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Effects of successful percutaneous lower extremity revascularization on cardiovascular outcome in patients with peripheral arterial disease

Giuseppe Giugliano [a], Luigi Di Serafino [a], Cinzia Perrino [a], Vittorio Schiano [a], Eugenio Laurenzano [a], Salvatore Cassese [a], Mario De Laurentis [a], Gabriele Giacomo Schiattarella [a], Linda Brevetti [a], Anna Sannino [a], Giuseppe Gargiulo [a], Anna Franzone [a], Ciro Indolfi [b], Federico Piscione [a], Bruno Trimarco [a], Giovanni Esposito [a,*]

[a] Division of Cardiology, Department of Clinical Medicine, Cardiovascular and Immunological Sciences, Federico II University, Naples, Italy
[b] Division of Cardiology, Magna Graecia University, Catanzaro, Italy

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ABSTRACT

Background: Lower extremity peripheral arterial disease (LE-PAD) reduces walking capacity and is associated with an increased cardiovascular risk. Endovascular revascularization of LE-PAD improves walking performance and quality of life. In the present study, we determined whether successful lower limbs revascularization also impacts cardiovascular outcome in LE-PAD patients.

Methods: 479 consecutive LE-PAD patients at stage II of Fontaine's classification, with ankle/brachial index ≤0.90 and one or more stenosis >50% in at least one leg artery, were enrolled in the study. According to the Trans-Atlantic Inter Society Consensus II recommendations, 264 (55.1%) underwent percutaneous lower extremity angioplasty (PTA group), while 215 (44.9%) were managed with conservative therapy (MT group). The incidence of major cardiovascular events (including cardiovascular death, myocardial infarction, ischemic stroke, coronary and carotid revascularizations) was prospectively analyzed by Kaplan–Meier curves. Crude and adjusted HRs (95% CI) of developing a cardiovascular event were calculated by Cox analysis.

Results: No baseline differences were observed among the groups, except for a lower maximum walking distance in the PTA group. During a median follow-up of 21 months (12.0–29.0), the incidence of cardiovascular events was markedly lower in PTA compared to MT patients (6.4% vs. 16.3%; p = 0.003), and patients in the MT group showed a 4.1-fold increased cardiovascular risk compared to patients in the PTA group, after adjustment for potential confounders (95% CI 1.22–13.57, p = 0.023).

Conclusions: This study shows that successful revascularization of LE-PAD patients affected by intermittent claudication, in addition to improving functional status, reduces the occurrence of future major cardiovascular events.

1. Introduction

Lower extremity peripheral arterial disease (LE-PAD) is a common clinical manifestation of atherosclerosis, affecting ~20% of the population aged 55 and older [1], and represents a major cause of acute and chronic illness with decrement in functional capacity and quality of life up to limb amputation [2]. The major clinical relevance of this condition is principally represented by its association with a high risk of developing athero-thrombotic events, mainly myocardial infarction and stroke [3,4]. Indeed, large epidemiologic studies have shown that LE-PAD patients have a three-fold to six-fold higher risk of a fatal cardiovascular event than those with similar risk factors but without lower extremity ischemia [3,5,6].

Numerous strategies, both pharmacological and invasive, have been developed to reduce the enormous toll of the disease [7]. With respect to functional disability, in LE-PAD patients with limited exercise performance and walking capacity, limb revascularization procedures represent the first-choice therapeutic strategy when exercise and/or drug therapy fail to improve symptoms [2,3,7–10]. Both open repair/bypass surgery and percutaneous trans-luminal angioplasty (PTA) are effective revascularization approaches, and the choice is based upon the number, length and localization of the stenosis/occlusion, surgery risk score and patient preference [2].

While PTA of the lower limbs is widely recognized to be effective in improving functional status and quality of life in claudicants [8,10], no data are currently available regarding its impact on cardiovascular outcome in this high-risk population. Interestingly, PTA in LE-PAD entails an increase of ankle/brachial index (ABI) [11], the most consistent and

* Corresponding author at: Division of Cardiology, Department of Clinical Medicine, Cardiovascular and Immunological Sciences, University of Naples "Federico II", Via Pansini, 5, 80131 Naples, Italy. Tel.: +39 081 746 2216; fax: +39 081 746 2223.
E-mail address: espogiov@unina.it (G. Esposito).

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powerful prognostic indicator in these patients [12]. Moreover, PTA in LE-PAD patients improves endothelial dysfunction [13], which plays a key role in the pathophysiology and natural history of the disease [14], and reduces the ischemia–reperfusion injury which promotes systemic inflammation [15]. Thus, in this study we hypothesized that effective endovascular revascularization by PTA might reduce cardiovascular events compared to medical therapy in LE-PAD patients. To test this, we conducted a prospective study aimed at evaluating whether the correction of leg ischemia by endovascular revascularization of lower extremity arteries is associated with a reduction in the cardiovascular risk in a homogeneous cohort of LE-PAD patients with intermittent claudication.

2. Materials and methods

2.1. Study population

Consecutive patients referred to our vascular laboratory for suspected intermittent claudication from June 2007 through June 2009 (n = 678) were screened for enrollment in this prospective, single-institution study. Criteria for study entry were all of the following: 1) LE-PAD at stage II of Fontaine's classification (intermittent claudication); 2) ABI ≤0.90; and 3) one or more stenosis >50% in at least one leg artery at B-mode ultrasound. All patients underwent history and clinical examination to document the presence of coronary artery disease (CAD) and cerebrovascular disease and, among patients without history of CAD, to identify those with indication to further noninvasive/invasive diagnostic testing. Exclusion criteria were: 1) critical limb ischemia; 2) previous lower limb revascularization; 3) recent acute coronary or cerebrovascular ischemic events (6 months); 4) recent coronary or carotid revascularization procedures (6 months); 5) abnormal myocardial ischemia stress test at enrollment; 6) de-compensated heart failure; and 7) malignant neoplasia or significant hepatic, renal, or inflammatory disease.

According to the inclusion/exclusion criteria, 544 consecutive LE-PAD patients were selected. All patients were treated with maximal medical therapy and encouraged to engage regular physical exercise for at least 3 months. After this time, patients complaining a severe disability caused by claudication, unable to perform normal work or with very serious impairment of daily life activities despite maximal medical therapy and regular physical exercise (n = 329) were selected for angiography and eventually revascularization, while the remaining 215 patients were managed with medical therapy only (MT group). Among the patients initially selected for revascularization, 15 patients refused to undergo angiography, and were excluded from the study. Based on the angiograms, 34 patients displaying TASC D lesions were excluded from the study, while 280 underwent endovascular revascularization. Following PTA, only 264 patients displayed a successful angiographic result (16 patients showed a residual stenosis >30%), and therefore were included in the study (PTA group).

All patients were treated according to the most recent guidelines [2,9], and response to therapy (including side effects) was evaluated at regular clinical evaluations during follow-up; when necessary, therapeutic adjustments were performed on these occasions. All women were postmenopausal, and none was receiving hormone replacement therapy. All participants gave written informed consent to the study, which was approved by our institutional ethics committee.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Clinical assessment

In each patient, clinical history and risk factors were assessed at first visit. Smokers included current and former smokers. Hypertension was diagnosed if systolic arterial pressure exceeded 140 mm Hg and/or diastolic arterial pressure exceeded 90 mm Hg on repeated measurements, or if the patient used antihypertensive drugs. Hypercholesterolemia was diagnosed if plasma total cholesterol exceeded 200 mg/dl, plasma low-density lipoprotein cholesterol exceeded 130 mg/dl, or if the patient used lipid-lowering drugs because of a history of hypercholesterolemia. Diabetes mellitus was diagnosed if plasma fasting glucose exceeded 126 mg/dl or if the patient used hypoglycemic agents. Hospital records documented previous cardiovascular events.

2.3. ABI and maximum walking distance assessment

ABI was measured at the first visit after participants had rested supine for 5 min. The systolic blood pressure in both brachial arteries and the ankle systolic blood pressure for the right and left posterior tibial and dorsalis pedis arteries were measured using a Doppler probe. The ABI for each leg was then determined using the higher of the two readings from either the posterior tibial or dorsalis pedis arteries, and the higher of the two brachial readings. The lower ABI of the two legs was used for diagnostic purposes and as predictor of future cardiovascular events. Maximum walking distance (MWD) was tested by treadmill (speed 3 km/h, inclination 10%) at the first visit.

2.4. Inflammatory markers

At the first visit, leukocyte count was measured by the Bayer H*2 hematology analyzer in all patients enrolled in the study. In 30 patients of both the PTA and MT groups, C-reactive protein (CRP) and myeloperoxidase (MPOx) serum levels were measured at the first visit and, only in the PTA group, 3 months after successful PTA. CRP was determined using a high sensitivity assay (Dade Behring Diagnostics). MPOx was measured by ELISA according to procedures recommended by the manufacturer (Calbiochem). After blind assessment of the inflammatory markers, test results were merged with the database.

2.5. Endovascular procedure

PTA was performed after diagnostic angiography and intra-venous injection of 70 U/kg of unfractionated heparin. Bailout nitinol self-expanding stent implantation was performed when a suboptimal angiographic result was obtained. Successful angioplasty was defined by a final angiogram with residual stenosis <30%. When possible, baseline medications remained unchanged during follow-up, except for the addition of clopidogrel for at least 1 month in patients with stent implantation.

2.6. Assessment of cardiovascular events

Patients underwent regular follow-up clinical examinations at our institution at 3-month intervals. The occurrence of cardiovascular death, myocardial infarction, ischemic stroke and coronary or carotid revascularizations was prospectively assessed. Cardiovascular deaths comprised fatal myocardial infarction, fatal stroke, sudden death, and death secondary to arrhythmia or refractory heart failure. The minimum follow-up period was 6 months. Medical records and death certificates of all patients who had an event were obtained and validated by a physician unaware of the patient's peripheral treatment. For patients who had more than 1 event, only the first was considered in the analysis.

2.7. Statistical analysis

Statistical analyses were performed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). Variables were expressed as absolute numbers and percentage or mean ± SD, with the exception of leukocyte count, CRP and MPOx, which were expressed as median and inter-quartile range because of their skewed distribution. Comparisons were made by *t*-test for unpaired samples, χ^2 test, or Mann–Whitney *U* test, as appropriate. Cumulative event rates in the PTA vs. MT group were estimated by Kaplan–Meier curves and probability values by log-rank test.

Cox proportional hazard analyses were performed to verify if endovascular treatment was associated with a lower incidence of future cardiovascular events. The following covariates, known to be potential contributors of cardiovascular risk, were included in the adjusted model: age, sex, smoking, diabetes mellitus, hypercholesterolemia, hypertension, previous MI or stroke, baseline ABI, baseline maximum walking distance, and leukocyte count. A second adjusted model including cardiovascular drugs known to affect cardiovascular outcome in LE-PAD was created to evaluate whether differences in drug assumption between the two groups may influence outcome.

Next, to control for possible systematic differences in the groups of patients managed by endovascular or medical therapy, which would bias the comparison of cardiovascular outcome, a logistic regression model with endovascular treatment as the dependent variable was developed [16]. This "propensity" model [17] included all the patient specific demographic and clinical data detailed above. The propensity model was developed using the entire population, and yielded for each patient the estimated probability of being treated with endovascular therapy, expressed as a continuous variable between 0 and 1. This score was then included in the Cox proportional hazard models as an additional independent variable to explicitly adjust for selection bias.

All statistical tests were two-sided. For all tests, a p-value<0.05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

Table 1 reports the baseline characteristics of the patients in the PTA and MT groups. Not surprisingly, the MT group was characterized by a better functional capacity (maximum walking distance: 403.0 ± 532.1 vs. 123.6 ± 306.5 m, p<0.001). Conversely, no difference between the two groups was observed with respect to the prevalence of classic cardiovascular risk factors, cardiovascular co-morbidity, baseline ABI, and use of cardiovascular drugs.