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Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events

Lasse Jespersen[1]*, Anders Hvelplund[2,3], Steen Z. Abildstrøm[1], Frants Pedersen[4], Søren Galatius[3], Jan K. Madsen[3], Erik Jørgensen[4], Henning Kelbæk[4], and Eva Prescott[1,5]

[1]Department of Cardiology, Bispebjerg University Hospital, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark; [2]National Institute of Public Health, University of Southern Denmark, Øster Farimagsgade 5A, 1399 Copenhagen, Denmark; [3]Department of Cardiology, Gentofte University Hospital, Niels Andersens Vej 65, 2900 Hellerup, Denmark; [4]Department of Cardiology, Rigshospitalet University Hospital, Blegdamsvej 9, 2500 Copenhagen, Denmark; and [5]Copenhagen City Heart Study, Bispebjerg University Hospital, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark

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Aims Patients with chest pain and no obstructive coronary artery disease (CAD) are considered at low risk for cardiovascular events but evidence supporting this is scarce. We investigated the prognostic implications of stable angina pectoris in relation to the presence and degree of CAD with no obstructive CAD in focus.

Methods and results We identified 11 223 patients referred for coronary angiography (CAG) in 1998–2009 with stable angina pectoris as indication and 5705 participants from the Copenhagen City Heart Study for comparison. Main outcome measures were major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, stroke or heart failure, and all-cause mortality. Significantly more women (65%) than men (32%) had no obstructive CAD ($P < 0.001$). In Cox's models adjusted for age, body mass index, diabetes, smoking, and use of lipid-lowering or antihypertensive medication, hazard ratios (HRs) associated with no obstructive CAD were similar in men and women. In the pooled analysis, the risk of MACE increased with increasing degrees of CAD with multivariable-adjusted HRs of 1.52 (95% confidence interval, 1.27–1.83) for patients with normal coronary arteries and 1.85 (1.51–2.28) for patients with diffuse non-obstructive CAD compared with the reference population. For all-cause mortality, normal coronary arteries and diffuse non-obstructive CAD were associated with HRs of 1.29 (1.07–1.56) and 1.52 (1.24–1.88), respectively.

Conclusion Patients with stable angina and normal coronary arteries or diffuse non-obstructive CAD have elevated risks of MACE and all-cause mortality compared with a reference population without ischaemic heart disease.

Keywords Chest pain • Gender • Prognosis • Coronary artery disease • Angiography

Introduction

Patients with chest pain in the absence of obstructive coronary artery disease (CAD) remain a challenge. More than half of women with stable chest pain undergoing coronary angiography (CAG) are found to have no obstructive CAD, while this is true for only one-third of men.[1,2] Until recently, the prognosis was thought to be benign and many of these patients have been offered little more than reassurance that they do not have serious heart disease.[3] However, the perception of the benign

* Corresponding author. Tel: +45 21380964, Fax: +45 35312004, Email: lasjes@gmail.com

nature of the condition in women has been challenged with evidence from the Women's Ischemia Syndrome Evaluation (WISE) study showing that women with symptoms and signs suggestive of myocardial ischaemia but without obstructive CAD are at elevated risk for cardiovascular events.[4] Furthermore, these patients often continue to have chest pain leading to anxiety, limited physical capacity, and reduction in quality of life and making them more likely to be readmitted to repeated procedures and medical assessment.[5,6] Some patients with no obstructive CAD might have chest pain due to cardiac diseases other than ischaemic heart disease due to coronary atherosclerosis. In the WISE study, it was hypothesized that the increased risk of cardiovascular outcomes was due to endothelial dysfunction not seen by traditional CAG.[4] This is in line with other studies that have addressed the long-term prognostic value of endothelial function testing in patients with no obstructive CAD and demonstrated that endothelial dysfunction is associated with increased numbers of adverse cardiovascular events.[7–9] Importantly, however, the WISE study only enrolled women. Therefore, it is unknown whether these results are gender-specific and whether women suspected of myocardial ischaemia but without obstructive CAD might differ from men in terms of prognosis.

We investigated the prognostic implications of cardiac symptoms of stable angina pectoris in patients with no obstructive CAD in a cohort of women and men referred for CAG and compared them with a reference sample from the background population and with patients with obstructive CAD.

Methods

Study population

The study was designed as a retrospective cohort study of all patients in Eastern Denmark having CAG performed for the first time with suspected stable angina pectoris in 1998–2009. Eastern Denmark constitutes a catchment area of 2.4 million persons, i.e. 43% of the entire Danish population.[10]

All residents in Denmark have a unique personal identification number that allows for linkage between national registers on an individual level. Information regarding prior morbidity and outcomes was obtained from the Danish National Patient Registry which has registered all admissions to all Danish hospitals since 1977 according to the International Classification of Diseases, the 8th edition (ICD-8) until 1994 and from 1994 onwards ICD-10. Revascularization procedures are registered according to The Nordic Classification of Surgical Procedures from 1996 onwards.[11] Before 1996, The Classification of Operations and Treatments version 1–3 were used for both procedures and operations.[12] Information on the patient's vital status (alive or date of death) was obtained from The Danish Civil Registration System, where all persons residing in Denmark are registered from birth or time of immigration.

Symptomatic population

Since 1998, data on all patients who underwent CAG have been recorded at five invasive centres in Eastern Denmark and registered in two databases. From these databases, we identified 17 435 patients with stable angina pectoris as the referral reason for their first CAG, a valid personal identification number, and an age ≥20 years (*Figure 1*). A

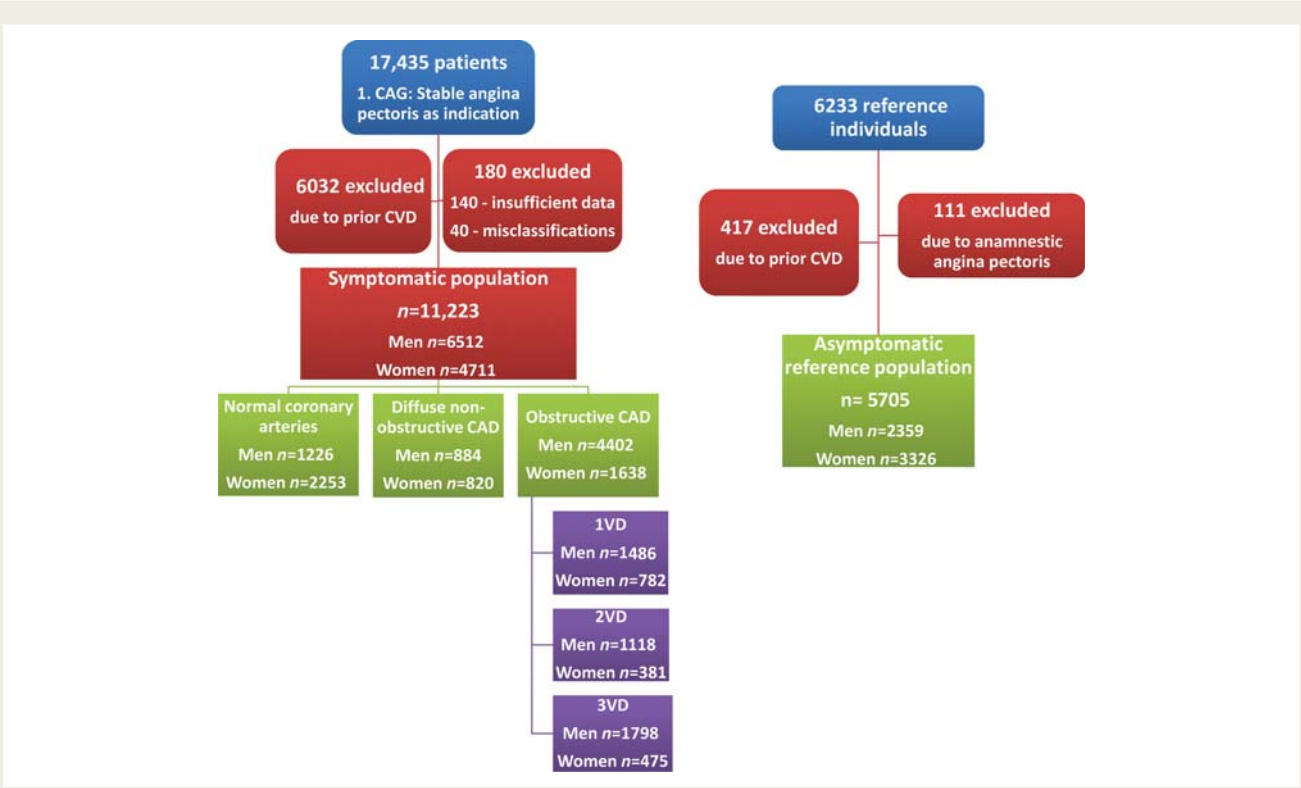


Figure 1 Derivation of the study population. CAG, coronary angiography; CAD, coronary artery disease; VD, vessel disease (indicates ≥50% stenosis); CVD, cardiovascular disease (i.e. prior stroke, revascularization, myocardial infarction, or unstable angina pectoris).

total of 6212 patients were excluded mainly due to prior diagnoses of cardiovascular disease. All patients were followed from the date of the CAG till 31 December 2009. The median and maximum follow-up time were 4.6 and 11.1 years, respectively (inter-quartile range 2.0–6.9 years).

Asymptomatic reference population

The asymptomatic reference population came from the fourth examination (2001–04) of the Copenhagen City Heart Study (CCHS), described in detail elsewhere.[13] Briefly, the CCHS was initiated in 1976 primarily to study the impact of lifestyle factors on cardiovascular diseases. The population was an age-stratified sample of men and women, aged 20 years or more, randomly selected from a defined area of Copenhagen, Denmark. The population was re-invited and new participants were included in 1981, 1991, and 2001.

The asymptomatic reference population included 6233 individuals with a valid personal identification number and an age of ≥20 years (*Figure 1*). A total of 528 were excluded mainly due to prior cardiovascular disease. All individuals were followed from the date of examination until 17 May 2009. The median follow-up time was 6.6 years (inter-quartile range 6.1–7.1 years).

Exclusion criteria

Individuals previously discharged from a Danish hospital with a diagnosis of myocardial infarction (MI) (ICD-8: 410; ICD-10: I21–22), unstable angina pectoris (ICD-8: 411; ICD-10: I20.0), stroke (ICD-8: 430–434 + 436; ICD-10: I61–I64), or a registered revascularization procedure, i.e. percutaneous coronary intervention or coronary artery bypass graft (The Classification of Operations and Treatments version 1–3: 30009–30200, 30240–30245, 30280, 30350, 30354, 30359, 30850 except 30160; The Nordic Classification of Surgical Procedures: KFNA–KFNG) at the time of inclusion were excluded. Additionally, in sensitivity analyses, individuals were excluded if they had previously been discharged from a Danish hospital with a diagnosis of aortic stenosis (ICD-8: 39500, 39502, 39590, 39592, 39603, 39693, 42410; ICD-10: I06.0, I06.2, I35.9, and I35.2), paroxysmal atrial fibrillation or atrial flutter (ICD-8: 42793, 42794; ICD-10: I48.9BB, I48.9A), hypertrophic cardiomyopathy (ICD-8: 42900, 42599; ICD-10: I42.1 and I42.2), or myocarditis (ICD-8: 42299; ICD-10: I01.2, I09.0, I40, I41, I42.3, I51.4, and I51.4B) or if this occurred within 6 months of the time of inclusion.

Patients with missing data regarding CAG results, CAG date, and hospitalizations prior to inclusion and patients with CAD misclassifications were excluded. Misclassifications were suspected if patients recorded as having either normal coronary arteries or diffuse non-obstructive CAD had a revascularization procedure within 90 days of the examination date. Data from these patients were systematically examined for discrepancies between the angiographic descriptions and the final conclusions, and as a result, 40 patients were excluded.

Individuals within our reference population with stable angina measured with the WHO (Rose) Angina Questionnaire as part of the Copenhagen City Heart Study were excluded.

Explanatory variables

Extent of coronary artery disease

Six degrees of CAD were defined based on conclusions registered by the invasive cardiologist performing the CAG. No obstructive CAD comprised the two groups of our main interest: normal coronary arteries (defined as 0% stenosis in all coronary arteries) and diffuse non-obstructive CAD (defined as 1–49% stenosis in any epicardial coronary artery). For comparison, four groups were defined: The asymptomatic reference population and three groups with obstructive CAD (i.e. ≥50% stenosis in any epicardial coronary artery): one- (1VD), two- (2VD), and three-vessel disease and/or left main stem stenosis (3VD).

Co-morbidity and cardiac risk factors

Information on co-morbidity and cardiovascular risk factors recorded at the time of inclusion included age, diabetes, lipid-lowering or antihypertensive medication, smoking, body mass index (BMI) (weight in kilograms divided with height in square metres), Canadian Cardiovascular Society Functional classification of angina (CCS class), and left ventricular ejection fraction (LVEF). Smoking status was categorized as active smokers vs. prior/never smokers. Body mass index was categorized into BMI < 25, $25 \leq$ BMI ≤ 30, and BMI > 30. There were few missing values for all covariates (0–5%) except CCS class and LVEF (available for 88 and 47% of the symptomatic population, respectively).

Outcome data

The primary composite endpoint consisted of major adverse cardiovascular events (MACE), defined as cardiovascular mortality (ICD-10: I00–I99), hospitalization for MI, heart failure (ICD-10: I50.0–I50.9), or stroke. The time frame in the survival analysis was defined as time from the date of inclusion till the date of the first event. The secondary endpoint was all-cause mortality.

Statistical analysis

Baseline data are reported as counts, percentages, or means ± SD and are compared with the use of the χ^2 or ANOVA. Comparisons of baseline data were adjusted for age by logistic or linear regression as appropriate.

The primary analysis was based on the Cox proportional hazards method and was concerning the relationship of stable angina to outcome among men and women with normal coronary arteries or diffuse non-obstructive CAD, respectively, when compared with an apparently normal reference population. The Cox proportional hazards method was used to describe these different levels of CAD as potential risk factors for events with time since inclusion as the underlying time scale. We used two different Cox's models, a crude model adjusted for age only and a multivariable-adjusted model based on the following major risk factors for cardiovascular events: age, diabetes, smoking status, BMI, and antihypertensive and lipid-lowering medication. Thorough age adjustment was ensured by entering in the model as a categorical variable after splitting each observation in 2-year age groups above the age of 40. The other covariates were treated as categorical variables with missing values in specific categories to avoid losing data. For patients with obstructive CAD, the relative risk of future outcomes compared with the reference population changed over time. Therefore, in a secondary multivariable-adjusted Cox model, we compared risk among patients with five different degrees of CAD compared with the reference population in two defined follow-up periods, i.e. from Days 0 to 365 and from Day 366 onwards. In this model, we split the follow-up into these two periods, so that risk in each patient group was described by hazard ratios (HRs). Model assumptions were tested and found valid. Since a larger proportion of women than men had no obstructive CAD and this may reflect differences in referral or disease characteristics, we tested for interaction between gender and degree of CAD by likelihood ratio tests comparing Cox's models with and without the interaction terms (2 df in the primary analysis and 10 df in the secondary analysis).

Significance testing was two-sided and based on a 5% probability level.

All analyses were performed using the Stata 11.1 software (StataCorp, 4905 Lakeway Drive, College Station, TX, USA).

Ethics

The Danish National Board of Health and the Danish Data Protection Agency approved the project. The Copenhagen City Heart Study was approved by The Danish National Committee on Biomedical Research Ethics and informed consent was given by all participants. Register-based studies do not require ethical approval in Denmark.

Results

Baseline characteristics

Baseline characteristics of the study population are shown in *Table 1* and *Figure 1*. Within the symptomatic population of 4711 women and 6512 men, a larger proportion of women than men had no obstructive CAD ($P < 0.001$). Among women and men, respectively, 48 vs. 19% had normal arteries and 17 vs. 14% had diffuse non-obstructive CAD. Over the study period, the proportion of patients with no obstructive CAD increased from 54 to 73% in women and from 19 to 41% in men (*Figure 2*), while the total annual numbers of CAGs performed increased from 704 to 1516.

Women were 2.4–4.3 years older than men when comparing within groups with the same degree of CAD, and the mean ages of both men and women rose with increasing degrees of CAD. Body mass indexes varied only a little between genders and the different levels of CAD with the reference groups having the lowest values ($P < 0.001$).

With the exception of smoking, cardiac risk factors were more prevalent in the symptomatic cohort compared with the reference cohort, and additionally, they tended to be more prevalent with higher degrees of CAD. Within the symptomatic population, the most pronounced differences were found between groups with normal coronary arteries and the other groups. Fewer patients with normal coronary arteries had diabetes or used antihypertensive drugs or lipid-lowering drugs, fewer were CCS class 2 or above, and among women, fewer were active smokers. Patients with 2VD and 3VD more often had LVEF < 40.

Major adverse cardiovascular events

The primary MACE outcome (cardiovascular mortality, hospitalization for MI, heart failure, or stroke) occurred in 1351 men and 837 women. Survival functions with respect to the MACE outcome for a 60-year-old woman/man during 7.5 years of follow-up are shown in *Figure 3*. Overall, survival free of MACE was better in women than in men, but for both genders, there was a graded increase in risk with increasing degrees of CAD.

Hazard ratios for normal coronary arteries and diffuse non-obstructive CAD are shown for age- and multivariable-adjusted Cox models in *Table 2*. Both Cox's models showed increased risks for both levels of CAD compared with the reference population with respect to the primary MACE endpoint ($P < 0.01$), with a graded increase in risk with increasing severity of CAD. There were no systematic gender differences in the estimated HRs for men and women with no obstructive CAD ($P = 0.88$ for interaction). Thus, pooling analyses of men and women yielded HRs for angina with normal coronary arteries of 1.52 (95% confidence interval, 1.27–1.83, $P < 0.001$) and for diffuse non-obstructive CAD of 1.85 (1.51–2.28, $P < 0.001$) (multivariable-adjusted model) (*Figure 4*). The increased risk of MACE in symptomatic patients with normal coronary arteries or diffuse non-obstructive CAD was largely accounted for by increased rates of cardiovascular death and either hospitalization with heart failure or MI.

Results of the secondary analyses (Days 0–365 and 366 onwards) showed significantly increased risk of MACE for patients with normal coronary arteries and patients with diffuse non-obstructive CAD compared with the reference population in both periods ($P < 0.001$; *Table 3*). Patients with no obstructive CAD had lower HRs from Days 0 to 365 than patients with obstructive CAD. All patients had higher risk of MACE from Days 0 to 365 than from Day 366 onwards. Overall, there was no gender interaction ($P = 0.14$). The 5-year MACE-free survival probabilities were 0.98, 0.94, 0.92, 0.91, 0.89, and 0.86 in women and 0.94, 0.89, 0.86, 0.86, 0.86, and 0.85 in men for the reference population, patients with normal coronary arteries, diffuse non-obstructive CAD, 1VD, 2VD, and 3VD, respectively (*Figure 3*).

All-cause mortality

In both men and women, angina with diffuse non-obstructive CAD was associated with a higher mortality rate than the reference population. There were no systematic gender differences ($P = 0.13$ for interaction). Pooling men and women yielded a mortality ratio for angina with normal coronary arteries of 1.29 (1.07–1.56, $P = 0.007$) and for diffuse non-obstructive CAD of 1.52 (1.24–1.88, $P < 0.001$) (*Figure 4*).

Patients with no obstructive CAD showed lower HRs from Days 0 to 365 than patients with obstructive CAD (*Table 3*) with a graded increase in risk of death with increasing degrees of CAD. Risk of death was higher for all patients from Days 0 to 365 than from Day 366 onwards. Overall, there was no gender interaction ($P = 0.47$).

Sensitivity analyses

Restricting data to patients residing in the same geographical area as the reference group did not change the results markedly (data not shown).

Patients with no obstructive CAD might suffer from chest pain due to other cardiac diseases than atherosclerotic CAD which might explain an increased cardiovascular risk. Therefore, we tested the robustness of our results by excluding all individuals with a previous diagnosis of aortic stenosis, paroxysmal atrial fibrillation, atrial flutter, hypertrophic cardiomyopathy, or myocarditis or if such a diagnosis was made within 6 months of the time of inclusion. This slightly attenuated the results, but HRs for patients with no obstructive CAD remained increased (*Figure 4*). Additionally, we tried limiting the analyses to patients with LVEF ≥ 40. This further lowered HRs and widened confidence intervals, but patients with no obstructive CAD still showed elevated risks of MACE ($P < 0.05$) (*Figure 4*).

Table 1 Baseline demographic and clinical characteristics

Degree of CAD	Symptomatic men (n = 6512)					Asymptomatic men	P-value[c]	Symptomatic women (n = 4711)					Asymptomatic women	P-value[c]
	3VD, n = 1798 (28%)	2VD, n = 1118 (17%)	1VD, n = 1486 (23%)	Diffuse CAD,[a] n = 884 (14%)	Normal CA,[b] n = 1226 (19%)	Reference population, n = 2359		3VD, n = 475 (10%)	2VD, n = 381 (8%)	1VD, n = 782 (17%)	Diffuse CAD,[a] n = 820 (17%)	Normal CA,[b] n = 2253 (48%)	Reference population, n = 3346	
Age, mean (SD), years	65.3 (9)	63.8 (9)	61.8 (10)	62.8 (10)	55.9 (11)	56.5 (16)	<0.001[d]	69.6 (10)	68.0 (9)	64.6 (10)	65.0 (10)	58.5 (11)	58.9 (17)	<0.001[d]
BMI, mean (SD)	27.5 (4)	27.5 (4)	27.4 (4)	27.7 (4)	27.8 (5)	26.3 (4)	<0.001	26.7 (5)	26.8 (5)	26.7 (5)	26.9 (5)	26.6 (5)	25.4 (5)	<0.001
Diabetes mellitus (%)	408 (23)	213 (19)	231 (16)	189 (22)	151 (13)	124 (5)	<0.001	120 (26)	64 (17)	135 (18)	147 (18)	221 (10)	103 (3)	<0.001
Active smoking (%)	462 (27)	302 (29)	413 (29)	260 (31)	343 (30)	818 (35)	0.002	113 (25)	82 (23)	219 (30)	194 (25)	409 (19)	1038 (31)	<0.001
Antihypertensive medication use (%)	954 (54)	563 (52)	699 (48)	453 (52)	461 (38)	300 (13)	<0.001	307 (65)	224 (60)	460 (60)	494 (61)	967 (44)	602 (18)	<0.001
Lipid-lowering medication use (%)	1,286 (77)	742 (72)	963 (69)	536 (65)	516 (45)	63 (3)	<0.001	341 (76)	262 (74)	547 (75)	540 (71)	1062 (50)	116 (4)	<0.001
CCS class (%)														
≤CCS1	263 (16)	203 (20)	349 (26)	342 (43)	473 (48)	—	—	51 (12)	51 (15)	144 (20)	257 (34)	729 (40)	—	—
≥CCS2	1,377 (84)	823 (80)	985 (74)	456 (57)	516 (52)	—		391 (88)	288 (85)	564 (80)	506 (66)	1,086 (60)		
LVEF (%)														
≥40	898 (90)	537 (93)	696 (95)	334 (94)	465 (94)	—	0.003[e]	259 (95)	190 (94)	368 (98)	335 (99)	885 (98)	—	0.011[e]
<40	104 (10)	42 (7)	36 (5)	22 (6)	28 (6)			54 (5)	12 (6)	7 (2)	4 (1)	18 (2)		
Ex_diagnosis,[f] (%)	141 (8)	87 (8)	117 (8)	123 (14)	177 (15)	18 (1)	—	34 (7)	30 (7)	47 (6)	76 (9)	181 (8)	20 (1)	—

[a]Diffuse non-obstructive CAD.
[b]Normal coronary arteries.
[c]Overall age-adjusted comparison of the prevalence of risk factors between the six different levels of CAD (the reference group included).
[d]Overall comparison of ages between the six different levels of CAD (the reference group included) from ANOVA.
[e]Overall age-adjusted comparison of the prevalences of LVEF < 40 in symptomatic groups only. There were 0–5% missing values for each covariate except CCS class and LVEF which explains for discrepancies between counts and percentages.
[f]Ex_diagnosis: individuals with a diagnosis of aortic stenosis, atrial flutter, paroxysmal atrial fibrillation, hypertrophic cardiomyopathy, or myocarditis previously or within 6 months of the inclusion date.

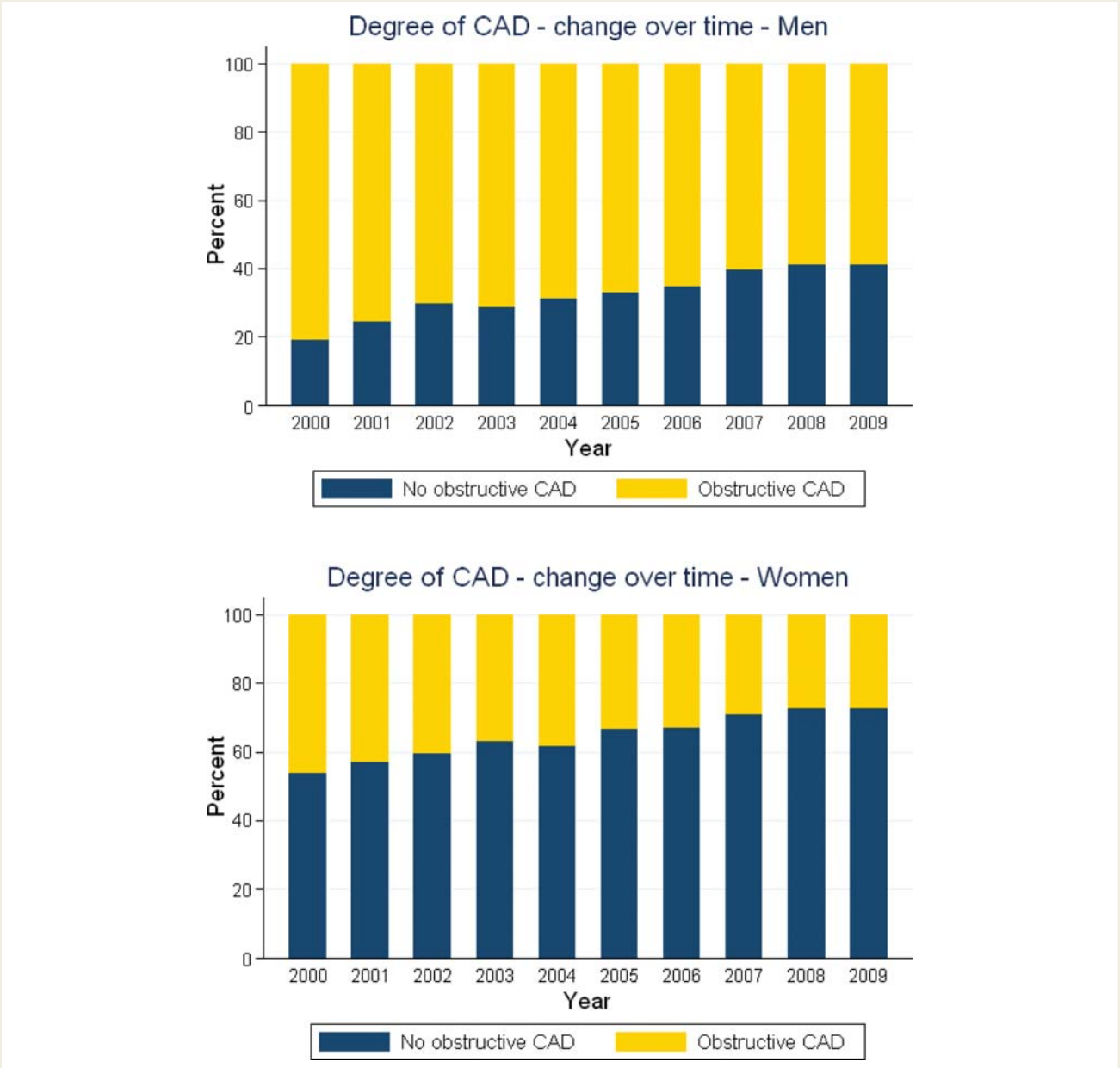
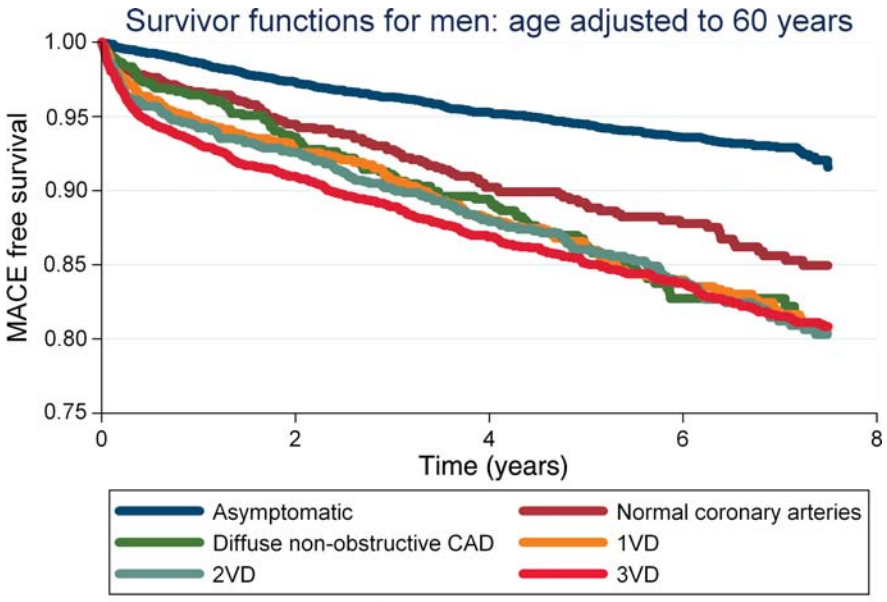


Figure 2 Degree of coronary artery disease by examination year and gender. No obstructive coronary artery disease, normal coronary arteries or diffuse non-obstructive coronary artery disease. Obstructive coronary artery disease, one or more significant coronary artery stenoses (indicates ≥50% stenosis).

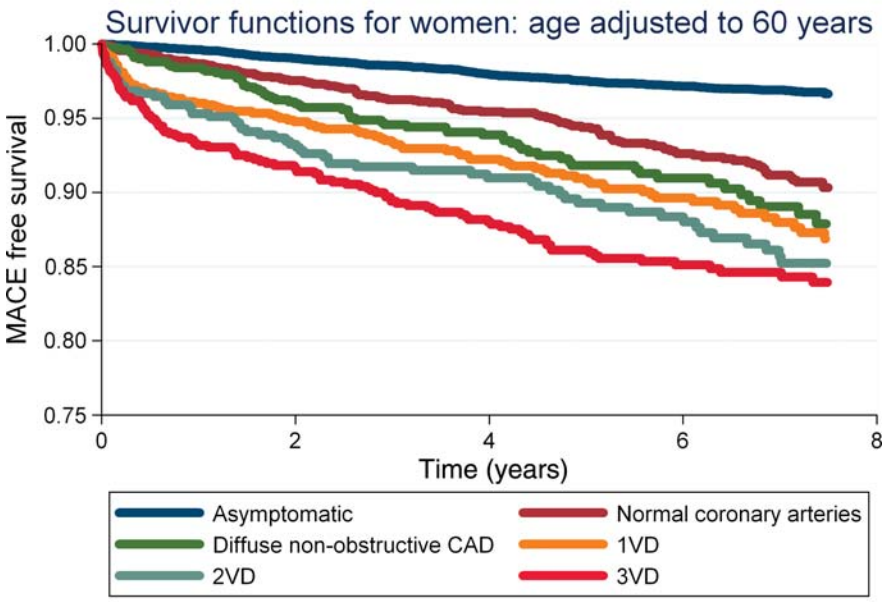
Discussion

This is the first study demonstrating that both men and women suspected of stable angina pectoris and categorized with either normal coronary arteries or diffuse non-obstructive CAD have increased risks of cardiovascular disease outcomes compared with a background population without known ischaemic heart disease, even after controlling for traditional cardiac risk factors and cardiac co-morbidity. Normal coronary arteries and diffuse non-obstructive CAD were associated with 52 and 85% increased risk of MACE (cardiovascular mortality, hospitalization for MI, heart failure, or stroke) and with 29 and 52% increased risk of all-cause mortality, respectively, with no differences between men and women. For both men and women, a graded increase in risk of future MACE and all-cause mortality with increasing levels of CAD was demonstrated.

Our study also demonstrates that patients suspected of stable angina pectoris frequently have no obstructive CAD, i.e. 65% women compared with 32% of men with an increasing trend over time. This probably reflects a lowering of the threshold for



Numbers at risk	0	2	4	6
Asymptomatic	2359	2231	2101	1738
Normal CA	1214	854	597	367
Dif. non-obstr. CAD	869	557	362	174
1VD	1475	1072	783	474
2VD	1105	806	583	342
3VD	1783	1312	984	632



Numbers at risk	0	2	4	6
Asymptomatic	3346	3213	3044	2600
Normal CA	2237	1597	1155	721
Dif. non-obstr. CAD	809	527	336	187
1VD	777	567	411	252
2VD	377	274	209	143
3VD	471	333	256	161

Figure 3 Major adverse cardiovascular event-free survivor functions for men and women. Age adjusted to 60 years. VD, vessel disease (indicates $\geq$50% stenosis).

Table 2 Hazard ratios (95% confidence interval) for patients with no obstructive coronary artery disease compared with asymptomatic women and men, respectively, in successively adjusted models

MACE	Events, *n*	Model 1[a]		Model 2[b]	
Degree of CAD	Women/men	Women	Men	Women	Men
Reference population	302/256	—	—	—	—
Normal coronary arteries	156/127	1.34 (1.08–1.66)	1.50 (1.19–1.89)	1.57 (1.21–2.02)	1.53 (1.18–2.00)
Diffuse non-obstr. CAD	87/132	1.62 (1.25–2.10)	1.79 (1.43–2.25)	1.86 (1.35–2.56)	1.87 (1.43–2.46)
All-cause mortality					
Reference population	356/298	—	—	—	—
Normal coronary arteries	105/103	0.97 (0.77–1.23)	1.30 (1.02–1.65)	1.20 (0.92–1.57)	1.44 (1.11–1.88)
Diffuse non-obstr. CAD	66/95	1.31 (1.00–1.71)	1.33 (1.05–1.69)	1.56 (1.13–2.15)	1.52 (1.15–2.01)

[a]Adjusted for age.
[b]Adjusted for age, BMI, diabetes, smoking status, and use of lipid-lowering and antihypertensive medication.

performing CAG.[14] In a much larger register-based study of 375 886 patients suspected of stable angina pectoris, 51% of the women and 33% of the men had no significant coronary artery stenosis (defined as <70% stenosis) which is largely in accordance with our findings.[1]

Several studies have reported that chest pain with a normal CAG is associated with an excellent prognosis.[15–19] These studies were published more than 15 years ago and do not reflect a contemporary clinical setting. In studies making comparisons with the background population, other endpoints than the composite MACE endpoint were used and small numbers of patients were included.[15,17] Thus, too little power might have been an issue in these studies.

Recently, data from the WISE study documented that women with stable symptoms of myocardial ischaemia and normal CAGs have an increased risk of future cardiovascular events compared with asymptomatic women.[2] In The Women's Health Initiative Observational Study, it was demonstrated that post-menopausal women hospitalized with a diagnosis of non-specific chest pain were at an increased risk of a future cardiovascular event (11.0% compared with 9.5% in those without such a hospitalization over 8 years of follow-up).[20] Results of these studies and ours support the view that symptoms of stable ischaemic heart disease is predictive of increased risk of adverse cardiovascular outcomes even in the absence of obstructive CAD. This is parallel to what is seen in patients with acute coronary syndrome (ACS) and no obstructive CAD. In one study, patients with initial non-ST-segment elevation ACS had a 2.1% risk of death and MI after 1 year,[21] and even higher numbers of different major adverse events have been reported in a few other studies.[22–24]

Why stable angina should predict increased risk of future adverse cardiovascular outcomes in the absence of obstructive CAD has several possible explanations. Some of these patients possibly have aortic stenosis, hypertrophic cardiomyopathy, perimyocarditis, rhythm disturbances, or heart failure but excluding such individuals only slightly lowered our estimated risks of MACE. Another possibility is that some of these patients have 'microvessel' disease causing characteristic symptoms of ischaemia. Several studies have demonstrated that coronary microvascular dysfunction is associated with increased risk of major adverse outcomes in patients with no obstructive CAD,[7,8,25] but at present, there is no standardized algorithm for further examination beyond CAG or evidence-based treatment beyond risk factor modification.[26]

Among patients with chest pain and no obstructive CAD, risk factor modification might be poor for different reasons. Since Blumgart and others in 1940 established obstructive coronary atherosclerosis as the underlying pathological condition in patients with angina pectoris, the primary evaluation focus of these patients has been to verify obstructive CAD.[27] Consequently, patients with no obstructive CAD are often not followed by cardiologists. There is little help to be found in guidelines. In the latest updated guidelines on the management of stable angina pectoris from The European Society of Cardiology in 2006, only two different possible cardiac conditions associated with having chest pain without obstructive CAD are considered: (i) atypical angina including vasospastic angina and (ii) the Cardiac Syndrome X. The latter is associated with an overall good prognosis, though it is recognized, that a subgroup with impaired endothelial function might be at increased risk for the future development of atherosclerotic coronary disease.[28] Still, it is recommended that the treatment focuses on symptomatic relief. Furthermore, the prognosis of vasospastic angina depends on the extent of underlying CAD and this condition should be managed accordingly, often combined with pharmacological therapy to improve symptoms.[26] Thus, focus is on symptomatic treatment and not on risk stratification or prognostic improvement.

Strengths and limitations

Our study reflects practice in a nationwide sample of patients. The large sample size of 11 223 symptomatic patients and 5705 asymptomatic reference individuals, the wide range of ages, and the 2188 major cardiovascular events during 6 years (median) of follow-up are important strengths of this study.

Our study has several limitations. Probably, the symptomatic population included both appropriate and inappropriate referrals,

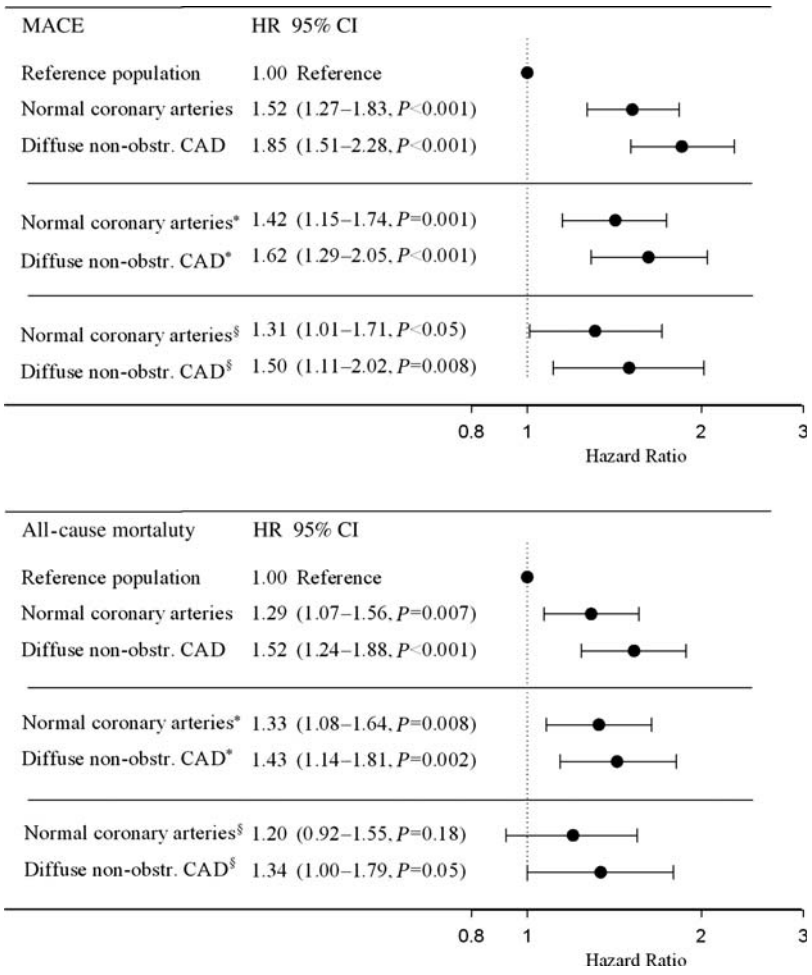


Figure 4 Hazard ratios for major adverse cardiovascular events and all-cause mortality by degree of coronary artery disease in pooled Cox's proportional hazards models adjusted for age, gender, body mass index, diabetes, smoking status, and use of antihypertensive and lipid-lowering medication. *Analyses limited to 10 304 individuals with no diagnosis of aortic stenosis, atrial flutter, paroxysmal atrial fibrillation, hypertrophic cardiomyopathy, or myocarditis previously or within 6 months of inclusion. §Analyses limited to 7485 individuals with no diagnosis of aortic stenosis, atrial flutter, paroxysmal atrial fibrillation, hypertrophic cardiomyopathy, or myocarditis previously or within 6 months of inclusion and for the symptomatic population an LVEF of ≥40. Diffuse non-obstr. CAD, diffuse non-obstructive coronary artery disease.

but such a referral pattern reflects what is normally seen in angiographic laboratories and our results would be applicable to other angiographic populations. The symptomatic population came from a larger geographical area than the reference population. Different geographical areas might have different rates of cardiovascular disease. However, sensitivity analyses yielded no markedly geographical effect. Detailed information on blood pressure and cholesterol levels was not available. Instead, we adjusted for the use of antihypertensive and lipid-lowering medication with minor effects on our estimates. Probably, the pain experienced by included patients was due to a variety of causes. In sensitivity analyses, we excluded all individuals with an eventual confounding cardiac disease with only little effect on our results. Left ventricular ejection fraction was only available for 47% of the symptomatic population. However, even when further restricting analyses to symptomatic individuals with LVEF ≥ 40, our analyses yielded significantly increased risks of MACE for both patients with normal coronary arteries and diffuse non-obstructive CAD.

Conclusions and implications

In conclusion, our study shows that among patients suspected of stable angina pectoris and referred to CAG, nearly two-thirds of women and one-third of men have no obstructive CAD. Both normal coronary arteries and diffuse non-obstructive CAD were associated with significantly increased risks of future MACE and all-cause mortality compared with a normal population without ischaemic heart disease, even after adjusting for traditional cardiac risk factors. Thus, future research should focus on the value of further risk stratification and treatment strategies of patients with stable chest pain associated with no obstructive CAD.

Table 3 Hazard ratios (95% confidence interval) for patients with different degrees of coronary artery disease compared with asymptomatic women and men, respectively, in two different time intervals

MACE	Events, *n*	Days 0–365			Day 366–		
Degree of CAD	**Women/men**	**Women[a]**	**Men[a]**	**Pooled[b]**	**Women[a]**	**Men[a]**	**Pooled[b]**
Reference population	302/256	—	—	—	—	—	—
Normal coronary arteries	156/127	2.15 (1.28–3.60)	2.03 (1.29–3.19)	1.98 (1.41–2.78)	1.48 (1.15–1.90)	1.26 (0.96–1.66)	1.31 (1.09–1.58)
Diffuse non-obstr. CAD	87/132	2.34 (1.27–4.28)	2.00 (1.26–3.17)	2.19 (1.52–3.16)	1.90 (1.38–2.61)	1.78 (1.35–2.34)	1.78 (1.45–2.19)
1VD	103/229	6.13 (3.77–9.96)	3.03 (2.05–4.46)	4.03 (2.97–5.46)	1.54 (1.12–2.13)	1.45 (1.14–1.84)	1.45 (1.20–1.76)
2VD	70/194	7.04 (4.11–12.07)	3.14 (2.11–4.68)	4.25 (3.09–5.86)	1.74 (1.21–2.51)	1.40 (1.08–1.80)	1.47 (1.20–1.81)
3VD	119/413	10.56 (6.68–16.69)	4.49 (3.14–6.42)	6.09 (4.58–8.10)	1.77 (1.29–2.43)	1.60 (1.29–2.00)	1.64 (1.37–1.95)
All-cause mortality							
Reference population	356/298	—	—	—	—	—	—
Normal coronary arteries	105/103	1.42 (0.60–3.35)	1.73 (0.84–3.56)	1.55 (0.89–2.69)	1.18 (0.91–1.54)	1.33 (1.03–1.72)	1.22 (1.02–1.47)
Diffuse non-obstr. CAD	66/95	3.03 (1.39–6.62)	2.12 (1.09–4.12)	2.47 (1.49–4.10)	1.49 (1.07–2.06)	1.45 (1.11–1.90)	1.44 (1.17–1.77)
1VD	72/136	3.27 (1.50–7.16)	2.39 (1.33–4.30)	2.75 (1.72–4.39)	1.31 (0.95–1.79)	0.94 (0.73–1.20)	1.03 (0.85–1.25)
2VD	46/162	4.58 (2.00–10.51)	3.03 (1.71–5.40)	3.56 (2.23–5.69)	1.22 (0.84–1.78)	1.35 (1.06–1.71)	1.30 (1.07–1.59)
3VD	85/325	7.56 (3.93–14.56)	4.11 (2.47–6.83)	5.02 (3.35–7.53)	1.32 (0.97–1.81)	1.36 (1.11–1.68)	1.33 (1.12–1.58)

These models show two HRs for every degree of CAD, the first one from Days 0 to 365 and the second one from Day 366 onwards.
[a]Adjusted for age, BMI, diabetes, smoking status, and use of lipid-lowering and antihypertensive medication.
[b]Adjusted for age, BMI, diabetes, smoking status, use of lipid-lowering and antihypertensive medication, and gender.

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