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

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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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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

and outcomes. Adjusted Cox regression models included potential confounders and outcome risk factors available in this study, avoiding intermediate variables on a plausible causal path between ECAD and outcome (estimated glomerular filtration rate [eGFR] and medication) [23]. To facilitate comparison with previous studies, we also evaluated the fully adjusted Cox model by redefining the subclinical ECAD group to comprise only those patients with an asymptomatic ABI of ≤0.9 or >1.4, leaving the patients with subclinical carotid artery disease or abdominal aortic disease to be considered as having no ECAD.

To evaluate the possible influence of gender, atrial fibrillation, or the type of myocardial infarction (STEMI or non-STEMI) on the association between any ECAD and outcome, separate analyses including multiplicative interaction terms were performed. Further, the influence of treatment start of statins, beta blockers, or ASA at the index event *versus* chronic use on the association between ECAD and outcome was evaluated in separate fully adjusted Cox regression analyses by including multiplicative interaction terms. The proportional hazard assumption was assessed and judged acceptable for every covariate by visual inspection of log–log plots or weighted plots of Schoenfeld residuals, and for the whole models using a global test of linear departure from the proportional hazard. Results are presented as the hazard ratio (HR) and 95% confidence interval (CI). Post-hoc power analyses were performed using the method of Latouche et al. [24].

Statistical analyses were performed using Stata version 14 (StataCorp LP, College Station, TX, USA) and R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) using the package powerSurvEpi. Two-sided p values of <0.05 were defined as significant.

3. Results

3.1. Baseline characteristics

The study population included 654 patients with a mean age of 65.6 ± 9.7 years and 70.8% (n = 463) were men. The prevalence of ECAD was 35.9% (n = 235), among whom 141 (60.0%) had a subclinical and 94 (40.0%) had a clinical ECAD. Among the latter patients, the occurrences of prior TIA/stroke, claudication, and peripheral vascular interventions were 44.7% (n = 42), 55.3% (n = 52), and 30.8% (n = 29), respectively. The prevalence of carotid artery disease, lower extremity artery disease, and abdominal aortic disease was 31.9% (n = 45), 61.7% (n = 87), and 23.4% (n = 33), respectively, among the patients with a subclinical ECAD, of whom 83.7% (n = 118) had a single vascular and 16.3% (n = 23) a polyvascular subclinical ECAD.

Baseline characteristics are presented in Table 1. Compared with patients without ECAD, patients with clinical or subclinical ECADs were older, with more frequent hypertension and prior myocardial infarctions, and they had worse renal function and lower haemoglobin levels. The index AMI was less often a STEMI among the patients with a clinical ECAD compared with the other two ECAD groups.

3.2. Medication

Patients with an ECAD were more often under medication with aspirin, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), statins, and beta blockers at admission than patients without an ECAD (Table 2). Further, patients with a clinical ECAD were more often receiving the above-mentioned drugs, as well as clopidogrel and warfarin, at admission compared with patients with a subclinical ECAD. At discharge, there were no significant differences in medication use between the ECAD groups except for clopidogrel, which was less often prescribed to the patients with a clinical ECAD compared with those without an ECAD (79.3% *vs.* 92.0%, $p = 0.002$). Information on warfarin medication at discharge was missing. A clear majority of patients on statins, both at admission and at discharge, were prescribed simvastatin with median dosage of 40 mg per day.

3.3. Follow-up

During a median follow-up time of 5.2 years, 166 patients (25.4%) experienced the primary composite endpoint, of whom 50 were hospitalized for recurrent AMI, 40 for heart failure, 20 for stroke, and 56 died from cardiovascular causes. The secondary endpoint, all-cause death, was reached by 146 patients (22.3%) during a median follow-up of 7.8 years. One patient was lost after 11 days and 4 patients after 1.5, 3.8, 5.0, and 9.1 years of follow-up, respectively, all because of emigration.

In the Kaplan–Meier analyses, ECAD was significantly associated with worse long-term prognosis regarding both the primary composite outcome ($p<0.001$; Fig. 1) and all-cause death ($p<0.001$; Fig. 1).

In the unadjusted Cox regression analysis, both clinical and subclinical ECADs were significantly associated with the primary endpoint (Table 3). After adjustment for age and gender, these associations remained statistically significant. In the fully adjusted model, clinical ECAD (HR 2.10, 95% CI, 1.34–3.27, $p=0.001$) remained significantly associated with future cardiovascular events. By contrast, in the fully adjusted model, a subclinical ECAD was not significantly associated with the composite outcome (HR 1.35, 95% CI 0.89–2.05, $p = 0.164$). Fig. 2 shows the detailed results of the Cox regression analyses, including the individual endpoints of the primary composite outcome.

When redefining the subclinical ECAD group to comprise only those patients with an asymptomatic ABI of ≤0.9 or >1.4, the fully adjusted Cox regression model showed that clinical (HR 1.85, 95% CI 1.21–2.83, $p = 0.004$), but not subclinical ECAD (HR 1.07, 95% CI 0.66–1.72, $p=0.782$), was associated with the primary composite outcome.

Regarding the secondary outcome (all-cause mortality), patients with clinical and subclinical ECADs had significantly worse prognoses compared with those without ECADs in the unadjusted analysis (Table 3). However, after adjustment, only clinical ECADs remained independently associated with outcome.

There was no significant influence of gender, atrial fibrillation, or type of myocardial infarction (STEMI/non-STEMI) on the associations of ECAD with the primary or secondary outcomes. In addition, there was no significant interaction between ECAD and treatment start of statins, beta blockers, or ASA at the index event *versus* chronic treatment on the association between ECAD and outcome.

4. Discussion

We found here that clinical ECADs were significantly and independently associated with the long-term risk of adverse cardiovascular events after hospitalization for AMI, while subclinical ECADs were not. This was true even though patients with a clinical ECAD had a higher frequency of guideline-based medical therapy at admission and a similar frequency of such therapy at discharge compared with patients without an ECAD.

Several previous studies have shown that patients with CAD and concomitant clinical ECADs are at increased risk of recurrent adverse cardiovascular events and mortality [4,5,7,9,10,18]. The frequency of ECAD among patients with AMI is substantial and vary between 13 and 43%, depending on study population and definition

Table 1
Baseline characteristics according to extracoronary artery disease (ECAD) status.

	Absence of ECAD (n = 419)	Subclinical ECAD (n = 141)	Clinical ECAD (n = 94)	p value[a]
Men, n (%)	296 (70.6)	103 (73.0)	64 (68.1)	0.71
Age (years)	63.1 ± 9.6	69.2 ± 8.2[d]	71.1 ± 7.9[d]	<0.001
Current smoking, n (%)	95 (22.7)	40 (28.4)	20 (21.3)	0.33
Body mass index (kg/m^2)	27.8 ± 4.7	27.1 ± 4.6	27.1 ± 4.6	0.21
Hypertension, n (%)	195 (46.5)	87 (61.7)[c]	75 (79.8)[df]	<0.001
Systolic blood pressure (mmHg)	124 ± 19	125 ± 20	131 ± 20[ce]	0.007
Diastolic blood pressure (mmHg)	73 ± 11	71 ± 11	72 ± 11	0.10
Hypercholesterolemia, n (%)	122 (29.1)	52 (36.9)	51 (54.3)[de]	<0.001
Diabetes mellitus, n (%)	56 (13.4)	24 (17.0)	35 (37.2)[df]	<0.001
Glycated haemoglobin (%)	4.91 ± 1.05	5.04 ± 0.97[b]	5.59 ± 1.42[df]	<0.001
Atrial fibrillation, n (%)	20 (4.8)	19 (13.5)[c]	14 (14.9)[c]	<0.001
Prior myocardial infarction, n (%)	56 (13.4)	38 (27.0)[d]	38 (40.4)[d]	<0.001
ST elevation MI, n (%)	166 (39.6)	49 (34.8)	12 (12.8)[dg]	<0.001
Maximum troponin I (μg/L)	18.1 ± 23.6	15.6 ± 18.1	13.2 ± 19.1	0.09
LV ejection fraction < 45%, n (%)	70 (16.7)	35 (24.8)	39 (41.5)[de]	<0.001
eGFR (ml/min/1.73 m^2)	80.7 ± 17.1	72.1 ± 19.4[d]	62.5 ± 24.1[dg]	<0.001
Haemoglobin (g/L)	146 ± 15	142 ± 16[b]	136 ± 18[df]	<0.001
PCI during hospitalization, n (%)	254 (60.6)	81 (57.4)	41 (43.6)[c]	0.011
CABG during hospitalization, n (%)	12 (2.9)	18 (12.8)[d]	9 (9.6)[b]	<0.001

[a]*p* value for comparison across ECAD categories; [b]$p < 0.05$ *vs.* No ECAD; [c]$p < 0.01$ *vs.* No ECAD; [d]$p < 0.001$ *vs.* No ECAD; [e]$p < 0.05$ *vs.* Subclinical ECAD; [f]$p < 0.01$ *vs.* Subclinical ECAD; [g]$p < 0.001$ *vs.* Subclinical ECAD.
eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting.

Table 2
Medication at admission and at discharge during the baseline hospitalization according to ECAD status.

Variable	Absence of ECAD n/total (%)	Subclinical ECAD n/total (%)	Clinical ECAD n/total (%)	p value[a]
Medication at admission				
Aspirin	96/417 (23.0)	63/139 (45.3)[d]	61/94 (64.9)[df]	<0.001
Clopidogrel	7/417 (1.7)	7/139 (5.0)	14/94 (14.9)[de]	<0.001
Warfarin	9/417 (2.2)	6/139 (4.3)	12/94 (12.8)[de]	<0.001
ACE-I/ARB	104/414 (25.1)	50/138 (36.2)[b]	60/94 (63.8)[dg]	<0.001
Statins	91/419 (21.7)	53/140 (37.9)[d]	59/94 (62.8)[dg]	<0.001
Beta blockers	103/414 (24.9)	59/138 (42.8)[d]	69/94 (73.4)[dg]	<0.001
Medication at discharge				
Aspirin	401/412 (97.3)	136/139 (97.8)	89/92 (96.7)	0.87
Clopidogrel	378/411 (92.0)	125/140 (89.3)	73/92 (79.3)[b]	0.003
ACE-I/ARB	392/410 (95.6)	132/141 (93.6)	86/92 (93.5)	0.47
Statins	402/412 (97.6)	140/140 (100.0)	89/91 (97.8)	0.13
Beta blockers	382/412 (92.7)	131/140 (93.6)	91/92 (98.9)	0.06

Information on warfarin medication at discharge was missing.
[a]*p* value for comparison across ECAD categories; [b]$p < 0.05$ *vs.* No ECAD; [c]$p < 0.01$ *vs.* No ECAD; [d]$p < 0.001$ *vs.* No ECAD; [e]$p < 0.05$ *vs.* Subclinical ECAD; [f]$p<0.01$ *vs.* Subclinical ECAD; [g]$p < 0.001$ *vs.* Subclinical ECAD.
ACE-I, angiotension converting enzyme inhibitor; ARB, angiotensin receptor blocker.

of ECAD [4,7,8,12]. Furthermore, an association has been demonstrated between asymptomatic abnormal ABI and cardiovascular mortality after acute coronary syndrome [12,25]. Therefore, in patients with AMI, there might be a rationale to screen for subclinical ECADs to obtain accurate prognostic information for guiding specific therapies. However, the present study does not support routine screening for subclinical ECADs in patients with AMI as the added prognostic information seems weak. In contrast, Morillas et al. examined 1054 patients hospitalized for an acute coronary syndrome and found that those having an asymptomatic ABI of ≤0.9 or >1.4 were at significantly higher risks of major adverse cardiovascular events than patients with a normal ABI, during a 1-year follow-up [12]. One important difference between their study and ours was the definition of subclinical ECAD. When we redefined subclinical ECAD to comprise only an asymptomatic abnormal ABI, the estimated HRs were even lower for both clinical and subclinical ECADs. This suggests that to classify carotid artery disease and abdominal aortic disease as not being ECADs dilutes the prognostic difference between the ECAD groups. In comparison with our study, the prevalence of a subclinical abnormal ABI in the study by Morillas et al. was considerably larger (28% *vs.* 13%), and their patients with a subclinical abnormal ABI had greater prevalences of hypertension (85% *vs.* 62%), hypercholesterolemia (86% *vs.* 37%), and diabetes mellitus (39% *vs.* 17%) at baseline, indicating a larger atherosclerotic burden in their population.

Multiple mechanisms have been suggested to explain the poor prognosis for patients with ECAD compared with those without, including older age, more cardiovascular risk factors, a greater atherosclerotic burden, more severe CAD, inflammatory markers, and underuse of evidence-based treatment [4,7,8,10,16,26].

Here, we did not find any evidence for an especially poor adherence to guideline-recommended therapy in the clinical and subclinical ECAD groups. At admission, patients with clinical ECADs had significantly higher prescription rates for ASA, beta blockers, ACE-I/ARB, clopidogrel, statins, and warfarin compared to both those with a subclinical ECAD and those without ECAD. This can

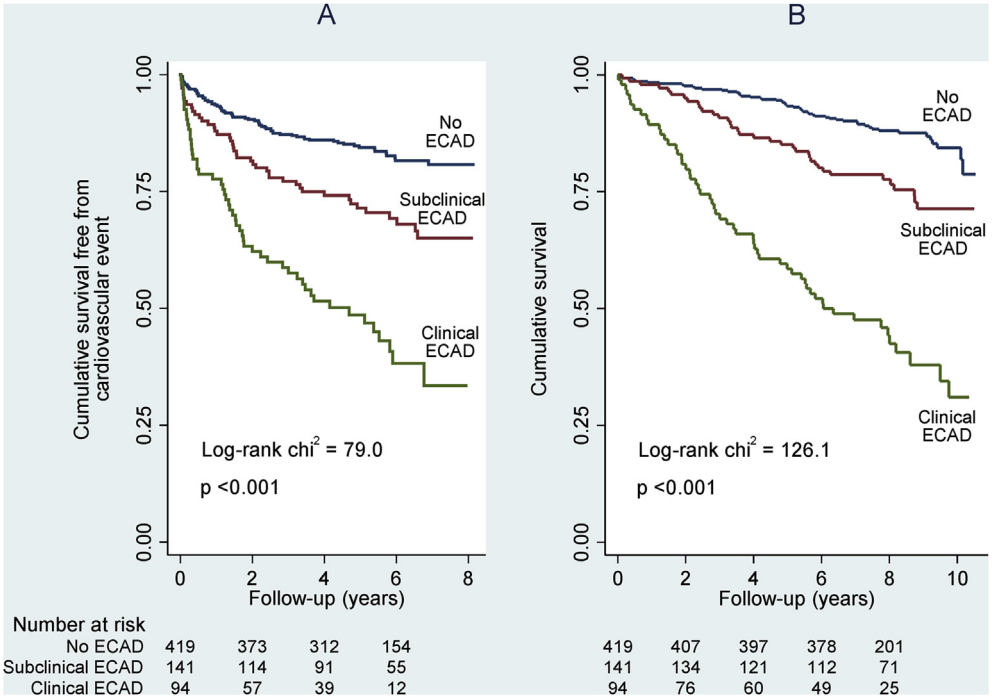

Fig. 1. Kaplan–Meier curves.
Kaplan–Meier curve showing (A) the cumulative survival free from cardiovascular events according to extracoronary artery disease (ECAD) status and (B) the cumulative survival according to ECAD status.

Table 3
Unadjusted and adjusted hazard ratios (HRs) and confidence intervals (CIs) for the associations between ECAD status and outcome.

		Cardiovascular events			All-cause mortality		
		HR (95% CI)	*p* value	*Post-hoc* power	HR (95% CI)	*p* value	*Post-hoc* power
Unadjusted	Absence of ECAD	Reference			Reference		
	Subclinical ECAD	1.98 (1.36–2.89)	<0.001	0.888	2.05 (1.34–3.12)	0.001	0.841
	Clinical ECAD	4.55 (3.17–6.53)	<0.001	>0.999	6.64 (4.56–9.66)	<0.001	>0.999
Adjusted for age and gender	No ECAD	Reference			Reference		
	Subclinical ECAD	1.74 (1.18–2.58)	0.005	0.713	1.53 (0.99–2.36)	0.055	0.405
	Clinical ECAD	3.80 (2.59–5.60)	<0.001	>0.999	4.70 (3.17–6.97)	<0.001	>0.999
Fully adjusted[a]	No ECAD	Reference			Reference		
	Subclinical ECAD	1.35 (0.89–2.05)	0.164	0.282	1.21 (0.75–1.93)	0.436	0.119
	Clinical ECAD	2.10 (1.34–3.27)	0.001	0.875	3.12 (1.98–4.92)	<0.001	0.995

Results based on 654 patients at baseline, 166 events for composite cardiovascular outcome (cardiovascular death or hospitalization due to myocardial infarction, heart failure, or stroke), and 146 events for all-cause mortality.
[a] Fully adjusted models included age, gender, current smoking habit, body mass index, diabetes, HbA_{1c} level, hypercholesterolaemia, hypertension, systolic blood pressure, diastolic blood pressure, atrial fibrillation, prior myocardial infarction, type of myocardial infarction (STEMI *versus* non-STEMI), maximum troponin I level, LVEF <45%, PCI at index hospitalization, and CABG at index hospitalization.

probably be explained by higher rates of comorbidities and is also in line with the guideline-recommended therapy for ECAD. Moreover, patients with subclinical ECADs were more often on ASA, beta blockers, ACE-I/ARB, and statins at admission than those without ECAD. However, medication at admission was not accounted for in most previous studies [4,5,7,12,16,25].

Participants with clinical ECAD had higher frequency of statin treatment at admission. At discharge, there were no significant differences in statin treatment according to the ECAD status. The LDL-hypothesis, were lower LDL-levels are associated with reduced cardiovascular morbidity and mortality, has recently got further support by showing that it is not just a class effect of statins [27,28]. Despite this, we found clinical ECAD significantly associated with cardiovascular events and all-cause mortality in our study. Thereby, this negative association seems to be beyond pharmacological stabilization of the atherosclerotic plaque, at least with medications frequently used at the setting of this study. On the other hand, subclinical ECADs were not found associated with an increase in cardiovascular events, and might mirror a population where plaque stabilization is still an available target for risk reduction.

In the present study, 63%, 70%, and 53% of patients with no ECAD, subclinical ECADs, and clinical ECADs, respectively, underwent revascularization (PCI or CABG) during hospitalization. Previous studies have found similar or lower revascularization rates [4,7,10,18]. Our patients with clinical ECADs were less likely to be revascularized with PCI at hospitalization than those without ECAD, which is in line with previous findings [4,7,10]. This could be explained by a greater occurrence of non-revascularizable CAD,

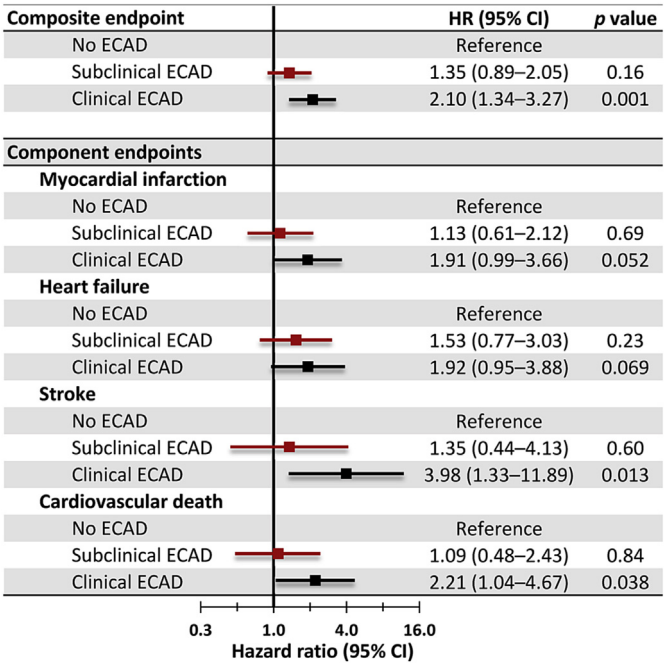

Fig. 2. Detailed results of the Cox regression analyses for the associations of extracoronary artery disease (ECAD) status with the primary composite endpoint and its component endpoints.
ECAD status was adjusted for age, gender, current smoking habit, body mass index, diabetes, HbA1c level, hypercholesterolemia, hypertension, systolic blood pressure, diastolic blood pressure, atrial fibrillation, prior myocardial infarction, type of myocardial infarction (STEMI *versus* non-STEMI), maximum troponin I level, LVEF <45%, PCI at index hospitalization, and CABG at index hospitalization.

greater frequency of comorbidities, and an increased risk for bleeding complications [7].

4.1. Strengths and limitations

We believe that the most important strengths of this study were its prospective design, a well-characterised study population representing patients in daily practice, and the long follow-up period. Valid data regarding medication at admission are very scarce in previous studies and our findings add new knowledge. Many of the patients, regardless of their ECAD status, were pharmacologically-treated according to post-AMI guideline recommendations at discharge, allowing us the evaluation of the prognostic impact of ECADs beyond current evidence-based medical therapy.

There are limitations to be recognized. Our conclusions are limited to AMI patients, 80 years or younger, willing to undergo a vascular screening examination. One-third of the eligible patients were excluded because of dementia, confusion, logistical problems, or declining to participate. For these patients, we have no baseline characteristics or follow-up data, as they did not give written consent to participate. However, it is most likely that they were more burdened with disease at baseline and had a worse prognosis compared with the study population. A clear majority of the participants excluded due to age >80 and/or missing data declined to participate in the vascular screening examination. The patients, 80 years or younger, excluded due to missing data (n = 135) did not differ from the study population regarding age, sex, smoking, previous hypertension, diastolic BP, hyperlipidemia, BMI, diabetes, or previous MI. However, they did have higher systolic BP (130 *vs.* 125 mmHg, p=0.011) and lower eGFR (71.5 *vs.* 76.3 mL/min/1.73 m^2, p=0.014). In addition, they had significantly higher rates of both CV events (92 *vs.* 53 events per 1000 person-years, log-rank Chi [2] 11.2, p<0.001) and all-cause death (62 *vs.* 30 deaths per 1000 person-years, log-rank Chi [2] 20.8, p<0.001) compared to the included patients. Our findings cannot be generalized to all AMI patients, but we do believe that our study population is an unbiased sample of daily practice AMI patients, ≤80 years of age that are willing to undergo vascular ultrasonographic screening.

The extent of coronary atherosclerosis was not quantified in our study and could probably co-vary with the extension of ECAD, as found in some previous studies, and thereby be an unaccounted confounder [5,7,12]. The links between CAD severity, ECADs, and prognosis in this patient group will be addressed by our group in a separate study. Unfortunately, data on prescription of warfarin at discharge were not available, but one could assume that the significantly higher frequency of warfarin use among patients with clinical ECADs at admission remained even at discharge, in accordance with previous studies [5,12]. Finally, long-term adherence to medication at baseline was not monitored and our results could be affected by compliance with guidelines and the target achievements of secondary prevention.

4.2. Conclusions

Among the patients hospitalized for AMI, we found that those with clinical ECADs had a worse prognosis than patients without ECAD, despite a higher use of evidence-based therapy at admission and no important differences in the guideline-recommended therapy after discharge. By contrast, the prognostic impact of subclinical ECADs was not statistically significant, so our findings do not support screening for subclinical ECADs in such patients. Future studies aiming at improving secondary prevention efforts and developing novel therapeutic methods are needed, to reduce the poor prognosis in patients with an AMI and a concomitant clinical ECAD.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

All authors were responsible for conception and design of the study. PH contributed to the collection of the data. PH and AR were responsible for the statistical analyses and compilation of the tables and figures. All authors contributed to the interpretation of the findings. MEÖ, FC, and PH drafted the manuscript, which was revised and approved by all authors. All authors take responsibility for all aspects of the reliability and freedom of bias of the data presented and their discussed interpretation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2017.05.027.

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