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Predictive value of Type D personality for impaired endothelial function in patients with coronary artery disease

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ABSTRACT

Background: Type D personality (high negative affectivity and social inhibition) is associated with cardiovascular events and coronary plaque severity. Whether Type D is also related to functional vasomotion abnormalities is unknown. We examined concurrent and predictive associations of Type D with endothelial dysfunction in patients with coronary artery disease (CAD).
Methods: At baseline, 180 CAD patients (90% men; M = 58.0 years) completed Type D (DS14) and depression scales, and entered a 12-week exercise program. Flow-mediated dilation (FMD) of the brachial artery and circulating $CD34^{+}/KDR^{+}/CD45^{+}_{dim}$ endothelial progenitor cells (EPCs) were assessed at baseline, 3 months, and 12 months. Logistic regression and linear mixed models were used to analyze endothelial function.
Results: Type D personality was associated with decreased FMD across baseline, 3 months, and 12 months (mixed model analysis, p = 0.04), after adjustment for clinical characteristics, exercise training and depression. There was no significant association between Type D and decreased EPCs (p = 0.07). Age and smoking were other significant correlates of FMD and EPCs. Using a FMD <5.5% cut-off, Type D patients more often had endothelial dysfunction at baseline (24/37 = 65%) than non-Type Ds (63/143 = 44%); OR = 3.03, 95% CI 1.04–8.80. This significant Type D effect was confirmed in prospective analyses of endothelial dysfunction at 12 months (OR = 3.43, 95% CI 1.01–11.64), and in subgroup analyses of male patients.
Conclusions: Type D personality was associated with impaired endothelial function in men with CAD. This association was robust across time, independent from depressive symptoms, and supports the notion that Type D has an adverse effect on cardiovascular health in patients with CAD.
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1. Introduction

Despite major advances in treatment, patients with coronary artery disease (CAD) continue to suffer cardiac events [1] that can also be stress-related. Patients with Type D (*distressed*) personality are prone to stress [2]; i.e., they tend to experience negative emotions (negative affectivity) and inhibit self-expression (social inhibition). Type D is related to adverse events in cardiac patients [2], and the European Society of Cardiology [3] and its cardiac rehabilitation section [4] have included Type D as a psychosocial risk marker. Yet, some studies found no effect of Type D on all-cause mortality [5]. A meta-analysis showed that Type D predicted a 2-fold increased risk of cardiac events [6], but also indicated heterogeneity among studies.

This heterogeneity relates to the biological plausibility of Type D [7]. Re-analysis of studies on CAD showed that Type D predicted cardiac events/death but not non-cardiac death [8]. Hence, Type D may be related to specific cardiovascular pathways [7]. Type D is related to increased coronary plaque severity [9,10] but its role in functional coronary abnormalities is unknown. Endothelial cells regulate vascular and inflammatory responses, and endothelial dysfunction induces functional coronary abnormalities that play a key role in the development of CAD [11,12]. Flow-mediated dilation (FMD) is a measure of endothelial function that reflects vasodilation through release of nitric oxide in response to a hyperemia-induced increase in endothelial shear stress [13,14]. FMD of the brachial artery is related to coronary endothelial dysfunction [12], and has a strong prognostic value in predicting cardiovascular events [15].

Acute [16,17] and chronic [18,19] stress can lead to endothelial dysfunction. Type D individuals [2] report more stress but it is unclear whether Type D is directly related to endothelial function. Type D predicted poor FMD in patients with lung disease [20] while studies in

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healthy subjects found mixed results [21,22]. Type D was also related to biomarkers of endothelial activation [23]. Type D might contribute to endothelial dysfunction through different candidate pathways. Increases in superoxide anions formation [24], oxidative stress [25], TNF-α [26], and cortisol [27] have been observed in Type D individuals, and may induce endothelial dysfunction [1,12,13,28].

Therefore, our aim was to examine the predictive value of Type D for endothelial dysfunction in CAD. We also examined the link between Type D and endothelial progenitor cells (EPC) as marker of endothelial repair [13]. Because endothelial dysfunction [29,30] and the effect of Type D on cardiovascular stress [31] may occur more in men than in women, we also wanted to study Type D and endothelial dysfunction among men in particular. Diabetes, hypertension, smoking and depression are associated with Type D [23,32–34] and were included as covariates.

2. Methods

2.1. Study design and participants

Patients from the Study on Aerobic INTerval EXercise training in CAD (SAINTEX-CAD) were included at the Antwerp University Hospital (n = 100) or Leuven University Hospital (n = 100) in Belgium. Rationale and methodology of this prospective trial are described elsewhere [35]. In brief, 200 patients (90% men; m = 58.4 ± 9.1y) were randomized to a supervised 12-week exercise program of aerobic *interval* or *continuous* training. Inclusion criteria were: 1) angio-graphically documented CAD (stenosis ≥75% in any branch) or acute myocardial infarction (AMI), 2) left ventricular ejection fraction (LVEF) >40%, 3) on optimal medical treatment, 4) stable regarding symptoms and medication for at least 4 weeks, and 5) included between 4 and 12 weeks following AMI, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) [35,36].

Patients underwent assessment of endothelial function by FMD and blood sampling for quantification of EPCs at baseline, after 3 months, and after 12 months. Blood sampling was performed in the morning, in fasting conditions and patients refrained from exercise at least 8 h before the measurements. Flow cytometric analyses were performed in the Antwerp Laboratory of Cellular and Molecular Cardiology that served as the core laboratory [36]. The SAINTEX-CAD trial complied with the World Medical Association Declaration of Helsinki on ethics in medical research. The study was approved by the local ethics committees of both participating hospitals, and all participants gave written informed consent [35].

2.2. Type D personality and depressive symptoms

Personality was assessed at baseline with the 14-item Type D Scale (DS14) [32]. The DS14 comprises two 7-item measures; negative affectivity (NA) and social inhibition (SI). Items are rated on a 5-point scale ranging from 0 = false to 4 = true. A cut-off ≥10 on the NA and SI measures identifies individuals with elevated trait levels, and individuals with a score ≥10 on both scales are categorized as Type D [32–34]. The NA and SI scales are uni-dimensional and internally consistent (Cronbach's α = 0.88 and 0.86), and have good test-retest reliability [32].

To compare the separate and combined effects of high and low trait levels, the cut-off ≥10 was used to define four distinct personality subgroups [33]; i.e., low on both traits (NA ≤ 9 and SI ≤ 9; reference group), SI only (SI ≥ 10 but NA ≤ 9), NA only (NA ≥ 10 but SI ≤ 9), and Type D (NA ≥ 10 and SI ≥ 10). Previously, we showed that this classification scheme was successful in predicting prognosis in CAD patients, and that Type D was associated with adverse cardiac events while patients of the NA only or SI only subgroups were not at increased risk [8,33].

The Dutch 7-item depression measure [37] of the Hospital Anxiety and Depression Scale was used to assess depressive symptoms and control for these symptoms in statistical analyses. The 7 items are rated on 4-point scale (0–3), and the total score ranges between 0 and 21.

2.3. FMD assessment of endothelial function

Endothelial function was assessed by FMD of the brachial artery [36]. Ultrasound scanning was used to measure endothelium-dependent vasodilation in response to reactive hyperemia [14]. To control environmental factors that could influence FMD assessment, all analyses were performed in the morning, in fasting conditions and in a quiet temperature-controlled room (21–24 °C) by a trained operator that was blinded for the study intervention. Subjects refrained from exercise, food and caffeine at least 8 h before the measurements. Patients were in supine position and the brachial artery was imaged above the antecubital fossa. Blood pressure was obtained after 10 min of rest with an automated blood pressure monitor (Omron M6). The forearm was occluded during 5 min with a cuff placed on the forearm distal to the brachial artery, at a cut-off pressure of at least 200 mm Hg or 60 mm Hg supra-systolic. Images were continuously recorded from 1 min before cuff inflation to 3 min after cuff deflation and were analyzed using edge-detection software FMD-i by Flomedi (Brussels, Belgium). FMD was expressed as the percentage change in diameter of the brachial artery [14]. Measurements were performed by two experienced investigators and analyses of the measurements were blinded to the treatment allocation and study visits.

2.4. Clinically relevant endothelial dysfunction

In addition to analyzing continuous FMD values, we also examined impairment in endothelial function in both concurrent (baseline) and prospective (12 months) analyses. There is a wide variability in FMD levels across studies [38], and a lack of consensus for a clinical relevant cut-off value [14]. In a study of patients with CAD, impaired FMD as defined by a cut-off <5.5% predicted an increased risk of adverse cardiovascular events [39]. In our study, the median value of FMD was 5.6% and 6.1% at baseline and 12 months. This corresponds well to the median of 5.2% reported in a meta-analysis of 16 studies [38] and to the cut-off <5.5% that has been related to poor prognosis in CAD [39]. Therefore, we used the FMD <5.5% cut-off to define clinically relevant endothelial dysfunction both at baseline and 12 months follow-up.

2.5. Assessment of circulating EPCs

Circulating EPC numbers, defined as $CD34^+/KDR^+/CD45^+$dim cells, were quantified by multi-parametric flow cytometry [36]. Whole blood was fixed (TransFix, Caltag Medsystems, Buckingham, UK) and processed 2 to 3 days after sampling. After pretreatment with Fc receptor blocking reagent (Miltenyi Biotec, Bergisch Gladbach, Germany), samples were incubated with CD34-PE-Cy7 (BD Pharmingen, Erembodegem, Belgium), KDR-APC (R&D Systems, Minnesota), and CD45-APC-H7 (BD Pharmingen) antibodies. Addition of the nucleic acid dye SYTO 13 (Life Technologies, Ghent, Belgium) allowed identification of non-nucleated cells and cellular debris. At least one million total events were recorded on a FACSCanto II flow cytometer (Becton Dickinson, New Jersey). Fluorescence-minus-one samples and unstained samples served as negative controls. Numbers of EPCs were analyzed using FACSDiva software (Becton Dickinson, version 6.1.2) and expressed as cells per million $CD45^+$ mononuclear cells with low forward (FSC) and side scatter (SSC) [36].

2.6. Statistical analyses

One-way analyses of variance and chi-square tests were used to examine differences in continuous and categorical baseline variables as a function of personality. Two separate linear mixed models were used to assess the association of the different personality profiles with FMD and EPC markers of endothelial function across 3 time points (baseline, 3 months, 12 months). In the linear mixed model analyses, all three time points were included and modeled according to an unstructured covariance matrix. Demographics (age, sex), exercise treatment (interval or continuous training), standard cardiovascular risk factors (hypertension, diabetes, smoking), and depressive symptoms were included as covariates in these analyses. Next, we used multiple logistic regression models to assess the concurrent (baseline) and prospective (12 months) relationships between personality profiles and endothelial dysfunction as defined by the FMD cut-off <5.5% [39]. These models included the covariates mentioned above. Logistic regression models of endothelial dysfunction were replicated in the group of men with CAD. All statistical analyses were performed using SPSS 24.0 for Mac and SPSS 22.0 for Windows (IBM SPSS Statistics for Windows, Armonk, NY). All tests were 2-tailed, and p-values <0.05 were considered to be statistically significant.

3. Results

3.1. Baseline characteristics

For 12 of the 200 participants, personality assessment was missing; Table 1 presents the characteristics of the 188 patients included in this study. The mean age was 58.0 years, 90% were men, 60% had survived an AMI, and the large majority of patients underwent PCI or CABG. Based on the standard cut-off ≥10 on the NA and SI measures of the DS14 [32], 39 patients (21%) were classified as Type D personality, 29 (15%) as NA only, 37 (20%) as SI only, and 83 (44%) as the reference group with low scores on both traits. Type D personality was not significantly related to age, sex, diagnosis of an index AMI, invasive treatment with CABG or PCI, hypertension, diabetes, smoking or medication use (statins, acetylsalicylic acids, beta-blockers, angiotensin-converting enzyme inhibitors, anti-diabetic medication, diuretics, nitrates). However, patients with Type D personality displayed significantly higher levels of depressive symptoms than non-Type D patients did (Table 1).

3.2. FMD and EPC measures of endothelial function

Mean scores (±standard deviation) of FMD were 5.61 ± 2.83, 6.68 ± 2.97 and 6.29 ± 3.22 at baseline, 3 months and 12 months. FMD was missing for 8, 30, and 45 patients at these 3 time points. Median

Table 1
Baseline characteristics and medical treatment.

	Total group n = 188	Non-Type D n = 149	Type D n = 39	p-Value
Clinical characteristics				
Age (years; mean ± SD)	58.0 ± 9.1	58.2 ± 9.2	57.6 ± 9.2	0.73
Male sex	170 (90%)	136 (91%)	34 (87%)	0.44
AMI	113 (60%)	93 (62%)	20 (51%)	0.21
PCI	125 (67%)	99 (66%)	26 (67%)	0.98
CABG	57 (30%)	44 (30%)	13 (33%)	0.65
Duration CAD > 3 months	42 (22%)	33 (22%)	9 (23%)	0.90
Peak VO2 (ml/kg/min)	22.7 ± 5.7	22.9 ± 5.7	22.4 ± 5.8	0.49
Hypertension	98 (52%)	75 (50%)	23 (59%)	0.34
Diabetes	34 (18%)	27 (18%)	7 (18%)	0.98
Smoking	23 (12%)	15 (10%)	8 (21%)	0.20
Depressive symptoms	3.5 ± 3.3	2.6 ± 2.7	6.9 ± 3.3	0.0001
Medication				
Statins	184 (98%)	146 (98%)	38 (97%)	0.83
Acetylsalicylic acids	176 (94%)	140 (94%)	36 (92%)	0.71
Beta-blockers	158 (84%)	128 (86%)	30 (77%)	0.17
ACE-inhibitors	130 (69%)	107 (72%)	23 (59%)	0.12
Oral antidiabetic	27 (14%)	19 (13%)	8 (21%)	0.22
Insulin	9 (5%)	8 (5%)	1 (3%)	0.47
Diuretics	15 (8%)	10 (7%)	5 (13%)	0.21
Nitrates	8 (4%)	6 (4%)	2 (5%)	0.76

Type D personality defined by the combination of a negative affectivity score ≥10 and a social inhibition score ≥10 on the DS14 [32]; all other patients classified as non-Type D. Data are expressed as means ± standard deviation (SD) for continuous variables or as number and percentages for dichotomous variables.
ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CAD = coronary artery disease; PCI = percutaneous coronary intervention; Peak VO2 = peak oxygen uptake.

Table 2
Mean FMD and EPC levels, and mixed model analyses of FMD and EPC levels across baseline, 3 months and 12 months assessments.

(2a) FMD/EPC Mean (SD)	Reference group n = 83	Negative affectivity only n = 29	Social inhibition only n = 37	Type D personality n = 39
FMD baseline	6.2 (2.9)	5.4 (2.5)	5.3 (2.4)	4.9 (3.0)
FMD 3 months	6.9 (3.0)	7.6 (3.5)	6.0 (2.4)	6.1 (2.9)
FMD 12 months	6.3 (2.8)	6.7 (4.6)	6.9 (3.0)	5.3 (2.9)
EPC baseline	12.4 (9.0)	11.6 (8.6)	12.3 (12.0)	9.0 (6.5)
EPC 3 months	12.3 (15.0)	9.2 (7.3)	13.3 (9.3)	11.5 (7.7)
EPC 12 months	11.4 (9.9)	9.7 (10.3)	11.1 (9.4)	10.5 (9.4)

	β	t	p	95% CI
(2b) FMD mixed model				
Age (years)	−0.07	−3.57	0.001	[−0.11, −0.03]
Male sex	0.52	0.82	0.41	[−0.74, 1.78]
Hypertension	0.32	0.89	0.38	[−0.39, 1.02]
Diabetes	−0.29	−0.66	0.51	[−1.18, 0.59]
Smoking	0.14	0.25	0.80	[−0.96, 1.24]
Training program	0.12	0.34	0.73	[−0.56, 0.80]
Depressive symptoms	−0.01	−0.18	0.86	[−0.15, 0.12]
Negative affectivity only	−0.27	−0.48	0.64	[−1.41, 0.86]
Social inhibition only	−0.62	−1.36	0.18	[−1.53, 0.28]
Type D personality	−1.14	−2.00	0.047	[−2.27, −0.02]
(2c) EPC mixed model				
Age (years)	−0.05	−0.91	0.37	[−0.16, 0.06]
Male sex	−3.25	−1.76	0.08	[−6.90, 0.39]
Hypertension	0.51	0.51	0.61	[−1.49, 2.51]
Diabetes	−1.66	−1.32	0.19	[−4.15, 0.82]
Smoking	−3.35	−2.08	0.039	[−0.29, −0.01]
Training program	−0.71	−0.73	0.47	[−2.65, 1.22]
Depressive symptoms	0.29	1.40	0.16	[−0.12, 0.71]
Negative affectivity only	−2.63	−1.59	0.11	[−5.90, 0.63]
Social inhibition only	−0.26	−0.20	0.84	[−2.80, 2.29]
Type D personality	−3.03	−1.81	0.07	[−6.33, 0.27]

SD = standard deviation; FMD was missing for 8, 30 and 45 patients, and EPC for 23, 33 and 43 patients at these 3 time points, respectively. Personality subgroups defined by the cut-off ≥10 on the negative affectivity (NA) and social inhibition (SI) traits of the DS14 [32,33]. *Negative affectivity only* = NA ≥ 10 but SI ≤ 9, *Social inhibition only* = SI ≥ 10 but NA ≤ 9, *Type D personality* = NA ≥ 10 and SI ≥ 10, patients scoring low on both traits (NA ≤ 9 and SI ≤ 9) were used as a reference group to estimate the effects of the NA only, SI only, and Type D personality profiles.

EPC levels were 11.61 ± 9.27, 11.89 ± 11.71 and 10.92 ± 9.66 at baseline, 3 months and 12 months; EPC levels were missing for 23, 33 and 43 patients, respectively. Index AMI, PCI, CABG, and medication (statins, aspirin, beta-blockers, diuretics, nitrates, angiotensin-converting enzyme inhibitors, diabetic medication) were not associated with FMD or EPCs at baseline or follow-up, and were not included in further statistical analyses.

3.3. Personality differences in endothelial function

Table 2a presents the mean FMD and EPC levels at three time points (baseline, 3 months, 12 months), stratified by the 4 different personality profiles. Mixed model analysis showed that Type D personality was significantly associated with decreased FMD across these time points, after adjustment for age, sex, hypertension, diabetes, smoking, training program, and depressive symptoms (Table 2b). In contrast, the NA only or SI only personality profiles were not significantly related to FMD. Increasing age was also independently associated with decreased FMD levels, but depressive symptoms were not associated with FMD.

Smoking was the only significant covariate of decreased EPC levels across the baseline, 3 months and 12 months assessments (Table 2c). Type D (p = 0.07), NA only, SI only, and depression were not significantly associated with EPCs across time. In further concurrent and prospective analyses, we examined the extent to which personality profiles were related to clinically significant endothelial dysfunction as indicated by a cut-off <5.5% on FMD [39].

3.4. Personality and endothelial dysfunction

The median FMD at baseline was 5.6%. Using a cut-off <5.5% on FMD [39], 48% of the patients had endothelial dysfunction at baseline and 38% patients at 12 months follow-up. At baseline, 42% (11/26) of patients with NA only had endothelial dysfunction, 54% (20/37) of those with SI only, and 40% (32/80) of those with low levels on both traits; these frequencies of endothelial dysfunction were not significantly different. In contrast, Type D patients had a higher frequency of endothelial dysfunction (24/37 = 65%; OR = 3.03, p = 0.042), after adjustment for age, sex, exercise, and depression (Table 3a). Hypertension, diabetes and smoking were unrelated to FMD (Table 2b) and were not included in further analyses. Prospective analyses confirmed that Type D personality (OR = 3.43, p = 0.048), but not NA or SI only, was independently associated with endothelial dysfunction at 12 months (Table 3b).

Subgroup analysis in men with CAD (n = 164; 91% of patients) yielded similar findings; i.e., Type D was associated with endothelial dysfunction at baseline (OR = 4.75, p = 0.01), while the NA only or SI only subgroups were not at increased risk (Table 3c). We could not show an association between Type D and endothelial function in women (n = 16; 9% of CAD patients). The prospective findings on Type D and increased risk of endothelial dysfunction were also replicated in the subgroup analysis of male patients with CAD (Table 3d; OR = 4.25, p = 0.03).

3.5. Type D versus non-Type D dichotomy in men with CAD

In a final subgroup analysis of men with CAD, we pooled 3 profiles (NA only, SI only, and reference with low levels of both traits) in one composite non-Type D personality profile. This dichotomous approach [33] yielded a clear association of Type D with a higher frequency of endothelial dysfunction both at baseline (Fig. 1a) and 12 months follow-up (Fig. 1b). Logistic regression analysis confirmed that increasing age (OR = 1.05, 95% CI 1.02–1.09) and the Type D dichotomy (Type D vs non-Type D; OR = 3.72, 95% CI 1.32–10.53), but not training program (p = 0.35) or depression (p = 0.65), were independent correlates of

Table 3
Logistic regression models of endothelial dysfunction at baseline and 12 months in the total group, and in the subgroup of men with CAD.[a]

	(3a) Total group - baseline			(3b) Total group - 12 months		
	OR	95% CI	p	OR	95% CI	p
Age (years)	1.06	[1.02–1.10]	0.001	1.02	[0.98–1.06]	0.33
Male sex	1.07	[0.35–3.28]	0.91	2.14	[0.47–9.77]	0.32
Training program	0.71	[0.38–1.33]	0.29	1.03	[0.52–2.07]	0.93
Depressive symptoms	1.01	[0.89–1.15]	0.85	0.93	[0.81–1.08]	0.37
Negative affectivity only	1.28	[0.45–3.67]	0.64	1.56	[0.49–4.95]	0.45
Social inhibition only	1.92	[0.85–4.33]	0.12	0.67	[0.26–1.71]	0.40
Type D personality	3.03	[1.04–8.80]	0.042	3.43	[1.01–11.64]	0.048
	(3c) Male patients - baseline			(3d) Male patients – 12 months		
	OR	95% CI	p	OR	95% CI	p
Age (years)	1.06	[1.02–1.10]	0.005	1.01	[0.97–1.05]	0.60
Training program	0.72	[0.37–1.40]	0.34	1.18	[0.58–2.42]	0.65
Depressive symptoms	0.97	[0.85–1.11]	0.66	0.92	[0.79–1.07]	0.26
Negative affectivity only	1.26	[0.41–3.88]	0.69	1.63	[0.49–5.36]	0.42
Social inhibition only	2.01	[0.87–4.62]	0.10	0.69	[0.27–1.79]	0.45
Type D personality	4.75	[1.45–15.57]	0.01	4.25	[1.15–15.75]	0.03

Type D = NA ≥ 10 and SI ≥ 10, Negative affectivity only = NA ≥ 10 but SI ≤ 9, Social inhibition only = SI ≥ 10 but NA ≤ 9. Patients scoring low on both traits (NA ≤ 9 and SI ≤ 9) were used as a reference group to estimate the effects of the Type D, NA only and SI only personality profiles.
CI = confidence interval; OR = odds ratio.
[a] Endothelial dysfunction was defined by a FMD cut-off <5.50 [39] at baseline and at 12 months, respectively. Personality subgroups were defined by the standard cut-off ≥10 on the negative affectivity (NA) and social inhibition (SI) traits of the DS14 [32,33].

endothelial dysfunction at baseline in men with CAD. In prospective analysis, the Type D dichotomy was the only predictor of endothelial dysfunction at 12 months (OR = 3.59, 95% CI 1.15–11.16).

4. Discussion

In patients with CAD who have a Type D personality profile, endothelial function was impaired across baseline, 3 months and 12 months assessment, as compared to non-Type D patients. This adverse Type D effect remained significant after adjustment for clinical characteristics, exercise training and depressive symptoms. Type D was related to endothelial dysfunction as defined by a FMD cut-off <5.5% [39] in concurrent analyses, and was prospectively associated with endothelial dysfunction at 12 months follow-up. The association of Type D with EPCs was not significant (p = 0.07), and depressive symptoms were not related to FMD or EPCs.

Older age [30] was also related to a decreased FMD levels across the 3 time points. Hypertension, diabetes, and smoking can interfere with the endothelial response [13], but these covariates were not related to continuous FMD levels in our study. The link between Type D and endothelial function was not influenced by type of exercise training [13]. Endothelial function improved in the SAINTEX-CAD trial [35] but this improvement was not accompanied by altered levels of EPCs, and FMD was not related to EPC levels at baseline or 3 months [36]. Low circulating EPCs levels predict increased mortality in patients with CAD [40]. Type D has been related to low EPC levels in patients with heart failure [41] but this link between Type D and decreased EPCs was not statistically significant in the current study ($\beta = -3.03$, p = 0.07).

This is the first study to report on Type D and endothelial dysfunction in CAD. None of the patients participated in other Type D studies, allowing for replication of findings on the role of Type D in CAD. Previously, others showed that Type D was related to increased coronary plaque severity [9,10]. Our study suggests that Type D is also involved in functional vasomotion abnormalities that further increase cardiovascular risk in CAD patients [11]. Brachial FMD is closely related to coronary endothelial function and predicts cardiac events [15]. Our median FMD value of 5.6% corresponds to the median of 5.2% in the literature [38] and to the cut-off <5.5% that predicts poor prognosis in patients with CAD [39]. Using this cut-off in concurrent and prospective models, Type D patients, who are high in both NA and SI, were at increased risk of endothelial dysfunction. Patients with NA or SI only were not at risk, suggesting that it is the combination of both traits that drives the effect of Type D on endothelial dysfunction.

Evidence suggests that chronic stress and repeated exposure to transient stress may lead to endothelial dysfunction [16–19,42–44]. Mental stress causes transient [16] and prolonged [42] endothelial dysfunction, which was also confirmed in meta-analysis [17]. The chronic burden of caregiving [18], posttraumatic [19] and social [43] stress, and suppressed anger [44] have all been related to endothelial dysfunction. Hence, the vulnerability of Type D individuals to chronic distress [2], posttraumatic [45] and social [46] stress, and suppressed anger [47] supports the psychological plausibility of the link between Type D and impaired endothelial function.

Increases in superoxide anions formation, oxidative stress, TNF-α, and cortisol are biological pathways by which Type D can contribute to endothelial dysfunction [1,12,28]. Previous studies showed increased

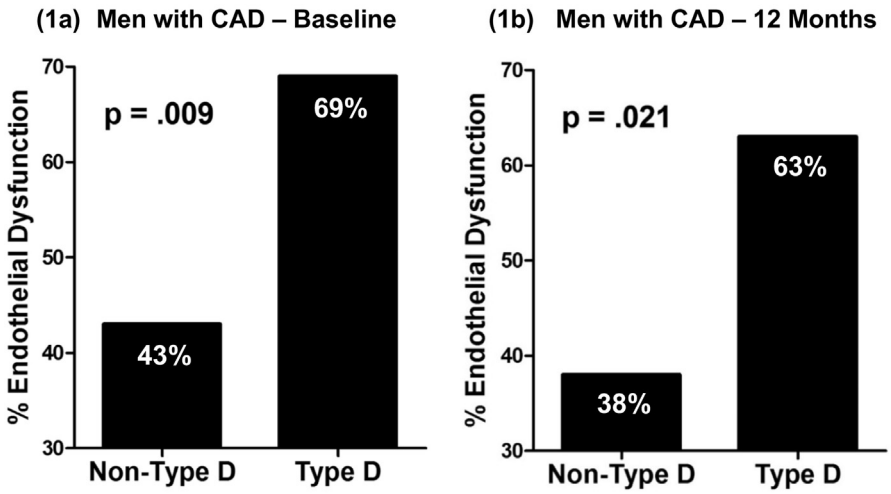

Fig. 1. Percentage of male patients with endothelial dysfunction at baseline (1a) and at 12 months follow-up (1b), stratified by Type D personality.[(a)] [(a)]Endothelial dysfunction: FMD cut-off <5.5% [39]. Percentages of patients with endothelial dysfunction are presented within each bar. Type D personality defined by the cut-off ≥10 on both the negative affectivity and social inhibition traits of the DS14 [32,33]; all other personality profiles classified as non-Type D.

macrophage activity and superoxide anion production [24], higher levels of oxidative stress [25], and a pro-inflammatory cytokine profile with higher TNF-α levels [26] in cardiac patients with Type D than in non-Type D patients. Type D is also related to increased cortisol and hypothalamic-pituitary-adrenal axis function after an acute cardiac event [27] and in response to acute stress [46]. Endothelial-leukocyte adhesion molecule-1 (E-Selectin) is an important adhesion molecule for endothelial cell activation that promotes atherosclerosis [13]. In the Maastricht Study, Type D was related to biomarkers of endothelial activation, including E-Selectin [23]. Overall, these findings on biological pathways support the role of endothelial dysfunction as a possible mechanism that connects Type D to increased cardiovascular risk.

There are also behavioral pathways by which Type D can promote endothelial dysfunction, including increased vulnerability to depression [2,23]. Depressive symptoms have been related to decreased FMD in some studies [48]. This was not the case in our study of cardiac patients, and there are other studies that found no link between depressive symptoms and FMD [18,44]. Yet, our findings are consistent with the notion that Type D and depression are different forms of distress, and may have incremental prognostic value in patients with CAD [49].

FMD has been used to compare endothelial function in age, sex and disease subgroups [14]. Personality is another individual difference variable that can explain heterogeneity in endothelial function. In general populations, Type D was not related to FMD in one study [22], but was related to endothelial dysfunction as measured by FMD of the brachial artery [21] and an endothelial biomarker sum-score [23] in 2 other studies. Our study extends this previous research by studying patients with CAD, and looking at this association across 3 time points. There are also sex differences in CAD [29] and endothelial function [29,30]. Men have worse endothelial function than women until about age 70 [29], and Type D is related to a sensitized cardiovascular stress-response in men but not women [31]. Our sex-subgroup analyses yielded a clear association between Type D and endothelial dysfunction in men with CAD. We could not show this association between Type D and endothelial function in women, which is due to the very small number of women ($n = 16$) included in the current study.

Limitations of this study include the lower participation and higher drop-out rates in women compared to men [35], and the relatively high number of missing values of FMD at follow-up. There is a lack of consensus for a clinical cut-off value on FMD and the definition of EPCs remains a matter of debate. Our findings provide no direct evidence of a causal relationship between Type D and risk of CAD. However, they are consistent with the notion that endothelial dysfunction is a candidate pathway that should be studied in future Type D research. Finally, Type D was not significantly related to number of EPCs. Strengths of our study include the standard assessment of four distinct personality subtypes, and the repeated assessment of FMD to study the robustness of the Type D effect across time. Most previous studies on psychological factors and FMD report on cross-sectional or retrospective analyses [48], and the literature would be strengthened by prospective studies such as ours.

Coronary arteries represent a functional conduit system [11]. Others showed that Type D was associated with structural coronary abnormalities [9,10]. Our study suggests that another possible mechanistic basis for the link between Type D and coronary events resides at the level of endothelial dysfunction. Together with findings from clinical research linking Type D with a higher risk of cardiac events in coronary patients [8,33], it is becoming apparent that the adverse effect of Type D might involve cardiovascular pathways that contribute to CAD.

In conclusion, endothelial dysfunction [38,39] emerges as a key factor that may link Type D to a higher risk of cardiac events in male patients with CAD [8]. Research needs to confirm that disease-specific pathways contribute to poor prognosis in patients with CAD and Type D. Yet, our findings suggest that the combination of plaque severity and endothelial dysfunction in the coronary arteries render Type D patients at increased risk, and support the notion that perceived stress during social interaction has a direct influence on cardiovascular health [43].

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Conflict of interest

No conflict of interest exists for any of the authors.

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