTA ≥50% | 229 | 11 | 2.1 (0.9-4.5) | 0.06 |
| Smoking | | | | |
| CTA <50% | 175 | 4 | 1.0 (reference) | |
| CTA ≥50% | 98 | 19 | 8.9 (3.0-26.5) | <0.001 |

# Discussion

The main finding of the current study comparing the prognostic value of CTA in smokers and non-smokers is that the prognostic value of significant CAD on CTA was significantly influenced by smoking status. The event rate in patients with significant CAD was approximately 4-fold higher in smokers compared to non-smokers. On the other hand, in patients without significant CAD, the event rate was similar in smokers and non-smokers.

Although several studies have been published on the prognostic value of CTA, to our knowledge this is the first report to describe the effect of smoking on risk stratification with CTA. The effect of smoking on the prognostic value of atherosclerosis as detected by CS has been studied.[10] CS is generally used in asymptomatic cohorts as a measure of atherosclerotic plaque burden, and elevated CS are associated with an increased risk of events. In the study by Shaw et al. in a large cohort of 10,377 asymptomatic individuals, the value of CS for risk stratification has been compared between smokers and non-smokers. The authors observed a significant interaction between smoking and CS for the prediction of all cause mortality. In each CS category the event rates in smokers were higher than observed in non-smokers. In addition to this imaging study in asymptomatic individuals, elevated event rates in

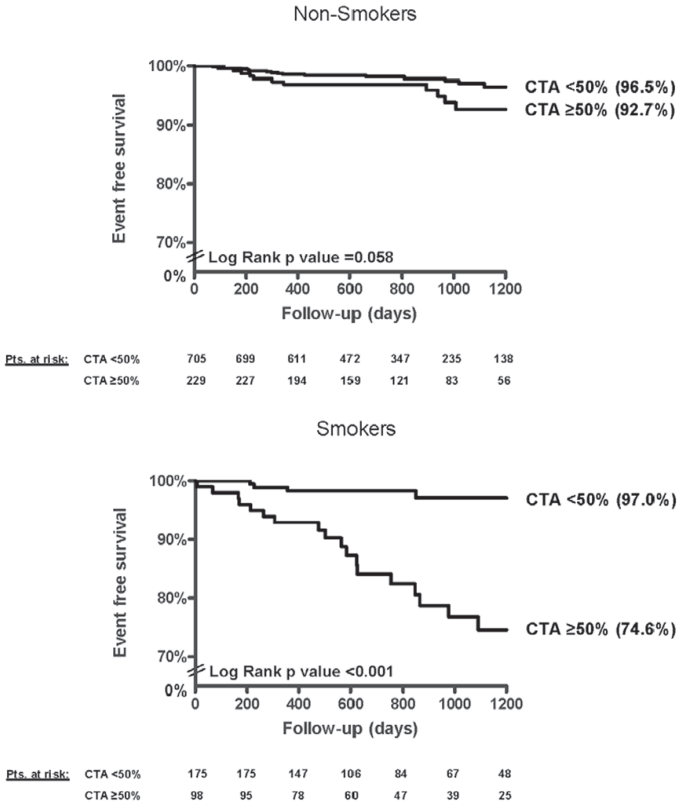


**Figure 2.** Survival according to CTA in non-smokers (panel a) and smokers (panel b).

smokers as compared to non-smokers have also been reported in symptomatic patients with established CAD. For instance, several studies have shown that following revascularization, smokers have a higher event rate than non-smokers.[16-18] The results of the current study are in line with these findings and further strengthen the evidence that smokers with CAD have a higher risk of events than non-smokers with similar levels of CAD.

The observations in the current study may be explained in part by the influence of smoking on the formation and progression of atherosclerosis through its negative effects on vasomotor dysfunction, inflammation and lipid modification.[19] Indeed multiple reports have described the effects of smoking on the formation of atherosclerosis both at autopsy, [20] as well as in clinical studies using coronary angiography, [21, 22] CS [23-25] and intima media thickness (IMT) measurements.[26, 27] Coronary angiography studies have described that smoking is an important and independent predictor of CAD, which is in line with the increased prevalence of significant CAD observed in the current study.[21, 22] Of interest, the atherosclerotic process seems to occur earlier in life in smokers.[25, 28] Earlier formation of CAD explains the

increased levels of CAD observed in smokers; however this may also be linked to increased progression of CAD. Smoking has been associated with CAD progression both on coronary angiography, IMT, and CTA. In a sub study of the CCAIT trial, Waters et al. observed that smoking resulted in both plaque progression and new plaque formation on serial quantitative coronary angiography.[29]

The rapid decrease in the risk of myocardial infarction observed after smoking cessation suggests that in addition to the effects of smoking on CAD formation and progression, smoking may also be seen as a trigger for myocardial infarction.[30] Smoking may affect all three major factors defining high risk patients that are vulnerable to myocardial infarction or sudden cardiac death: vulnerable plaque, vulnerable blood, and vulnerable myocardium.[31] Smoking has been associated with inflammatory processes, and endothelial dysfunction which may increase plaque vulnerability resulting in a higher risk of intracoronary thrombus formation. In addition platelet function, antithrombotic/prothrombotic and fibrinolytic factors may be altered by smoking resulting in an increased thrombotic tendency which in turn may cause more frequent and severe thrombus formation in response to plaque rupture.[32-35] Finally, smoking results in activation of the sympathetic nervous system thereby increasing heart rate and myocardial contractility resulting in increased oxygen demand, while at the same time decreasing myocardial oxygen supply due to vasoconstriction of the coronary arteries.[36] This mismatch in oxygen demand/supply may increase the myocardial vulnerability to ischemia thereby unfavorably altering myocardial response to thrombotic occlusions.

## Clinical implications

Further studies are needed to confirm our finding that the relative risk of events associated with significant CAD on CTA is significantly higher in smokers compared to non-smokers. Nevertheless, our results do suggest that strategies aimed at preventing future cardiovascular events should be intensified in patients with significant CAD who smoke. This is further strengthened by the fact that smoking is a modifiable risk factor, and that smoking cessation has been shown to improve survival.[37, 38]

Interestingly, when regarding patients without significant CAD, the risk of events in smokers without significant CAD was similar to the risk observed in their non-smoking counterparts. Based on previous studies assessing effect of smoking on CAD, it is expected that new formation and progression of (non-significant) CAD should also be increased in patients without significant CAD who smoke. The similar event rates observed in the current study suggest that this effect may be more gradual. Longer follow-up studies are necessary to determine the influence of smoking status in patients without significant CAD.

### Limitations

A limitation of the current study is that no exact data regarding quantification of smoking were available. This would have been of interest as several studies have suggested a dose response relationship between smoking and the severity of CAD. In addition, the occurrence of passive smoking in the non-smoking sub group was not systematically recorded. Because passive smoking has also been associated with an increased risk of events, [39-42] a similar interaction as observed between significant CAD and active smoking may exist in passive smokers. Future studies are necessary to further study these concepts.

A general limitation of CTA imaging is the high radiation dose associated with traditional 64-slice CTA protocols, although the radiation dose of CTA has decreased substantially with the implementation of dose saving algorithms and novel acquisition techniques.[43-46] Importantly, low-dose CTA with prospective ECG-triggering has recently been shown to reduce radiation burden while maintaining image quality and a high diagnostic accuracy.[47] Currently, the radiation burden with these novel acquisition techniques is approaching ≤2 mSv.[48]

## Conclusion

The prognostic value of CTA was significantly influenced by smoking status. The event rates in patients with significant CAD were approximately 4-fold higher in smokers compared to non-smokers. These results need to be confirmed in larger follow-up studies, but suggest that smoking cessation needs to be aggressively pursued, especially in smokers with significant CAD.

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