European Heart Journal (2017) **38**, 413–421
doi:10.1093/eurheartj/ehw548

Prognostic assessment of stable coronary artery disease as determined by coronary computed tomography angiography: a Danish multicentre cohort study

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Received 11 March 2016; revised 26 August 2016; editorial decision 21 October 2016; accepted 23 October 2016; online publish-ahead-of-print 9 December 2016

See page 422 for the editorial comment on this article (doi: 10.1093/eurheartj/ehw634)

Aims To examine the 3.5 year prognosis of stable coronary artery disease (CAD) as assessed by coronary computed tomography angiography (CCTA) in real-world clinical practice, overall and within subgroups of patients according to age, sex, and comorbidity.

Methods and results This cohort study included 16,949 patients (median age 57 years; 57% women) with new-onset symptoms suggestive of CAD, who underwent CCTA between January 2008 and December 2012. The endpoint was a composite of late coronary revascularization procedure >90 days after CCTA, myocardial infarction, and all-cause death. The Kaplan–Meier estimator was used to compute 91 day to 3.5 year risk according to the CAD severity. Comparisons between patients with and without CAD were based on Cox-regression adjusted for age, sex, comorbidity, cardiovascular risk factors, concomitant cardiac medications, and post-CCTA treatment within 90 days. The composite endpoint occurred in 486 patients. Risk of the composite endpoint was 1.5% for patients without CAD, 6.8% for obstructive CAD, and 15% for three-vessel/left main disease. Compared with patients without CAD, higher relative risk of the composite endpoint was observed for non-obstructive CAD [hazard ratio (HR): 1.28; 95% confidence interval (CI): 1.01–1.63], obstructive one-vessel CAD (HR: 1.83; 95% CI: 1.37–2.44), two-vessel CAD (HR: 2.97; 95% CI: 2.09–4.22), and three-vessel/left main CAD (HR: 4.41; 95% CI :2.90–6.69). The results were consistent in strata of age, sex, and comorbidity.

Conclusion Coronary artery disease determined by CCTA in real-world practice predicts the 3.5 year composite risk of late revascularization, myocardial infarction, and all-cause death across different groups of age, sex, or comorbidity burden.

Keywords Stable angina • Coronary atherosclerosis • Comorbidity • Prognosis • Coronary computed tomography angiography

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Introduction

Coronary computed tomography angiography (CCTA) is increasingly used in the diagnostic work-up of patients suspected of coronary artery disease (CAD).[1] Guidelines from the European Society of Cardiology recommend CCTA as a non-invasive alternative to functional stress testing in patients suspected of stable CAD and with a low-to-intermediate pretest likelihood of obstructive CAD.[2]

As people age, the likelihood of developing chronic medical conditions increases. Moreover, patients with CAD frequently suffer from concurrent diseases potentially influencing treatment decisions and the risk of mortality.[3] As ageing of the population will increase over coming decades,[4] the number of patients with multiple conditions, who undergo CCTA, is expected to increase.

Large-scale prospective studies and one meta-analysis[5–7] have demonstrated that disease severity determined by CCTA provides valuable information on clinical outcomes in patients with suspected stable CAD. However, whether sex, age, and comorbidity modify the prognostic value of CCTA determined CAD in real-world clinical practice remains uknown.[5–7] Therefore, we examined in real-world practice the prognosis of stable CAD as assessed by CCTA, overall and within subgroups of patients according to age, sex, and comorbidity.

Methods

Patients

This study was based on data from the Western Denmark Heart Registry (WDHR). This data source has been audited and validated.[8,9] All nine sites collaborating in the WDHR register patients consecutively in a catchment area of 3.3 million inhabitants (55% of the Danish population). We included all patients ≥18 years of age with symptoms (angina/dyspnoea) suggestive of CAD, who underwent CCTA between 1 January 2008 and 31 December 2012. Exclusion criteria were known CAD [prior myocardial infarction (MI) or coronary revascularization], or a missing CCTA result. If a patient had more than one CCTA examination, only the first was included in the analysis. The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to hospitals and general practitioners, as well as partial reimbursement for costs of prescribed medications.[10] A Civil Personal Registration (CPR) number is assigned to each Danish citizen at birth and to residents upon immigration.[10] This allowed accurate linkage of information among the registries used in this study.

This study was approved by the Danish Data Protection Agency (record numbers: 2008-58-0035 and 2012-41-0914). Use of data obtained from Danish registries for research does not require informed consent or approval from an ethics committee.

Patient clinical history, comorbidity, and medication

All participating WDHR sites use uniform data collection methods predefined in the WDHR electronic data entry form. Data regarding family history of premature CAD (defined as a first-degree relative with a diagnosis of CAD early in life, i.e. father aged ≤55 years or mother aged ≤65 years), smoking, hypertension, dyslipidaemia, and diabetes are collected. Symptoms were classified as typical, atypical, non-anginal chest pain, or dyspnoea (see Supplementary material online, *Table S1*). The pretest likelihood of obstructive CAD was computed according to the Diamond and Forrester risk algorithm.[11] The Danish National Patient Registry (DNPR) contains information on dates of admission to and discharge from all Danish hospitals, emergency departments, and outpatient specialist clinics.[12] Based on diagnosis codes the Charlson Comorbidity Index (CCI) score was computed for each patient (see Supplementary material online, *Table S2*)[13,14] and then categorized as low (CCI score = 0), moderate (CCI score = 1), or severe (CCI score ≥ 2). The Danish National Health Service Prescription Database (DNHSPD) contains information on all reimbursed prescriptions redeemed at Danish pharmacies using the International Anatomical Therapeutic Chemical system.[15] We identified use of aspirin, statins, renin–angiotensin system inhibitors, beta-blockers, diuretics, calcium channel blockers, and/or glucose-lowering drugs, up to 6 months prior to the CCTA procedure date. Hypertension, dyslipidaemia and diabetes were defined using codes from the WDHR, DNPR and/or DNHSPD, respectively (see Supplementary material online, *Table S1*). Registry quality has previously been audited and validated.[8,9,12,15]

Coronary computed tomography angiography acquisition and analysis

Patients were referred to non-emergent CCTA from outpatient clinics and private cardiologist practices (time between referral and CCTA <6 weeks). CCTA was performed on a variety of scanners with a minimum of 64-detector rows. A non-contrast scan was used to assess the Agatston score.[16] All sites used standardized protocols for contrast-enhanced image acquisition.[17] Oral and/or intravenous beta-blockers or ivabradin were recommended for heart rate control (targeting a heart rate <65 b.p.m.), and sublingual nitroglycerin was recommended in all patients. Data acquisition was performed with tube voltage 80–120 kV. Dose-reduction strategies included electrocardiogram (ECG)-gated tube current modulation in retrospective acquisition protocols, reduced tube voltage, use of prospective ECG triggering, and use of prospective ECG-triggered high-pitch acquisition. Experienced local cardiologists or radiologists analysed all CCTA examinations and reported the results to the WDHR. Severity of CAD was categorized as 'no CAD' (0% luminal stenosis and Agatston score = 0), 'non-obstructive CAD' (1–49% luminal stenosis and/or Agatston score > 0), or 'obstructive CAD' (≥50% luminal stenosis). Patients with obstructive disease were subdivided further into those with one-, two-, or three-vessel/left main (LM) CAD.

Posttest treatment

Coronary revascularization [defined as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) procedures] and preventive treatment with aspirin and statins were defined as present when occurring <90 days after the CCTA. This timeframe is consistent with treatment based upon test findings.[18] Coronary revascularizations were identified from the DNPR or WDHR using codes from the Nordic Medico-Statistical Committee's Classification of Surgical Procedures.[19]

Clinical outcome

The study endpoint was a composite of revascularization procedures performed >90 days after the CCTA, MI, and all-cause mortality. We used a hospital diagnosis (primary and/or secondary) in the DNPR to identify patients with MI.[11] All-cause death was ascertained from the Civil Registration System, which maintains complete data on mortality.[9]

Statistical analysis

Patients were characterized in terms of CAD severity. To avoid immortal time bias, we included only time that passed after the posttest treatment window (0–90 days after the CCTA examination) in our calculation of person-time. Using the Kaplan–Meier method, we computed the 91 day–

3.5 year risk of the composite endpoint for patients according to CAD severity. We used Cox proportional-hazards regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs) as a measure of relative risk for the composite endpoint, using patients with no CAD as the reference. Models were adjusted by age (as a continuous variable), sex, comorbidity categories, hypertension, dyslipidaemia, current smoking, family history of premature CAD, diabetes, comorbidity categories, concomitant medications, posttest coronary revascularization, and preventive treatment with aspirin and statins, respectively. We repeated the analyses within age groups (≤55, 56–64, and ≥65 years), sex and comorbidity categories. In sub-analyses, we examined the individual outcomes included in the composite endpoint. The Kaplan–Meier method was used to compute 91 day–3.5 year all-cause mortality risk and Fine and Gray's proportional subhazards model[20] was used to illustrate the cumulative incidence function for non-fatal outcomes, considering all-cause death as a competing risk. The incremental prognostic value of CCTA, in relation to the Diamond–Forrester risk score as well as clinical risk factors (hypertension, dyslipidaemia, current smoking, family history of premature CAD, diabetes) for the composite endpoint, was evaluated by using Harrell's *C*-statistics. Linearity of the continuous variable and the proportional hazards assumption were tested and found to be valid. Missing values for smoking status (16%) and family history of premature CAD (17%) were derived through multiple imputation using chained equations with bootstrapping for each model.[21] All statistical analyses were performed using the STATA statistical software package, version 14.0 (Statacorp, College Station, TX, USA).

Results

Patient characteristics

Coronary computed tomography angiography was performed in 18 414 patients. Of these, 1465 patients were excluded from the analyses (missing CCTA report, *n* = 711; prior revascularization or prior MI, *n* = 754). The remaining 16 949 patients comprised the study cohort. Median (interquartile range, IQR) patient age was 57 (49–65) years and 57% were women. CAD was absent in 9305 (55%) patients, 4900 (29%) patients had non-obstructive CAD, and 2744 (16%) had obstructive CAD. Among patients with obstructive CAD, 1888 (11%) had one-vessel disease, 613 (4%) had two-vessel disease, and 243 (1%) had three-vessel/LM disease. *Table 1* provides detailed characteristics of patients according to the CAD severity.

The estimated median (IQR) effective radiation dose associated with CCTA (including scout, calcium score, test bolus, and the contrast-enhanced scan) was 4.8 (2.1–5.9) mSv. For the purpose of the scan, 67% of the patients received heart rate-lowering medication. Median (IQR) heart rate during CT acquisition was 59 (54–64) b.p.m. Sinus rhythm was present in 99.4% of patients.

During the first 90 days following CCTA, a total of 734 (4.3%) patients underwent coronary revascularization (PCI, *n* = 619; CABG, *n* = 135; both, *n* = 20). Among patients without or non-obstructive CAD, aspirin prescription decreased by 11% (2076 vs. 986 patients) and 2% (1581 vs. 1467 patients), respectively. Among patients with obstructive CAD, aspirin utilization increased by 9% (1115 vs. 1366 patients). Among patients without CAD, statin utilization decreased by 7% (2328 vs. 1639 patients). In patients with non-obstructive or obstructive CAD, statin utilization increased by 5% (1921 vs. 2163 patients) and 19% (1279 vs. 1815 patients), respectively.

Clinical outcomes

Patients were followed for a minimum of 2.0 years (median: 3.57, IQR: 2.75–4.53). Seventeen patients died and two patients were lost to follow-up due to emigration within 90 days following CCTA. The remaining 16 930 patients were followed for the composite endpoint. Overall, 173 (1.0%) patients underwent coronary revascularization (PCI, *n* = 136; CABG, *n* = 46; both, *n* = 9), 105 (0.6%) evolved an MI, and 261(1.5%) died. The cumulative 3.5 year risk of the composite endpoint was positively associated with the severity of CAD (*Table 2* and *Figure 1*). In Cox-regression analyses, the presence of both non-obstructive and obstructive CAD was associated with increasing risk of the composite endpoint, and higher relative risk was associated with more vessels with obstructive lesions (*Table 2* and *Figure 1*). In sub-analyses, the presence of each outcome increased with the severity of CAD (see Supplementary material online, *Tables S3–S5*). By adding CAD severity as assessed by CCTA to a model including the Diamond–Forrester risk score and risk factors improved the *C*-index from 0.64 to 0.72 ($P < 0.0001$) (see Supplementary material online, *Table S6*).

Clinical outcome in relation to age, sex, and comorbidity

Increasing severity of CAD was positively associated with the composite endpoint at all age (*Table 3* and *Figure 2*), sex (*Table 4* and *Figure 3*), and comorbidity categories (*Table 5* and *Figure 4*). The relative risk of the composite endpoint did not differ substantially between women and men, or among comorbidity groups. Of note, differences in 3.5 year cumulative risk between patients without CAD and patients with obstructive CAD were pronounced among patients ≤55 years of age.

Discussion

We showed that, absence of CAD determined by CCTA is associated with a favourable 3.5 year prognosis in patients with suspected CAD and intermediate pretest risk. The presence and extent of CAD convey an increased risk irrespective of age, sex, and burden of comorbidity, even after adjustment for posttest treatment and patient characteristics. Finally, CCTA improved prediction for risk of future events beyond clinical risk assessment.

Our study represents a strategy of real-world practice CCTA testing. Patients had unfettered access to health care with high-quality registry data[8–10,12] hence attenuating issues related to referral and measurement bias. Merging data from these registries by the CPR number enabled us to overcome limitations by adjusting for several important clinical factors, e.g. comorbidity and posttest medication. We ascertained clinical outcome following CCTA testing in patients with new-onset symptoms suggestive of CAD for whom CCTA testing is considered appropriate.[1]

Consistent with the high negative predictive value of CCTA for identification of obstructive CAD,[5–7] we observed that the risk of late coronary revascularization, MI, or all-cause death was low with mean annualized event rates of 0.1%, 0.1%, and 0.3%, respectively, in patients without CAD. Moreover, in accordance with previous literature, we found that the risk of adverse events was associated with CAD severity.[5–7,18] In a single-centre study

Table 1 Patient characteristics by coronary artery disease severity

	No. CAD (n = 9305)	Non-obstructive CAD (n = 4900)	Obstructive CAD (n = 2744)	P-value
Male sex	3452 (37.1)	2371 (48.4)	1493 (54.4)	<0.001
Age (years)				
≤ 55	5369 (57.8)	1434 (29.3)	719 (26.3)	<0.001
56–65	2468 (26.5)	1645 (33.6)	884 (32.3)	<0.001
>65	1462 (15.7)	1815 (37.1)	1134 (41.4)	<0.001
Comorbidity level[a]				
Low	7239 (77.9)	3431 (70.1)	1853 (67.7)	<0.001
Moderate	1370 (14.7)	869 (17.8)	534 (19.5)	<0.001
Severe	690 (7.4)	594 (12.1)	350 (12.8)	<0.001
Cardiac risk factors				
Hypertension	2892 (31.1)	2230 (45.5)	1393 (50.8)	<0.001
Dyslipidaemia	2732 (29.4)	2198 (44.9)	1448 (52.8)	<0.001
Current smoking	1804 (22.6)	1023 (24.0)	618 (25.6)	0.007
Family history of premature CAD	3588 (46.9)	1883 (46.8)	1165 (50.4)	0.008
Diabetes	492 (5.3)	406 (8.3)	285 (10.4)	<0.001
Median body mass index (IQR)	26 (23–29)	26 (23–29)	26 (22–29)	0.12
Concomitant pharmacotherapy				
Aspirin	2073 (22.3)	1580 (32.3)	1109 (40.5)	<0.001
Statins	2325 (25.0)	1919 (39.2)	1278 (46.7)	<0.001
Beta-blockers	1868 (20.1)	1217 (24.9)	795 (29.1)	<0.001
Calcium channel blockers	1094 (11.8)	964 (19.7)	585 (21.4)	<0.001
Renin–angiotensin system inhibitors	2033 (21.9)	1582 (32.3)	1013 (37.0)	<0.001
Diuretics	1206 (13.0)	900 (18.4)	567 (20.7)	<0.001
Coronary CTA indication				
Typical angina	554 (8.8)	397 (11.0)	455 (23.3)	<0.001
Atypical angina	2701 (43.6)	1641 (45.6)	890 (45.5)	0.098
Non-anginal chest pain	2614 (42.2)	1276 (35.5)	456 (23.3)	<0.001
Dyspnoea	335 (5.4)	283 (7.9)	154 (7.9)	<0.001
Pretest likelihood of CAD				
Low	1696 (27.4)	349 (9.7)	117 (6.0)	<0.001
Intermediate	4498 (72.6)	3239 (90.0)	1823 (93.2)	<0.001
High	0	9 (0.2)	15 (0.8)	<0.001
Median Agatston calcium score (IQR)	0 (0–0)	38 (10–115)	136 (27–339)	0.01

Data are numbers (%) unless otherwise indicated. Proportion of patients with missing covariate values: type of angina/equivalent: 5203 (31%), family history of CAD: 2968 (17%), smoking: 2729 (16%), body mass index: 2299 (14%).
CAD, coronary artery disease; CTA, computed tomography angiography; IQR, interquartile range.
[a]Levels of comorbidity burden were based on Charlson Comorbidity Index scores of 0 (low), 1 (moderate), and ≥ 2 (severe).

following 1584 patients suspected of CAD for 5 years, Hadamitzky *et al.*[18] reported a positive association between CAD severity and risk of late revascularization, MI, or death. We added to these findings by demonstrating that the extent of CAD conveys an increased risk of an unfavourable clinical outcome even after adjusting for contemporary posttest treatment.

The overall changes in subsequent preventive treatment (26%) in this study are in line with the 18% change in preventive treatment utilization observed in the multicentre 'Scottish Computed Tomography of the Heart' (SCOT-HEART) study.[22] These findings emphasize the value of frontline CCTA testing in identifying individuals with CAD, who may benefit from preventive medication in clinical practice. The rate of early revascularization in patients with obstructive CAD is in line with the 'Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicentre' (CONFIRM) Registry, which reported 24% of patients with obstructive CAD underwent revascularization.[23] Our finding reflects moderate specificity of CCTA in diagnosing obstructive CAD.[2] Moreover, it may be speculated that among patients with obstructive CAD and severe comorbidity, increased physiological frailty with concomitant increased susceptibility to treatment complications creates reluctance to intensify medical and interventional therapy.

In accordance with previous studies,[6,7] we observed that CCTA is predictive of adverse events within different sex- and age-groups. Regardless of age (<65 vs. ≥65 years), a CONFIRM study comprising 15 187 patients demonstrated that increasing severity of CAD was associated with a higher risk of the composite endpoint including late

Table 2 91 day–3.5 year cumulative risk and hazard ratios with 95% confidence intervals for the composite endpoint

	No. patients	No. events	Risk[a] % (95% CI)	Hazard ratio (95% CI)	
				Unadjusted	Adjusted[b]
No CAD	9299	140	1.51 (1.28–1.78)	1 (reference)	1 (reference)
Non-obstructive CAD	4894	161	3.29 (2.83–3.83)	2.20 (1.76–2.76)	1.28 (1.01–1.63)
Obstructive CAD	2737	185	6.76 (5.88–7.77)	4.62 (3.71–5.75)	2.25 (1.73–2.92)
One-vessel	1885	92	4.88 (4.00–5.96)	3.30 (2.53–4.29)	1.83 (1.37–2.44)
Two-vessel	612	57	9.32 (7.27–11.91)	6.46 (4.75–8.80)	2.97 (2.09–4.22)
Three-vessel/left main	240	36	15.00 (11.06–20.18)	10.71 (7.43–15.45)	4.41 (2.90–6.69)

Composite endpoint comprising late coronary revascularization, myocardial infarction, and all-cause death.
[a]The probability of the endpoint within 3.5 years.
[b]Adjusted for age, sex, comorbidity categories, hypertension, dyslipidaemia, family history of premature CAD, current smoking, diabetes, concomitant medications, posttest coronary revascularization, and preventive treatment with aspirin and statins, respectively.
CAD, coronary artery disease; CI, confidence interval.

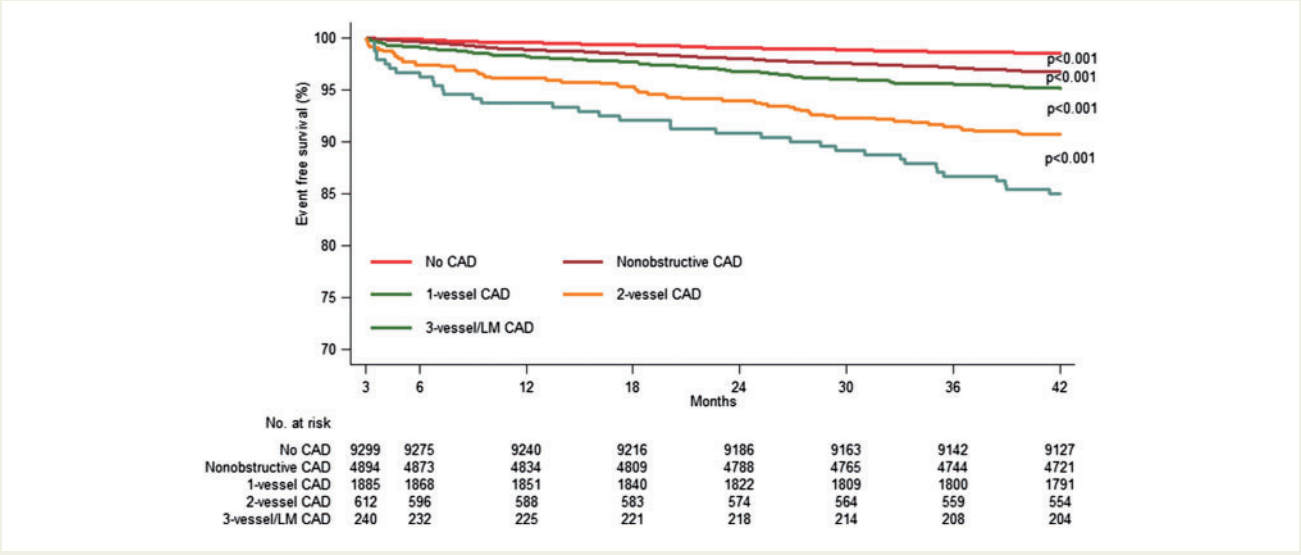

Figure 1 Unadjusted event-free survival from the composite endpoint according to the extent of coronary artery disease. Composite endpoint comprising late coronary revascularization, myocardial infarction, and all-cause death.

revascularization, MI, and all-cause death.[7] However, the fact that patients treated with coronary revascularization within 90 days following CCTA were excluded from the survival analyses in the CONFIRM study[7] may explain the differences between studies (HR: 11.2 vs. 2.25 in this study), because treatment initiated as a consequence of the CCTA findings may modify the natural course of CAD and hence clinical outcomes.[22]

An important novel finding of our study is that CAD severity is predictive of future adverse events irrespective of patients' comorbidity burden. Notably, among patients with severe comorbidity, absence of CAD was associated with a 5.8% cumulative 3.5 year risk of adverse events. This underscores that these patients are *per se* at increased risk of adverse events, resulting in less pronounced HRs in patients with CAD. Accordingly, studies have shown that the presence of conditions such as chronic obstructive pulmonary disease is associated with accelerated atherosclerosis and adverse cardiovascular events.[24]

Evidence on the utility of CCTA beyond traditional risk assessment in patients with suspected CAD is limited. In accordance with a CONFIRM study,[25] we found that CCTA adds an incremental value over Diamond–Forrester risk score and clinical risk factors for predicting future adverse events. Thus, CCTA may be considered for risk reclassification in patients with symptoms suggestive of CAD in real-world practice.

Limitations

Despite the large study population, the rarity of the components of the composite endpoint limited statistical precision in our

Table 3 91 day–3.5 year cumulative risk and hazard ratios with 95% confidence intervals for the composite endpoint according to age

	Age ≤ 55 years			Age 56–65 years			Age > 65 years		
	Risk[a] % (95% CI)	Hazard ratio (95% CI)		Risk[a] % (95% CI)	Hazard ratio (95% CI)		Risk[a] % (95% CI)	Hazard ratio (95% CI)	
		Unadjusted	Adjusted[b]		Unadjusted	Adjusted[b]		Unadjusted	Adjusted[b]
No. CAD	0.86 (0.64–1.15)	1 (reference)	1 (reference)	1.66 (1.23–2.25)	1 (reference)	1 (reference)	3.64 (2.79–4.73)	1 (reference)	1 (reference)
Nonobstructive CAD	1.54 (1.02–2.33)	1.80 (1.08–2.99)	1.31 (0.76–2.25)	3.41 (2.63–4.41)	2.06 (1.38–3.09)	1.69 (1.11–2.58)	4.58 (3.71–5.64)	1.26 (0.89–1.78)	0.94 (0.66–1.33)
Obstructive CAD	4.87 (3.52–6.72)	5.80 (3.73–9.00)	3.31 (1.89–5.79)	4.98 (3.73–6.63)	3.04 (1.99–4.66)	2.22 (1.35–3.66)	9.35 (7.80–11.20)	2.66 (1.91–3.70)	1.81 (1.25–2.61)
1-vessel	4.14 (2.77–6.16)	4.91 (2.98–8.10)	3.03 (1.67–5.48)	3.25 (2.11–5.00)	1.97 (1.15–3.35)	1.63 (0.92–2.91)	6.87 (5.24–8.99)	1.93 (1.31–2.85)	1.38 (0.91–2.10)
2-vessel	6.56 (3.33–12.68)	7.90 (3.72–16.74)	4.08 (1.72–9.64)	8.08 (4.95–13.04)	5.08 (2.81–9.17)	3.89 (2.01–7.54)	11.18 (8.12–15.30)	3.20 (2.08–4.93)	2.24 (1.39–3.60)
3-vessel/ left main	9.76 (3.78–23.94)	11.67 (4.20–32.41)	5.80 (1.84–18.22)	10.84 (5.80–19.80)	6.82 (3.32–14.04)	3.69 (1.59–8.59)	19.83 (13.65–28.31)	6.05 (3.71–9.87)	4.07 (2.38–6.95)

Composite endpoint comprising late coronary revascularization, myocardial infarction, and all-cause death.
CAD, coronary artery disease; CI, confidence interval.
[a]The probability of the endpoint within 3.5 years.
[b]Adjusted for age, sex, comorbidity categories, hypertension, dyslipidaemia, current smoking, family history of premature CAD, diabetes, concomitant medications, posttest coronary revascularization, and preventive treatment with aspirin and statins, respectively.

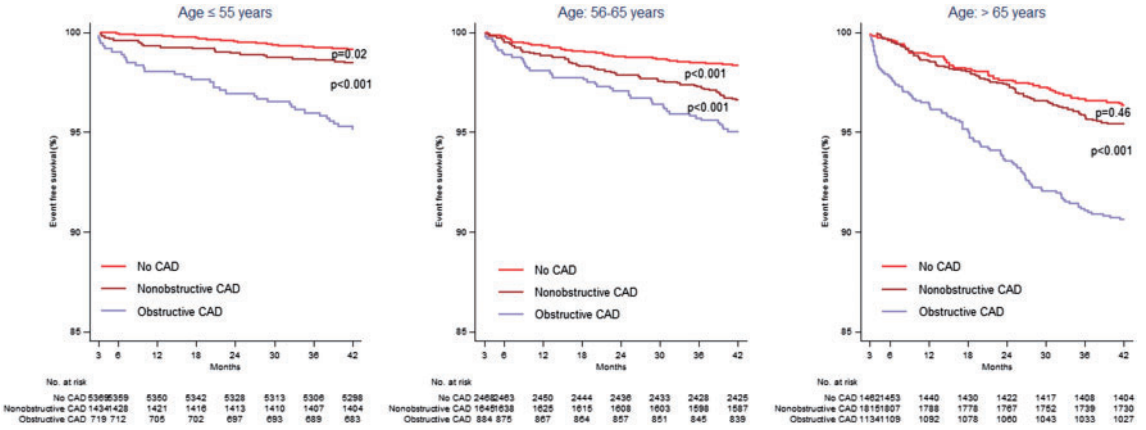

Figure 2 Unadjusted event-free survival from the composite endpoint according to age and severity of coronary artery disease. Composite endpoint comprising late coronary revascularization, myocardial infarction, and all-cause death.

Table 4 91 day–3.5 year cumulative risk and hazard ratios with 95% confidence intervals for the composite endpoint according to sex

	Women			Men		
	Risk[a] % (95% CI)	Hazard ratio (95% CI)		Risk[a] % (95% CI)	Hazard ratio (95% CI)	
		Unadjusted	Adjusted[b]		Unadjusted	Adjusted[b]
No CAD	1.44 (1.16–1.78)	1 (reference)	1 (reference)	1.63 (1.26–2.11)	1 (reference)	1 (reference)
Non-obstructive CAD	3.01 (2.41–3.76)	2.11 (1.55–2.88)	1.20 (0.86–1.67)	3.60 (2.92–4.43)	2.23 (1.59–3.13)	1.34 (0.94–1.92)
Obstructive CAD	5.84 (4.67–7.30)	4.16 (3.04–5.69)	2.17 (1.51–3.13)	7.53 (6.30–9.00)	4.78 (3.47–6.57)	2.32 (1.59–3.39)
One-vessel	3.96 (2.86–5.47)	2.79 (1.88–4.13)	1.62 (1.05–2.48)	5.70 (4.43–7.33)	3.59 (2.48–5.19)	1.99 (1.32–3.00)
Two-vessel	9.19 (6.31–13.30)	6.65 (4.25–10.39)	3.32 (2.02–5.46)	9.42 (6.76–13.06)	6.08 (3.94–9.39)	2.74 (1.66–4.51)
Three-vessel/ left main	13.98 (8.37–22.85)	10.68 (5.96–19.16)	4.42 (2.32–8.41)	15.65 (10.69–22.60)	10.22 (6.29–16.60)	4.48 (2.56–7.84)

Composite endpoint comprising late coronary revascularization, myocardial infarction, and all-cause death.
CAD, coronary artery disease; CI, confidence interval.
[a]The probability of the endpoint within 3.5 years.
[b]Adjusted for age, comorbidity categories, hypertension, dyslipidaemia, current smoking, family history of premature CAD, diabetes, concomitant medications, posttest coronary revascularization, and preventive treatment with aspirin and statins, respectively.

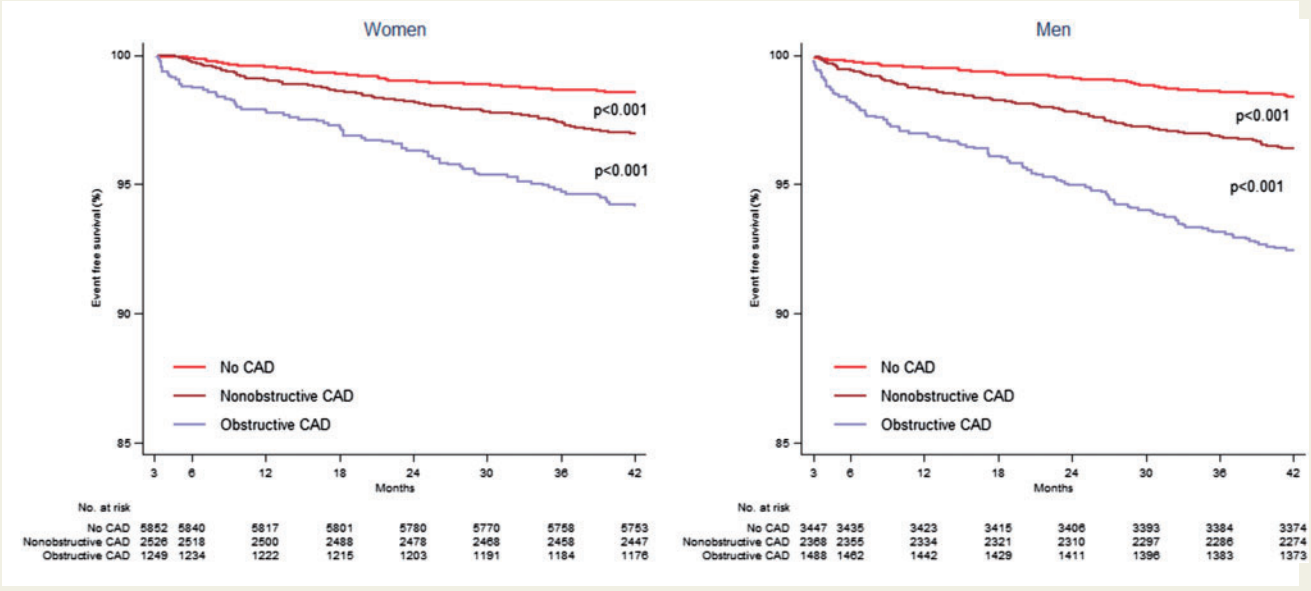

Figure 3 Unadjusted event-free survival from the composite endpoint according to sex and severity of coronary artery disease. Composite endpoint comprising late coronary revascularization, myocardial infarction, and all-cause death.

subgroup analyses. Data for individual coronary artery segments were not available for this study. Moreover, data regarding cardiac death were not available. However, use of all-cause death reduces detection bias. Any misclassification of covariates resulting from incomplete registration most likely would be independent of the diagnosis of CAD. Data related to CCTA non-evaluability were not available. We cannot exclude inter-observer and inter-site variability in CCTA diagnosis and posttest treatment. However, this study was based on multiple sites within the same country, and therefore, heterogeneity regarding CCTA education and choice of treatment may be small.

Conclusion

The extent of CAD determined by CCTA in clinical practice predicts clinical outcome for up to 3.5 years, across different groups of age, sex, or comorbidity burden. The present findings substantiate the real-world use of CCTA testing in patients suspected of CAD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Table 5 91 day–3.5 year cumulative risk and hazard ratios with 95% confidence intervals for the composite endpoint according to comorbidity burden

	Low comorbidity[a]			Moderate comorbidity[a]			Severe comorbidity[a]		
	Risk[b] % (95% CI)	Hazard ratio (95% CI)		Risk[b] % (95% CI)	Hazard ratio (95% CI)		Risk[b] % (95% CI)	Hazard ratio (95% CI)	
		Unadjusted	Adjusted[c]		Unadjusted	Adjusted[c]		Unadjusted	Adjusted[c]
No CAD	1.04 (0.83–1.30)	1 (reference)	1 (reference)	1.83 (1.24–2.70)	1 (reference)	1 (reference)	5.80 (4.29–7.82)	1 (reference)	1 (reference)
Nonobstructive CAD	2.13 (1.70–2.67)	2.06 (1.50–2.85)	1.25 (0.88–1.76)	4.04 (2.91–5.58)	2.22 (1.33–3.72)	1.55 (0.90–2.65)	8.93 (6.90–11.53)	1.56 (1.03–2.35)	1.06 (0.69–1.64)
Obstructive CAD	4.80 (3.92–5.88)	4.73 (3.48–6.42)	2.24 (1.54–3.25)	9.38 (7.19–12.19)	5.36 (3.32–8.66)	3.51 (2.01–6.10)	13.14 (10.01–17.15)	2.35 (1.54–3.60)	1.48 (0.90–2.44)
1-vessel	3.69 (2.80–4.86)	3.61 (2.52–5.17)	1.92 (1.28–2.89)	6.04 (3.94–9.21)	3.38 (1.88–6.08)	2.40 (1.27–4.54)	10.18 (6.88–14.92)	1.80 (1.08–3.00)	1.23 (0.70–2.15)
2-vessel	7.48 (5.26–10.59)	7.51 (4.89–11.52)	3.14 (1.91–5.18)	13.42 (8.88–20.03)	7.87 (4.37–14.17)	5.75 (2.91–11.36)	10.67 (5.48–20.20)	1.85 (0.87–3.95)	1.19 (0.53–2.70)
3-vessel/ left main	7.97 (4.50–13.93)	7.88 (4.18–14.83)	3.26 (1.61–6.59)	18.87 (10.63–32.23)	11.53 (5.54–24.01)	8.29 (3.63–18.96)	30.61 (19.72–45.55)	6.22 (3.44–11.26)	3.99 (1.98–8.03)

Composite endpoint comprising late coronary revascularization, myocardial infarction, and all-cause death.
CAD, coronary artery disease; CI, confidence interval.
[a]Levels of comorbidity burden were based on Charlson Comorbidity Index scores of 0 (low), 1 (moderate), and ≥ 2 (severe).
[b]The probability of the endpoint within 3.5 years.
[c]Adjusted for age, sex, hypertension, dyslipidaemia, current smoking, family history of premature CAD, diabetes, concomitant medications, posttest coronary revascularization, and preventive treatment with aspirin and statins, respectively.

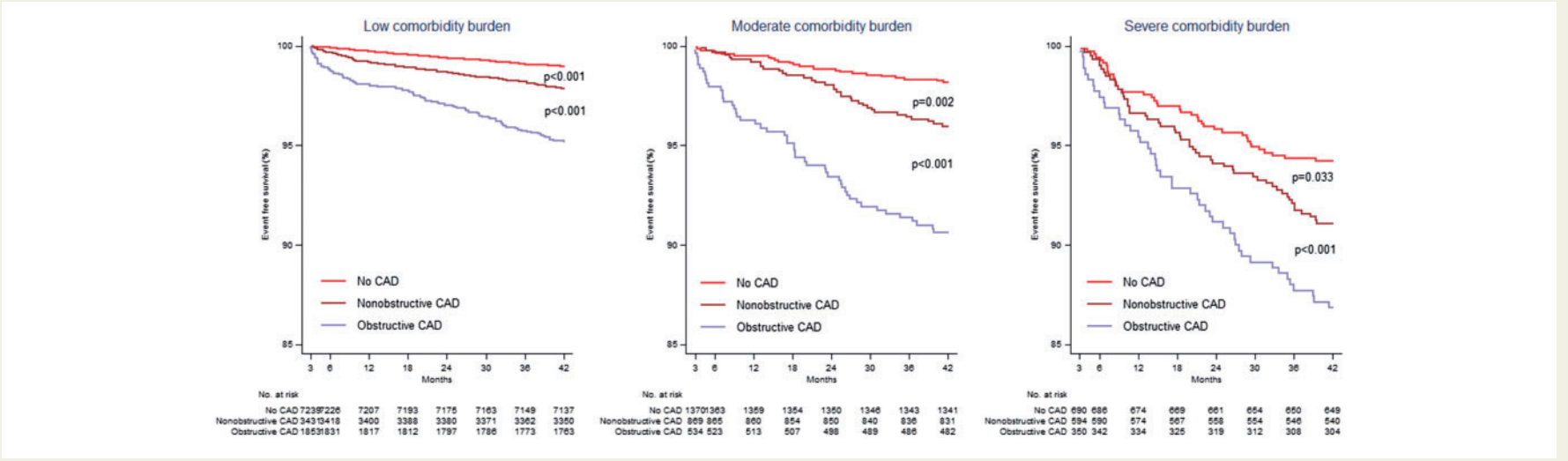

Figure 4 Composite endpoint comprising late coronary revascularization, myocardial infarction, and all-cause death. Levels of comorbidity burden were based on Charlson Comorbidity Index scores of 0 (low), 1 (moderate), and ≥ 2 (severe).

Funding

Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation. The funding source had no role in the design, conduct, analysis, or reporting of the study.

Conflict of interest: B.L.N. has received unrestricted research grants from Siemens, Edwards Lifescience, and HeartFlow. J.M.J. has received speaker compensation from Bracco. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

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