International Journal of Cardiology 201 (2015) 561–567

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Prognostic impact of high residual platelet reactivity after chronic total occlusion percutaneous coronary intervention in patients with diabetes mellitus☆

Renato Valenti [a], Giulia Cantini [a], Rossella Marcucci [a,b,c], Marco Marrani [a], Angela Migliorini [a], Nazario Carrabba [a], Vincenzo Comito [a], Ruben Vergara [a], Giampaolo Cerisano [a], Guido Parodi [a,b], Rosanna Abbate [a,b,c], Anna Maria Gori [a,c,d], Gian Franco Gensini [a,b,c,d], David Antoniucci [a,*]

[a] Department of Heart and Vessels, Careggi Hospital, Florence, Italy
[b] Post-graduate School in Cardiology, University of Florence, Italy
[c] Department of Clinical and Experimental Medicine, University of Florence, Italy
[d] Don Carlo Gnocchi Foundation, Centro S. Maria agli Ulivi, Onlus IRCCS, Florence, Italy

ARTICLE INFO

Article history:
Received 4 February 2015
Received in revised form 6 April 2015
Accepted 8 April 2015
Available online 10 April 2015

Keywords:
Coronary occlusion
Diabetes mellitus
Platelet reactivity

ABSTRACT

Background: The study sought to determine the impact of high residual platelet reactivity (HRPR) on long-term cardiac mortality in diabetic patients treated with PCI for CTO. No data exist about the impact of HRPR after 600 mg clopidogrel loading on long-term clinical outcome in patients with diabetes mellitus and treated with percutaneous coronary angioplasty (PCI) for chronic total occlusion (CTO).
Methods: From the Florence CTO-PCI registry, we identified consecutive diabetic patients with available in vitro platelet reactivity assessment by light transmittance aggregometry after a loading dose of 600 mg of clopidogrel. HRPR was defined as residual platelet aggregation by 10 μmol/L ADP test ≥70%. The primary end point of the study was long-term cardiac mortality.
Results: Two-hundred and three diabetic patients underwent CTO-PCI. The incidence of HRPR was 23%. The 3-year cardiac survival was lower in the HRPR group than the low residual platelet reactivity (LRPR) group (70 ± 7% and 92 ± 3%, respectively; $p = 0.001$). Within the oral antidiabetic patients there were no significant differences in long-term survival between HRPR and LRPR groups. Conversely, the association of insulin therapy and HRPR was related to a dramatic decrease in survival compared to the LRPR group (34 ± 14% vs. 89 ± 4%; $p < 0.001$). At multivariable analysis insulin therapy (HR 4.31; $p = 0.001$) and HRPR (HR 3.26; $p = 0.004$) were significantly related to long-term mortality, while completeness of revascularization was inversely related to cardiac mortality (HR 0.40; $p = 0.029$).
Conclusion: HRPR is a strong marker of increased risk of cardiac death in patients with DM who underwent PCI for CTO.

1. Introduction

Studies have shown a reduced in vitro responsiveness to standard antiplatelet therapy in patients with diabetes mellitus (DM) [1–3]. DM is also frequently associated with coronary multivessel disease and chronic total occlusion (CTO) [4–6]. CTO is a predictor of incomplete coronary revascularization [7–9], while successful CTO percutaneous coronary intervention (PCI) and complete coronary revascularization provide a strong survival benefit [8–10]. Conversely, in patients with non-revascularized CTO, the presence of DM was associated with a higher risk of cardiac death [11]. High residual platelet reactivity (HRPR) on clopidogrel treatment is associated with a poor outcome in patients treated with PCI [12–26]. Indeed, the current guidelines [27,28] don't cover specific recommendations for the use of new antiplatelet therapy (prasugrel or ticagrelor) in the setting of stable coronary disease PCI, even in the high risk patients. This study sought to determine the clinical relevance of HRPR on clopidogrel treatment in the particular high risk setting of patients with diabetes mellitus who underwent non-urgent PCI for CTO.

2. Methods

From the Florence CTO-PCI registry [10,29,30] we retrospectively identified consecutive diabetic patients who underwent PCI for CTO,

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Division of Cardiology, Careggi Hospital, Viale Pieraccini 17, I-50134 Florence, Italy.
E-mail address: david.antoniucci@virgilio.it (D. Antoniucci).

http://dx.doi.org/10.1016/j.ijcard.2015.04.052
0167-5273/

and who received platelet reactivity assessment by light transmittance aggregometry (LTA) after a loading dose of 600 mg of clopidogrel. Patients were divided according to residual platelet reactivity after clopidogrel loading in HRPR group and low residual platelet reactivity (LRPR) group. All patients included in the study had a previous diagnosis of DM (according to the criteria of the American Diabetes Association) [31] and were divided in 2 subgroups according to antidiabetic therapy: insulin therapy and oral antidiabetic agents alone. Patients who received new antiplatelet drugs (prasugrel or ticagrelor) for acute coronary syndrome from 2011 were excluded from the study.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the study was thus approved by the institutional review committee; all patients gave informed written consent to intervention and to the study.

CTO was defined as a coronary obstruction with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 and an estimated duration of >3 months. The indication for the percutaneous treatment of CTO was the demonstration of viable myocardium in the territory of the occluded vessel by echographic or scintigraphic provocative tests, whereas no CTO angiographic characteristic was considered as an absolute contraindication to PCI attempt. Patients underwent PCI instead of coronary surgery because of high surgical risk or patient's preference. Most CTOs were attempted using the antegrade approach and dedicated coronary wires and devices. All successfully recanalized CTO vessels were treated with drug-eluting stents (DES). Procedural success was defined as a final diameter of stenosis <30% with a TIMI flow grade 3 of all CTO and non-CTO treated lesions without death, non Q-wave or Q-wave myocardial infarction (MI), or emergency coronary surgery.

Platelet responsiveness to clopidogrel was assessed by light transmittance aggregometry (APACT4, Helena Laboratories, Milan, Italy) with the use of ADP as agonist. Blood samples anticoagulated with 0.129 mol/L sodium citrate (ratio 9:1) were obtained 12 to 18 h after 600-mg clopidogrel loading and before PCI. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 200 g, was stimulated with 10 μmol/L of ADP. The 100% line was set with the use of platelet-poor plasma, and the 0 baseline was established with platelet-rich plasma (adjusted from 18×10^9/L up to 30×10^9/L). Platelet aggregation (according to the Born method) was evaluated with consideration of the maximal percentage of platelet aggregation in response to stimulus. Coefficient of variation within day: 3.1%; coefficient of variation day to day: 2.2% [32]. Patients with platelet aggregation by 10 μmol ADP ≥ 90th percentile of controls were considered abnormal. HRPR was defined as residual platelet aggregation by ADP ≥ 70% [17,26].

All patients had scheduled clinical follow-up at 6 and at 12 months and yearly thereafter. Patients with CTO-PCI success had scheduled angiographic follow-up at 6 to 9 months. Unscheduled angiography was allowed on the basis of clinical evaluation. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries was entered into the prospective database.

The primary end point of the study was long-term cardiac mortality. All deaths were considered cardiac unless otherwise documented [33]. All other outcome end points were exploratory.

2.1. Statistical methods

Discrete data are summarized as frequencies, whereas continuous data as mean ± SD or median (interquartile range), as appropriate. The chi-square or Fisher exact test when appropriate were used for comparison of categorical variables, and the unpaired 2-tailed Student *t* test or Mann–Whitney rank sum test was used to test differences among continuous variables. Survival curves were generated using the Kaplan–Meier method, and the difference between groups was assessed by a log-rank test. The multivariable analysis to evaluate the independent contribution of clinical, angiographic, and procedural variables to the primary end points was performed by a forward stepwise Cox proportional hazards model. The variables entered into the model were age (years), male gender, insulin therapy, HRPR ≥ 70%, hypercholesterolemia, hypertension, previous myocardial infarction, acute coronary syndrome, previous coronary surgery, creatinine >250 μmol/L, 3-vessel disease, left ventricular ejection fraction (LVEF) <0.40, successful CTO-PCI, complete coronary revascularization, year of index procedure. A Cox proportional hazards model was also used to test interaction among covariates. In order to minimize the bias due to the nonrandomized nature of the study, two models of propensity score analysis were performed using a logistic regression model from which the probability for the insulin therapy and for HRPR were calculated for each patient; variables entered into both propensity score models were: age (years), male gender, smokers, hypertension, hypercholesterolemia, previous myocardial infarction, acute coronary syndrome, creatinine >250 μmol/L, LVEF < 0.40, 3-vessel disease, and also HRPR for the propensity model of insulin therapy; and insulin therapy for the propensity model of HRPR. Model discrimination was assessed with the c-statistic and goodness-of-fit with Hosmer and Lemeshow test. Thereafter, Cox multivariable analyses were performed to adjust insulin therapy and HRPR for the propensity score.

Furthermore, the net reclassification improvement (NRI) analysis was performed to assess if platelet function testing (HRPR) increased the discriminative value of the model with established and validated predictors of adverse events.

A p value < 0.05 was considered significant. Analyses were performed using the software packages SPSS version 11.5 (SPSS Inc., Chicago, Illinois) and STATA 10.1 (Stata Corporation, College Station, TX).

3. Results

From 2003 to 2012, 1142 consecutive patients underwent CTO-PCI, with a PCI success rate of 78%. Diabetic patients were 293 (26%), and PCI success rates were identical in patients with or without DM (78%). From 2005 routine assessment of in vitro platelet reactivity after a 600-mg loading dose of clopidogrel by LTA was performed and the results were available for 203 patients.

Baseline clinical characteristics of the 203 patients are shown in Table 1. Mean age was 68 ± 9 years, with 25% of patients aged ≥75 years. Out of the 203 patients, 75 (37%) had insulin-requiring DM, while the 128 (63%) remaining patients were in therapy with oral antidiabetic agents. Multivessel disease was present in 87% of patients, and 3-vessel disease in 55%. Insulin-requiring patients had lower LVEF on admission (37 ± 14% vs. 45 ± 13%; p < 0.001) and a higher prevalence of 3-vessel disease (64% vs. 49%; p = 0.026) compared to patients treated with oral antidiabetic agents alone. HRPR after clopidogrel loading was revealed in 47 patients (23%) and the incidence of HRPR was similar in patients treated with insulin or oral antidiabetic agents alone. Patients with HRPR were older (mean age: 71 ± 9 vs. 67 ± 9 years; p = 0.014), and had a more frequent history of coronary surgery (23% vs. 11%; p = 0.029) compared to those with LRPR.

Procedural characteristics are summarized in Table 2. CTO-PCI was successful in 80% of the attempted lesions, and a complete coronary revascularization by PCI was achieved in 63% of patients. Multivessel PCI was performed in 68% of patients. There were no significant differences in the rates of successful CTO-PCI with regard to the type of antidiabetic treatment (83% in the insulin-treated patients, and 78% in the oral antidiabetic agents alone) and to the residual platelet reactivity (80% in the LRPR group, and 79% in the HRPR group).

Patients had a median follow-up of 36 months (IQ range 14–51 months) and all patients had a clinical follow-up of at least 1 year. One-year clinical outcomes are summarized in Table 3. The 1-year cardiac mortality rate was 6.4%: 8 patients died of refractory congestive heart failure, while the other 5 cardiac deaths were due to probable or possible stent thrombosis according to the Academic Research Consortium definition [33]. Nonfatal myocardial infarction occurred in 3