"The Belgian Registry on Coronary Function Testing (BELmicro Registry): Study Population, Prevalence of Coronary Vascular Dysfunction and Procedural Safety."

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Highlights:

- A significant proportion of patients are affected by coronary vascular dysfunction.
- Comprehensive CFT plays a pivotal role in the diagnostic work-up of ANOCA patients.
- Applicability of CFT in clinical practice demonstrates a low rate of complications.

"The Belgian Registry on Coronary Function Testing (BELmicro Registry): Study Population, Prevalence of Coronary Vascular Dysfunction and Procedural Safety."

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Abstract:

Coronary function testing (CFT) plays a pivotal role in the diagnosis of coronary vascular dysfunction and in providing patients with tailored therapy. The Belgian registry on coronary function testing (BELmicro registry) is a prospective, observational, multicenter registry including 14 centers in Belgium. All patients undergoing clinically indicated CFT were included in the registry. Baseline characteristics, CFT data, and clinical outcomes were collected. The aims of the current analysis were to describe the baseline characteristics of a real-world population of patients undergoing CFT, to evaluate the prevalence of coronary vascular dysfunction and to assess the safety of CFT in daily clinical practice. Between October 2021 and September 2023, 449 patients were enrolled. The mean age was 65 ± 10 years, and 47.4% of patients were male. Fifty-nine percent of patients had hypertension, 18.7% diabetes, 69.5% hypercholesterolemia, and 40.1% smoking habit. Angina and non-obstructive coronary arteries (ANOCA) were identified in 85.1% of patients. Microvascular physiology assessment was performed in 95.5% of patients, vasoreactivity test in 28.5%, and both in 24.0%. CMD was diagnosed in 23.4% of ANOCA patients, epicardial vasospasm in 26.3%, and microvascular spasm in 14.9%. Rates of major complications were 0.7% for microvascular physiology assessment and 0% for vasoreactivity test. In conclusion, participants in the BELmicro registry represented a real-world population of patients, characterized by a high burden of cardiovascular risk factors. Both CMD and coronary vasospasm were frequent in ANOCA patients. Performing CFT in daily clinical practice was feasible with a low rate of complications.

Keywords: coronary function testing, coronary physiology, coronary microvascular dysfunction, vasospastic angina, coronary flow reserve, index of microcirculatory resistance.

Abbreviations and acronyms:

ACH: acetylcholine

ANOCA: angina with non-obstructive coronary arteries

CAD: coronary artery disease

CAG: coronary angiography

CCS: chronic coronary syndromes

CFR: coronary flow reserve

CFT: coronary function testing

CMD: coronary microvascular dysfunction

ECG: electrocardiogram

FFR: fractional flow reserve

IMR: index of microcirculatory resistance

INOCA: ischemia with non-obstructive coronary arteries

LAD: left anterior descending coronary artery

LCx: left circumflex coronary artery

MVA: microvascular angina

MVS: microvascular spasm

RCA: right coronary artery

RFR: resting full-cycle ratio

Tmn_{hyper}: hyperemic mean transit time

Tmn_{rest}: resting mean transit time

VSA: vasospastic angina

Introduction

For many decades, coronary artery disease (CAD) has been considered the main cause of angina.[1] Therefore, ruling out obstructive CAD is considered the primary goal in the management of ischemic heart disease. Nevertheless, about 50% of patients undergoing elective coronary angiography (CAG) have normal coronary arteries or non-obstructive CAD.[2] A significant proportion of these patients have angina or ischemia with non-obstructive coronary arteries (ANOCA and INOCA).[3,4] Recently, two clinical entities have been proposed that may be responsible for patients' symptoms: (1) microvascular angina (MVA) caused by coronary microvascular dysfunction (CMD) and/or microvascular spasm (MVS), and (2) vasospastic angina (VSA) due to inappropriate epicardial vasoconstriction.[5] The CORonary MICrovascular Angina (CorMicA) trial was the first randomized trial in which improved clinical outcome, defined as relief of angina symptoms and higher quality of life, was demonstrated in patients who recieved stratified medical therapy.[6,7] Consequently, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) consensus document on INOCA and the European Society of Cardiology (ESC) guidelines on CCS recommend coronary function testing (CFT) consisting of both guidewire-based microvascular function evaluation and vasoreactivity tests in patients with ANOCA or INOCA.[3,5] Despite these recommendations, CFTs are performed in only a minority of patients in a real-world setting. The Belgian registry on coronary function testing, the BELmicro registry (NCT06089031), has been developed to promote the uptake of CFT in clinical practice and to collect data on coronary vascular function in a real-world population of patients undergoing coronary microvascular assessment and/or vasoreactivity tests. Moreover, the BELmicro registry is expected to offer further evidence on coronary microvascular and vasomotor disorders in a broader clinical setting than ANOCA and

INOCA, such as cardiomyopathies, heart failure with preserved ejection fraction, acute coronary syndrome, and obstructive CAD.[8,9]

Methods

1. Study design

The BELmicro study is a prospective, observational, multicenter registry conducted in 14 centers in Belgium. Patient-level baseline characteristics, clinical outcome data, and vessel-level CFT data were collected in a fully compliant web-based clinical data platform, Research Electronic Data Capture (REDCap). Standardized definitions were used for all variables. CFT could consist either of bolus thermodilution measurements and/or a vasoreactivity test, at the operator's discretion. Clinical follow-up data were collected during routine outpatient evaluations or consulting the internal medical archives. The study protocol was in accordance with ethical principles consistent with the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice guidelines, and the applicable legislation on non-interventional studies. The central ethics committee of the Antwerp University Hospital (Project ID 2021-0522) and the ethics committees of the participating centers approved the study protocol.

2. Study population

All patients who underwent clinically indicated CFT and provided written informed consent were included in the registry. Patients unable to understand, read, and sign the informed consent were excluded.

3. Coronary function testing

CFT could be performed *ad hoc* after diagnostic CAG or in a separate procedure. A comprehensive CFT consisted of both a microvascular assessment with the bolus thermodilution technique and vasoreactivity testing. Given the observational nature of the

study, the tests performed (microvascular assessment, vasoreactivity test, or both) and their sequence were at the discretion of the operator.

3.1 Acetylcholine vasoreactivity test

The study recommendations for vasoreactivity assessment on the left anterior descending coronary artery (LAD) included intracoronary (IC) administration of incremental doses of ACH (2, 20, 100, 200 μg) by manual injection over 20-30 seconds. In the right coronary artery (RCA), the recommended maximal ACH dose was 80 μg. The manual injection speed could be adjusted when bradyarrhythmia occurred. After one minute, symptoms, ECG changes, and reduction of coronary artery diameter on coronary angiogram were to be assessed. At the end of the procedure, IC nitroglycerine or isosorbide dinitrate were delivered and repeated if necessary. In the event of refractory vasospasm or hemodynamic instability, intravenous (IV) atropine could be administered.

3.2 Bolus thermodilution method

For the assessment of coronary microvascular physiology, all measurements had to be performed with a dedicated pressure-temperature sensor equipped guidewire (Pressure Wire X, Abbott Vascular). The use of six-French guiding catheters was recommended, however, five-French was allowed in the case of radial artery spasm.[10] IC nitrates were administered prior to the measurements. After equalization of the guidewire's pressure sensor with the aortic pressure, coronary physiology measurements were performed with the distal pressure sensor advanced at least 6 cm into the coronary artery. It was recommended to start with the non-hyperemic resting full-cycle ratio (RFR), which allows to evaluate the presence of obstructive CAD. Basal and hyperemic mean transit time values (Tmn) were obtained by rapid IC bolus injections of 3 mL of room-temperature saline at rest and during maximal hyperemia. Recorded transit time measurements were within the 30% variation margin. Maximal hyperemia was routinely achieved by either 140 μg/kg/min of IV adenosine or 12-

16 mg of IC papaverine, according to the standard practice of the participating center. It was recommended to record fractional flow reserve (FFR) values during the hyperemic state in all patients undergoing bolus thermodilution assessment. In the case of pressure drift, defined as ≥ 0.03 FFR units during manual pullback, re-equalization and repeat measurement of pressure-derived indices were advised. All physiologic measurements were automatically calculated in dedicated software (Coroflow, Coroventis). Coronary flow reserve (CFR) was calculated as the ratio between the mean of resting and hyperemic Tmn values ($CFR=Tmn_{rest}$ / Tmn_{hyper}).[11,12] The index of microcirculatory resistance (IMR) was derived from Ohm's law by dividing the distal pressure (Pd) with the inverse of the Tmn during hyperemia ($IMR=Pd_{hyper}/\frac{1}{Tmn_{hyper}}$).[13,14] CFR values < 2.0 and IMR values ≥ 25 were considered abnormal.[5]

3.3 Definition of ANOCA patients

ANOCA patients were defined by the presence of non-obstructive CAD. Non-obstructive CAD was defined by <50% diameter stenosis and/or FFR values >0.80. For those patients in whom FFR values were not available, ANOCA was defined on the basis of <50% diameter stenosis on coronary angiography.

3.4 Coronary vascular function endotypes

The following definitions of coronary vascular function endotypes were adopted:

- **Coronary microvascular assessment**
  - Absence of CMD:
    - Normal coronary physiology: CFR ≥ 2.0 and IMR < 25.
  - Presence of CMD:
    - Structural CMD: CFR < 2.0 and IMR ≥ 25.
    - Functional CMD: CFR < 2.0 and IMR < 25.
- **Coronary vasoreactivity assessment**

- Negative test: no spasm, no angina, and no ischemic ECG changes. Isolated mild (< 90%) spasm was also considered a negative test result.
- Definite epicardial vasospasm: recognizable angina symptoms, ischemic ECG changes, and focal or diffuse reduction of the coronary vessel diameter of at least 90% assessed visually with the angiogram after nitrates as a reference.[15]
- MVS: recognizable angina symptoms, ischemic ECG changes, and no or less than 90% epicardial coronary obstruction.

- **Mixed endotype**: CMD and coronary vasospasm (either epicardial or microvascular).

3.5 Procedural complications

Major complications were defined as death, ventricular fibrillation, ventricular tachycardia, peri-procedural myocardial infarction and cardiogenic shock. Minor complication included atrial tachyarrhythmias and bradycardia requiring medical intervention. Transient atrioventricular block following ACH administration was not considered a procedural complication.

4. Aim of the current analysis

The aims of the current analysis were to describe the baseline characteristics of a real-world population of patients included in the BELmicro registry, to evaluate the prevalence of coronary vascular dysfunction, and to assess safety and feasibility of CFT in daily clinical practice.

5. Statistical analysis

Continuous variables are reported as mean ± standard deviation or median and interquartile range depending on data distribution. Normal data distribution was tested by the Shapiro-Wilk normality test. Categorical variables are reported as counts and percentages.

Data analyses were performed using R software, version 4.2.2 (R Foundation for Statistical Computing, Vienna).

Results

1. Baseline characteristics

Between October 2021 and September 2023, 449 patients were included in the BELmicro registry (Table 1). The mean age was 65 ± 10 years, and 47.4% of patients were male. The study population was characterized by a high burden of cardiovascular risk factors: 58.8% had hypertension, 18.7% diabetes mellitus, 69.5% hypercholesterolemia, 40.1% were current or former smokers, and 15.1% had a family history of CAD. Notably, 42.8% of patients already underwent at least one CAG in their past medical history, 12.7% had prior myocardial infarction, and 21.2% underwent prior myocardial revascularization.

Anginal symptoms were the main complaint in 70.6% of patients, while dyspnea in 20.0%. On transthoracic echocardiography, mean left ventricular ejection fraction was 57 ± 10%, and regional wall motion abnormalities were detected in 16.5% of cases. Inducible myocardial ischemia was identified in 32.4% of stress tests performed. On CAG, 20.3% of patients presented with ≥ 50% diameter stenosis in one or more coronary arteries.

ANOCA patients, characterized by < 50% diameter stenosis and/or FFR value > 0.80, were 85.1% (n = 382) of the BELmicro registry population. Patients with obstructive CAD, defined as ≥ 50% diameter stenosis and/or FFR value ≤ 0.80, were 14.9% (n = 67) (Figure 1).

2. CAG and CFT procedural details

In 61.5% of patients, the CFT was performed *ad hoc*, the remainder as an elective procedure. In 24% of patients, a comprehensive CFT including vasoreactivity and coronary microvascular function tests was carried out, and the vasoreactivity test was performed prior to the bolus thermodilution measurements in 61.1% of cases. Coronary microvascular

function assessment was performed in 95.5% of patients and vasoreactivity test in 28.5% (Table 2 and Figure 1).

2.1 Microvascular physiology measurements

Coronary microvascular physiology assessment with the bolus thermodilution technique was performed in 429 patients (95.5%) and 437 vessels (Table S1). Maximal hyperemia was achieved with IV adenosine and IC papaverine in 72% and 28.0% of the cases, respectively. Most measurements were performed in the LAD (93.8%), followed by the RCA (4.2%) and left circumflex coronary artery (LCx; 2.0%). Combined measurements of the LAD and RCA were performed in eight patients (1.9%). One assessment was interrupted due to a complication occurred during hyperemia induction.

2.2 Vasoreactivity test

The vasoreactivity test was performed in 128 patients (28.5%) and 131 vessels, mainly in the left coronary artery (LCA; 95.4%). Evaluation of both left and right coronary systems was performed in three patients (2.3%). In the LCA, the highest administered dose of ACH was 100 μg in 38.4% of the cases and 200 μg in 53.6%; only 1 patient was evaluated with methylergonovine (maximal dose of 300 μg). In the RCA, the maximal dose of ACH was 50 μg in 66.7% of the cases and 80 μg in the remainders. Recognizable chest discomfort was reproduced in 67.2% of patients, ischemic ECG changes in 44.5%, and ≥ 90% vasoconstriction in 39.8% (Table S2).

3. Prevalence of coronary vascular function endotypes among ANOCA patients

Among ANOCA patients, 363 were tested for coronary microvascular dysfunction. The majority was characterized by normal coronary microvascular function (61.8%), 8.0% were affected by functional CMD and 15.4% by structural CMD, while 14.8% presented with isolated abnormal IMR values. Vasoreactivity test was performed in 114 ANOCA patients.

Definite epicardial vasospasm was diagnosed in 26.3% of patients, while microvascular spasm in 14.9% (Figure 2).

A comprehensive CFT (bolus thermodilution and vasoreactivity test) was performed in 96 ANOCA patients, and a mixed pattern characterized by both coronary microvascular dysfunction and coronary vasospasm was diagnosed in 9.4% of patients (Table 3).

4. Coronary function testing among CAD patients

A considerable proportion of patients (14.9%) underwent CFT in the presence of obstructive CAD. Obstructive CAD, defined as ≥ 50% coronary stenosis and/or FFR ≤ 0.80, could be present either in the target vessel or in non-target vessels for CFT. Sixty-five patients underwent bolus thermodilution assessment, 24.6% showed abnormal CFR values and 16.9% abnormal IMR values. Vasoreactivity test was performed in 14 patients, 35.7% were affected by epicardial vasospasm and 7.1% by microvascular spasm (Table S3).

5. Procedural complications related to CFT

The overall complication rate of bolus thermodilution measurements was 1.4% (6/429), including three major and three minor complications. The three major complications (0.7%) occurred after IC papaverine: one patient developed sustained ventricular tachycardia and two others ventricular fibrillation. All of them were treated successfully with electrical defibrillation without any subsequent clinical implications. The three minor complications (0.7%) included adenosine-induced atrial tachyarrhythmia, adenosine-induced mild bronchospasm, and cluster headache, all of which required medical intervention.

The complication rate of the vasoreactivity test was 6.3% (8/128), including only minor complications. Seven patients developed acetylcholine-induced arrhythmia requiring medical intervention, and one patient developed a minor peri-procedural myocardial injury characterized by an increase of high-sensitive troponin I levels below the threshold of 5-fold the upper limit of normal (Table 4 and Figure 3).

Discussion

The current study sought to describe the baseline characteristics of a real-world population of patients undergoing CFT, to evaluate the prevalence of different coronary vascular function endotypes among ANOCA patients, and to assess safety and feasibility of CFT in daily clinical practice. The main findings of our study can be summarized as follows: 1) Participants in the BELmicro registry represented a real-world population of patients undergoing CFT, characterized by a relatively high burden of cardiovascular risk factors. 2) Epicardial and microvascular physiology measurements were performed in the majority of patients, while a comprehensive CFT, including vasoreactivity testing, were performed in only one out of four patients. 3) Coronary vascular dysfunction was frequent among ANOCA patients, with 23% of patients affected by CMD and 41% affected by vascular spasm, if vasoreactivity test was performed. 4) Performing CFT was feasible in daily clinical practice and characterized by a very low rate of major complications.

Several studies investigating the prevalence of CMD and coronary vasospasm are available in the current literature. Most of these included relatively young patients without evidence of obstructive CAD.[16–18] Participants in the BELmicro registry represented a real-world population of older patients characterized by a higher rate of cardiovascular risk factors. Moreover, a considerable rate of obstructive CAD and prior coronary revascularization were observed in our study population. In patients affected by obstructive CAD, CMD is thought to contribute to the total burden of ischemia in myocardial regions supplied by the stenosed epicardial arteries, and coronary vasospasm may co-exist.[19] Therefore, this subpopulation of patients included in the BELmicro registry may provide additional insights into the role of coronary vascular dysfunction among patients affected by obstructive CAD.

One of the main goals of the registry was to promote CFT as a key investigation in the diagnostic work-up of ANOCA, which allows for a more accurate diagnosis and customized treatment plans for these patients. This approach has been shown to improve patient-reported outcomes, as it is cost-effective.[6,20,21] Of note, almost half of the BELmicro patients underwent at least one prior CAG in their past medical history. Even after considering those patients with a prior history of coronary revascularisation and/or myocardial infarction, the proportion of patients who underwent prior diagnostic CAG and remained underdiagnosed for coronary vascular dysfunction seems high. This finding underlines the pivotal role of CFT in providing patients with a definite diagnosis, especially in the case of repeat CAG which showed non-obstructive CAD.

Notably, uptake of ACH vasoreactivity tests was low (28.5%), suggesting that many patients might remain underdiagnosed for VSA. Several explanations were considered. First, the vasoreactivity test ideally requires a time window free from vasoactive drugs of at least 48 hours. In addition, the test is best performed in the morning, as suggested in the Japanese guidelines.[22] Both the no-drug window and the diurnal consideration should, however, be a reason to perform the test in an elective fashion but not to forgo the test. Second, ACH is not available for intravascular use in Belgium. Therefore, the off-label use of ACH for intra-ocular injection is required. Third, operators might hesitate to perform vasoreactivity test out of fear for complications. However, no major complications occurred during ACH vasoreactivity test in our patients cohort, consistently with larger registries that showed the safety of this procedure.[23] Fourth, operators might consider the presence of vasospastic angina irrelevant for patients prognosis, although, the contrary has been reported.[24] Fifth, longer procedural time with higher radiation and contrast exposure might pose another barrier. Lastly, physiological measurements during maximal hyperemia require the administration of IC nitrates, which may decrease the sensitivity of the ACH vasoreactivity

test for epicardial vasospasm. The available guidelines contradict each other regarding the order of tests, as the COVADIS consensus recommendation is to perform bolus thermodilution measurements first and the Japanese guidelines recommend to perform ACH vasoreactivity first.[15,22] In our patient cohort, bolus thermodilution measurements were performed prior to ACH testing in 38.9% of patients. In half of those patients, no nitrates were given prior to the pressure wire measurements, which is actually 'off-protocol' and might have influenced the hyperemic coronary pressure-indices obtained.

CMD was diagnosed in almost one out of four ANOCA patients enrolled in the BELmicro registry. This prevalence was lower compared to the pooled prevalence of CMD presented in a recent meta-analysis by Mileva N. et al.[4] However, this metanalysis included studies in which the presence of CMD was diagnosed by IMR assessment only. Multiple registries did not show a difference in the rate of adverse cardiac events for isolated increased microcirculatory resistance compared to normal measurements, therefore, it remains unclear whether this an isolated elevated IMR value is truly pathological.[25–27] Functional CMD was less frequent than the structural form (respectively 8.0% vs. 15.4%). Conversely, a recent analysis of the ILIAS (Inclusive Invasive Physiological Assessment in Angina Syndromes) registry, in which a CFR cut-off of 2.5 was adopted, revealed that functional CMD was the most frequent CMD endotype.[25].

In the BELmicro population, the rates of epicardial vasospasm and MVS were lower compared to those reported in the meta-analysis by Mileva N. et al. [4] However, equivocal test results occurred in almost one in three patients tested. It has been suggested that these equivocal test results may represent an endotype of VSA not to be ignored, as (1) the hemodynamic response to high-dose acetylcholine appears similar to that of MVS, suggestive of vascular smooth muscle cells hyperreactivity; (2) the response to nitroglycerine is similar between the equivocal and epicardial vasospastic endotype, with similar increases in coronary

blood flow and epicardial diameter, as well as a similar decrease in vascular resistance; (3) during ACH rechallenge, nitroglycerin improves coronary blood flow, vascular resistance, and symptoms similar to those of epicardial vasospasm; (4) post-spastic reactive hyperemia occurs in a similar extent in equivocal, epicardial, and MVS endotypes; (5) patients with equivocal test results have similar rates of recurrent angina as those with MVS or epicardial VS.[28–31] Simultaneous measurement of coronary blood flow during ACH provocation may serve as a good alternative, however, the doppler-wire is currently not commercially available.[32]

Finally, both the bolus thermodilution technique and the vasoreactivity test are considered to have a low rate of major complications in the literature.[33,34] The results of the BELmicro registry support this, as major complications occurred in only 0.7% of patients after papaverine administration. All these complications were promptly managed and solved without subsequent clinical implications.

Study limitations

First, a selection bias of the patients included in the BELmicro registry cannot be excluded. Second, since the BELmicro registry was designed to collect data on CFT performed in daily clinical practice, participating centers could apply slightly different approaches from the study protocol to perform coronary physiology assessment. Third, given the observational nature of the registry, the tests performed during coronary physiology assessment were at the discretion of the operator, and a limited number of patients underwent ACH vasoreactivity testing. Therefore, the prevalence data on epicardial vasospasm and MVS may be affected by the relatively small sample size. In addition, the results of vasoreactivity testing may not be unequivocal, leading to conflicting interpretations by different operators. Fourth, core laboratory analysis was not performed in the current study. However, coronary

physiology assessments were performed by experienced operators at all participating centers. Fifth, the CFR cut-off value of 2.0 was adopted for the diagnosis of CMD in the current analysis, however, recent studies showed that a cut-off value of 2.5 is more reliable for the bolus thermodilution technique.[21].

Conclusions

Participants in the BELmicro registry represented a real-world population of patients characterized by a high burden of cardiovascular risk factors and a considerable rate of obstructive CAD. Most of the patients were evaluated with epicardial and microvascular physiology assessment, and only a minority of them with a comprehensive CFT including vasoreactivity testing. The BELmicro population showed a high prevalence of CMD and coronary vasospasm among ANOCA patients. The applicability of CFT in daily clinical practice was found to be feasible and safe.

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Figures legend:

Figure 1. Study population of the BELmicro registry and flow chart of the study protocol.

ANOCA: angina and non-obstructive coronary arteries; CAD: coronary artery disease; CAG: coronary angiography.

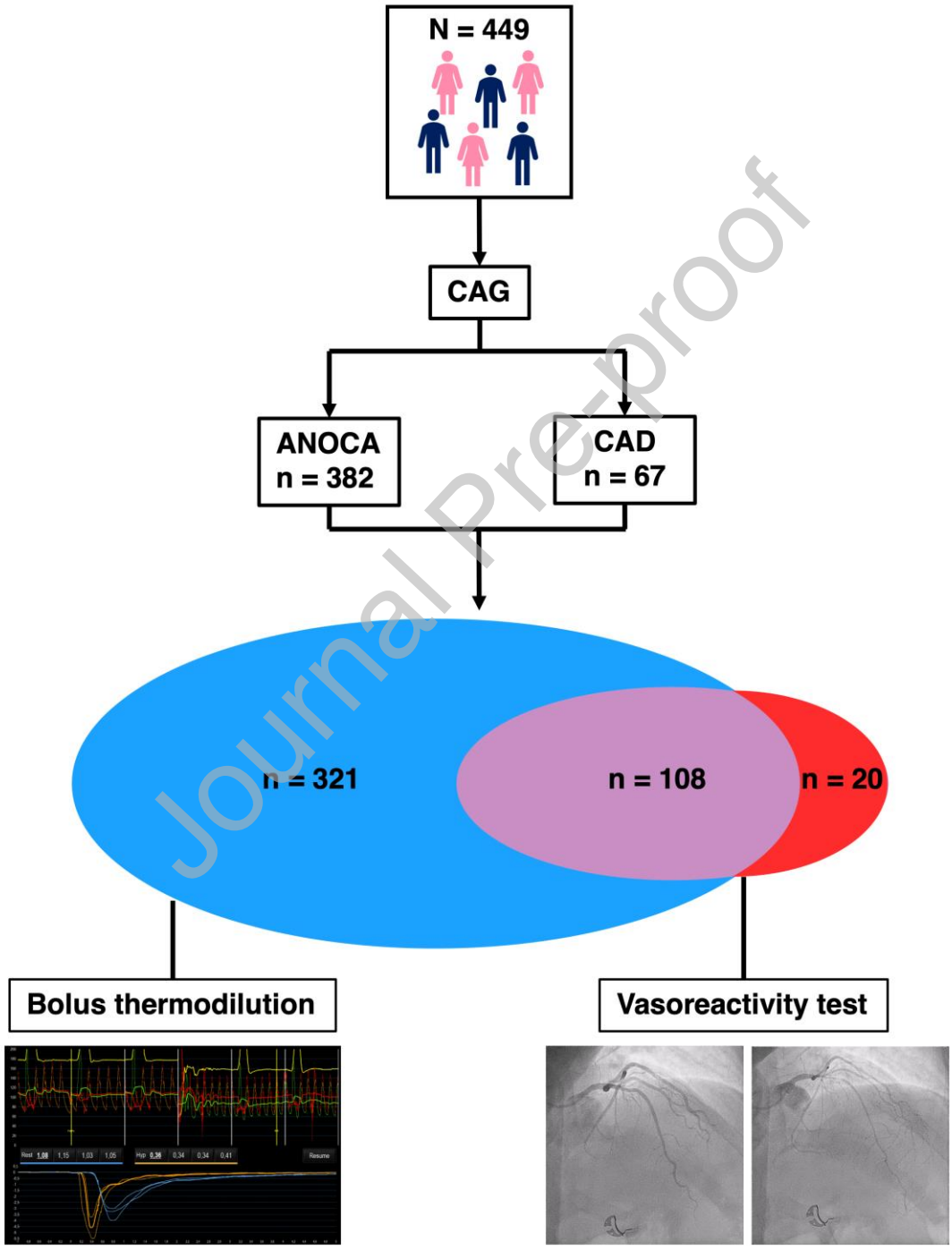


Figure 2. Prevalence of coronary microvascular dysfunction and vascular spasm in ANOCA patients.

ANOCA: angina and non-obstructive coronary arteries; CMD: coronary microvascular dysfunction.

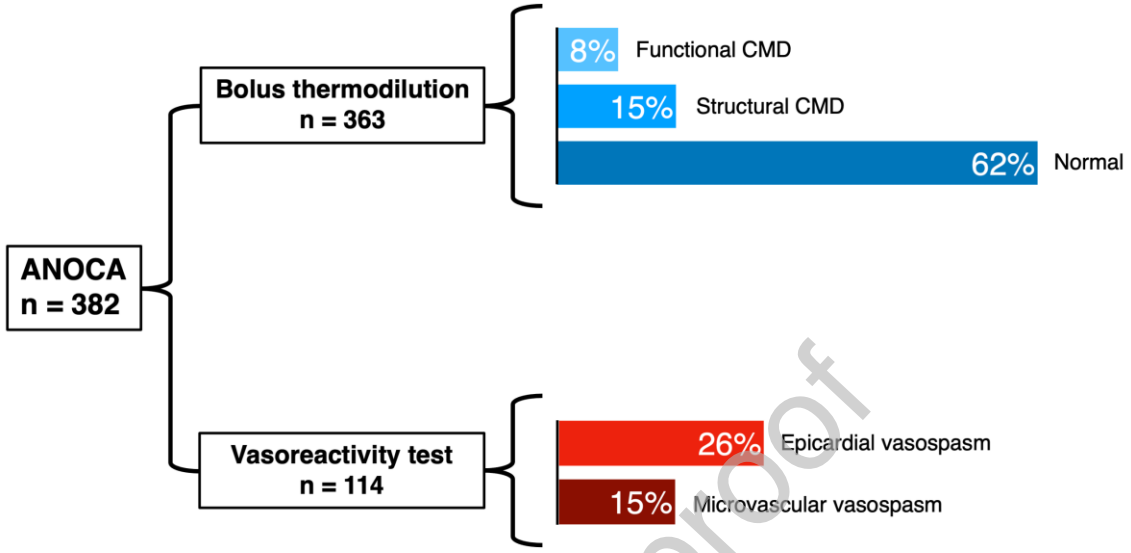
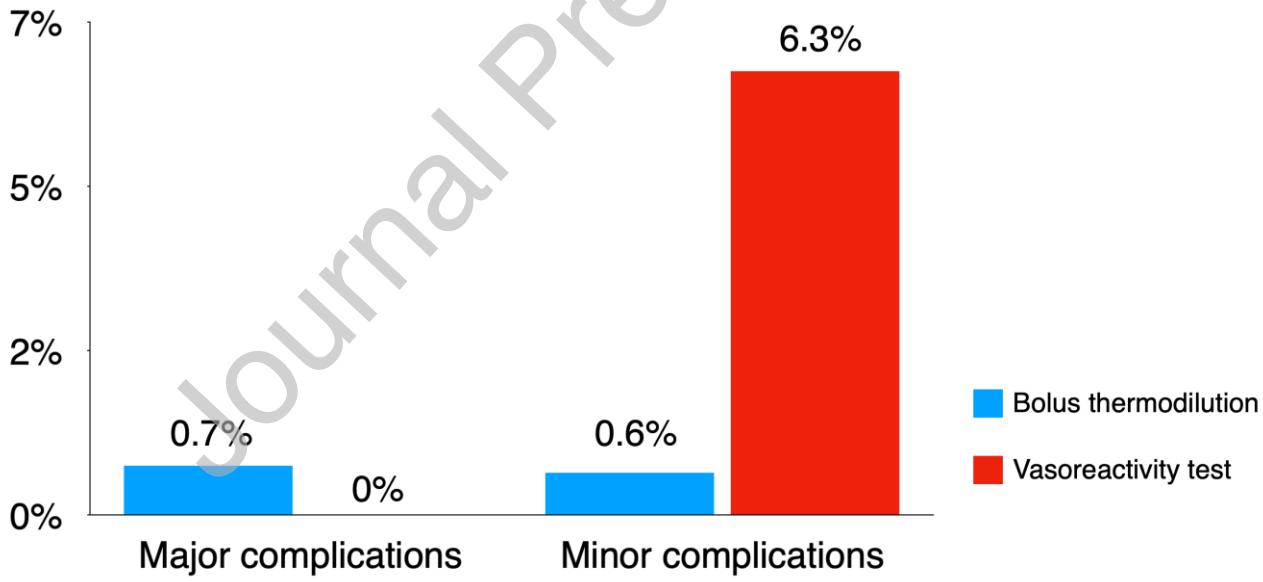


Figure 3. Rates of major and minor complications for bolus thermodilution and vasoreactivity tests.



Tables:

Table 1. Baseline characteristics of the BELmicro registry population.

	N = 449
Age, years	65 ± 10

	N = 449
Male sex	213 (47.4%)
BMI, kg/m²	27.6 ± 4.9
eGFR, ml/min/1.73 m^2	79 ± 19
Cardiovascular risk factors	
Hypertension	264 (58.8%)
Diabetes mellitus	84 (18.7%)
Dyslipidaemia	312 (69.5%)
Current or former smokers	180 (40.1%)
Family history of CAD	68 (15.1%)
Medical history	
Prior CAG	192 (42.8%)
Prior myocardial infarction	57 (12.7%)
Prior coronary revascularization	95 (21.2%)
Percutaneous coronary intervention	91 (20.3%)
Coronary artery bypass grafting	4 (0.1%)
Atrial fibrillation	74 (16.5%)
Clinical presentation	
Angina	317 (70.6%)
Dyspnea	90 (20.0%)
Asymptomatic	29 (6.5%)
Other	13 (2.9%)
Seattle Angina Questionaire (n = 212)	
Angina limitation	67 ± 31
Angina frequency	71 ± 24
Angina quality of life	42 ± 39
Non-invasive investigations	
ECG repolarization abnormalities	53 (11.8%)
LVEF, % (n = 382)	57 ± 10

	N = 449
Regional wall-motion abnormalities (n = 382)	63 (16.5%)
Inducible myocardial ischemia (n = 259)	84 (32.4%)
Coronary angiography	
One vessel with epicardial stenosis ≥ 50%	66 (14.7%)
Two vessels with epicardial stenosis ≥ 50%	18 (4.0%)
Three vessels with epicardial stenosis ≥ 50%	7 (1.6%)

n (%); mean ± sd.

BMI: body max index; CAD: coronary artery disease; CAG: coronary angiography; ECG: electrocardiogram; eGFR: estimate glomerular filtration rare; LVEF: left ventricular ejection fraction.

Table 2. CFT procedural details.

	N = 449
Timing of CFT	
Elective	173 (38.5%)
Ad hoc	276 (61.5%)
Coronary function test performed	
Coronary microvascular function (CFR/IMR)	429 (95.5%)
Vasoreactivity test	128 (28.5%)
Comprehensive CFT	108 (24.0%)
Vascular approach	
Radial	432 (96.2%)
Femoral	16 (3.6%)
Ulnar	1 (0.2%)
Size of guiding catheter	
5 Fr	18 (4.0%)
6 Fr	429 (95.6%)
7 Fr	2 (0.4%)

n (%).

CFR: coronary flow reserve; CFT: coronary function testing; Fr: French; IMR: index of microcirculatory resistance.

Table 3. Prevalence of coronary vascular function endotypes among ANOCA patients.

	N = 382
Coronary microvascular function (n = 363)	
Functional CMD	29 (8.0%)
Structural CMD	56 (15.4%)
Normal microvascular function	224 (61.8%)
Isolated abnormal IMR	54 (14.8%)
Vasoreactivity test (n = 114)	
Epicardial vasospasm	30 (26.3%)
Microvascular spasm	17 (14.9%)
Comprehensive CFT (n = 96)	
Mixed pattern	9 (9.4%)

n (%).

ANOCA: angina and non-obstructive coronary arteries; CFT: coronary function testing; CMD: coronary microvascular dysfunction; IMR: index of microcirculatory resistance.

Table 4. Procedural Complications.

	N = 449
Coronary angiography complications (n = 449)	**5 (1.1%)**
Access site bleeding or large hematoma	2 (0.4%)
Symptomatic radial artery occlusion	2 (0.4%)
Peripheral artery perforation	1 (0.2%)
Bolus thermodilution complications (n = 429)	**6 (1.4%)**
Ventricular fibrillation	2 (0.5%)
Sustained ventricular tachycardia	1 (0.2%)
Atrial tachyarrhythmia	1 (0.2%)
Mild bronchospasm	1 (0.2%)
Cluster headache	1 (0.2%)
Vasoreactivity test complications (n =128)	**8 (6.3%)**
Atrial tachyarrhythmia	6 (4.7%)
Bradyarrhythmia	1 (0.8%)
Minor peri-procedural myocardial injury (hs Tn I < 5x ULN)	1 (0.8%)

n (%).

ACH: acetylcholine; hs Tn I: high sensitive troponine I; ULN: upper limit of normal.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Vincent Frans Maria Segers reports financial support was provided by Fund for Scientific Research Flanders. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.