Circulating Biomarkers Predict Symptomatic but Not Asymptomatic Carotid Artery Stenosis

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Abstract

Background: Subjects exposed to risk factors such as age, gender, hypertension, diabetes mellitus, and smoking are prone to atherosclerotic events. Aims: The main aim of this longitudinal cohort study was to determine whether the role of novel plasma biomarkers for atherosclerotic carotid artery disease is different in subjects developing symptomatic carotid artery stenosis (CAS), as opposed to those with incident asymptomatic CAS. Methods: The following biomarkers were measured in 5,550 middle-aged subjects in a population-based cohort study: C-reactive protein (CRP), lipoprotein-associated phospholipase A2 mass and activity, pro-neurotensin, midregional proadrenomedullin (MR-proADM), midregional proatrial natriuretic peptide, N-terminal pro-brain natriuretic peptide, copeptin, and cystatin C. After exclusion of those with prevalent CAS, subjects were thereafter followed in national patient registers for 23.4 (interquartile range 19.5–24.3) years regarding incident symptomatic and asymptomatic CAS. Results: Among 110 patients with confirmed incident CAS, 56 were symptomatic and 54 were asymptomatic. When including conventional risk markers in a Cox regression analysis, NT pro-BNP (hazard ratio [HR] 1.59; 95% confidence interval [CI]: 1.20–2.11), MR-proADM (HR 1.40; CI: 1.13–1.73), cystatin C (HR 1.21; CI: 1.02–1.43), and CRP (HR 1.53; CI: 1.13–1.73) were independently associated with incident symptomatic CAS, whereas no plasma biomarker was associated with incident asymptomatic CAS. Conclusion: Plasma biomarkers NT pro-BNP, MR-proADM, cystatin C, and CRP were independently associated with incident symptomatic CAS, whereas no such association could be demonstrated with incident asymptomatic CAS. As these biomarkers indicate future development of clinically relevant atherosclerotic CAS, their potential utility in relation to intensified preventive measures and selection of potential candidates for carotid surgery should be further evaluated.

Keywords
Carotid artery stenosis · Symptomatic · Asymptomatic · Biomarkers · C-reactive protein · Lipoprotein-associated phospholipase A2 · Pro-neurotensin · Midregional proadrenomedullin · Midregional proatrial natriuretic peptide · N-terminal pro-brain natriuretic peptide · Copeptin · Cystatin C
Introduction

Carotid artery stenosis (CAS) is an atherosclerotic narrowing of the artery and one of the primary causes of ischemic stroke [1]. The prevalence of CAS in an elderly population is between 4 and 5 percent, and the disorder has been calculated to result in ischemic stroke in around 7 percent [1], meaning that most patients remain neurologically asymptomatic. As stroke preventive effects of carotid surgery or stenting are better established in symptomatic CAS [2, 3] than in unsellected asymptomatic cases [3, 4], identification of the small proportion of CAS patients later developing focal neurological deficits such as sudden unilateral numbness or weakness in the face or limbs, aphasia, dysarthria, or amaurosis fugax is of great clinical importance to select the proper patients for surgery or stenting [3].

Vascular inflammation as a sign of an ongoing atherosclerotic process has been related to increased levels of lipoprotein-associated phospholipase A2 (Lp-PLA2), an inflammatory enzyme produced by macrophages strongly associated with cardiovascular disease and ischemic stroke in meta-analysis [5]. C-reactive protein (CRP) synthesized in the liver and playing an important role during inflammation has been found to positively correlate cross-sectionally with CAS [6]. Several other novel biomarkers have been identified as predictors for atherosclerotic cardiovascular events. The hormones proneurotensin [7] and the midregional peptides proadrenomedullin (MR-proADM) and proatrial natriuretic peptide (MR-proANP) are all potential candidates for detection and predicting development of cardiovascular events [8].

Markers for congestive heart failure (CHF) have also been used to predict atherosclerosis. Elevated concentration of the hormone N-terminal pro-B-type natriuretic peptide (NT pro-BNP) synthesized by the heart in CHF has also been cross-sectionally related to CAS [9]. Copeptin has been shown to correlate with vasopressin during inflammatory processes and has been found to be elevated during ongoing acute myocardial infarction [10]. Cystatin C reflecting kidney function has also been cross-sectionally associated with CAS [11]. We recently reported that NT pro-BNP and MR-proADM were strong indicators of incident CAS [12]. The aim of this study was to determine whether the predictive values of plasma biomarker levels adjusted for conventional risk factors are different in symptomatic CAS for which surgery is clearly indicated [2, 3] and in asymptomatic CAS where the indication for surgery is debatable.

Materials and Methods

Study Sample
The population-based Malmö Diet and Cancer Study (MDCS) [13] included 30,446 middle-aged individuals from Malmö, Sweden. A random subsample from this cohort was included in the MDCS cardiovascular cohort [14], of whom 5,550 individuals underwent clinical examination and fasting blood sampling between November 1991 and February 1994 (Fig. 1).

Baseline Examination
Current smoking was defined as self-reported regular smoking or smoking cessation within the last year. Diabetes mellitus was defined as self-reported physician’s diagnosis, use of antidiabetic medication, or fasting whole blood glucose >6.0 mmol/L. Hypertension was defined as use of antihypertensive medication or blood pressure ≥140/90 mm Hg.

Laboratory Measurements
Glycosylated hemoglobin was determined by ion-exchange chromatography, using the Swedish Mono-S standardization system; reference values were 3.9–5.3% in nondiabetic individuals. Plasma biomarkers were measured from fasting plasma samples frozen at −80°C immediately after collection [14]. CRP was measured by a high-sensitivity Tina-quant® latex assay (Roche Diagnostics, Basel, Switzerland). The average coefficient of variation (CV) was 4.6% [15]. Lp-PLA2 was expressed as enzymatic activity and mass (quantity) [15]. Lp-PLA2 activity was measured in duplicate using [3H]-platelet activating factor as substrate. The range of detection was 8–150 nmol/min/mL and average CV 5.8%. Lp-PLA2 mass measurements were performed using the commercially available second generation PLAQTM test (diaDexus Inc., South San Francisco, CA, USA) enzyme-linked immunoabsorbt assay kit [16]. Plasma-EDTA samples are stable for Lp-PLA2 activity and mass measurements within 7 days of collection for refrigerated samples and for more than 10 years from collection when stored at −70°C [16]. Proneurotensin was measured using a chemiluminesometric sandwich immunoassay to detect a proneurotensin fragment [7]. Levels of MR-proADM were measured using immunoluminometric sandwich assays targeted against amino acids in the midregions of the peptide (BRAHMS AG, Hennigsdorf, Germany) [17]. Lower and upper limits of detection were 0.08 and 25 nmol/L, respectively. MR-proANP was measured using immunoluminometric sandwich assays targeted against amino acids in the midregion of the peptide (BRAHMS, Berlin, Germany). NT pro-BNP was measured using the automated Dimension Vista Intelligent Lab System method (Siemens Diagnostics, Nürnberg, Germany) [14]. Mean inter-assay CVs were ≤10% for MR-proADM, ≤10% for MR-proANP, and 2.7% for NT pro-BNP. Copeptin was measured using commercially available assay in the chemiluminescence/coated tube format (BRAHMS AG). Lower detection limit was 0.4 pmol/L, and functional assay sensitivity (<20% inter-assay CV) was <1 pmol/L [18]. Cystatin C was measured using a particle-enhanced immune-nephelometric assay (N Latex Cystatin; Siemens Diagnostics, Dade Behring, Deerfield, IL, USA) with a mean inter-assay CV of 4.3%.

Endpoint Ascertainment and Validation
After exclusion of seven individuals with a diagnosis of CAS already at baseline, individuals with a first registered diagnosis of
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CAS were identified from Swedish national registers (the Inpatient and Outpatient Register and the Cause of Death Register) by linkage of the ten-digit personal identification number unique to each Swedish resident. Follow-up was extended until December 31st, 2016. In both Inpatient and Cause of Death registers, CAS is coded using a Swedish revision of the International Classification of Disease, version 8 (432.00; 432.90), version 9 (443B), and version 10 (I65.2). Surgical procedures performed on carotid arteries are coded using a Swedish classification system (24) (Op6: 8831, KKÅ97: PAF21, PAK21, PAQ21).

Among 125 patients with registered diagnosis of CAS, 4 patients were misdiagnosed, of which 3 had other atherosclerotic manifestations and 1 had carotid artery dissection. In 11 patients, records were incomplete and the diagnosis of CAS could not be confirmed (Fig. 1). 110 patients had confirmed CAS; 56 had been judged as having symptomatic stenosis by a multidisciplinary round comprising a neurologist, a vascular surgeon, and a vascular physician whereas 54 had been judged as having asymptomatic CAS. This decision was based on evaluation of radiological findings and neurological symptoms such as aphasia, dysphasia, unilateral weakness and/or numbness of face or limbs, or ocular symptoms with CAS as the probable cause of the symptoms.

**Statistical Analysis**
Quantitative normal and skewed distributed variables are presented as mean with standard deviation and median with interquartile range, respectively. Dichotomous variables are presented as count and proportion. Individuals with a diagnosis of CAS at baseline were excluded from the current study and prospective analyses included only incident CAS. Plasma biomarkers and confounders for incident symptomatic or asymptomatic CAS were assessed using Cox regression models, and hazard ratios (HRs) were expressed per 1 standard deviation increment of each respective log transformed plasma biomarker (skewed distributed) in the Cox regression models. Analyses were performed using SPSS for Windows, version 24.0 (SPSS Inc, Chicago, IL, USA). A p value less than 0.05 was considered significant.

**Results**

**Baseline Conventional Risk Factor Assessment**
After exclusion of individuals with known CAS at baseline, the cumulative incidence of symptomatic CAS during follow-up was 1.0% (56/5,539), 1.5% (34/2,269) for men, and 0.7% (22/3,270) for women (p < 0.001), and the cumulative incidence of asymptomatic CAS was 1.4% (31/2,269) for men and 0.7% (23/3,270) for women (p < 0.001) during median follow-up of 23.4 (interquartile range).
range 19.5–24.3) years. Baseline risk factor characteristics for individuals in the cohorts with symptomatic or asymptomatic CAS, or without CAS, are shown in Table 1. When including the conventional risk factors for atherosclerotic disease listed in the footnote of Table 2 into a Cox regression analysis, male gender (HR 3.02; 95% confidence interval [CI]: 1.61–5.66), current smoking (HR 3.07; CI: 1.70–5.54), hypertension (HR 2.75; CI: 1.20–6.28), and diabetes mellitus (HR 2.75; CI: 1.20–6.28) were independently associated with incident symptomatic CAS. When the same risk factors were entered into a Cox regression analysis, male gender (HR 2.35; CI: 1.29–4.28), current smoking (HR 2.13; CI: 1.18–3.84), hypertension (HR 2.40; CI: 1.13–5.07) were independently associated with incident asymptomatic CAS. There was also a trend that elevated cholesterol (HR 1.27; CI: 0.99–1.63; \( p = 0.063 \)) was associated with incident asymptomatic CAS.

**Plasma Biomarkers**

Plasma biomarker levels at baseline in individuals with and without incident symptomatic or asymptomatic CAS are shown in Table 1. In the Cox regression analysis, NT pro-BNP (HR 1.59; CI: 1.20–2.11), MR-proADM (HR 1.40; CI: 1.13–1.73), cystatin C (HR 1.21; CI: 1.02–1.43), and CRP (HR 1.53; CI: 1.13–1.73) were independently associated with incident symptomatic CAS (Table 2), whereas there were trends toward such associations for Lp-PLAS2 mass (HR 1.28; 95% CI: 0.97–1.69) and Lp-PLAS2 activity (HR 1.34; 95% CI: 0.99–1.81). No plasma biomarker was associated with incident asymptomatic CAS (Table 2).

**Discussion**

The plasma biomarkers NT pro-BNP, MR-proADM, cystatin C, and CRP were all independently associated with incident symptomatic CAS during a median follow-up of 23.4 years. These biomarkers which have previously been established as risk markers for ongoing atherosclerosis in coronary arteries and CHF [14] also appear to be longitudinally linked with development of symptomatic CAS. We have previously only been able to link NT pro-BNP and MR-proADM to incident CAS [12], and despite the comparably lower number of subjects with incident symptomatic CAS in the present study, cystatin C and CRP were now also identified as predictors of future symptomatic CAS, whereas no such link could be established for asymptomatic CAS. This demonstrates that there might indeed be complex and significant dif-

### Table 1. Baseline characteristics in subjects with and without incident symptomatic or asymptomatic CAS

| Characteristic | Without CAS \((n = 5,429)\) | Symptomatic CAS \((n = 56)\) | Asymptomatic CAS \((n = 54)\) |
|---------------|---------------------------|-----------------------------|-----------------------------|
| Age, years, mean (SD) | 57.6 (5.9) | 59.1 (5.7) | 58.6 (5.1) |
| Male sex, n (%) | 2,235 (41.2) | 34 (60.7) | 31 (57.4) |
| Body mass index, kg/m², mean (SD) | 25.7 (4.0) | 26.7 (3.9) | 25.5 (3.5) |
| History of hypertension, n (%) | 3,446/5,413 (63.7) | 48/56 (85.7) | 42 (77.8) |
| History of diabetes, n (%) | 140/4,458 (3.1) | 4/46 (8.7) | 2/47 (4.3) |
| Current smoking, n (%) | 1,533/5,424 (28.3) | 24 (42.9) | 21 (38.9) |
| Total cholesterol, mmol/L, median (IQR) | 6.1 (5.4–6.8; n = 5,356) | 6.5 (5.8–7.4) | 6.6 (5.4–7.3) |
| Triglycerides, mmol/L, median (IQR) | 1.2 (0.9–1.6; n = 5,355) | 1.5 (1.0–1.9) | 1.3 (1.1–1.8) |
| Hemoglobin A1c, %, median (IQR) | 4.8 (4.5–5.1; n = 5,352) | 5.0 (4.7–5.3) | 4.9 (4.6–5.2; n = 53) |
| Lp-PLA2 (mass), ng/mL | 255.6 (214.1–317.8; n = 5,271) | 282.1 (228.3–357.3; n = 55) | 270.2 (217.1–320.4; n = 54) |
| Lp-PLA2 (activity), nmol/min/mL | 44.1 (36.2–52.8; n = 5,276) | 49.7 (41.5–57.2; n = 55) | 46.5 (39.4–55.7; n = 54) |
| Proneurotensin, pmol/L | 104.6 (75.7–148.6; n = 4,525) | 103.3 (83.1–137.6; n = 45) | 109.8 (73.2–146.9; n = 48) |
| MR-proADM, nmol/L | 0.45 (0.38–0.53; n = 5,140) | 0.48 (0.44–0.60; n = 53) | 0.45 (0.39–0.54; n = 53) |
| MR-proANP, pmol/L | 66.3 (51.0–86.6; n = 5,141) | 67.9 (46.8–93.7; n = 53) | 57.0 (44.3–84.2; n = 53) |
| NT pro-BNP, pg/mL | 61.0 (34.0–112.0; n = 5,045) | 85.0 (48.9–158.0; n = 52) | 51.0 (31.0–107.0; n = 51) |
| Copeptin, pmol/L | 5.2 (3.2–8.2; n = 5,134) | 7.1 (5.4–9.4; n = 53) | 6.1 (3.5–10.6; n = 53) |
| Cystatin C, mg/L | 0.76 (0.69–0.85; n = 5,043) | 0.78 (0.72–0.95; n = 50) | 0.75 (0.68–0.82; n = 50) |
| CRP, mg/L | 1.4 (0.7–2.8; n = 5,184) | 2.8 (1.2–4.5; n = 53) | 1.6 (0.8–3.2; n = 53) |

CAS, carotid artery stenosis; SD, standard deviation; IQR, interquartile range; Lp, lipoprotein.
ferences between the pathophysiology in asymptomatic CAS with dormant atherosclerotic plaques and symptomatic CAS featuring active atherosclerotic embolization and neurological symptoms [19, 20].

As symptomatic and asymptomatic atherosclerotic plaques differ in composition [19], it is important to study different biomarkers separately in relation to these two plaque types. Earlier studies have proven that symptomatic and progressive atherosclerotic plaques reflect an inflammatory process whereas asymptomatic atherosclerotic plaques are more inert and more often exhibit calcification [20]. Both such morphological differences and our results imply that it might not be adequate to only take the degree of stenosis into account when relating CAS to biomarkers, potential neurological symptoms related to the stenosis are also of relevance.

As the incidence of neurological symptoms among patients with high-degree asymptomatic CAS is low and declining [21], and as the incidence of stroke after carotid endarterectomy is 3% [22], it is crucial to select the right patients for surgery [3]. This longitudinal cohort study with long follow-up in which plasma biomarkers were strongly linked with symptomatic CAS may together with neurological and radiological findings help us select candidates for carotid endarterectomy. It is also important to recognize potential benefits of measuring the above plasma biomarkers in the asymptomatic population to identify individuals in need of tailored risk factor control, such as smoking cessation and beneficial lifestyle habits such as healthy diet and more physical activity.

It is worth mentioning that the diagnoses of both symptomatic and asymptomatic CAS in the present study were validated by reviewing expert clinical opinion in patient files, leading to removal of the 12% of cases in which a registered diagnosis of CAS could not be validated. This was not unexpected, however, since it has been shown that more than 30% of the diagnoses of peripheral arterial disease entered into the Danish National Patient Registry were incorrect [23], stressing the importance of validation when using registry information for research purposes.

The long follow-up with a median of 23.4 years together with the multidisciplinary round determining the diagnosis of symptomatic or asymptomatic CAS strengthens the findings of this study. As study participants were not systematically examined with bilateral carotid ultrasound, asymptomatic CAS already at baseline cannot be completely excluded. Another study limitation is that as the Cox regression captured the first CAS diagnosis, a subject with asymptomatic CAS later developing symptoms was analyzed in the asymptomatic group. Furthermore, conventional risk factors and medication were only assessed at baseline and might have changed during follow-up. Another aspect that should be taken into consideration is the limited size of the study material; only few patients developed CAS despite the comparatively long fol-

| Variable                  | Symptomatic CAS (N = 56) HR* (95% CI) | p value | Asymptomatic CAS (N = 54) HR* (95% CI) | p value |
|---------------------------|--------------------------------------|---------|--------------------------------------|---------|
| Plasma inflammatory biomarkers |                                       |         |                                      |         |
| Lp-PLA2 (mass)            | 1.28 (0.97–1.69)                     | 0.080   | 0.87 (0.64–1.18)                     | 0.36    |
| Lp-PLA2 (activity)        | 1.34 (0.99–1.81)                     | 0.061   | 0.95 (0.68–1.33)                     | 0.77    |
| Proneurotensin            | 0.90 (0.63–1.28)                     | 0.55    | 0.96 (0.70–1.30)                     | 0.77    |
| MR-proADM                 | 1.40 (1.13–1.73)                     | 0.002   | 0.98 (0.69–1.40)                     | 0.92    |
| MR-proANP                 | 1.12 (0.83–1.52)                     | 0.47    | 0.79 (0.58–1.09)                     | 0.15    |
| NT pro-BNP                | 1.59 (1.20–2.11)                     | 0.001   | 1.08 (0.80–1.47)                     | 0.61    |
| Copeptin                  | 1.35 (0.88–2.06)                     | 0.17    | 1.16 (0.80–1.67)                     | 0.43    |
| Cystatin C                | 1.21 (1.02–1.43)                     | 0.030   | 0.75 (0.50–1.10)                     | 0.14    |
| CRP                       | 1.53 (1.13–2.05)                     | 0.005   | 1.08 (0.80–1.46)                     | 0.63    |

The following baseline variables were entered in the multivariable analysis besides each respective plasma biomarker: age, sex, body mass index, current smoking, diabetes mellitus, hypertension, cholesterol. Asymptomatic patients were excluded when assessing symptomatic CAS, and symptomatic patients were excluded when assessing asymptomatic CAS. * HRs were expressed per one SD increment of each respective log transformed plasma biomarker.
low-up and a larger material might have revealed significances also for other variables. Nevertheless, differences in biomarker patterns could be demonstrated between subjects later developing symptomatic and asymptomatic CAS.

In conclusion, the plasma biomarkers NT pro-BNP, MR-proADM, cystatin C, and CRP were independently associated with incident symptomatic CAS whereas no such associations could be established in asymptomatic CAS. As these biomarkers indicate future development of clinically relevant atherosclerotic CAS, their potential utility in relation to intensified preventive measures and selection of potential candidates for carotid surgery should be further evaluated.

Statement of Ethics
The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written and oral informed consent was obtained from the study participants, and ethical approval was obtained from the Regional Ethical Review Board in Lund, Sweden (Dnr § LU 51-90, 2013/566).

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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