Atherosclerosis 263 (2017) 53–59

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Prognostic impact of subclinical or manifest extracoronary artery diseases after acute myocardial infarction

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ARTICLE INFO

Article history:
Received 3 February 2017
Received in revised form
5 May 2017
Accepted 23 May 2017
Available online 26 May 2017

Keywords:
Extracoronary artery disease
Myocardial infarction
Prognosis

ABSTRACT

Background and aims: In patients with coronary artery disease (CAD), clinically overt extracoronary artery diseases (ECADs), including claudication or previous strokes, are associated with poor outcomes. Subclinical ECADs detected by screening are common among such patients. We aimed to evaluate the prognostic impact of subclinical *versus* symptomatic ECADs in patients with acute myocardial infarction (AMI).

Methods: In a prospective observational study, 654 consecutive patients diagnosed with AMI underwent ankle brachial index (ABI) measurements and ultrasonographic screening of the carotid arteries and abdominal aorta. Clinical ECADs were defined as prior strokes, claudication, or extracoronary artery intervention. Subclinical ECADs were defined as the absence of a clinical ECAD in combination with an ABI $\leq$0.9 or >1.4, carotid artery stenosis, or an abdominal aortic aneurysm.

Results: At baseline, subclinical and clinical ECADs were prevalent in 21.6% and 14.4% of the patients, respectively. Patients with ECADs received evidence-based medication more often at admission but similar medications at discharge compared with patients without ECADs. During a median follow-up of 5.2 years, 166 patients experienced endpoints of hospitalization for AMI, heart failure, stroke, or cardiovascular death. With ECAD-free cases as reference and after adjustment for risk factors, a clinical ECAD (hazard ratio [HR] 2.10, 95% confidence interval [CI] 1.34–3.27, p=0.001), but not a subclinical ECAD (HR 1.35, 95% CI 0.89–2.05, p=0.164), was significantly associated with worse outcomes.

Conclusions: Despite receiving similar evidence-based medication at discharge, patients with clinical ECAD, but not patients with a subclinical ECAD, had worse long-term prognosis than patients without an ECAD after AMI.

1. Introduction

Atherosclerotic cardiovascular diseases, especially coronary artery disease (CAD), are the leading causes of death worldwide [1]. Clinical manifestations of extracoronary artery diseases (ECADs), such as claudication or cerebrovascular disease, are linked to CAD and are associated with worse prognosis in patients with manifest CAD [2–8]. In addition, the burden of atherothrombotic disease (i.e., the number of arterial beds affected) increases the risk of recurrent ischemic events in patients with overt cardiovascular disease [8,9]. More severe coronary atherosclerosis, a greater burden of comorbidities, and the underuse of evidence-based treatment have been suggested as causes for the increased risk of morbidity and mortality in patients with CAD and a concomitant ECAD [7,9,10].

Several studies have documented that many patients with CAD have a lower limb artery disease, as detected by an abnormal ankle–brachial index (ABI) [11–13]. Subclinical lower limb artery disease in patients with CAD is related to the complexity of CAD and is associated with a poor prognosis during the first year after an acute coronary syndrome event [12,14]. Furthermore, subclinical ECADs in other vascular beds, such as carotid artery stenotic disease

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http://dx.doi.org/10.1016/j.atherosclerosis.2017.05.027

or an abdominal aortic aneurysm, have been associated with CAD [15–17]. Therefore, in patients with acute myocardial infarction (AMI), there might be a rationale to screen for subclinical ECAD to obtain accurate prognostic information and direct therapy. Data are limited regarding the long-term prognostic impact of subclinical ECAD in relation to clinically overt ECAD in patients with CAD.

In this prospective study, we aimed to investigate the associations of clinical and subclinical ECADs with long-term prognosis in patients hospitalized with AMI.

2. Materials and methods

2.1. Study population

The study participants were part of the Västmanland Myocardial Infarction Study (VaMIS; Clinical Trials.gov Identifier NCT 01452178). All patients ≥18 years of age admitted to the coronary care unit of Västmanland County Hospital, Västerås, Sweden, from November 2005 through May 2011, resident in the hospital catchment area, and diagnosed with AMI were eligible for inclusion. AMI was diagnosed if a patient had a troponin I level ≥0.4 μg/L, with a subsequent decline, in combination with at least one of the following: ischemic symptoms, electrocardiographic (ECG) changes indicative of ischemia (ST segment elevation or depression), development of Q waves on the ECG, or the need for coronary intervention [18].

From a total of 1459 eligible patients, 451 (30.9%) were excluded because of dementia, acute confusion, language difficulties, other severe diseases, logistical problems, or declining to participate (see Supplementary Materials). Initially, all eligible patients were scheduled for screening for a subclinical ECAD, but it soon became apparent that many older subjects declined to participate. Therefore, we decided to limit ECAD screening to patients ≤80 years of age (n = 789). Data regarding subclinical ECAD and covariates were missing in 82 and 53 subjects, respectively, leaving 654 subjects for analysis. All patients gave their written informed consent. The study was approved by the Ethics Committee of Uppsala University, Sweden (Dnr 2005:169) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki with later revisions.

2.2. Clinical evaluation

A standard questionnaire was used during the index hospitalization to assess each patient's medical history and lifestyle. Self-reported data on hypercholesterolemia, hypertension, diabetes, and previous cardiovascular disease were confirmed from the medical records. Medications used at admission and at discharge were noted. Acute clinical blood samples, including measures of troponin I and haemoglobin levels, were drawn at admittance to the hospital. Troponin I was assessed on two additional occasions during the first 24 h of hospitalization. Blood samples for glycated haemoglobin (HbA_{1c}) analysis and measurements of sitting right arm systolic and diastolic blood pressures were performed at the time of inclusion in the study (1–5 days after admission). In a few cases with missing sitting blood pressures, supine blood pressures taken at the time of ankle pressure measurements were recorded.

The left ventricular ejection fraction (LVEF) was obtained by echocardiography and assessed using the biplane Simpson's rule within a median of 3 days from admission [19]. Left ventricular systolic dysfunction was defined as LVEF <45%. In subjects for whom it was not possible to obtain the Simpson LVEF (132, 20.8%), a visual estimation of LVEF was made and classified as above or below 45%.

2.3. Diagnosis and definition of ECADs

One of three experienced vascular technicians with no prior knowledge of the participants' clinical history performed ultrasonographic examinations of the carotid arteries and abdominal aorta. Significant carotid artery disease was defined as the presence of a plaque in the internal carotid artery causing a reduction of the lumen diameter in combination with flow turbulence in the colour flow Doppler scan and a spectral Doppler peak systolic velocity ≥1.5 m/sec corresponding to an at least moderate stenosis, or no detectable flow corresponding to occlusion [20]. Significant abdominal aortic disease was defined as a diameter of ≥30 mm, a stenosis ≥50%, occlusion, or dissection of the abdominal aorta [21]. The ankle–brachial index (ABI) was calculated to estimate lower limb arterial disease. Supine systolic and diastolic blood pressures were measured in each arm. Ankle systolic blood pressures in the bilateral dorsalis pedis and tibial posterior arteries were obtained by an appropriate-sized leg cuff, an aneroid sphygmomanometer, and a hand-held Doppler-instrument with a 5 MHz-probe. The leg-specific ABI was calculated as the higher of the two pedal artery systolic pressures divided by the highest systolic blood pressure of the two arms. Significant lower limb arterial disease was defined as an ABI ≤0.9 or >1.4 in either limb [22]. Reproducibility tests for the vascular screening are presented in Supplementary Materials.

Clinical ECAD was defined as a prior documented transient ischemic attack (TIA) or stroke, claudication, vascular surgery or percutaneous intervention of the abdominal aorta, of the carotid or lower extremity arteries, or amputation because of peripheral artery disease. Subclinical ECADs were defined as significant carotid artery disease, lower limb arterial disease, or abdominal aortic disease, in the absence of a clinical ECAD.

2.4. Follow-up

The primary composite endpoint was cardiovascular death (International Classification of Diseases 10th revision code I00-I99) or hospital admission because of recurrent AMI (code I21), heart failure (codes I11.0 or I50), or stroke (codes I61 or I63). The secondary endpoint was all-cause mortality. Patients were followed from the index examination until any end-point or at the latest 31 December 2013 for the composite endpoint, and to 26 May 2016 for all-cause death. Endpoint information was determined from the Swedish National Cause of Death Register for cardiovascular death, the Swedish National Inpatient Register for causes of hospitalization, and the Swedish Population Register for all-cause mortality. The registers were linked to the participants by the unique personal identification number assigned to each Swedish resident.

2.5. Statistics

Data are presented as frequencies (percentages) or mean ± standard deviation. Unpaired Student's *t* tests were used to compare differences between the means of two groups and analysis of variance for differences between three groups for continuous variables with approximately normal distributions. The Wilcoxon rank-sum test was used to compare two groups and the Kruskal–Wallis rank test was used for three groups for continuous variables with a skewed distribution (troponin I and HbA_{1c} levels). Fisher's exact test was used to compare differences in categorical variables. *Post-hoc* tests are presented with Bonferroni-corrected p values.

The cumulative incidence of the endpoints was analysed using the Kaplan–Meier method and differences between groups were evaluated by the log-rank test. Cox regression models were used to evaluate the crude and adjusted associations between ECAD status