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Severity of stable coronary artery disease and its biomarkers differ between men and women undergoing angiography

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ABSTRACT

Background: Coronary artery disease (CAD) affects both men and women. Cardiovascular biomarkers have been suggested to relate to CAD severity, but data on sex-specificity is scarce. Therefore, we investigated the association of established biomarkers with the severity of CAD in stable patients undergoing coronary angiography in a sex-specific manner.
Methods: We studied stable patients undergoing coronary angiography and measured CAD severity by SYNTAX score and biomarker levels (N-terminal pro-brain natriuretic peptide (NT pro-BNP), high-sensitivity CRP (hsCRP), cystatin C (CysC), myeloperoxidase (MPO), high-sensitivity troponin I (hsTnI) and von Willebrand factor (VWF)). We tested for sex differences in SYNergy between percutaneous coronary intervention with TAXUS™ and cardiac surgery (SYNTAX) scores and biomarker levels using multivariable ANCOVA. We investigated the association of biomarker levels with SYNTAX score in a multivariable linear regression with interaction terms for sex.
Results: We analysed data on 460 men and 175 women. SYNTAX scores were significantly lower in women (9.99 points vs. 11.88 points). Univariably, hsCRP and hsTnI levels were significantly associated with SYNTAX scores (both β 2.5). In multivariable analysis only hsCRP associated with SYNTAX score (β 1.9, p = 0.009). Sex did not modify the association of biomarkers with SYNTAX score.
Conclusion: CAD severity as quantified by SYNTAX score is lower in women than men based on coronary angiography. The association of biomarkers with CAD severity did not differ between the sexes.

1. Introduction

CAD is the leading cause of mortality in both men and women worldwide [1]. Morbidity and death are attributed to the growth, destabilization or rupture of atherosclerotic plaques. Several mechanisms are implicated in the complex process of atherosclerosis; of most importance are inflammation [2], endothelial dysfunction and myocardial ischemia. Several biomarkers relating to these processes have been studied and implemented as non-invasive tools for the diagnosis of CAD and for the prediction of future cardiovascular events in primary prevention. Established biomarkers include: NT pro-BNP, which is associated with ventricular dilatation and pressure overload [3–5]; hsCRP [6,7], involved in the inflammatory process; CysC [8–11], a marker of renal dysfunction; MPO, linked to both inflammation and oxidative stress [12–14]; hsTnI [15–17], associated with myocardial ischemia and VWF [18], which is known to be involved in coagulation.

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Sex-specific analyses on biomarkers for CAD may provide more insight into the underlying mechanisms of sex differences in CAD. Women represent less than 30% of the population included in cardiovascular research [19], yet evidence is accumulating that women develop more "stable" atherosclerosis when compared to men [20] and are more likely to have plaque erosion as compared to plaque rupture [21] as the underlying substrate for sudden death and myocardial damage.

For the purpose of this study we measured SYNTAX scores in men and women presenting with stable CAD (either stable angina, dyspnoea complaints or silent ischemia), undergoing coronary angiography. The SYNTAX score [22] is currently the most widely used method to quantify the complexity and severity of CAD. Furthermore, the SYNTAX score is predictive of future cardiovascular events [23].

We hypothesize that there are sex differences in established CAD biomarker levels and that they associate differently with the severity of CAD between men and women with stable complaints.

2. Methods

2.1. Study population

We analysed data from the UCORBIO cohort (clinicaltrials.gov identifier: NCT02304744), a biobank of patients undergoing coronary angiography with or without coronary intervention in the University Medical Center in Utrecht, the Netherlands. From October 2011 to April 2013 we enrolled patients from the catheterization laboratories (n = 1030). For the current study only patients presenting with stable complaints (either stable angina, dyspnoea complaints or silent ischemia) were selected (n = 635). Demographical data was collected at baseline (age, sex, cardiovascular risk factors, indication for angiography, treatment and medication use at the moment of angiography).

All patients provided written informed consent. This study conforms to the declaration of Helsinki.

2.2. CAD severity

Angiographic data was collected and categorized into three categories: no CAD, minor CAD (wall irregularities, <50% stenosis) and significant CAD (at least one epicardial vessel with >50% stenosis) based on visual assessment.

Two independent observers, using SYNTAX score calculator version 2.11, measured the SYNTAX scores. The SYNTAX score allows for the characterization of coronary vasculature with respect to the number of lesions involved, the location and complexity of the lesions. Lesions are only scored if they meet the required criteria (>50% stenosis and vessel diameter >1.5 mm) [22]. Higher scores are allocated to the most complex lesions. The observers were blinded to the biomarker levels of the patient. The two observers had unlimited access to quantitative coronary angiography [24] (QCA) software (CAAS, Siemens) to measure the percentage of stenosis or the dimension of the vessel if they were unsure about significance of a lesion by eyeballing. When the two observers were more than 5 SYNTAX points apart, the case was discussed in order to reach consensus and, if needed, QCA was performed in order to determine the significance of a lesion (>50% stenosis and vessel diameter >1.5 mm).

The average of the SYNTAX scores of the two observers was used for the current analysis. Patients, who the interventional cardiologists classified as having significant CAD, but ended up with an SYNTAX score of 0 (because of not meeting the criteria of >50% stenosis or vessel <1.5 mm or only lesions in non-dominant right coronary artery) were discarded from the analysis, as this is not considered significant CAD in terms of the SYNTAX classification.

2.3. Biomarkers

Blood was drawn from the arterial sheath that was inserted for the angiographic procedure, before any procedure-related drugs were administered. The sample was immediately centrifuged and plasma was frozen at −80 °C. Levels of NT pro-BNP, hsCRP, CysC, MPO and VWF were measured from thawed EDTA plasma using validated in-house sandwich ELISA assays performed in the University Medical Center Utrecht, the Netherlands. Quality controls were used in each plate. Inter- and intra-assay coefficients of the assays are <10%. Levels of hsTnI were measured in the Gelre Ziekenhuis, Apeldoorn, the Netherlands using the clinically validated ARCHITECT *STAT* High Sensitive Troponin-I assay (Abbott Laboratories, Lisnamuck, Longford, Ireland).

Table 1
Patient characteristics of men and women presenting with stable complaints. Continuous variables are presented in means ± standard deviation (sd). Categorical variables are presented in percentages. P-values are the result of ANOVA or chi-square testing. Biomarker levels are presented in medians with interquartile ranges in square brackets. Biomarkers were compared using a Mann–Whitney U test, as they were non-normally distributed. The SYNTAX score was only measured in people with significant CAD.

	Men	Women	p-Value
N	460	175	
Age (mean ± sd)	64.8 ± 10.1	67.0 ± 10.5	0.013
Risk factors			
BMI (mean ± sd)	27.4 ± 4.1	26.8 ± 5.1	0.171
Diabetes (%)	25.8	20.6	0.208
Hypertension (%)	61.2	64.9	0.437
Hypercholesterolemia (%)	57.9	53.2	0.336
Smoking (Current %)	19.7	22.4	0.003
Quit	39.3	24.4	
Non-smoker	41.0	53.2	
Family history (%)	53.5	60.9	0.183
Medical history			
History of ACS (%)	41	27.6	0.003
History of PCI (%)	45.8	30.3	0.001
History of CABG (%)	20.2	6.9	<0.001
History of CVA (%)	11.0	8.6	0.463
History of PAD (%)	15.9	10.9	0.144
Kidney failure (%)	3.0	2.3	0.805
COPD (%)	8.7	5.7	0.279
Angiography			
CAD severity (no %)	4.0	15.4	<0.001
Minor CAD	17.8	28.0	
Significant CAD	78.2	56.6	
SYNTAX score (mean ± sd)	12.3 ± 8.2	10.8 ± 6.7	0.148
Treatment (Conservative %)	35.7	52.0	0.001
PCI	59.6	43.4	
CABG	4.8	4.6	
Medication			
Platelet inhibitor (%)	83.7	74.3	0.010
Statin (%)	82.1	70.3	0.002
Beta blocker (%)	72.9	70.9	0.674
RAAS (%)	59.8	57.1	0.607
Biomarkers			
NT pro-BNP (pmol/L)	35.7 [7.7, 105.5]	42.7 [17.1, 105.6]	0.104
hsCRP (μg/mL)	1.2 [0.5, 2.8]	1.5 [0.7, 3.1]	0.017
CysC (μg/mL)	0.8 [0.7, 1.1]	0.8 [0.6, 1.0]	0.642
MPO (ng/mL)	24.5 [18.7, 32.9]	25.1 [19.8, 33.0]	0.471
hsTnI (ng/L)	5.3 [3.3, 10.6]	4.3 [2.6, 8.1]	0.004
VWF (μg/mL)	13.4 [10.5, 17.4]	13.9 [10.4, 17.8]	0.891

Abbreviations: BMI: body mass index, ACS: acute coronary syndrome, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, PAD: peripheral arterial disease, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, RAAS: renin–angiotensin–aldosteron system, NT pro-BNP: N-terminal pro-brain natriuretic peptide, hsCRP: high-sensitivity C-reactive protein, CysC: cystatin C, MPO: myeloperoxidase, hsTnI: high-sensitivity troponin I, VWF: von Willebrand factor.