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## The association between circulating endostatin levels and incident myocardial infarction

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### ABSTRACT

**Objective.** Increased levels of circulating endostatin have been observed in patients with prevalent ischemic heart disease. However, the association between circulating endostatin, and incident myocardial infarction (MI) is less studied. Our main aim was to study the association between circulating endostatin and incident MI in the community adjusted for established cardiovascular risk factors in men and women. **Design.** Circulating endostatin was measured in a nested case control study based on three large community-based Swedish cohorts, including 533 MI cases, and 1003 age-, sex- and cohort-matched controls. Odds ratios (OR) with 95% confidence intervals (CI) were calculated with adjustments for established cardiovascular risk factors. **Results.** Higher endostatin was associated with a higher incidence of MI independently of established cardiovascular risk factors (OR 1.19, 95% CI 1.03–1.37,  $p = .02$ ), but this association was abolished after additional adjustment for C-reactive protein. Sex-stratified analyses suggest that the association was substantially stronger in women as compared to men. **Conclusions.** In our community based sample, higher endostatin predicted incident myocardial infarction predominantly in women but not independently of CRP. Thus, our findings do not support a broad utility of endostatin measurements for the prediction of incident myocardial infarction in clinical practice.

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### KEYWORDS

Inflammation; extra cellular matrix; oxidative stress; myocardial infarction; community based cohort; endostatin

### Introduction

Collagen XVIII is a major component of the basal membranes and cleavage of collagen XVIII during extra cellular matrix remodelling increases the levels of endostatin, a biologically active fragment with anti-angiogenic and antifibrotic activity [1]. Endostatin has been thoroughly studied in the field of malignant diseases, and the circulating levels have been suggested to reflect extra cellular matrix turnover in patients with malignant diseases [2].

Experimental studies suggest a causal role for endostatin in the development of atherosclerosis [3,4] and previous clinical studies have shown that patients with prevalent atherosclerotic disease also portray elevated circulating endostatin levels [5–7]. Other studies have shown that higher endostatin levels is associated with a higher risk of cardiovascular events and mortality [8] but the specific association between endostatin and incident MI has not been reported previously. In the present study, we hypothesized that elevated levels of endostatin are causally involved in the development of MI. Accordingly, we investigated the association

between endostatin and incident MI in a nested case control analyses in three large community-based cohorts, with pre-specified stratified analyses in men and women.

### Methods

#### Study population

We used a prospective nested case control design. Participants were recruited from the Northern Sweden MONitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) project [9], the Västerbotten Intervention Program (VIP) [10], and the Mammmary Screening Program (MSP) [11].

In the MONICA project, randomly selected samples of 2000–2500 25–74-year-old inhabitants of Västerbotten and Norrbotten counties (with a target population of 316,015 in 1999) were invited to participate in a health survey in 1986, 1990, 1994 and 1999. The mean participation rate in the four surveys was 77.2%.

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The VIP is an ongoing community intervention program targeting cardiovascular disease and diabetes prevention in the Västerbotten County in Sweden. Men and women are asked to participate in a health examination, with a similar design as for the MONICA population surveys, at their primary health care center the year they turn 30, 40, 50, and 60 years old (since 1996, 40, 50 and 60 years) [12]. The participation rate was 56% in 1995 to 65% towards the end of the period studied. Between 1985 and 2000, about 66,300 individuals took part in the VIP health surveys. Differences in education level and urbanization between participants and non-participants in VIP were minimal.

Regular mammography screening (MSP) is offered to all women older than 50 years in the Västerbotten county, and 28,400 unique women participated between 1995 and 2000.

In both MONICA and VIP, participants were asked to complete a questionnaire in respect to living conditions and cardiovascular risk factors, anthropometry and blood pressure were measured, and OGTT was performed together with blood sampling for blood lipids and glucose. A modified protocol including anthropometry and blood pressure was used in the MSP.

As part of these programs, participants in all surveys were requested to donate a fasting blood sample to be stored at the Northern Sweden Medical Research Bank for future research. Thus all analyzed blood samples were collected prior to the myocardial infarction.

### Case selection

All (in-hospital and out-of-hospital) cases with acute MI (in the age group 25–64 years) in the MONICA area (i.e., Västerbotten and Norrbotten) have since 1985 been included in the Northern Sweden MONICA register using WHO criteria and validated MONICA methodology.

Possible MI events were identified through screening of hospital discharge records, general practitioners' reports, and death certificates, with ICD 8 and 9 codes 410–413 corresponding to ICD 10 codes I20–I24. For death certificates, the codes 414 and 798–799 (ICD 8 and 9), and I25 and R96–99 (ICD 10) were also extracted from the data bases. Data collection included information on medical history, symptoms, examinations, and presenting electrocardiogram (ECG). The number of subjects with MI included in the registry not willing to participate in further studies after information has averaged two per year (0.2%).

Originally, MI diagnoses were based on typical chest pain, cardiac enzymes and ECG findings. Criteria for MI were typical ECG progression, probable ECG progression together with elevated cardiac enzymes to more than twice the upper limit of normal, or typical symptoms of MI together with elevated cardiac enzymes as above. From the late 1990s troponins were introduced for diagnosis of MI. An event was considered to be first ever for the patient if the patient's history was free from a previous clinically recognized MI.

Two referents per case were randomly selected and matched for sex, age ( $\pm 2$  years), cohort (MONICA, VIP or

MSP) and date ( $\pm 4$  months) of health examination, and geographical area. All cases and referents with a previous history of MI or stroke (any time before survey), or cancer (less than 5 years before or 1 year after MI) were excluded.

The study protocol was approved by the Research Ethics Committee of Umeå University, Umeå, and the data handling procedures by the National Computer Data Inspection Board, Stockholm, Sweden. All participants gave informed consent.

### Clinical examinations and biochemical analysis

Subjects were classified as smokers (daily smokers), ex-smokers, and non-smokers. Blood pressure was recorded in the sitting position after 5 min of rest using a mercury sphygmomanometer. In the VIP survey, blood pressure was measured after 5 min of rest in the recumbent position, until 1 September 2009; thereafter, it was measured in the sitting position with the device described above. Measurements obtained with participants in the recumbent position were adjusted with a sex- and age-specific formula [10]. Hypertension was defined as systolic BP  $\geq 140$  mmHg and/or diastolic BP  $\geq 90$  mmHg, and/or on anti-hypertensive medication.

An oral glucose tolerance test, with measurements of fasting and post-load glucose levels, was performed routinely in the VIP, in 60% of MONICA participants, but not in the MSP. Diabetes mellitus (DM) was determined based on self-reported usage of anti-diabetic medication, fasting plasma glucose levels  $\geq 7.0$  mmol/L, and/or post-load plasma glucose levels  $\geq 11.1$  mmol/L (or  $\geq 12.2$  mmol/L based on capillary plasma measurements in the VIP). Impaired fasting glucose (IFG) was defined as a fasting glucose level  $\geq 6.1$  and  $< 7.0$  mmol/L. Impaired glucose tolerance (IGT) was defined as a post-load glucose level  $\geq 7.8$  and  $< 11.1$  mmol/L (or  $\geq 8.9$  and  $< 12.2$  mmol/L in the VIP), combined with a non-diabetic fasting glucose level. The definition of glucose intolerance was IFG, IGT, or DM.

Plasma samples were obtained after fasting for a minimum of 4 hours (extended to 8 hours 1992), and kept stored in a deep-freeze blood bank at  $-80^\circ\text{C}$  until analyses.

Apolipoprotein A-1 and B were determined by immunoturbidimetry (Dako, Glostrup, Denmark). An ELISA assay was used to measure CRP (IMMULITE, Diagnostic Products Corporation, USA). All measurements were made by laboratory staff, unaware of participants' disease status. Serum levels of endostatin were analysed using a commercially available ELISA kit for endostatin (DY1098, R&D Systems, Minneapolis, MN). The patient samples were all diluted 1:40 in 0.02 M  $\text{Na}_2\text{HPO}_4$ , 0.15 M NaCl, pH 7.2 containing 10 g/L of bovine serum albumin. The assay had a total coefficient of variation (CV) of approximately 7% and an intra assay variation of 4.5%. Routine blood samples including blood lipids and glucose intolerance were collected immediately after visit. Endostatin and CRP samples were analyzed in stored samples. Average storage time for CRP was 11.0 years and for Endostatin 21.7 years. CRP was analysed in one batch run at the follow up.

**Table 1.** Baseline characteristics for cases and controls.

Variable	Cases	Controls
	Mean and 95% confidence interval or %	Mean and 95% confidence interval or %
Number of participants	533	1003
Female	28%	28%
Age at survey (years)	54.9 (54.3–55.6)	54.8 (54.3–55.2)
Mean follow up (years)	4.0 (3.8–4.2)	4.0 (3.8–4.2)
Endostatin (ng/mL)	47.9 (46.6–49.3)	43.4 (42.6–44.2)
C-reactive protein (CRP, mg/L)	2.1 (1.9–2.3)	1.3 (1.2–1.4)
Apolipoprotein A1/Apolipoprotein B	0.9 (0.89–0.93)	0.8 (0.77–0.80)
BMI (kg/m <sup>2</sup> )	27.0 (26.6–27.4)	25.8 (25.6–26.1)
Glucose intolerance	31%	17%
Hypertension	64%	44%
Never smoked	25%	75%
Former smoker	32%	68%
Current smoker	53%	47%

Data are geometric means with 95% confidence intervals for continuous variables and *n* (%) for categorical variables.

**Table 2.** The associated risk between serum levels of standard deviation increments of endostatin and MI infarctions in conditional logistic regression models.

	Odds ratio	95% CI	<i>p</i> -Value
<b>Crude model</b>	1.50	1.32–1.71	<.001
<b>Established risk factors</b>	1.16	1.01–1.34	.04
<b>Established risk factors + CRP</b>	1.11	0.95–1.28	.18

All cases were matched for age, sex and cohort. The crude model was unadjusted and the established risk factor model was adjusted for all other variables in Table 1 except CRP (BMI, apolipoprotein ratio, smoking status, hypertension and glucose intolerance).

**Table 3.** The associated risk between serum levels of standard deviation increments of endostatin in men and women and endpoints in conditional logistic regression models.

	Men	Women
	Odds ratio 95% CI <i>p</i> -Value	Odds ratio 95% CI <i>p</i> -Value
<b>Crude model</b>	1.40 1.21–1.62 <.001	1.85 1.41–2.43 <.001
<b>Established risk factors</b>	1.11 .94–1.32 .20	1.42 1.04–1.93 .0
<b>Established risk factors + CRP</b>	1.060 .87–1.25 .50	1.285 .94–1.76 0.12

All cases were matched for age and cohort. The crude model was unadjusted and the established risk factor model was adjusted for all other variables in Table 1 except CRP (apolipoprotein ratio, smoking, hypertension and diabetes).

## Statistics

Endostatin was log-transformed and standardized by its own standard deviation. Within strata, the cases and referents had the same follow-up times, in this nested, matched case-referent study. Therefore, we estimated odds ratios (OR) and 95% confidence intervals (CI) with logistic regression analyses (rather than Cox regression) and the conditional maximum likelihood routine designed for matched analysis.

Missing observations were replaced by the median value of all real observations in controls. Since the controls were matched to the cases by age, sex and cohort, the following adjustments to the models were made. Crude model

(unadjusted), to see any effect of any higher risk of MI for a standard deviation higher level of endostatin. Established cardiovascular risk factors (BMI (body mass index), apolipoprotein ratio, smoking, hypertension and glucose intolerance), to see the risk estimates for endostatin when the risk associated with the established cardiovascular risk factors was accounted for [13,14]. Finally, we made additional adjustments to the established cardiovascular risk factor model, by adding CRP, the most widely used clinical marker of systemic inflammation. According to our aim, we also analyzed men and women separately, as formal interaction tests by sex was not possible, due to the matching by sex. All calculations were performed with the statistical program, SPSS version 24 (IBM, Armonk, NY, USA).

## Results

### Baseline characteristics

Baseline characteristics of the study populations are presented in Table 1.

### Conditional logistic regression analysis

Higher endostatin levels was associated with an increased incidence of MI when comparing cases and their age-, sex- and cohort-matched controls, as shown in Table 2. The OR estimates for the crude association between endostatin and outcome were similar when the three cohorts were investigated separately (VIP 1.44, 95% CI 1.25–1.66, MONICA 1.54, 95% CI 0.90–2.65, and MSP 1.91 95% CI 1.31–2.80). The association between higher levels of endostatin and a higher incidence of MI was attenuated albeit still statistically significant when adjusted for established cardiovascular risk factors. Further adjustments for CRP abolished the association.

As seen in Table 3, the association between endostatin and MI was predominantly seen in women.

## Discussion

### Main findings

In the present prospective community based nested case-control study, increased levels of circulating endostatin was associated with an increased incidence of MI independently of established cardiovascular risk factors. This association was predominantly seen in women but was abolished after additional adjustment for CRP, arguing against a broad utility of endostatin measurements for the prediction of MI in the community.

### Comparison with previous studies

Circulating endostatin has been shown to be increased in patients with acute MI [15,16] and expression of endostatin is increased in human heart biopsies from patients with non-ST elevation MI [16]. Also, higher levels of serum endostatin in the coronary circulation of patients with

ischemic heart disease was associated with poorer collateral formation [5].

Studies evaluating the association between circulating endostatin levels and cardiovascular events are scarce. We are aware of only one study that evaluated the association between circulating endostatin and the risk of cardiovascular mortality [8]. In that study, elevated serum endostatin was associated with increased cardiovascular mortality in two independent community-based cohorts of elderly. The association was more profound in participants with prevalent cardiovascular disease compared to those without cardiovascular disease. We have not been able to find any study reporting the association between circulating endostatin and its association with incident MI in the community.

### **Possible mechanisms for observed associations**

The pathophysiological role of increased circulating endostatin is not clear. One hypothesis is that increased circulating endostatin mirrors either an increased level of extra cellular matrix (ECM) remodelling as observed in patients with aortic aneurysms [17] or in patients with malignant diseases [2]. Local ECM remodeling in the heart, initiated for example by hypertension, cardiac stress, valve dysfunction, hypertrophy of the myocardium or by MI per se [18], leads to a substantial pathological deposition of extra cellular matrix proteins in the myocardium and results in cardiac fibrosis [18,19]. Cardiac fibrosis has been suggested to be associated with a reduction in local capillary perfusion leading to tissue hypoxia and a subsequent activation of the angiogenic milieu [20]. Importantly, it has been shown that the expression of endostatin is increased in rat cardiomyocytes exposed to hypoxia [21].

Alternatively, it is also possible that circulating endostatin reflects a systemic increased angiogenic activity initiated by an angiogenic stimulus involving extra cellular matrix remodulation and release of endostatin. Vascular endothelial growth factor (VEGF), one of the most potent endogenous stimulators of angiogenesis, is regulated by hypoxia, inflammatory cytokines as well as oncogenes [22,23]. Initiation of angiogenesis by VEGF involves extracellular matrix degradation and leads to an imbalance in the local angiogenic milieu favoring angiogenesis. As a consequence to the extra cellular matrix breakdown, endostatin is released in order to maintain homeostasis in the angiogenesis. Alteration in the systemic balance of pro and anti-angiogenic homeostasis has been shown to be involved in the destabilization of atherosclerotic plaques [24].

Taken together, it is possible that atherosclerotic changes in the coronary circulation causes an increased expression of endostatin in the circulation either via an increased ECM remodeling or a change in the local angiogenic milieu. Speculatively, the association between high levels of circulating endostatin and incident MI could mirror an advanced state of atherosclerosis in the coronary circulation and thus explain our findings in the models where CRP was not included. Interestingly, the association between circulating endostatin and incident of MI was still robust after

adjustment for diabetes, apolipoprotein ratio, smoking and hypertension, all traditionally strong risk factors for incident MI [25–28].

Yet, the association between endostatin and MI incidence was abolished after adjustment for the inflammatory marker CRP. Inflammation is a key factor in most stages of the development of atherosclerosis, from the formation of atherosclerotic lesions to the initiation of plaque rupture (the “vulnerable plaque”) [19]. In the present study it is not possible to differentiate between whether CRP mediates the association between endostatin and MI (i.e. implicating a causal association) or whether the association is between endostatin and MI is merely confounded by CRP (indicating a non-causal association). Our data suggest that it may be worthwhile to pursue additional studies that clarify the interplay between endostatin and inflammation in the development of atherosclerotic disease.

Finally, we observed an increased association between endostatin and incident MI predominantly in women. The mechanism behind this finding is difficult to explain as we have found no previous reports suggesting an effect modification by sex. Both risk factors for acute coronary syndrome, as well as the pathophysiological mechanism behind acute MI, differ in men and women. For example, plaque rupture is much less common in women compared to men [29]. Our observational data do not allow us to further elucidate this finding and subsequent analyses have to be performed to study the specific role of circulating endostatin as a risk factor for ischemic heart disease in women.

### **Strengths and limitations**

The present study has several strengths. National Swedish Registers on cardiovascular events have been shown to be 99.8% complete [30], and the present register was likely even better since MI deaths outside hospitals were included in the present study. The fact that all participants in the study originated from cohort studies where blood samples were drawn before the MI further strengthen the present results. Limitations include the unknown generalizability to other age- and ethnic groups. Thus, additional large-scale studies in other ethnicities and in other age groups are needed to properly validate our findings and to establish optimal thresholds in order to identify individuals at an increased risk. Another possible limitation is the long storage time for endostatin and CRP. We do not know the effect of storage on the stability of endostatin and CRP however, we expect the effects of storage to be similar for both controls and cases due to identical follow up time (as part of the study design cases and controls were matched to have identical follow up time which, i.e identical storage time).

### **Conclusion**

Even though circulating endostatin levels predicted incident MI independently of established cardiovascular risk factors, the clinical implications of our findings appear limited in men and if data on CRP is available.

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## Disclosure statement

The funding sources did not play any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Årnlöv is the guarantor of this work. Dr. Söderberg had full access to all the data, and takes full responsibility for the integrity of data and the accuracy of data analysis.

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