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Regular Article

Cilostazol and outcome in outpatients with peripheral artery disease

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ABSTRACT

Background: Cilostazol increases the walking distance in patients with intermittent claudication, but there is scarce evidence of any effect on the risk for subsequent ischemic events, bleeding or death.
Patients and Methods: We used data from the FRENA Registry to compare the clinical outcome in stable outpatients with intermittent claudication, according to the use of cilostazol.
Results: As of January 2013, 1,317 patients with intermittent claudication were recruited in FRENA, of whom 191 (14.5%) received cilostazol. Over a mean follow-up of 18 months, 39 patients developed myocardial infarction, 23 ischemic stroke, 20 underwent limb amputation, 15 had major bleeding and 70 died. There were no significant differences in the rate of subsequent ischemic events, major bleeding or death between patients receiving or not receiving cilostazol. On multivariate analysis, the use of cilostazol had no influence on the risk for subsequent myocardial infarction (hazard ratio [HR]: 0.97; 95% CI: 0.33-20.8), ischemic stroke (HR: 1.46; 95% CI: 0.48-4.43), limb amputation (HR: 0.34; 95% CI: 0.04-20.6), major bleeding (HR: 1.52; 95% CI: 0.33-7.09) or death (HR: 0.90; 95% CI: 0.40-20.0).
Conclusions: In stable outpatients with intermittent claudication, the use of cilostazol was not associated with increased rates of subsequent ischemic events, major bleeding or death.

Introduction

Cilostazol is a phosphodiesterase III inhibitor that is primarily used for relief of intermittent claudication in patients with peripheral artery disease due to its antiplatelet and vasodilatation function [1,2]. A number of randomized clinical trials (and two pooled analyses) demonstrated that patients with intermittent claudication receiving cilostazol experienced a significant improvement in maximal walking distance compared with those receiving placebo [3–6], but there is scarce evidence of any effect of cilostazol on the risk for subsequent myocardial infarction, stroke or death. Moreover, there is scarce evidence either of any effect of cilostazol on the risk of bleeding in patients who are already receiving antiplatelets, anticoagulants or both.

The Factores de Riesgo y ENfermedad Arterial (FRENA) Registry was initiated in March 2003 to prospectively record the current clinical management and outcome of patients with arterial disease in several Spanish centers. It is an ongoing, multicenter, observational registry of consecutive patients designed to gather and analyze data on treatment patterns and outcomes in stable outpatients with symptomatic ischemic disease of the heart, brain, and/or major peripheral arteries. Data from this registry have been used to assess the influence of body weight, smoking habit, alcohol consumption or glucose control on outcome [7–11]. The aim of the current study was to compare the clinical outcome in stable outpatients with symptomatic intermittent claudication according to the use of cilostazol.

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Patients and Methods

Inclusion Criteria

Participating centers in the FRENA registry prospectively enrolled consecutive outpatients with symptomatic artery disease with at least one recent (<3 months prior to enrollment) episode of coronary (manifesting as angina or acute coronary syndrome); cerebrovascular (manifesting as transient ischemic attack or ischemic stroke); or peripheral artery disease (either intermittent claudication with an ankle-brachial index <0.9, or previous vascular intervention or limb amputation). Patients were excluded if they would not be available for follow-up or if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients provided written or oral consent prior to their participation in the registry, according to the requirements of the ethics committee within each hospital.

Study Design

For this study, only patients with intermittent claudication were considered. The Fontaine classification was used for categorization [12]. The primary outcome was the incidence of subsequent ischemic events (myocardial infarction [MI], ischemic stroke or limb amputation), major bleeding or death during the study period. All events were adjudicated by the attending physicians. In case of doubt, the event was adjudicated by the FRENA Adjudication Committee.

Definitions

Subsequent MI was defined as the presence of typical chest pain in combination with a transient increase of creatine kinase-MB or troponin and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression) [13]. Ischemic stroke was diagnosed if the patient had an appropriate clinical event not resolving completely within 24 hours, and had an acute cerebrovascular lesion on brain CT or MRI. Bleeding complications were classified as 'major' if they were overt and required a transfusion of 2 units of blood or more, or if they were retroperitoneal, spinal or intracranial, or when they were fatal. A patient was classified as having diabetes when there was a clinical history of diabetes or when they were taking insulin or oral antidiabetic agents. Patients were classified as having hypertension when there was a clinical history of hypertension or when they were taking antihypertensive medications. Creatinine clearance was calculated according to the Cockcroft and Gault formula [14].

Follow-Up

A detailed history was performed on all patients at study entry (<3 months after an acute ischemic episode). Co-morbid conditions were characterized, including a history of coronary, cerebrovascular or peripheral artery disease, diabetes, hypertension, hyperlipidemia, chronic lung disease, heart failure, cancer, smoking status, and alcohol consumption. Pain free walking distance in patients with Fontaine stage II was assessed by asking the patient at each visit. Then, physical examination was performed comprising weight, height, heart rate and blood pressure levels on standard conditions, after 5 min of rest. An electrocardiogram was also recorded. After the initial visit, patients were followed-up at 4-month intervals in the outpatient clinic. At these visits, any change in medical history and data from physical examination was recorded, with special attention to lifestyle habits; blood pressure measurement; laboratory tests; the type, dose, and duration of treatment received, and clinical outcome. Physicians were allowed to use any and all appropriate medications, as dictated by their usual clinical practice patterns.

Most outcomes (including the causes of death) were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Data Collection

The attending physicians ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating centre through a secure website. Patient identities remain confidential because they were identified by a unique number assigned by the study coordinating centre, which was responsible for all data management. Data quality was regularly monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality was also monitored by periodic visits to participating hospitals, by contract research organizations, which compared the medical records with the data in the web. A data audit was performed at periodic intervals.

Statistical Analysis

Categorical variables were compared using the chi-square test (two-sided) and Fisher´s Exact Test (two-sided). Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated, and a p value <0.05 was considered to be statistically significant. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the rate ratio [15]. The association between the use of cilostazol and outcome was assessed using the Cox proportional hazards regression model, estimated by a forward step method. All variables achieving a significance level of ≤0.1 in univariate analysis were considered for inclusion in the logistic regression model. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS, Inc).

Results

As of September 2013, 1,317 patients with intermittent claudication were recruited in FRENA, of whom 191 (14.5%) received cilostazol. Patients receiving cilostazol were more likely men, current smokers and were less likely to have prior coronary heart disease or heart failure than those not receiving cilostazol (Table 1). Moreover, patients receiving cilostazol had lower levels of creatinine clearance, total cholesterol or triglycerides than those not receiving the drug. Finally, patients receiving cilostazol were less likely to receive anticoagulants concomitantly, but concomitant use of cilostazol and antiplatelet drugs was found in 93% of patients.

Over a mean follow-up of 18 months, 39 patients developed myocardial infarction, 23 ischemic stroke, 20 underwent limb amputation, 15 had major bleeding and 70 died (Table 2). There were no significant differences in the rate of subsequent ischemic events, major bleeding or death between patients receiving or not receiving cilostazol, but when only considering patients with Fontaine stage IIa, patients on cilostazol had a lower mortality rate (0.51 vs. 3.44 deaths per 100 patient-years). Moreover, no patient with Fontaine stage IIb receiving cilostazol underwent limb amputation, compared with 16 patients not receiving the drug (2.93 events per 100 patient-years), as shown in Table 2. As to the causes of death, there were no differences either between patients receiving or not receiving cilostazol (Table 3).

On multivariate analysis, the use of cilostazol had no influence on the risk for subsequent myocardial infarction (hazard ratio [HR]: 0.97; 95% CI: 0.33-20.8), ischemic stroke (HR: 1.46; 95% CI: 0.48-4.43), limb amputation (HR: 0.34; 95% CI: 0.04-20.6), major bleeding (HR: 1.52; 95% CI: 0.33-7.09) or death (HR: 0.90; 95% CI: 0.40-20.0), as shown in Table 4.