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Coronary flow velocity reserve predicts adverse prognosis in women with angina and no obstructive coronary artery disease: results from the iPOWER study

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Aims Many patients with angina, especially women, do not have obstructive coronary artery disease (CAD) yet have impaired prognosis. We investigated whether routine assessment of coronary microvascular dysfunction (CMD) is feasible and predicts adverse outcome in women with angina and no obstructive CAD.

Methods and results After screening 7253, we included 1853 women with angina and no obstructive CAD on angiogram who were free of previous CAD, heart failure, or valvular heart disease in the prospective iPOWER (Improving Diagnosis and Treatment of Women with Angina Pectoris and Microvascular Disease) study. CMD was assessed by Doppler echocardiography in the left anterior descending artery as coronary flow velocity reserve (CFVR). Patients were followed for a composite outcome of cardiovascular death, myocardial infarction (MI), heart failure, stroke, and coronary revascularization. CFVR was obtained in 1681 patients (91%) and the median CFVR was 2.33 (quartiles 1–3: 2.00–2.74). During a median follow-up of 4.5 years, 96 events occurred. In univariate Cox regression, CFVR was associated with the composite outcome {hazard ratio (HR) 1.07 [95% confidence interval (CI) 1.03–1.11] per 0.1 unit decrease in CFVR; $P < 0.001$}, primarily driven by an increased risk of MI and heart failure. Results remained significant in multivariate analysis [HR 1.05 (95% CI 1.01–1.09) per 0.1 unit decrease in CFVR; $P = 0.01$]. In exploratory analyses, CFVR was also associated with the risk of repeated hospital admission for angina and all-cause mortality.

Conclusion Assessment of CFVR by echocardiography is feasible and predictive of adverse outcome in women with angina and no obstructive CAD. Results support a more aggressive preventive management of these patients and underline the need for trials targeting CMD.

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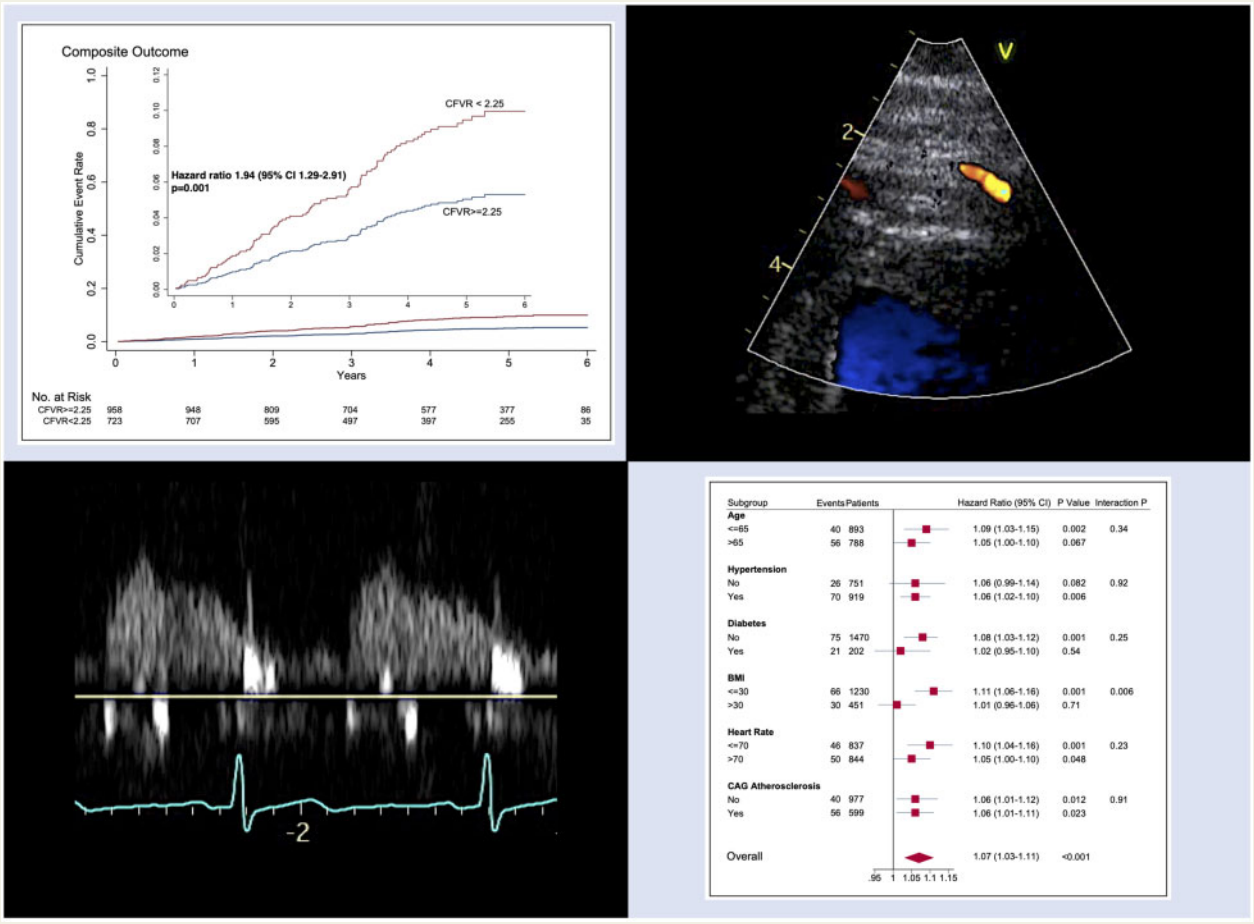
Graphical Abstract



Keywords Coronary flow velocity reserve • Coronary microvascular dysfunction • Prognosis • women • Coronary artery disease

Introduction

The current diagnostic approach in patients with angina pectoris is primarily focused on identifying epicardial coronary artery stenosis. However, >90% of angina patients referred for assessment and >2/3 of patients undergoing invasive coronary angiography (CAG) do not have obstructive coronary artery disease (CAD).[1–3] This condition, coined angina with no obstructive CAD (ANOCA), is predominantly seen in women. Patients with ANOCA are at increased risk of major adverse cardiovascular events compared with asymptomatic peers.[4–6]

Coronary microvascular dysfunction (CMD) has emerged as a possible cause of symptoms and a marker of poor prognosis in angina patients, and several diagnostic test modalities evaluating CMD have shown promise in risk stratification.[7–9] CMD is associated with cardiovascular disease (CVD) mortality, increased risk of myocardial infarction (MI) with no obstructive coronary artery disease (MINOCA), and heart failure with preserved ejection fraction (HFpEF).[5,6,10,11] Concurrently, recent studies are raising questions regarding the efficacy of coronary revascularisation even in angina patients with significant coronary stenosis.[12,13] This may lead to increased focus on CMD as a possible cause of angina and impaired prognosis.

Evaluation of CMD by transthoracic Doppler echocardiography (TTDE) coronary flow velocity reserve (CFVR) is a readily available non-invasive diagnostic test, and it has been shown that TTDE CFVR is a consistent outcome predictor in angina patients at large.[7,14,15] However, when considering the notable group of angina patients without obstructive CAD, CFVR studies have been retrospective and limited either by small size or heterogeneous patient populations including both patients with and without obstructive CAD.[16] Due to a lack of large-scale CFVR studies in angina patients without

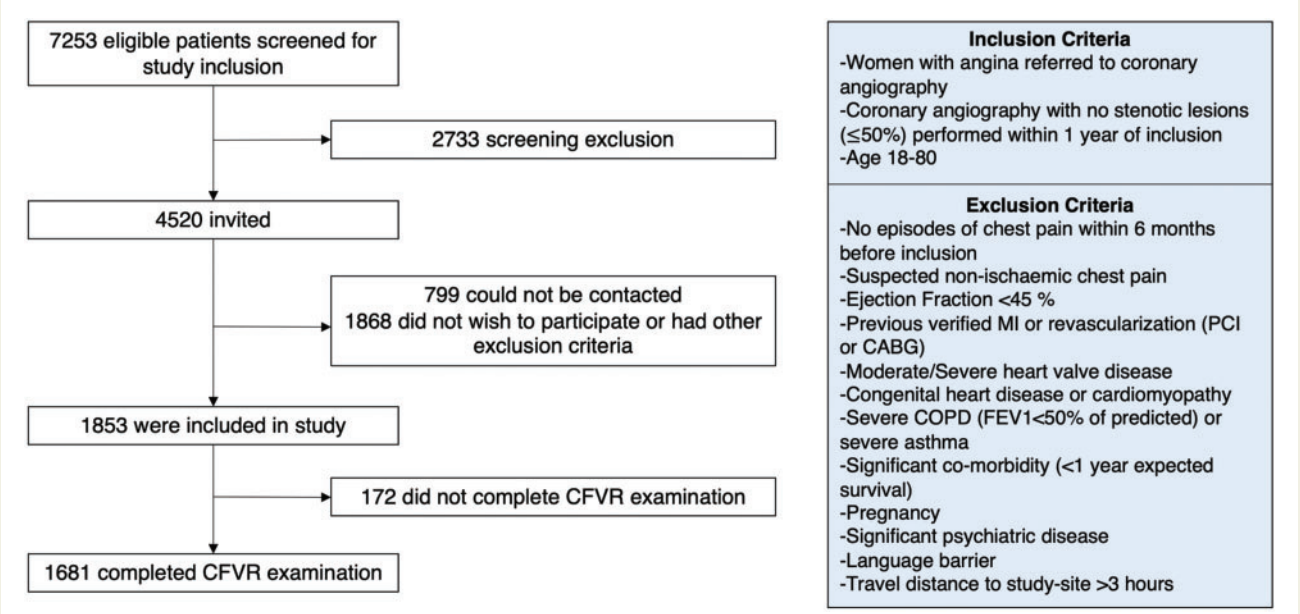


Figure 1 Patient enrolment and inclusion. CABG, coronary artery bypass graft; CFVR, coronary flow velocity reserve; COPD, chronic obstructive pulmonary disease; FEV, forced expiratory volume; MI, myocardial infarction; PCI, percutaneous coronary intervention.

significant stenosis at CAG, current guidelines rank echocardiographic CFVR at evidence level B, recommendation IIb.[1]

The aim of the iPOWER (Improving Diagnosis and Treatment of Women with Angina Pectoris and Microvascular Disease) study is to determine whether routine assessment of CFVR is feasible and identifies women with increased risk of major adverse cardiovascular events in a large homogeneous patient cohort of women with angina and no obstructive CAD.[17]

Patients and methods

Study design

The iPOWER study was an investigator-initiated prospective cohort study with a central diagnostic examination centre covering the entire Eastern Denmark region (≅3 million inhabitants). All patient interviews, clinical evaluations, and echocardiographic examinations were performed at a single centre to ensure consistency and quality of the specialized patient examination procedure.

The main aims of the study were to assess the prevalence of low CFVR and the prognostic value of CFVR measurement in women with angina and no obstructive CAD. The study was designed and overseen by a steering committee, and design, rationale and preliminary baseline data have been published previously.[17]

Patients

All women referred for a diagnostic CAG in Eastern Denmark between March 2012 and December 2017 due to stable or unstable angina and suspected obstructive CAD were screened in the comprehensive CAG database PATS (Patient Analysis & Tracking System, Dendrite Clinical Systems). Inclusion criteria were age 18–80 years and a CAG with no stenotic lesions (≤50%) demonstrated within 1 year of inclusion. This stenosis percentage cut-off was chosen to reasonably ensure that symptoms were not caused by flow-limiting stenosis, as fractional flow reserve data were not available. Electronic patient health records were screened to exclude individuals with prior ischaemic or significant structural heart disease, severe pulmonary disease, or other significant co-morbidity (*Figure 1*).

Baseline assessment included clinical and demographic data. Patients were interviewed regarding medical history, cardiovascular risk factors, medication, and symptom characteristics. Extensive clinical measurements and biochemical parameters were obtained, as previously described.[17]

Echocardiographic examination

All participants underwent TTDE of the left anterior descending artery during rest and high-dose dipyridamole stress (0.84 mg/kg) over 6 min to obtain coronary flow velocities at baseline and at maximal hyperaemia. Examinations were performed by the same experienced echocardiographers using GE Healthcare Vivid E9 Cardiovascular Ultrasound System (GE Healthcare), and images were analysed by Echopac v.112. Patients were abstinent from caffeine and foods containing significant amounts of methylxanthine 24 h prior to examination, and medication that could potentially impact results were paused prior to the examination. The left anterior descending artery was visualized with colour Doppler in an apical modified foreshortened 2- or 4-chamber view or in a modified short-axis view of the left ventricle. CFVR was calculated as the ratio between diastolic peak velocities during stress and rest. Examinations were assigned a quality grade of low, medium, or high as described.[18] In previous validation studies, we found a coefficient of variation of 7%. CFVR

readings were highly reproducible, and CFVR was obtainable in >90% of patients.[17–19]

Outcomes

The primary outcome was a composite of first occurrence of CVD death, MI, heart failure, stroke, or coronary revascularization. As secondary exploratory outcomes, we analysed all-cause mortality and hospital admissions for angina pectoris. Information about the underlying cause of death was obtained from the National Register of Causes of Death. The Danish National Patient Register, covering all somatic hospital admissions and procedures, provided hospitalization data. All registers have 100% coverage.

The main outcomes were classified into categories defining the primary composite outcome: hospitalization for MI [International Classification of Diseases (ICD) codes I21.0–I23.9], heart failure (ICD codes I50-50.9), stroke (ICD codes I60.0–I64.9), coronary revascularization (Nordic Classification of Surgical Procedures: KFNA–KFNG), or CVD death (ICD codes I00–I99). Hospital admission for angina pectoris was defined as any non-MI hospitalization for stable or unstable angina pectoris (ICD codes I20–I20.9, I24–I24.9, and I25–I25.1).

Statistical analysis

Baseline variable statistical significance was assessed with Wilcoxon tests, analysis of variance, and $\chi 2$ tests for continuous non-normal distributed, continuous normal distributed, and categorical variables, respectively. There was a significant relation between increased risk of the composite outcome and decreasing CFVR value, which was consistent across the full range of CFVR values, and accordingly, CFVR was treated as a continuous variable in primary regression analyses. However, for the purpose of comparisons between patient subgroups with low and high CFVR values, an optimal CFVR cut-off value was determined using the Youden index for maximization of the specificity and sensitivity sum. This cut-off was used for the presentation of baseline variable distribution and graphical illustrations.

For the primary composite outcome and individual outcomes with competing risk (i.e. non-CVD death and all-cause death as appropriate), cumulative incidence curves were calculated. The primary composite outcome, constituent individual outcomes, and all-cause mortality were analysed with Cox proportional hazards models. Hospital admissions for angina pectoris were analysed using a recurrent event Cox model with robust sandwich standard error estimates to adjust for multiple admissions for the same patient. The proportional hazard assumption was assessed graphically and with Schoenfeld residuals. Appropriate functional form of continuous variables was assessed graphically with martingale residuals.

The relation between the composite outcome, CFVR, known cardiovascular risk factors, and echocardiographic variables was assessed using univariate and multivariate procedures. The multivariate model included CFVR and age as prespecified variables. Only variables that were significantly associated with the composite outcome in the univariate analysis were examined in the multivariate model. To avoid overadjustment, the variable was then retained in the final model either if $P < 0.10$ or if the variable significantly impacted the relation between CFVR and the composite outcome. To ensure that results were consistent across different variable selection approaches, a model including all variables regardless of univariate *P*-value and a backward stepwise selection model were also fitted for comparison. Optimal model fit was evaluated using the likelihood ratio test. Subgroup analyses using an interaction effect were performed according to age group, hypertension, diabetes, body mass index (BMI), heart rate, and CAG atherosclerosis.

Two-sided *P*-values of 0.05 or less were considered to indicate statistical significance, with the exception of the *P*-value threshold of 0.10 for retainment in the multivariate model. Analyses were performed with STATA/IC 16 (StataCorp LP, College Station, TX, USA).

Ethics

This study was performed in accordance with the Declaration of Helsinki and was approved by the Danish Regional Committee on Biomedical Research Ethics (H-3-2012-005) and the Danish Data Protection Agency. All participants gave written informed consent on oral and written information.

Results

Patient characteristics

From May 2012 to December 2017, a total of 7253 women with angina pectoris and a CAG without significant epicardial stenosis (≤50%) were screened and 1853 women were enrolled in the study. A valid CFVR measurement was obtained in 1681 patients (91%) (*Figure 1*), and 93% of examinations were of medium or high quality (*Table 1*). The median CFVR was 2.3 [quartiles 1–3 (Q1–Q3) 2.0–2.7], and the median age was 64 (Q1–Q3 56–70).

For the comparison of baseline variables, patients were divided into two groups based on a CFVR cut-off value of 2.25 obtained from the Youden index for maximization of the specificity and sensitivity sum (*Table 1*). Patients with low CFVR were significantly older and a larger proportion had hypertension or diabetes. Furthermore, patients with low CFVR had a higher prevalence of diffuse atherosclerosis at CAG, were more frequently postmenopausal, and had higher diastolic blood pressure and resting heart rate and more frequent use of beta-blockers, angiotensin II receptor-blockers, statins, and aspirin. At echocardiographic examination, patients with low CFVR had both a higher resting coronary flow velocity (CFV) and a lower CFV during stress. E/e' index ≥12 was more prevalent in patients with low CFVR.

Follow-up and outcomes

Follow-up data for all outcomes were available in all patients through February 2019. The median follow-up period was 4.5 years (Q1–Q3 2.8–5.9), and no patients were lost to follow-up.

The primary composite outcome occurred in 96 patients, 56 in the group with CFVR < 2.25 (7.7%, 19.7 events per 1000 person-years) and 40 in patients with CFVR ≥ 2.25 (4.2%, 10.0 events per 1000 person-years). The hazard ratio (HR) for the composite outcome associated with a 0.1 unit decrease in CFVR value was 1.07 [95% confidence interval (CI) 1.03–1.11; $P < 0.001$] (*Table 2*), and the HR associated with CFVR < 2.25 was 1.94 [95% CI 1.29–2.91, $P = 0.001$] (*Figure 2*). For the individual outcomes, reduced CFVR

Table 1 Characteristics of the patients at baseline

Characteristic	All (*N* = 1681)	CFVR < 2.25 (*N* = 723)	CFVR ≥ 2.25 (*N* = 958)	*P*-value
Demographics and history				
Age (years), median (Q1–Q3)	64 (56–70)	66 (58–72)	62 (55–69)	<0.001
Family history of IHD, *n* (%)	880 (54)	362 (52)	518 (56)	0.07
Diabetes, *n* (%)	202 (12)	107 (15)	95 (10)	0.002
Hypertension, *n* (%)	919 (55)	443 (62)	476 (50)	<0.001
Dyslipidaemia, *n* (%)	1039 (62)	462 (64)	577 (61)	0.15
Smoking status, *n* (%)				0.44
Ex-smoker	691 (41)	305 (42)	386 (41)	
Current smoker	270 (16)	122 (17)	148 (16)	
CAG atherosclerosis, *n* (%)	599 (38)	299 (44)	300 (33)	<0.001
Postmenopausal, *n* (%)	1414 (85)	639 (89)	775 (82)	<0.001
Typical stable angina symptoms, *n* (%)	571 (34)	244 (34)	327 (34)	0.87
Medication				
Beta-blockers, *n* (%)	469 (28)	234 (33)	235 (25)	<0.001
Calcium-channel blockers, *n* (%)	377 (23)	172 (24)	205 (22)	0.27
Nitrates, *n* (%)	490 (32)	214 (33)	276 (31)	0.49
ACE inhibitors, *n* (%)	261 (16)	126 (18)	135 (14)	0.067
ARB, *n* (%)	309 (19)	156 (22)	153 (17)	0.004
Statins, *n* (%)	839 (51)	388 (54)	451 (48)	0.009
Aspirin, *n* (%)	674 (41)	326 (46)	348 (37)	<0.001
Clinical measurements				
BMI (kg/m^2), mean (SD)	27.1 (5.4)	27.2 (5.7)	27.1 (5.1)	0.75
High BMI (>30), *n* (%)	451 (27)	200 (28)	251 (26)	0.50
Diastolic blood pressure, mean (SD)	68 (12)	67 (12)	69 (12)	0.003
Systolic blood pressure, mean (SD)	131 (21)	131 (21)	130 (21)	0.66
Heart rate, mean (SD)	71 (11)	72 (11)	70 (10)	<0.001
Biochemical parameters				
eGFR (mL/min/1.73 m^2), mean (SD)	85 (16)	83 (16)	86 (15)	<0.001
Cholesterol (mmol/L), mean (SD)	5.0 (1.1)	5.0 (1.1)	5.0 (1.1)	0.64
LDL (mmol/L), mean (SD)	2.8 (1.0)	2.7 (1.0)	2.8 (1.0)	0.17
TSH, median (Q1–Q3), 10–3 IU/L	1.3 (0.8–2.0)	1.3 (0.8–1.9)	1.3 (0.8–2.0)	0.22
Hemoglobin (mmol/L), mean (SD)	8.3 (0.7)	8.2 (0.7)	8.3 (0.6)	0.05
Echocardiographic parameters				
CFV rest (m/s), median (Q1–Q3)	0.24 (0.20–0.29)	0.27 (0.22–0.33)	0.22 (0.18–0.26)	<0.001
CFV stress (m/s), mean (SD)	0.58 (0.17)	0.54 (0.16)	0.62 (0.16)	<0.001
CFVR, median (Q1–Q3)	2.3 (2.0–2.7)	2.0 (1.8–2.1)	2.7 (2.4–3.0)	<0.001
CFVR examination quality, *n* (%)				<0.001
Low quality	116 (7)	66 (9)	50 (5)	
Medium quality	812 (49)	375 (53)	437 (46)	
High quality	728 (44)	272 (38)	456 (48)	
LVEF, mean (SD)	58.6 (5.9)	58.8 (6.0)	58.4 (5.9)	0.26
GLS, mean (SD)	21.0 (2.8)	21.0 (2.9)	21.0 (2.7)	0.33
$E/e' \geq 12$	184 (11)	100 (14)	84 (9)	0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAG, coronary angiography; CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; IHD, ischaemic heart disease; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; TSH, thyroid-stimulating hormone

value was associated with the risk of MI and heart failure. For stroke, coronary revascularization, and CVD death, the excess risk did not reach statistical significance (*Table 2*). Only 5 out of 13 coronary revascularizations were performed during MI hospital admissions.

A total of 41 patients died during the follow-up period. The risk of all-cause mortality was associated with reduced CFVR value. In recurrent event survival analysis of angina pectoris hospital admissions, 123 admissions occurred and admission risk was associated with reduced CFVR value (*Table 2* and *Figure 3*).

Table 2 Patient outcomes

Outcome	Outcome numbers and rates by subgroups			Regression analysis results	
	All ($n = 1681$) n (event rate[a])	CFVR < 2.25 ($n = 723$) n (event rate[a])	CFVR ≥ 2.25 ($n = 958$) n (event rate[a])	Hazard ratio[b] (95% CI)	P-value[c]
Primary composite outcome	96 (14.1)	56 (19.7)	40 (10.0)	1.07 (1.03–1.11)	<0.001
Secondary outcomes					
Acute myocardial infarction	35 (5.1)	29 (10.1)	6 (1.5)	1.15 (1.07–1.24)	<0.001
Heart failure	25 (3.7)	17 (5.9)	8 (2.0)	1.15 (1.06–1.25)	0.001
Stroke	36 (4.7)	18 (6.3)	18 (4.5)	1.05 (0.99–1.12)	0.10
Coronary revascularization	13 (1.9)	8 (2.8)	5 (1.3)	1.08 (0.97–1.19)	0.15
CVD death	10 (1.5)	5 (1.8)	5 (1.3)	1.04 (0.95–1.14)	0.42
All-cause mortality	41 (5.8)	27 (9.1)	14 (3.4)	1.10 (1.03–1.17)	0.002
Angina pectoris hospital admission[d]	123 (17.5)	72 (24.2)	51 (12.6)	1.06 (1.03–1.10)	<0.001

CFVR, coronary flow velocity reserve; CI, confidence interval; CVD, cardiovascular disease.
[a]Event rate = annual event rate per 1000 person-years.
[b]CFVR treated as a continuous variable, hazard ratio per 0.1 unit decrease in CFVR.
[c]Unadjusted P-value.
[d]A total of 123 events divided among 83 patients.

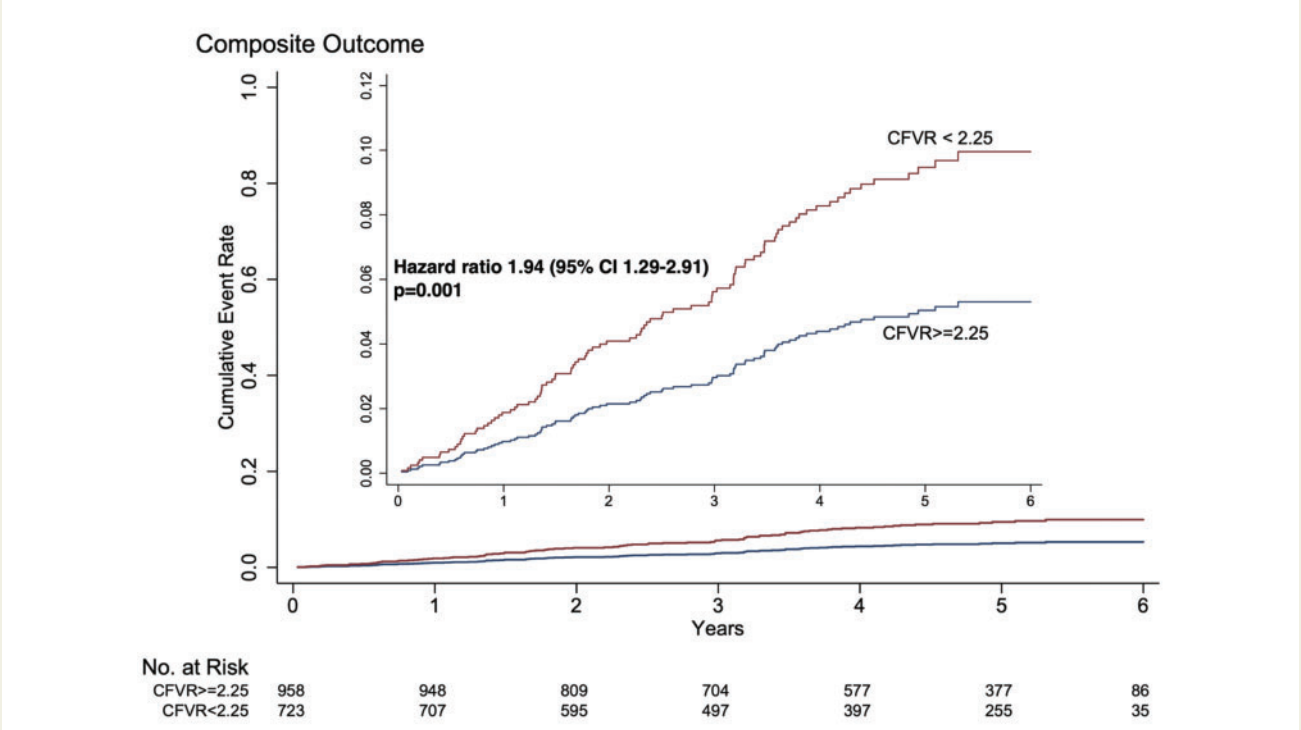


Figure 2 Time to event curve for composite outcome of cardiovascular disease mortality, myocardial infarction, heart failure, stroke, or coronary revascularization. Inset shows the same data on an expanded y-axis. CFVR, coronary flow velocity reserve.

Outcome predictors

The results of univariate and multivariate adjusted composite outcome HRs for CFVR and cardiovascular risk factors are shown in *Table 3*. In the univariate analysis, CFVR, age, hypertension, diabetes, and CAG atherosclerosis were associated with an increased composite outcome risk. In the multivariate analysis, significance was maintained for CFVR, CAG atherosclerosis, and hypertension. The relation between CFVR and the composite outcome was maintained in the fully adjusted and the stepwise regression models (results not shown).

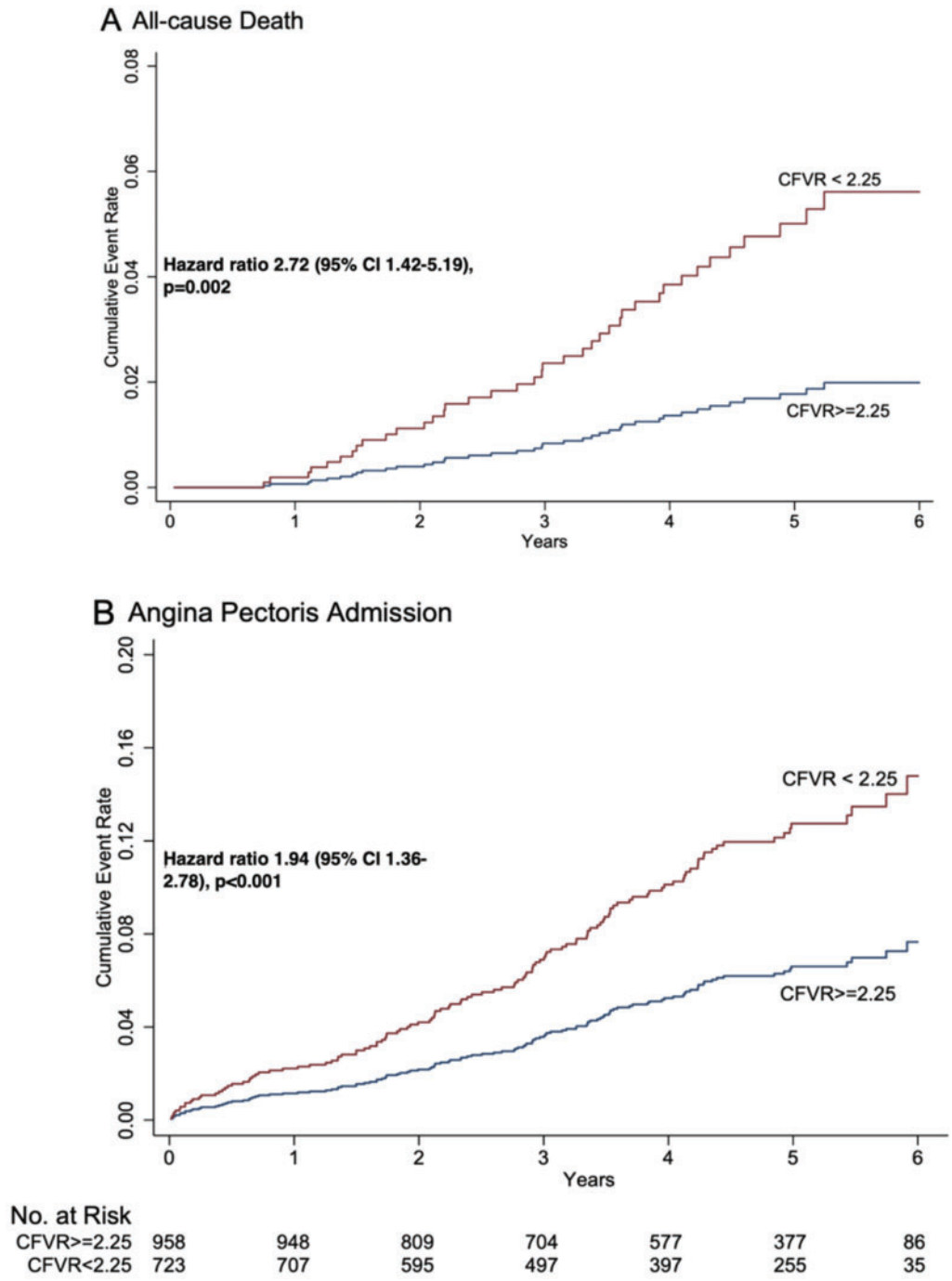


Figure 3 Time to event curves for secondary outcomes. CFVR, coronary flow velocity reserve.

Subgroup analyses

Subgroup analysis results for the association between CFVR and the composite outcome are presented in *Figure 4*. Overall, the increased risk associated with reduced CFVR was consistent across subgroups with the exception of BMI, for which there was a significant interaction. In patients with a BMI of >30, there was no increased risk related to a low CFVR value, while in patients with a BMI of ≤30, a low CFVR value was associated with an increased composite outcome risk. The interaction with BMI was also significant when BMI was treated as a continuous variable (result not shown). There was no difference attributable to BMI in CFV at rest (0.25 m/s in patients with BMI ≤ 30 and 0.24 m/s in patients with BMI > 30, $P = 0.86$) or in CFV during stress (0.59 m/s in patients with BMI ≤ 30 and 0.57 m/s in patients with BMI > 30, $P = 0.57$).

Table 3 Predictors of composite outcome

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CFVR, per 0.1 unit decrease[a]	1.07 (1.03–1.11)	<0.001	1.05 (1.01–1.09)	0.01
Age, per year	1.04 (1.01–1.06)	0.001	1.01 (0.99–1.04)	0.24
Family history of IHD	0.74 (0.50–1.12)	0.15		
Hypertension	2.35 (1.49–3.70)	<0.001	1.82 (1.14–2.91)	0.01
Dyslipidaemia	1.51 (0.97–2.36)	0.07		
Diabetes	2.10 (1.30–3.43)	0.003		
Smoking status				
Ex-smoker	1.12 (0.72–1.74)	0.62		
Current smoker	1.17 (0.66–2.07)	0.60		
Typical stable angina symptoms	1.20 (0.80–1.82)	0.37		
BMI (kg/m^2), per unit	1.01 (0.98–1.05)	0.48		
Heart rate, per 1 bpm	1.01 (0.99–1.03)	0.34		
CFVR examination quality[b]	0.80 (0.58–1.10)	0.17		
LVEF	0.99 (0.96–1.03)	0.64		
CAG atherosclerosis	2.49 (1.66–3.75)	<0.001	2.02 (1.32–3.09)	0.001

BMI, body mass index; CAG, coronary angiography; CFVR, coronary flow velocity reserve; CI, confidence interval; HR, hazard ratio; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction.
[a]CFVR treated as a continuous variable, HR per 0.1 unit decrease in CFVR.
[b]Hazard ratio per 1 unit increase in CFVR examination quality score (low = 1, medium = 2, and high = 3).

The increased risk related to a reduced CFVR value was independent of presence of diffuse atherosclerosis on CAG.

Discussion

The aim of the iPOWER study was to determine whether routine assessment of CFVR by Doppler echocardiography was feasible and whether this adds to risk stratification in patients with angina and no obstructive CAD. We found that CFVR could be assessed in the vast majority and that impaired CFVR, CAG atherosclerosis, and hypertension were independent predictors of the composite outcome of CVD death, MI, heart failure, stroke, and coronary revascularization. Impaired CFVR was also associated with all-cause mortality and an increased risk of repeated hospital admission for angina pectoris.

The composite outcome event rate in the current study was 14.1 per 1000 person-years overall, and 19.7 per 1000 person-years (7.7%) in patients with CFVR < 2.25. ANOCA has been shown to be associated with increased CVD risk in comparison with healthy populations.[2,4,20] A recent meta-analysis assessed long-term adverse CVD outcomes in 35 000 angina patients without obstructive CAD and reported an incidence rate per 1000 person-years of 9.8 for a pooled outcome of CVD mortality and MI, comparable to our findings.[4] In comparison, event rates in obstructive CAD patients are expectedly higher. In the recent ISCHEMIA trial, the cumulative 5-year event rate of the composite outcome was roughly 17%; however, unstable angina pectoris hospitalizations were included in the composite outcome, accounting for part of the observed difference compared to the present study.[13] Our finding that diffuse CAG atherosclerosis is an independent predictor of adverse outcome is consistent with previous studies in angina patients with no obstructive CAD.[4]

Despite no obstructive CAD and left ventricular ejection fraction >45% at study entry, the association between reduced CFVR and the composite outcome was driven primarily by an increase in the rates of MI and heart failure, while coronary revascularisation procedures were infrequent. Out of 35 observed MIs, only 5 were followed by short-term revascularisation. Consequently, MINOCA may be an important cause of the observed increase in MI associated with low CFVR. Possible mechanisms for MINOCA include chronic vascular inflammation with minor plaque rupture and microvascular dysfunction limiting myocardial perfusion.[5,10] Moreover, increased risk of HFpEF may explain part of the observed increase in heart failure risk associated with low CFVR. A recent cohort study in HFpEF patients found that 75% had CMD, and CMD was further associated with markers of heart failure severity.[11] We found that patients with low CFVR had a higher prevalence of increased filling pressure defined as $E/e' \geq 12$.

In subgroup analyses, the increased risk associated with impaired CFVR was consistent across all subgroups with the exception of BMI. CFVR was a significant outcome predictor in patients with BMI ≤ 30, but not in patients with BMI > 30. This may be related to the TTDE method. We have previously found that TTDE CFVR is feasible in >90% of obese patients and has good inter- and intra-observer variabilities with coefficients of variation ∼5–10%.[19,21,22] However, we have also found a weak association between higher BMI and lower quality of CFVR assessment.[18] Our current findings are consistent with possible underestimation of CFVR in obese patients, perhaps because acquisition of high-quality flow curves during stress can be particularly challenging in obese patients. As a consequence, the true

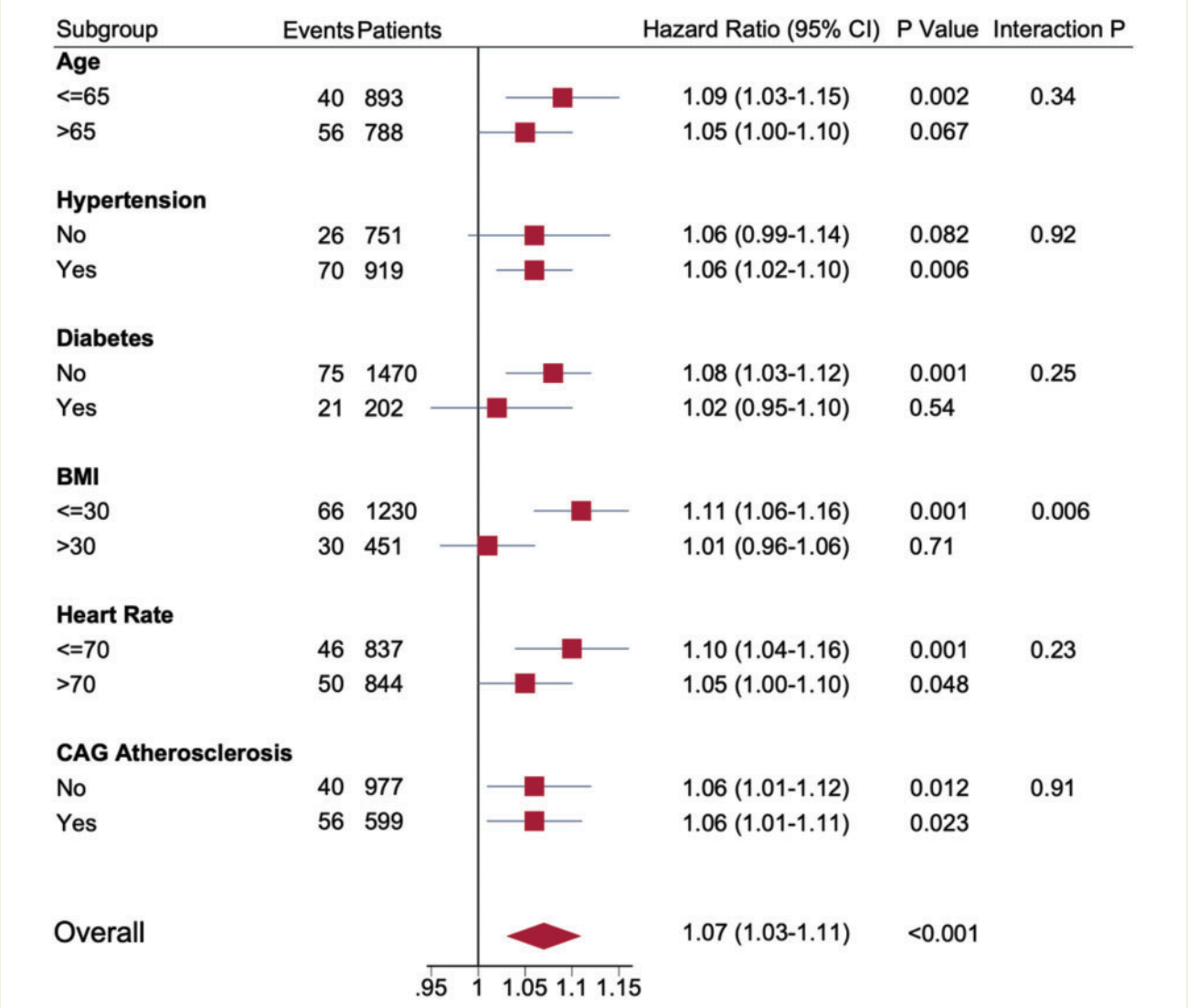
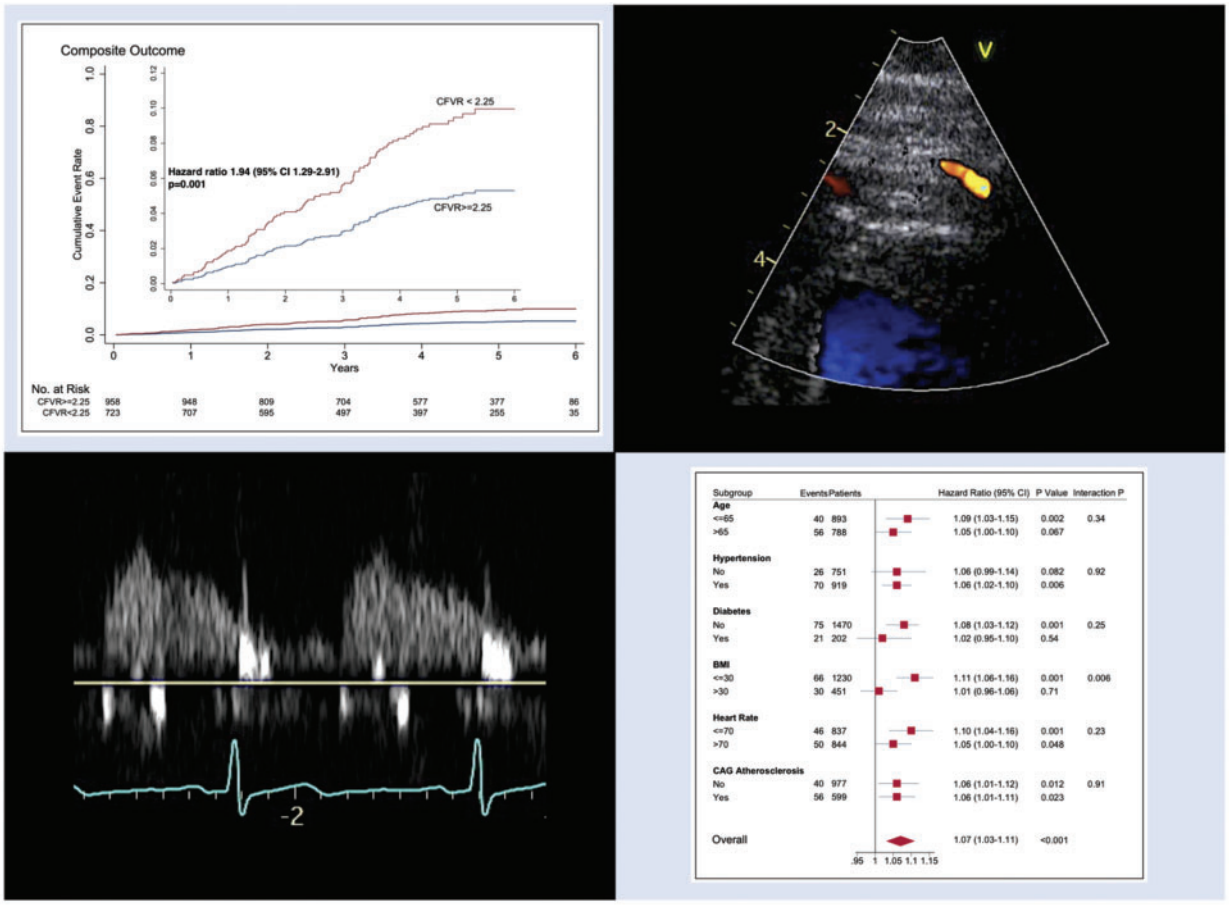


Figure 4 Composite outcome hazard ratios per 0.1 unit decrease in coronary flow velocity reserve in subgroups. BMI, body mass index; CAG, coronary angiography; CI, confidence interval.

maximum stress flow may not be identified in all subjects, which would result in underestimation of CFVR. Alternatively, CFVR assessments were valid, and low CFVR was not a predictor of adverse outcome in obese patients, perhaps because of differences in underlying pathophysiology as a parallel to the 'obesity paradox' or as a chance finding. Notably, high BMI was not associated with low CFVR or the composite outcome.

In exploratory analyses, we found a significant association between low CFVR and risk of hospital admission for angina pectoris and between low CFVR and all-cause mortality. Although increased risk of angina pectoris hospital admissions in ANOCA patients has been described in the past, our finding further suggests a possible role for low CFVR as a predictor of future angina pectoris admissions.[5,23] Regarding all-cause mortality, a previous large study in CAD patients found low CFVR was associated with a HR of 3.31 for all-cause mortality.[7] Another recent study specifically evaluated low CFVR and non-cardiac causes of death and found a considerable increase in the 8-year incidence of cancer mortality.[24] Thus, CFVR also seems to predict all-cause and non-CVD mortality. The underlying causes of this need further exploration.

Previous studies of non-invasive assessment of CMD in angina patients have focused on TTDE and positron emission tomography. TTDE CFVR studies were retrospective, conducted in heterogeneous patient populations including patients with obstructive CAD and heart failure, some in the context of stress echocardiography risk assessment before CAG. Furthermore, a notable proportion of patients in these studies underwent myocardial revascularisation shortly after the stress echocardiography due to new significant stenoses.[7,14,15,25] Positron emission tomography evaluation of CMD in angina patients has also been shown to predict an adverse outcome in heterogeneous retrospective cohorts.[8,16,26] By contrast, the present study investigates a well-defined patient population in a different clinical context. We



Take home figure. Assessment of coronary flow velocity reserve by echocardiography is feasible and predictive of adverse outcome in women with angina and no obstructive CAD

prospectively included patients with no history of obstructive CAD or any other significant cardiac disease. Accordingly, this is the first large study to demonstrate the risk stratification potential of TTDE CFVR in a specifically selected cohort of angina patients following a CAG without obstructive CAD. The timing of CFVR examination after CAG is in line with guidelines and White Papers recommending that obstructive CAD should always be ruled out by invasive CAG or coronary computed tomography angiography before considering a diagnosis of microvascular angina.[1,27,28]

Regarding optimal CMD threshold, many studies in both angina patients with and without obstructive CAD have chosen a value <2.0 to indicate CMD and have obtained higher HRs compared to our findings.[7,14,15] Since CFVR is a continuous variable with an inverse association with adverse outcomes, a lower cut-off will result in an increase in HR. Our data suggest an optimal discrimination threshold may be 2.25. This finding warrants replication in similar patient cohorts. The optimal CFVR cut-off value in patients without obstructive CAD may well be different from the optimal value in patients with suspected or established obstructive CAD, due to regional differences in epicardial and microvascular function in the latter group.

Clinical implications

The pivotal diagnostic challenge in patients classified as ANOCA following a CAG or coronary computed tomography angiography without significant stenosis is to differentiate between those with non-cardiac chest pain and a likely more benign prognosis, and those with microvascular (defined as abnormal CFVR) and/or vasospastic angina. Further distinction between vasospastic and microvascular angina is also relevant due to differences in treatment recommendations.[1] However, diagnosis of vasospastic angina requires intracoronary acetylcholine infusion during CAG, a procedure that is not conventionally performed in catheterization laboratories at present.[28] Moreover, the majority of angina patients are never evaluated with a CAG because non-invasive work-up is normal. A recent invasive study investigated angina aetiology in 151 patients without coronary stenosis and found that isolated microvascular angina was present in 52% of patients compared to isolated vasospastic angina in only 17%. This suggests that microvascular angina due to reduced coronary flow reserve is the dominant cause of angina in these patients.[29] Thus, although invasive assessment will provide a complete picture of vascular function, non-invasive assessment of microvascular angina is

available to a much larger proportion and will lead to a relevant diagnosis in many patients.

In the majority of women with angina pectoris, no aetiological explanation is found. In comparison with invasive CAG and positron emission tomography, TTDE CFVR is inexpensive, readily available in all cardiology departments, not associated with radiation and feasible in >90% of patients.[14,27] This study suggests that TTDE CFVR may be used to identify angina patients with no obstructive CAD for intensified preventive treatment, e.g. with a statin, and to select high-risk subgroups for participation in future interventional studies targeting microvascular dysfunction in angina patients. A shortcoming of TTDE CFVR is that correct interpretation requires that epicardial stenosis has been ruled out, but this is not a concern in the context of verified non-obstructive coronary arteries.

Strengths and limitations

The main strengths of this study were the multicentre consecutive inclusion of all women who met the criteria in a combined rural and urban region covering ~3.0 million inhabitants resulting in an externally valid cohort, and the careful selection of patients with no obstructive CAD or other significant cardiac disease. Furthermore, all TTDE procedures and readings were performed at a central diagnostic examination centre by the same trained operators.

The main limitation is that only non-endothelium-dependent CMD via dipyridamole stress was assessed. Intracoronary acetylcholine injection is rarely performed during routine invasive CAG in Denmark and elsewhere, and this prevented us from evaluating endothelium-dependent CMD and vasospastic angina in the current study. A further limitation was that fractional flow reserve data were not available, and although a low stenosis percentage (≤50%) was chosen, a number of patients may have had undetected flow-limiting stenoses, which would contribute to a lower CFVR.

Conclusion

We found that echocardiographic assessment of CFVR is feasible in most patients and that impaired CFVR is an independent predictor of a composite outcome of CVD death, MI, heart failure, stroke, and coronary revascularization in women with angina pectoris and no obstructive CAD. Assessment of CFVR should be considered in angina patients to identify subgroups likely to benefit from intensified treatment.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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