



Incremental prognostic value of coronary and systemic atherosclerosis after myocardial infarction☆☆☆

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ARTICLE INFO

Article history:

Received 24 October 2017

Received in revised form 18 January 2018

Accepted 9 February 2018

Keywords:

Atherosclerosis

Myocardial infarction

Coronary artery disease

Extra-cardiac artery disease

Prognosis

ABSTRACT

Background: The role of systemic atherosclerosis in myocardial infarction (MI) patients is not fully understood. We investigated the incremental prognostic value of coronary and systemic atherosclerosis after acute MI by estimating extra-cardiac artery disease (ECAD) and extent of coronary atherosclerosis.

Methods and results: The study included 544 prospective MI patients undergoing coronary angiography. For all patients, the longitudinal coronary atherosclerotic extent, expressed as Sullivan extent score (SES) was calculated. In addition, the patients underwent non-invasive screening for ECAD in the carotid, aortic, renal and lower limb. SES was found to be associated with ECAD independent of baseline clinical parameters [adjusted odds ratio (OR) 1.04 95% confidence interval (CI) 1.02–1.06, $P < 0.001$]. Extensive systemic atherosclerosis, defined as the combination of extensive coronary disease ($SES \geq 17$) and ECAD, was associated with higher risk for all-cause mortality compared to limited systemic atherosclerosis ($SES < 17$ and no ECAD) (hazard ratio [HR] 2.9 95% CI 1.9–4.5, $P < 0.001$, adjusted for Global Registry of Acute Coronary Events risk score parameters 1.8, 95% CI 1.1–3.0, $P = 0.019$). The risk for the composite endpoint of cardiovascular death or hospitalization was significantly higher in patients with extensive systemic atherosclerosis compared to patients with limited systemic atherosclerosis (HR 3.1, 95% CI 2.1–4.7, $P < 0.001$, adjusted HR 1.9, 95% CI 1.2–3.1, $P < 0.004$).

Conclusions: Visual estimation of the longitudinal coronary atherosclerotic extent at the time of MI predicts ECAD. Coexistence of extensive coronary disease and ECAD defines a group with particularly poor prognosis after MI.

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1. Introduction

Coronary artery disease may lead to myocardial infarction (MI), a major killer worldwide [1], but atherosclerosis in coronary arteries may also indicate disease in other vascular beds [2]. Angiographic findings in MI are heterogeneous, ranging from normal to severe disseminated

atherosclerosis in all coronary vessels [3]. There is an association between severity of coronary disease and both prognosis [4] and the presence and severity of extra-cardiac atherosclerotic disease (ECAD, in our study defined as significant atherosclerotic disease one or more of the carotid, aortic, renal or lower limb arteries) [2,5]. Systemic atherosclerosis (lesions in multiple arterial beds) is associated with poor cardiovascular prognosis [5], but less is known about the post-MI prognostic impact of the combined coronary and extra-cardiac atherosclerosis burden. The main objective of this study was to examine the incremental prognostic value of coronary and systemic atherosclerosis after MI.

The widely used coronary scoring system describing number of significantly diseased coronary vessels is a simple, yet powerful predictor of prognosis [6] but information of the longitudinal atherosclerotic extent and diffuse dissemination of coronary disease is discarded. We hypothesized that a simple scoring system based on coronary angiographic longitudinal extent would be helpful in identifying patients with systemic atherosclerosis, potentially impacting prognosis and with possible implications for preventive and therapeutic measures.

In a prospective cohort study, we used a combination of data from angiographic coronary scoring and non-invasive assessment of ECAD

* **Acknowledgement of grant support:** This work was supported by unrestricted grants from Sparbanksstiftelsen Nya [grant number 552, 693, 0932, 2297], the Collaboration fund (Counties of Örebro, Västmanland, and Sörmland) [grant number 100LL1951], the Research committee (Örebro County council) [grant number OLL-135611, OLL-202161], and the Uppsala/Örebro Regional Research Council, [grant number RFR-641271].

☆☆ **Conflicts of interest:** None of the authors declares conflicts of interest in relation to the subject of this paper, including related consultancies, shareholdings and funding grants.

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¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

at the time of MI to determine the association between longitudinal atherosclerotic extent in the coronary arteries and ECAD, and to evaluate the correlation between systemic atherosclerotic burden and prognosis.

2. Methods

2.1. Study population

The study was prospective and part of the Västmanland Myocardial Infarction Study (VaMIS) ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01452178) Identifier NCT 01452178). From November 2005 to May 2011, patients ≥ 18 years of age, admitted to the coronary care unit of Västmanland County Hospital, Västerås, Sweden were screened for participation. Inclusion criteria were a diagnosis of MI by electrocardiogram and a troponin I level $\geq 0.4 \mu\text{g/L}$ as the biomarker criterion [7]. The study complied with the Declaration of Helsinki. The regional ethical review board of Uppsala, Sweden, approved the study (protocol number 2005:169). All subjects provided written informed consent.

2.2. Baseline data

Medical history and lifestyle factors were assessed by questionnaire on day 2 to 4 following diagnosis of MI. Hypertension, hyperlipidaemia, diabetes mellitus, and prior MI were defined as history of physician-diagnosed disease. An additional follow-up interview was conducted with subjects who had provided incomplete data. Blood pressure and resting heart rate were measured between day 4 and 7. Systolic and diastolic blood pressure was measured twice in each arm with the patient sitting.

2.3. Extent of coronary atherosclerosis

All patients with an available coronary angiogram recorded for clinical reasons during the index hospitalization were included in analyses. Coronary angiograms for patients referred to a secondary hospital for angiography were, for logistical reasons, not available for this study. The longitudinal extent of coronary atherosclerosis was determined by systematic evaluation of coronary angiographies. We used the Sullivan extent score (SES) method [8] based on visual estimation. This score was designed to reflect the extent of endothelial surface involved in atheroma and has a superior correlation to cardiovascular risk factors than does scoring based on stenosis severity [8]. In brief, the coronary arterial tree was divided into 15 segments according to American Heart Association definitions [9]. The extent of coronary disease in each segment was determined based on information synthesized from all available series. All imaged native coronary segments were included in the analysis, including segments filled with contrast via collateral vessels or through coronary artery bypass grafts. Coronary arteries $< 1 \text{ mm}$ in diameter were not included in the analysis. Coronary atherosclerosis was defined as irregularities of $> 20\%$ of total lumen diameter. For each segment, we visually estimated the longitudinal extent of atherosclerosis as a percentage. An occlusion within a segment counted as at least 50% longitudinal atherosclerosis, and atherosclerotic extent was then determined in the remaining, non-occluded, portion of the segment, hence the total extent of atherosclerosis would range from 50 to 100% in an occluded segment. The segment percentage of longitudinal atherosclerosis was multiplied by a factor representing the surface area of the studied segment relative to the entire coronary arterial tree. The left main coronary artery accounted for 5%, the left anterior descending artery 35%, the left circumflex artery 30%, and right coronary artery 30% according to the SES definition, so that the each angiogram would confer a total SES value in the range 0 to 100.

All coronary angiograms were examined by an experienced invasive cardiologist or an experienced and specifically trained cardiac nurse. The investigators were blind to the patient's clinical data. Five percent of the angiograms were examined by two investigators to calculate inter-observer variability. We calculated the median SES for all subjects, and defined limited longitudinal coronary disease as $\text{SES} < \text{median value}$ and extensive longitudinal coronary disease as $\text{SES} \geq \text{median value}$.

2.4. Laboratory data

Blood samples were drawn at hospital admittance. Troponin I was assessed on two additional occasions during the first 24 h of hospitalization. HaemoglobinA1c, calcium, N-terminal pro B-type natriuretic peptide, and total cholesterol, triglycerides, and low and high density lipoproteins were measured within 3 days of hospital admission.

2.5. Physiology

Echocardiography and vascular ultrasound were performed within 25 days of enrolment in the study. Left ventricular ejection fraction (LVEF) was assessed according to the Simpson formula [10] when image quality permitted, or otherwise visually estimated. Vascular ultrasound of the carotid artery, infra-renal aorta, and renal arteries was performed by one of three experienced vascular technicians blinded to patient clinical history. If adequate visualization or pulsed Doppler flow measurement of a vessel segment could not be satisfactorily obtained, the examination was classified as non-diagnostic at the segment level. Significant carotid artery stenosis was defined as presence of plaque in the internal carotid artery resulting in reduction of the lumen diameter in combination with flow turbulence in the colour flow Doppler and a spectral Doppler peak systolic velocity $\geq 1.5 \text{ m/s}$, defined as at least moderate stenosis or no detectable flow, corresponding to

occlusion [11]. Significant atherosclerotic disease in the infra-renal aorta was defined as lumen diameter of $\geq 30 \text{ mm}$, stenosis $\geq 50\%$, or an occlusion or dissection of the abdominal aorta [12]. Significant renal artery stenosis was defined as peak systolic velocity $> 1.8 \text{ m/s}$ and renal aortic ratio > 3.5 , corresponding to stenosis $\geq 60\%$, or an occluded artery [12]. To estimate lower limb arterial disease, the ankle brachial index (ABI) was calculated. Ankle systolic blood pressures in the bilateral dorsalis pedis and tibial posterior arteries were obtained by a leg cuff, an aneroid sphygmomanometer, and a hand-held Doppler-instrument. ABI was calculated as the higher of the pedal artery systolic pressures divided by the highest systolic blood pressure in the arms. Significant lower limb arterial disease was defined as $\text{ABI} < 0.9$ or ≥ 1.4 in either limb [12,13]. ECAD was defined as significant disease in any of the examined extra-cardiac arterial beds.

2.6. Systemic atherosclerosis

We combined information of coronary atherosclerosis extent with information on ECAD to define groups with extensive, moderate, or limited systemic atherosclerosis. Extensive systemic atherosclerosis was defined as extensive coronary disease ($\text{SES} \geq \text{median}$) plus ECAD. Moderate systemic atherosclerosis was defined as either extensive coronary artery disease or ECAD. Limited systemic atherosclerosis was defined as limited coronary artery disease ($\text{SES} < \text{median}$) and no ECAD.

2.7. Registry data

Based on a Swedish citizen's unique 10-digit personal identification number, follow-up data on survival, emigration, and date of death until 9th of March 2017, were obtained by linking the database to the comprehensive Swedish National Population Registry. Information on hospitalization for cardiovascular disease and cardiovascular mortality until 31st December 2015 was obtained from the Swedish National Patient Register and the Cause of Death Register. Cardiovascular disease was defined as International Statistical Classification of Diseases and Related Health Problems (ICD) codes I21 (MI), I63 (ischemic stroke), I50 or I11 (heart failure). Cardiovascular death was defined as death caused by any diagnosis coded as ICD 100–199.

2.8. Statistical analysis

Continuous data were presented as mean $\pm$ standard deviation (SD) for approximately normally distributed data, or median and interquartile range for skewed data. Categorical variables were summarized as frequency and percentage. Differences among patient groups, defined according to level of atherosclerosis, were assessed with Student's *t*-test for approximately normally distributed continuous variables, Mann–Whitney *U* test for heavily non-normally distributed continuous variables, and Pearson's χ^2 -test for categorical variables. Inter-observer agreement of SES was estimated by calculating intraclass correlation (ICC) [14]. We used logistic regression to calculate the odds ratio (OR) for ECAD relative to SES. In the multivariable model we adjusted for sex, age, diabetes, hypertension, hyperlipidemia, smoking, previous percutaneous coronary intervention (PCI), and previous coronary artery bypass surgery (CABG). In addition, we adjusted for various baseline clinical characteristics with significant univariate association to ECAD. The Kaplan–Meier method was used for analysis of cumulative event rates throughout the study period. Differences were assessed with Log Rank test. Hazard ratios (HR) were calculated using the Cox proportional hazard method. To evaluate the incremental prognostic value of atherosclerosis burden, we adjusted for the majority of parameters included in the Global Registry of Acute Coronary Events (GRACE) risk score 2.0 as proposed by NICE guidelines [15,16] (age, heart rate, systolic blood pressure, creatinine level, ST-segment deviation), excluding cardiac arrest at admission, were no information was available, and biomarkers for cardiac injury since positive troponin was a criterion for inclusion in the study. We did not perform multiple adjustments for risk factors were atherosclerosis is in the probable causal chain linking the risk factor to cardiovascular events. All *P* values were two-sided, and $P < 0.05$ was regarded as statistically significant. Analyses were performed with IBM SPSS Statistics 20.0 (Chicago, IL).

3. Results

Of the 1008 patients included in the VaMIS study, a coronary angiogram was available for 544. A flow chart for the inclusion in this analysis is presented in Fig. 1. The mean age was 68.5 years (SD 10.7) and 31.7% were female. Echocardiography was performed in 526 (97%). In 416 patients, LVEF was assessed according to the Simpson formula, while it was visually estimated in 110 patients. The ICC for inter-observer agreement in SES calculations was 0.89 (95% confidence interval [CI] 0.77–0.95). The median SES for all subjects was 17 (interquartile range 17). Baseline clinical parameters of subjects with limited ($\text{SES} < 17$) and extensive ($\text{SES} \geq 17$) coronary disease are shown in Table 1. The one-year mortality rate was 7.9% ($n = 22$) in subjects with extensive coronary disease and 3.9% ($n = 11$) in the group with limited disease ($P = 0.049$). Mean follow-up for all-cause mortality was 7.7 years (SD 2.9). Mortality throughout the study period was 35.5% ($n = 94$) in the group with

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