Atherosclerosis 245 (2016) 43–49

Contents lists available at ScienceDirect

Atherosclerosis

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

Long-term prognostic role of cerebrovascular disease and peripheral arterial disease across the spectrum of acute coronary syndromes

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ARTICLE INFO

Article history:
Received 20 August 2015
Received in revised form
2 October 2015
Accepted 13 November 2015
Available online 1 December 2015

Keywords:
Acute coronary syndromes
Cerebrovascular disease
Peripheral artery disease
Long-term follow-up
Outcome

ABSTRACT

Background: In acute coronary syndromes (ACS), the influence of cerebro-vascular disease (CVD) and/or peripheral artery disease (PAD) on short-midterm outcome has been well established. Data on long-term outcome however, are limited. Our study aimed to explore the effect of CVD and PAD on long-term outcome in a cohort of unselected ACS patients, including ST-elevation (STE-ACS) and non-ST-elevation (NSTE-ACS).

Methods and results: The population consisted of 2046 consecutive patients with a confirmed final diagnosis of ACS; 896 (44%) had STE-ACS and 1150 (66%) NSTE-ACS. CVD alone was present in 98 patients (5%), 282 (14%) had PAD alone, and 30 (1.5%) had both. All cause mortality at 5 years was lowest in patients without CVD/PAD (33%), intermediate in patients with either CVD or PAD (62% and 63%, respectively) reaching 80% in those with both CVD and PAD. These findings were confirmed in the STE-ACS and NSTE-ACS subgroups. CVD and PAD remained independent predictors of mortality after multivariable analysis, the combined presence of both carrying the highest risk within each ACS type (HR 4.15, 95% CI 1.83–9.44 for STE-ACS; HR 2.14, 1.29–3.54 for NSTE-ACS). Patients with CVD and/or PAD were less likely to be treated invasively and received less evidence-based treatment at discharge.

Conclusions: Across the spectrum of ACS, extracardiac vascular disease harbors a negative long-term prognosis that worsens progressively with the number of affected arterial beds.

1. Introduction

Prior studies have shown that a history of cerebro-vascular disease (CVD) or peripheral artery disease (PAD) predicts the presence, extension and outcome of stable coronary disease [1–5]. In the setting of acute coronary syndromes (ACS), the influence of CVD and/or PAD on short-midterm outcome has been well established, as well as the relationship between number of affected arterial beds and increasingly worse prognosis [6–10]. Data on long-term outcome however, are limited to patients with non-ST-elevation myocardial infarction aged ≥65 [11].

The aim of our study was therefore to explore the effect of CVD and PAD on long-term outcome in a cohort of unselected patients with acute coronary syndromes (ACS), including those with ST-elevation (STE-ACS) and non-ST-elevation (NSTE-ACS).

2. Methods

2.1. Setting and patients

Sant'Orsola – Malpighi Hospital is a tertiary care centre located in Bologna, Italy (catchment area approximately 1 million people), equipped with a high volume catheterization laboratory, available on a 7 days/24 h basis.

All demographical, clinical, electrocardiographic, laboratory, therapeutic, and outcome data on ACS patients hospitalized at our Center were collected in the "Sant'Orsola – Malpighi ACS database", that was approved by the local ethics committee. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.11.014
0021-9150/

This analysis focused on consecutive patients hospitalized at our Institution between January 1st 2004 and December 31st 2005, with an audited final diagnosis of ACS. Patients aged <18 were excluded.

Patients were identified in two complementary ways in order to include all relevant cases, thus avoiding selection bias:

1) Patients prospectively screened and enrolled by a trained physician working at the Emergency Department (ED) or the Coronary Care Unit (CCU) during index hospitalization for ACS;
2) Patients identified through a systematic review (clinical audit) of all medical records of patients discharged between January, 1st 2004 through December, 31^{h} 2005 with the following ICD9CM diagnosis codes: 410.X1 or 4111. The audit was performed by an Endpoint Adjudication Committee (GM, FV, LC) and patients fulfilling the diagnostic criteria of ACS (see below) were included in the database.

Patients with symptoms suggesting myocardial ischemia were classified as having STE-ACS if the 12-lead electrocardiogram (ECG) disclosed a persistent (>20 min) ST segment elevation (STE) occurring in two contiguous leads ($\geq$0.2 mV in V2–V3, $\geq$0.1 mV in other leads) or a new (or presumably new) left-bundle-branch block (LBBB) or development of pathological Q waves in two contiguous leads [12].

A diagnosis of NSTE-ACS was made in case of symptoms suggestive of myocardial ischemia plus 1 of the following: a) ST-segment depression >0.05 mV in any lead, b) transient (<20 min) STE in 2 contiguous leads, c) inverted T waves >1 mm in 2 contiguous leads, d) positive cardiac biomarkers, and e) documentation of coronary artery disease [12]. Patients presenting with pacemaker rhythm and pre-existing LBBB were categorized as having NSTE-ACS.

An Endpoint Adjudication Committee that systematically reviewed all cases adjudicated the final diagnosis; disagreements were solved by consensus.

CVD was designated as a history of stroke defined as the sudden onset of a focal neurologic deficit lasting more than 24 h. PAD was defined as claudication (with exertion or at rest), prior peripheral vascular bypass surgery, angioplasty or stent, lower extremity amputation, documented abdominal aortic aneurysm, prior abdominal aortic aneurysm requiring surgical or endovascular repair.

GFR (Glomerular Filtration Rate) was estimated in every patient using the modified MDRD [13] equation [eGFR ml/min/1.73 m^2 of body surface area = 186 * (serum creatinine in mg/dl)$^{-1.154}$ * (age in years)$^{-0.203}$ * (0.742 if female gender)]. In all patients, renal failure stage was established in accordance to the National Kidney Foundation/Kidney Disease Outcome Quality Initiative guidelines [14] as stage 1, (normal renal function; GFR > 90 ml/min/1.73 m^2), stage 2 (mild CKD; GFR 60–89 ml/min/1.73 m^2), stage 3 (moderate CKD; GFR 30–59 ml/min/1.73 m^2), stage 4 (severe CKD; GFR < 30 ml/min/1.73 m^2) and stages 5 (kidney failure; GFR < 15 ml/min/1.73 m^2).

2.2. Study endpoints and definitions

The primary study endpoint was 5-year all-cause mortality. The secondary endpoints were recurrence of myocardial infarction (MI) and major bleeding.

In-hospital bleeding was classified as major or minor according to the TIMI classification [15]. Major bleeding occurring after discharge was defined as follows: intracranial hemorrhage, bleeding requiring transfusion or surgery or hospitalization, hemoglobin reduction > 5 g/dl when available. Five-year follow-up was complete for 1703/2046 (83.2%) patients.

2.3. Statistical analysis

Categorical data are expressed as proportions and continuous variables reported as mean (SD).

The overall study population was divided into four groups: no CVD/PAD; CVD only; PAD only; CVD + PAD. As regards categorical variables, the Chi-square test and adjusted pairwise comparisons were used. One way ANOVA and Bonferroni multiple comparison test were used to compare continuous variables in the four groups.

The Kaplan–Meier method was used to analyze the occurrence of death, recurrent MI, and major bleeding during follow-up and comparison between groups was conducted using the Log-rank test.

Multivariable Cox regression analysis was performed to identify predictors of 5-year mortality. The following variables were chosen on the basis of clinical judgment and included in the model: age, gender, diabetes, hypertension, dyslipidaemia, smoking status, CVD, PAD, CVD + PAD, prior MI, prior HF, prior coronary revascularization, systolic blood pressure on admission (SBP), heart rate on admission (HR), Killip class on admission, atrial fibrillation on admission, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 on admission, ST-segment elevation, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) performed during index-hospitalization.

Martingale residuals were used in determining the linear form of continuous covariates to be included in the Cox model (age, HR and SBP); a plot of a Lowess smooth of the Martingale residuals against each variable appeared nearly linear, supporting the inclusion of the untransformed variables. The proportional-hazards assumption of all variables has been checked on the basis of Schoenfeld residuals.

Interaction analysis between the impact of PAD and/or CVD and type of ACS (STE/NSTE) was performed.

All statistical analyses were performed using Stata/SE 12.1 for Windows (StataCorp LP, College Station, Texas, USA).

A p value < 0.05 (2-sided) was considered significant.

3. Results

3.1. Study population

The overall population consisted of 2046 patients with a confirmed final diagnosis of ACS. Mean age was 72 years and 64.5% were male; 896 (44%) patients had STE-ACS and 1150 (56%) NSTE-ACS.

Overall, 98 patients (5%) had CVD alone, PAD alone was present in 282 (14%), and 30 patients (1.5%) had both CVD and PAD. The prevalence of CVD was similar in STE-ACS and NSTE-ACS patients (5.1% vs. 4.5, p = 0.59), whereas PAD and CVD + PAD were more common in the latter group (6.7% vs. 19.3%, p = 0.0001 and 0.8% vs. 2%, p = 0.037 respectively).

Table 1 reports the baseline characteristics and clinical presentation of the overall population and according to the presence of CVD and/or PAD. Patients with polyvascular disease (CVD only, PAD only, CVD + PAD) were older, more often male, more frequently had a history of hypertension and diabetes, CKD and COPD. They also had a more frequent history of MI and/or revascularization. Patients with no CVD or PAD were more likely to have a family history of CAD or smoking. Killip class at presentation was more advanced in patients with CVD and/or PAD and atrial fibrillation was more frequent, particularly in patients with CVD.