Effectiveness of combined therapy with angiotensin-converting enzyme inhibitors and statins in reducing mortality in diabetic patients with critical limb ischemia: An observational study

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ABSTRACT

Aims: To investigate the effect of combined treatment with angiotensin-converting enzyme inhibitors (ACE) and statins on mortality in diabetic patients with critical limb ischemia (CLI).

Methods: Prospective observational study of 553 consecutive diabetic patients admitted because of CLI followed for a mean of 2.2 years. All patients underwent peripheral revascularization and antithrombotic therapy was prescribed or continued and therapy with statin and ACE was recorded. Mortality from any cause was assessed and Kaplan–Meier analyses were performed to compare the relationship between survival and recorded variables.

Results: One hundred thirty-nine patients did not have therapy with statin or an ACE, 78 had therapy with statin without ACE, 164 had therapy with ACE without statin and 172 patients had therapy with both statin and ACE. One hundred thirty-six patients died, 45/139 with neither statin nor ACE, 40/164 with ACE only, 26/78 with statin only, and 25/172 with both statin and ACE. Multivariate analysis confirmed the independent role of age, history of stroke, renal insufficiency and dialysis. Combined treatment with ACE and statin appeared to have a protective role.

Conclusions: In patients with diabetes and CLI mortality after two years is high. Life expectancy was better in patients receiving combined therapy with ACE and statin but not with therapy with only a statin or an ACE.

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1. Introduction

Critical limb ischemia (CLI) is a severe manifestation of peripheral atherosclerosis that puts at high risk survival of the limb and life [1–3]. Peripheral revascularization is the major goal to salvage the limb and risk-factor modification is the major goal to reduce mortality [4,5].

Although there have been studies on the amelioration of mortality risk in patients with PAD they are rarely performed in patients specifically with CLI [6–9]. Our Institute is a tertiary diabetic foot centre where patients are referred from other hospitals because of a foot lesion and once healed, they are returned to their original centre for ongoing care. These patients, however, remained in contact with our Centre for a regular update of their foot problem and their general state of health.

In October, 2008 we obtained authorization from the Ethics Committee of our Institute to start a prospective observational study on the adequacy of the treatment of glycaemia, with antidiabetic agents, of arterial hypertension with angiotensin-converting enzyme inhibitors (ACE) and of hyperlipidaemia with statins in diabetic patients admitted because of CLI to our foot centre. The study was conducted in the years 2009–2010 and was completed by June 30, 2012. This paper reports the results.

2. Methods

2.1. Study design

We performed a prospective study of the prognostic value of ACE-inibihors and statins therapy in a cohort of consecutive diabetic patients with critical limb ischemia who were referred to the Diabetic Foot Center of Multimedica hospital in Milan, Italy. The study was approved by the ethical committee of our Institution.

2.2. Protocol

All diabetic patients referred to our diabetic foot centre for foot lesions were assessed for the presence of CLI using the TASC II criteria [10]. CLI was detected if transcutaneous oxygen tension (TcPO$_2$; TCM^{TM}3, Radiometer GMBH, Copenhagen, Denmark) at the dorsum of the foot was < 30 mmHg and ankle pressure < 70 mmHg when measurable (absent foot pulses or non-compressible foot arteries were due to medial calcification) with a continuous wave Doppler instrument (DIADOP 50, Mediland s.r.l. Varedo, Milan, Italy). All patients with CLI were referred for an angiographic study and peripheral angioplasty or bypass graft was performed. After revascularization antithrombotic therapy with ticlopidine 500 mg plus acetylsalicic acid 100 mg was prescribed. In patients with previous anticoagulant or clopidrogel therapy the therapy was continued.

For each patient, all of the following variables were recorded: gender and age; duration and treatment of diabetes; history of diabetic retinopathy, cardiac disease, stroke, arterial hypertension and prior peripheral revascularization; current smoking, dialysis treatment.

The clinical laboratory variables considered in this study were: blood glucose level on admission, glycated hemoglobin (HbA$_{1c}$, mmol/mol), serum creatinine value (mg/dl, Jaffe, Roche, Milan, Italy), arterial systolic and diastolic blood pressure, low-density lipoprotein cholesterol (LDL, colorimetry, Boehringer Mannheim, Monza, Italy), high-density lipoprotein cholesterol (HDL, Polyethylene Glycol 6000, reagent made in laboratory) and triglycerides (colorimetry, Bayer, Milan, Italy).

Therapy with angiotensin-converting enzyme inhibitors (ACE) and statin at the time of admission was recorded and this therapy was not during follow up. The term ''ACE'' therapy included treatment with angiotensin-converting enzyme inhibitors or with angiotensin receptor blockers. The number of patients treated with both these drugs was very small (seven patients) and this did not allow stratification. Patients were considered to have been on statin therapy when taking any of these classes of drugs regardless of the type and dosage but the variation in agent used prevented stratification within this group.

2.3. Follow-up

After hospital discharge all the patients with a foot ulcer were examined at our centre until complete ulcer healing occurred and every two months thereafter. The vital status of all 553 patients was determined at the end of follow-up. The cause of death was established by communication with the patients' primary care physicians and diabetologists and review of medical records for patients who died while hospitalized.

2.4. Statistical analysis

We considered the consecutive series of patients as a cohort study and reported the descriptive statistics as average values and standard deviation for the continuous variables and as percentages and contingency tables for the qualitative and discrete variables. The 95% level were determined and 5% level used to test the null hypotheses. The time from the date of admission with CLI to death was studied by applying the Kaplan–Meier approach and the product/limit curve was built. The comparison between the survival curves was made by the log-rank test for equality of survivors function. The mean differences of the variables measured in studied groups of patients were compared by the analysis of variance (ANOVA). The relationship between the recorded variables and survival was evaluated by multiple logistic regression analysis and data were reported with odds ratio (OR) and 95% confidence interval (CI). Stata 10.0 (Statistics/Data Analysis, Stata Corporation, 4905 Lakeway Drive, College Station, TX, USA) was used for calculations.

3. Results

In the period 1 January 2009–31 December 2010, 554 diabetic patients were admitted to our diabetic foot centre because of chronic critical limb ischemia. A total of 553 (99.8%) patients were followed to June 30, 2012 with a mean follow-up of