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Associations between dyspnoea, coronary atherosclerosis, and cardiovascular outcomes: results from the long-term follow-up CONFIRM registry

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Aims The relationship between dyspnoea, coronary artery disease (CAD), and major cardiovascular events (MACE) is poorly understood. This study evaluated (i) the association of dyspnoea with the severity of anatomical CAD by coronary computed tomography angiography (CCTA) and (ii) to which extent CAD explains MACE in patients with dyspnoea.

Methods and results From the international COronary CT Angiography EvaluatioN for Clinical Outcomes: An InteRnational Multicenter (CONFIRM) registry, 4425 patients (750 with dyspnoea) with suspected but without known CAD were included and prospectively followed for ≥5 years. First, the association of dyspnoea with CAD severity was assessed using logistic regression analysis. Second, the prognostic value of dyspnoea for MACE (myocardial infarction and death), and specifically, the interaction between dyspnoea and CAD severity was investigated using Cox proportional-hazard analysis. Mean

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patient age was 60.3 ± 11.9 years, 63% of patients were male and 592 MACE events occurred during a median follow-up duration of 5.4 (IQR 5.1–6.0) years. On uni- and multivariable analysis (adjusting for age, sex, body mass index, chest pain typicality, and risk factors), dyspnoea was associated with two- and three-vessel/left main (LM) obstructive CAD. The presence of dyspnoea increased the risk for MACE [hazard ratio (HR) 1.57, 95% confidence interval (CI): 1.29–1.90], which was modified after adjusting for clinical predictors and CAD severity (HR 1.26, 95% CI: 1.02–1.55). Conversely, when stratified by CAD severity, dyspnoea did not provide incremental prognostic value in one-, two-, or three-vessel/LM obstructive CAD, but dyspnoea did provide incremental prognostic value in non-obstructive CAD.

Conclusion In patients with suspected CAD, dyspnoea was independently associated with severe obstructive CAD on CCTA. The severity of obstructive CAD explained the elevated MACE rates in patients presenting with dyspnoea, but in patients with non-obstructive CAD, dyspnoea portended additional risk.

Keywords coronary artery disease • coronary computed tomography angiography • dyspnoea • prognosis

Introduction

Patients presenting with dyspnoea comprise a diagnostic challenge, since symptoms can be caused by multiple cardiac and non-cardiac diseases, including coronary artery disease (CAD), heart failure, pulmonary disease (e.g. chronic obstructive pulmonary disease or lung fibrosis), neuro-muscular disease, or psychogenic disorders (e.g. hyperventilation syndrome). An extensive clinical evaluation may clarify the diagnosis, but often the symptoms remain unexplained and additional diagnostic testing is needed .

Dyspnoea can be secondary to CAD (also referred to as 'angina-equivalent') that causes myocardial ischaemia, ischaemic left ventricular (LV) dysfunction, and increased LV filling pressures.[1] Some studies that evaluated patients with suspected CAD who presented with dyspnoea reported a significant association with myocardial ischaemia[2,3] while other studies did not.[4–6] However, all studies consistently showed that dyspnoea has a significant impact on prognosis.[2–6] To which extent CAD (or its consequence, myocardial ischaemia) contributes to the association of dyspnoea and impaired outcome is therefore uncertain .

The presence and extent of myocardial ischaemia have traditionally been assessed with stress testing (stress echocardiography,[2,6] single-photon emission computed tomography,[3,4] or exercise stress testing[5]), which may underestimate CAD in the presence of balanced ischaemia.[7] Coronary computed tomography angiography (CCTA) is more sensitive for the detection of CAD because it directly visualizes coronary atherosclerosis (as compared with an indirect assessment of CAD with stress testing).[8] The COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) is the largest registry including patients undergoing CCTA for suspected CAD and has systematically collected prospective, long-term follow-up data for major cardiovascular events (MACE).[9,10] Accordingly, data from the CONFIRM registry were used to (i) evaluate the association of dyspnoea with the severity of anatomical CAD and vice versa and (ii) to which extent anatomical CAD severity contributes to the elevated rates of MACE among patients presenting with dyspnoea.

Methods

Patients

The CONFIRM registry is a dynamic, international, multicentre, observational cohort that prospectively collects clinical, procedural, and follow-up data from patients who underwent ≥64 slice CCTA for clinically suspected CAD, as previously described.[9] The current analysis concerned patients from the long-term follow-up cohort of the CONFIRM registry, which included patients with ≥5 years follow-up for major events from 17 participating sites from nine countries between 2002 and 2009. We included patients without known CAD [defined as previous myocardial infarction (MI), coronary artery bypass grafting, or coronary revascularization] before CCTA acquisition. The institutional review board approval was obtained for all participating sites, with either informed consent or waiver of informed consent.[11]

Clinical data collection

Standardized data collection was performed at the participating centres. Each patient was evaluated by a physician or nurse before CCTA and demographical and clinical information was systematically obtained.[9] Cardiovascular risk factors included diabetes, hypertension, hypercholesterolaemia, familial history of CAD, and current smoking as defined previously.[12–14] Suspected cardiac symptoms, such as CCTA indication, were categorized as non-anginal, atypical and typical chest pain, and dyspnoea. Dyspnoea was defined as whether patients experienced shortness of breath and was binary classified. Chest pain symptoms could be present together with dyspnoea.

CCTA image acquisition and interpretation

CCTA acquisition protocols at each site were in adherence with the Society of Cardiovascular Computed Tomography guidelines.[15] Specific details regarding the acquisition were previously described.[9] Level III-trained experts uniformly interpreted the CT images using a 16-segment coronary artery tree model. For each coronary artery segment, the presence of atherosclerosis was reported with corresponding stenosis severity. The stenosis severity of coronary artery atherosclerosis was categorized as normal (0% stenosis), non-obstructive (1–49% stenosis), or obstructive CAD (≥50% stenosis) by visual assessment. Subsequently, the severity of CAD was categorized as no CAD, non-obstructive CAD, one coronary artery with ≥50% stenosis in any coronary segment, two coronary arteries with ≥50% stenosis, and three coronary arteries and/or left main (LM) with ≥50% stenosis.[12] LV ejection fraction was calculated from CCTA as previously described.[16]

Outcomes

First, we evaluated the association of dyspnoea with CAD severity. Second, the relation of dyspnoea (and the influence of CAD) with MACE was assessed, defined as a composite endpoint of all-cause death and non-fatal MI. Each local institution systematically performed patient

follow-up by a dedicated physician or nurse.[9] The Social Security Index was reviewed for assessment of mortality within the United States or determined through email or telephone contact with the patients, family, or physician or review of medical records for the other countries. MI events were collected through a combination of direct interviewing of patients using scripted interview with confirmation of the event by screening patient's medical files, in accordance with the universal definition of MI.[9,17]

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD); categorical variables as frequencies with percentages. Continuous data were compared using the Student's *t*-test and one-way analysis of variance (ANOVA) analysis for multiple groups. Categorical variables were compared with the χ^2 test. The association of dyspnoea with CAD severity subgroups was evaluated using logistic regression analysis; odds ratios with 95% confidence intervals (CIs) were derived. Demographical and clinical variables, which were significantly associated with increasing CAD severity, were entered in multivariable models (multinominal logistic regression) to assess the independent association of dyspnoea with CAD. The Kaplan–Meier method was utilized to depict 5-year MACE-free survival rates for the presence vs. absence of dyspnoea and the CAD severity subgroups (normal, non-obstructive CAD, one-, two-, and three-vessel/LM CAD); comparisons were made with the log-rank test. Uni- and multivariable Cox-proportional hazard analyses were performed, and hazard ratios (HRs) were derived to assess the prognostic impact of dyspnoea on MACE, with significant univariate predictors ($P < 0.10$) entered in multivariable models. Adjusted MACE-free survival curves were provided for the presence or absence of dyspnoea among patients with no, non-obstructive, and obstructive CAD. Furthermore, whether the prognostic value of dyspnoea was modified by the severity of CAD was tested with an interaction term for dyspnoea and CAD severity, which was included in a multivariable model together with the two main effects. A two-sided *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS statistics (version 24, IBM, Armonk, NY, USA).

Table 1 Patient characteristics

	Dyspnoea ($n = 750$)	No dyspnoea ($n = 3675$)	*P*-value
Age (years)	62.1 ± 12.3	59.9 ± 11.8	<0.001
Male (gender)	416 (56)	2371 (64)	<0.001
BMI (kg/m^2)	28.1 ± 6.0	26.9 ± 4.5	<0.001
Chest pain symptoms			<0.001
No chest pain	229 (32.6)	1557 (42.7)	
Non-anginal	108 (15.4)	255 (7.0)	
Atypical	226 (32.2)	1287 (35.3)	
Typical	139 (19.8)	544 (14.9)	
Cardiovascular risk factors			
Diabetes	190 (25.5)	572 (15.6)	<0.001
Hypertension	487 (65.4)	1904 (52.0)	<0.001
Hypercholesterolaemia	422 (56.6)	1976 (53.9)	0.190
Family history for CAD	193 (26.4)	1111 (30.6)	0.023
Current smoker	134 (18.1)	679 (18.6)	0.747
Medication use			
Aspirin	265 (43.3)	954 (28.7)	<0.001
Beta blocker	210 (34.4)	933 (28.1)	0.002
ACE-I	125 (20.5)	653 (19.7)	0.655
Statin	270 (44.1)	1207 (36.2)	<0.001
Coronary CTA findings			<0.001
Non-obstructive CAD	214 (28.5)	1055 (28.7)	
One-vessel obstructive CAD	147 (19.6)	700 (19.0)	
Two-vessel obstructive CAD	90 (12.0)	330 (9.0)	
Three-vessel/left main obstructive CAD	78 (10.4)	272 (7.4)	

Values are expressed as mean ± standard deviation or counts (%).
ACE-I, angiotensin converting enzyme-inhibiter; BMI, body mass index; CAD, coronary artery disease.

Results

Patients

Of the 4425 patients included in the current analysis, 750 (17%) had dyspnoea as presenting symptom. Patients with dyspnoea were significantly older (62.1 ± 12.3 vs. 59.9 ± 11.8 years, $P < 0.001$), less often male (56% vs. 64%, $P < 0.001$), had a higher body mass index (BMI 28.1 ± 6.0 vs. 26.9 ± 4.5 kg/m^2), more frequently presented with concomitant typical angina (19.8% vs. 14.9%) and more often reported no chest pain (42.7% vs. 32.6%; overall $P < 0.001$) vs. absence of dyspnoea (*Table 1*). Patients with dyspnoea had a higher prevalence of two- and three-vessel/LM obstructive CAD than patients without dyspnoea: 12.0% vs. 9.0% and 10.4% vs. 7.4%, respectively, overall $P < 0.001$. Of interest, patients presenting with dyspnoea did not smoke more frequently (18.1% vs. 18.6%, $P = 0.747$).

Association of dyspnoea with CAD

The clinical characteristics associated with CAD are shown in *Table 2*. Dyspnoea was more prevalent with increasing severity of CAD; 16.9% in patients with non-obstructive CAD vs. 22.3% in patients with three-vessel/LM obstructive CAD ($P < 0.001$). Other clinical variables significantly associated with increasing CAD severity were age, male gender, typical chest pain, diabetes, hypertension, hypercholesterolaemia, and current smoking ($P < 0.001$ for all). In multivariable analysis adjusting for age, sex, chest pain typicality, and cardiovascular risk factors, two- and three-vessel/LM obstructive CAD were independently associated with dyspnoea: odds ratio (OR) 1.43 (95% CI: 1.04–1.98) and 1.56 (95% CI: 1.11–2.21), respectively (*Figure 1*). With further adjustment for statin, aspirin, and beta blocker use, only three-vessel/LM obstructive CAD remained significant (OR 1.48, 95% CI: 1.02–2.15). No significant association was observed between dyspnoea and non-obstructive, or one-vessel obstructive CAD.

Prognostic value of dyspnoea for MACE

During a median follow-up duration of 5.4 years (25–75% interquartile range 5.1–6.0 years), a total of 592 MACE events occurred. Dyspnoea was associated with a 57% increased risk for MACE (HR 1.57, 95% CI: 1.29–1.90; $P < 0.001$; *Table 3*). Other important prognostic factors on univariable analysis were age, sex, typical chest pain, diabetes, hypertension, currently smoking and CAD severity. After adjusting for these variables, dyspnoea remained significantly associated with MACE, but the effect magnitude was modified (HR 1.26, 95% CI 1.02–1.55; $P = 0.029$).

Table 2 Associations between clinical characteristics and CAD

	Normal ($n = 1539$)	CAD ≤50% ($n = 1269$)	1-VD ≥50% ($n = 847$)	2-VD ≥50% ($n = 420$)	3-VD/left main ≥50% ($n = 350$)	*P*-value
Age (years)	54.5 ± 12.6	61.9 ± 10.4	63.5 ± 10.0	64.9 ± 10.0	66.8 ± 9.6	<0.001
Male (gender)	791 (51.4)	811 (63.9)	600 (70.8)	101 (76.0)	263 (75.1)	<0.001
BMI (kg/m^2)	27.0 ± 4.9	27.6 ± 5.2	26.9 ± 4.7	27.3 ± 4.4	26.7 ± 3.7	0.003
Cardiac symptoms						<0.001
No chest pain	633 (41.8)	589 (47.2)	305 (36.8)	155 (37.5)	104 (30.5)	
Non-anginal	147 (9.7)	97 (7.8)	59 (7.1)	35 (8.5)	25 (7.3)	
Atypical	570 (37.6)	451 (36.1)	280 (33.8)	111 (26.9)	101 (29.6)	
Typical	164 (10.8)	111 (8.9)	185 (22.3)	112 (27.1)	111 (32.6)	
Dyspnoea	221 (14.4)	214 (16.9)	147 (17.4)	90 (21.4)	78 (22.3)	<0.001
Cardiovascular risk factors						
Diabetes	193 (12.6)	174 (13.7)	174 (20.6)	105 (25.3)	116 (33.3)	<0.001
Hypertension	662 (43.1)	703 (55.6)	504 (59.8)	277 (66.7)	245 (70.4)	<0.001
Hypercholesterolaemia	653 (42.5)	747 (59.0)	527 (62.4)	252 (60.4)	219 (63.3)	<0.001
Family history for CAD	463 (30.5)	375 (29.6)	243 (29.2)	117 (28.4)	106 (31.1)	0.878
Current smoker	248 (16.3)	214 (16.9)	177 (21.0)	89 (21.4)	85 (24.6)	<0.001

Values are expressed as mean ± standard deviation or counts (%).
BMI, body mass index; CAD, coronary artery disease; VD, vessel disease.

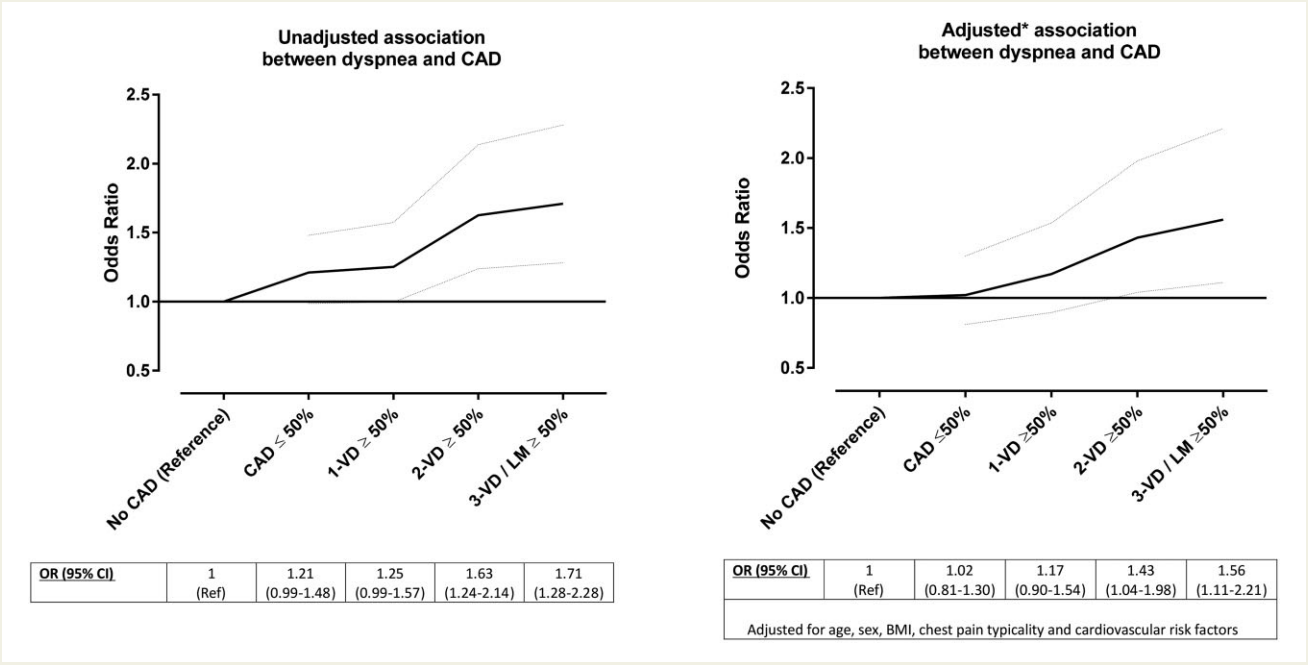

Figure 1 Association of dyspnoea with severity of CAD. On uni- and multivariable analysis, dyspnoea was significantly associated with two- and three-vessel/left main obstructive CAD. CAD, coronary artery disease.

Interaction between dyspnoea and CAD severity

Among patients with one-, two-, or three-vessel/LM obstructive CAD, dyspnoea did not portend independent prognostic value (*Table 4*). In patients with non-obstructive CAD, dyspnoea was independently associated with elevated MACE rates (HR 1.59, 95 CI: 1.09–2.32; $P = 0.017$), after adjusting for age, sex, chest pain typicality, diabetes, hypertension, and current smoking. When separating the primary outcome, dyspnoea was only significantly associated with all-cause mortality in patients with non-obstructive CAD (HR 1.83, 95% CI: 1.14–2.93; $P = 0.012$), but not with MI (HR 1.51, 95% CI:

Table 3 Cox proportional hazard analysis for MACE

	Univariable HR (95% CI)	*P*-value	Multivariable HR (95% CI)	*P*-value
Age (years)	1.04 (1.04–1.05)	<0.001	1.03 (1.02–1.04)	<0.001
Male (gender)	0.87 (0.74–1.03)	0.102	0.77 (0.64–0.93)	0.005
BMI (kg/m^2)	1.01 (1.00–1.03)	0.106	–	
Cardiac symptoms		0.001		0.681
No chest pain	Ref		Ref	
Non-anginal	1.41 (1.05–1.89)		1.17 (0.87–1.57)	
Atypical	1.15 (0.95–1.41)		1.11 (0.90–1.35)	
Typical	1.58 (1.25–1.29)		1.05 (0.82–1.33)	
Dyspnoea	1.57 (1.29–1.90)	<0.001	1.26 (1.02–1.55)	0.029
Cardiovascular risk factors				
Diabetes	1.75 (1.44–2.12)	<0.001	1.38 (1.13–1.68)	0.001
Hypertension	1.75 (1.46–2.01)	<0.001	1.35 (1.12–1.63)	0.002
Hypercholesterolaemia	0.87 (0.74–1.03)	0.115	–	
Family history for CAD	0.95 (0.79–1.15)	0.607	–	
Current smoker	1.44 (1.19–1.75)	<0.001	1.42 (1.16–1.74)	0.001
Coronary CTA findings				
Normal	Ref		Ref	Ref
Non-obstructive CAD	2.64 (2.01–3.46)	<0.001	2.21 (1.66–2.94)	<0.001
One-vessel obstructive CAD	4.69 (3.56–6.15)	<0.001	3.66 (2.73–4.92)	<0.001
Two-vessel obstructive CAD	5.39 (3.97–7.31)	<0.001	4.15 (2.98–5.78)	<0.001
Three-vessel/left main obstructive CAD	7.75 (5.74–10.4)	<0.001	5.28 (3.79–7.37)	<0.001

BMI, body mass index; CAD, coronary artery disease; MACE, major adverse cardiac events; Ref, reference category.

0.85–2.68; $P = 0.161$). When excluding patients with typical angina, results were similar and in non-obstructive CAD dyspnoea was associated with MACE (*Appendix Table A1*).

The Kaplan–Meier curves showed significant differences in 5-year cumulative event-free survival for the CAD severity subgroups (95.6% for no CAD vs. 70.8% for three-vessel/LM obstructive CAD, $P < 0.001$) and for the absence vs. presence of dyspnoea (88.0% vs. 82.5%, $P < 0.001$; *Figure 2*). Adjusted MACE-free survival analyses visualize the lowest event rates for patients without CAD, and the worst outcomes among patients with obstructive CAD, regardless of dyspnoea (*Figure 3*). Among patients with non-obstructive CAD, the presence of dyspnoea was significantly associated with increased MACE risk ($P = 0.017$). Exploratory analyses demonstrated that in non-obstructive CAD, dyspnoeic patients were more likely to be female, have diabetes, hypertension, had an elevated BMI, but did not have a lower LVEF (59.5 ± 18.7% vs. 60.7 ± 11.7%, $P = 0.539$; *Appendix Table A2*).

Discussion

Among patients without known CAD referred for CCTA, dyspnoea is independently associated with severely obstructive CAD. Secondly, dyspnoea was predictive for MACE, but this effect was significantly modified after adjusting for clinical variables and anatomical CAD severity. In patients with obstructive CAD, all-cause death and MI were determined by CAD severity and the presence of dyspnoea did not increase long-term risk for MACE. However, in patients with non-obstructive CAD, excess risk for MACE (especially all-cause mortality) existed for dyspnoea.

Dyspnoea and CAD

Dyspnoea as presenting symptom can be a sign of symptomatic CAD (angina equivalent); therefore, these patients frequently undergo diagnostic testing to detect or exclude CAD. Coronary atherosclerosis may lead to myocardial ischaemia which provokes diastolic dysfunction that subsequently leads to dyspnoea.[1] Ilia *et al.*[18] elegantly investigated the relationship between shortness of breath, LV filling pressures, and the severity of CAD assessed by invasive coronary angiography and observed that increasing severity of CAD was correlated with worsening grades of shortness of breath and increasing LV end-diastolic pressures. However, relatively little is known about the prevalence and severity of CAD among patients presenting with dyspnoea and unexpected results have been reported in comparison to patients presenting with chest pain. A meta-analysis including 24 491 patients with chest pain and 5753 patients with dyspnoea who underwent stress testing, observed myocardial ischaemia in 37.5% of patients with dyspnoea, which was similar to patients presenting with chest pain (36.5%).[19] Among 17 991 patients with suspected CAD, Abidov *et al.*[4] reported the prevalence of ischaemia in patients with dyspnoea vs. absence of symptoms, and observed only a minor increased incidence of ischaemia (19.4% vs. 16.7%) and no difference in percentage of ischaemia myocardium (2.4% vs. 2.2%). In contrast, the incidence of myocardial ischaemia and the percentage of ischaemia myocardium in the left ventricle were much higher in patients

Table 4 Prognostic value of dyspnoea according to CAD severity

	Adjusted HR for MACE (95% CI)[a]					
	Normal ($n = 1539$) events=77	**CAD ≤50% ($n = 1269$) events=161**	**1-VD ≥50% ($n = 847$) events=164**	**2-VD ≥50% ($n = 420$) events=90**	**3-VD/left main ≥50% ($n = 350$) events=100**	***P*-interaction[b]**
Dyspnoea	1.73 (0.99–3.02) $P = 0.053$	1.59 (1.09–2.32) $P = 0.017$	1.02 (0.65–1.59) $P = 0.994$	1.38 (0.83–2.31) $P = 0.219$	0.77 (0.46–1.31) $P = 0.341$	0.031

CAD, coronary artery disease; HR, hazard ratio; MACE, major adverse cardiac events; VD, vessel disease.
[a]Adjusted for age, sex, chest pain typicality, diabetes, hypertension, and current smoking.
[b]*P*-value for interaction term between CAD severity and dyspnoea when entered in the multivariable model with: age, sex, chest pain typicality, diabetes, hypertension, and current smoking, CAD severity, and dyspnoea.

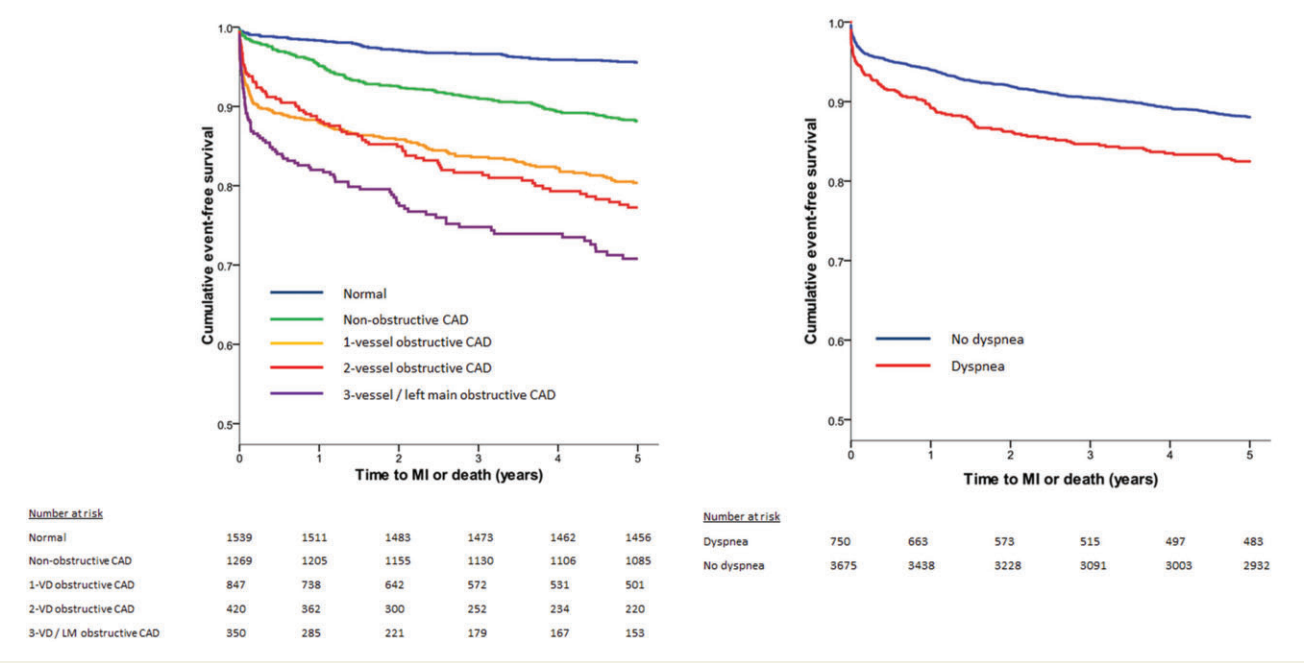

Figure 2 Kaplan–Meier MACE-free survival curves for patients according to CAD severity and dyspnoea. Five-year cumulative event-free survival curves show the graded increase of events with increasing CAD severity and higher MACE rates for dyspnoea vs. absence of dyspnoea (log-rank $P<0.001$). CAD, coronary artery disease; MACE, major adverse cardiac events.

presenting with typical angina (30.1% and 4.4%). These data did not convincingly support that patients presenting with dyspnoea can have a large burden of myocardial ischaemia. Nor did they identify myocardial ischaemia as a mediator in the relationship between dyspnoea and MACE.[4] Associations between dyspnoea and myocardial ischaemia have been largely investigated with relative perfusion imaging techniques (single-photon emission computed tomography), which may have reduced accuracy in the presence of balanced ischaemia, provoked by severe, multivessel disease.[7,20] Accordingly, the prevalence of CAD in patients presenting with dyspnoea may have even been underestimated.

This study examined this specific question using CCTA, which is highly sensitive test to quantify the extent and severity of coronary atherosclerosis. We observed an independent association of dyspnoea with two- and three-vessel/LM obstructive CAD only, which supports this hypothesis of anatomically severe CAD, leading to myocardial ischaemia, diastolic dysfunction, and dyspnoea. These findings are in line with Nakanishi *et al.*,[21] who demonstrated among 1443 patients without known CAD that dyspnoea is associated with ≥70% stenosis and proximal coronary plaque on CCTA. Given the strong prognostic value of CAD severity for MACE, obstructive CAD will likely interact in the association between dyspnoea and elevated rates of MACE.

Dyspnoea and prognosis

Studies have consistently shown that dyspnoea is associated with worse outcome among patients with suspected CAD.[2–6] The previously mentioned meta-analysis[19] reported a 2.57 times increased mortality risk for dyspnoea vs. chest pain among 30 244 patients. Also, the largest individual study which examined 17 991 patients

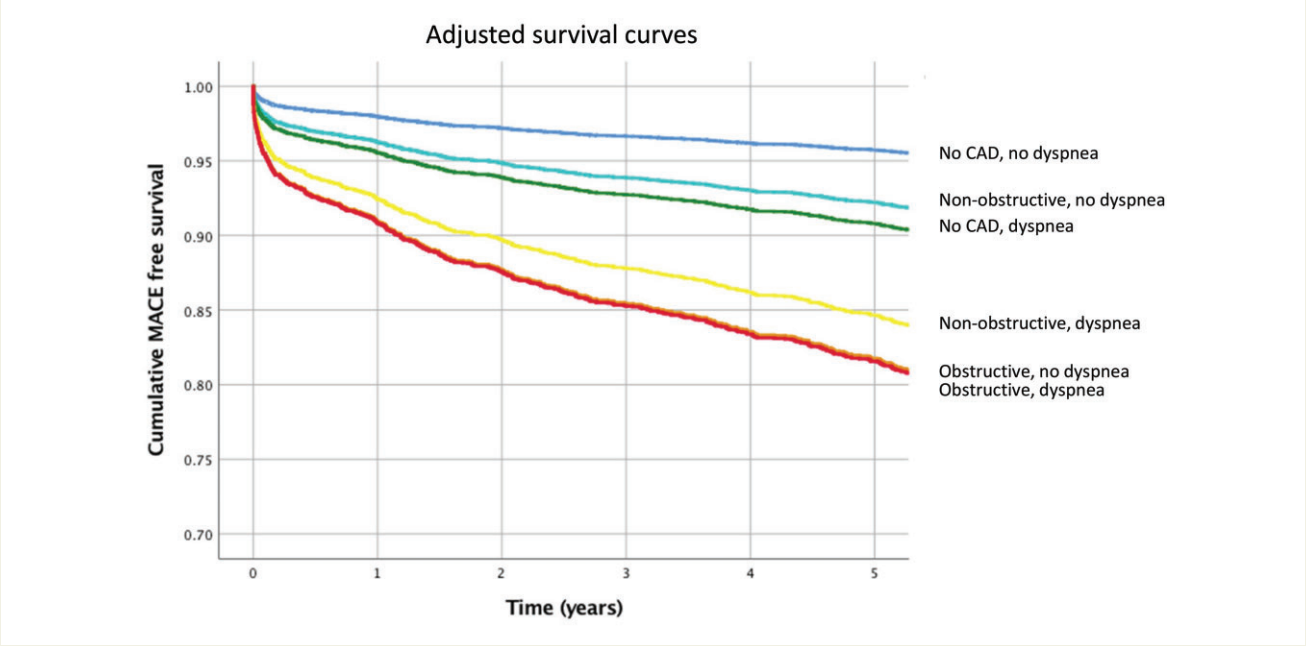

Figure 3 Interaction between dyspnoea and CAD severity on 5-year survival. Five-year cumulative event-free survival curves for the presence of dyspnoea among patients without CAD, with non-obstructive and obstructive CAD after adjusting for age, sex, chest pain typicality, diabetes, hypertension, and current smoking. Dyspnoea was associated with increased MACE risk in non-obstructive CAD only (P=0.017) and showed a trend in normal CCTA (P=0.053). The curves were overlapping in patients with obstructive CAD. CAD, coronary artery disease; MACE, major adverse cardiac events.

using single-photon emission computed tomography demonstrated a 1.82 (95% CI: 1.30–2.55) times increased risk for cardiac death of dyspnoea vs. absence of cardiac symptoms. After extensive multivariable modelling, including the percentage of myocardium with fixed defects and ischaemia, the effect was only little modified to 1.76 (95% CI: 1.25–2.47), which was consistent with the only mildly increased burden of ischaemia in patients with dyspnoea.

We observed that dyspnoea was associated with severely obstructive CAD, and among patients with obstructive CAD, all-cause death, and MI were determined by CAD severity, without additional prognostic effect of dyspnoea. Among patients with non-obstructive CAD, dyspnoea was significantly associated with increased MACE risk. Given the absence of association between dyspnoea with the presence vs. absence of non-obstructive CAD, the elevated MACE rates among this subgroup of patients are likely caused by other factors. Extra-cardiac deaths such as pulmonary, psychiatric, or vascular diseases may have occurred. However, CONFIRM included patients undergoing CCTA because of suspected cardiac pathology and heart failure, or microvascular coronary dysfunction may explain MACE in non-obstructive CAD. Recent work from Taqueti *et al.*[22] demonstrated that in symptomatic patients with normal LVEF and without overt CAD, the prevalence of coronary microvascular dysfunction [defined as coronary flow reserve <2 on positron emission tomography imaging (PET)] exceeded 50% and it was independently associated with diastolic dysfunction. Also, this study population consisted of predominantly women (65%), and the prevalence of diabetes and hypertension was high, similar to the patients with non-obstructive CAD in this study. As demonstrated by the same group, among 329 symptomatic patients referred for invasive coronary angiography after PET imaging, coronary flow reserve was associated with MACE, independently from the CAD prognostic index derived from angiography.[23] Importantly, the correlation between decreasing flow reserve and increasing CAD severity was only modest.

Clinically, our findings suggest that patients presenting with dyspnoea and obstructive CAD should be treated according to the severity of atherosclerosis with medical therapy with or without revascularization according to guideline directed care for symptomatic CAD. It is apparent that dyspnoea in these patients is associated with hemodynamically significant obstructive stenosis. This supports the guidelines that have included dyspnoea as increasing factor for pre-test probability for CAD.[24] However, when obstructive stenosis is excluded, the presence of dyspnoea increases the risk over CAD severity, which may be related to extra-cardiac causes or adverse coronary physiologically. Myocardial blood flow imaging in these patients may improve risk stratification.

Limitations

The current evaluation is an observational cohort study with all its inherent limitations including selection bias and unobserved confounders. Data regarding functional testing of CAD were unavailable, and therefore, whether the relationship between three-vessel/LM obstructive CAD and dyspnoea was mediated by myocardial ischaemia leading to subsequent LV dysfunction remains unresolved. Specific causes of death (coronary or cardiac) were not available for the current analyses. No further detailed information regarding the duration and severity of dyspnoea was available. The large group of

asymptomatic individuals may not fully represent an asymptomatic cohort because of their clinical indication for CCTA, which poses a limitation to interpretability of the results and potentially reduces the strength of the observed associations. Also, it would have been preferred if several grades of dyspnoea severity were available. Possibly, more severe symptoms relate more strongly with obstructive CAD. Finally, LVEF and heart failure status were not available for all patients and it cannot be excluded that some patients presented with symptomatic heart failure.

Conclusion

Among patients without known CAD referred for CCTA, dyspnoea was independently associated with two-vessel or three-vessel/LM obstructive CAD. In patients with obstructive CAD, all-cause death and MI were determined by CAD severity and the presence of dyspnoea did not increase long-term risk for MACE. In patients without obstructive CAD, dyspnoea associated with MACE independently from the presence or absence of non-obstructive CAD. Additional cardiac or non-cardiac investigations may improve risk stratifications of this subgroup.

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Conflict of interest: J.A.L. is a consultant to and has stock options in Circle CVI and HeartFlow. J.K.M. is employed by and owns equity interest in Cleerly, Inc. and has served on the Advisory Board at Arineta. All other authors have no conflict of interest to declare .

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Appendix

Table A1 Prognostic value of dyspnoea according to CAD severity excluding patients with typical angina

	Adjusted HR for MACE (95% CI)[a]				
	Normal	CAD ≤50%	1-VD ≥50%	2-VD ≥50%	3-VD/left main ≥50%
Dyspnoea	1.31 (0.65–2.65) $P = 0.450$	1.67 (1.03–2.71) $P = 0.038$	0.71 (0.33–1.48) $P = 0.358$	1.40 (0.66–2.98) $P = 0.384$	0.86 (0.40–1.85) $P = 0.692$

CAD, coronary artery disease; HR, hazard ratio; MACE, major adverse cardiac events; VD, vessel disease.
[a]Adjusted for age, sex, chest pain typicality, diabetes, hypertension, and current smoking.

Table A2 Sub-analysis in patients with non-obstructive CAD

	Dyspnoea (*N* = 214)	No dyspnoea (*N* = 1055)	*P*-value
Women	103 (48.1)	355 (33.6)	<0.001
Body mass index	29.2 ± 7.4	27.3 ± 4.6	0.001
Diabetes	48 (22.5)	126 (12.0)	<0.001
Hypertension	142 (67.0)	561 (53.3)	<0.001
LV ejection fraction (%)	59.5 ± 18.7[a]	60.7 ± 11.7[b]	0.539

CAD, coronary artery disease; LV, left ventricular.
[a]Available in 109 (50.9%) patients.
[b]Available in 321 (30.4%) patients.