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High Maintenance Dosage of Clopidogrel is Associated with a Reduced Risk of Stent Thrombosis in Clopidogrel-Resistant Patients†

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Abstract

Background: Stent thrombosis remains an important complication after stent implantation, despite the use of dual antiplatelet therapy with aspirin (acetylsalicylic acid) and clopidogrel. Several studies have shown an increased risk of thrombotic events in patients with resistance to clopidogrel. Some recent studies have suggested that a higher clopidogrel maintenance dosage could enhance *ex vivo* platelet inhibition and thereby overcome resistance to clopidogrel.

Objectives: To investigate whether a higher clopidogrel maintenance dosage is associated with a reduced risk of stent thrombosis after percutaneous coronary intervention (PCI) in clopidogrel-resistant patients and to evaluate the frequency of hemorrhagic accidents that could be associated with a high clopidogrel maintenance dosage.

Methods: An observational study was performed in 52 consecutive clopidogrel-resistant patients (resistance defined according to adenosine diphosphate-induced platelet aggregation assessment) who underwent a PCI with stenting at a tertiary referral center (Toulouse University Hospital, France). All patients received a clopidogrel loading dose of 300 mg, then 32 patients received a clopidogrel maintenance dosage of 75 mg/day (patients admitted between 2004–5) and 20 patients received 150 mg/day (patients admitted in 2006). We compared the occurrence of definite stent thrombosis and hemorrhagic accidents between these two groups, using a regression model.

Results: Among the patients treated with clopidogrel 75 mg/day, 26 (81.3%) had definite stent thrombosis versus seven (35.0%) treated with 150 mg/day (adjusted relative risk [RR] 2.46; 95% CI 1.63, 2.76; p = 0.002). The risk of major adverse cardiac events (MACE) was also significantly lower in patients treated with 150 mg/day (adjusted RR 2.63; 95% CI 1.82, 2.82; p = 0.001). There was no significant difference between the two groups regarding hemorrhagic accidents.

Conclusion: Our data suggest that a high maintenance dosage of clopidogrel (150 mg/day) is associated with a reduced risk of definite stent thrombosis and MACE compared with a maintenance dosage of 75 mg/day. The frequency of hemorrhagic accidents was similar between the two groups, underlining a positive benefit-risk ratio of this strategy in clopidogrel-resistant patients. These findings deserve confirmation in a prospective, well conducted study.

† In memory of Professor Jacques Puel.

Background

In patients with symptomatic coronary artery disease, percutaneous coronary intervention (PCI) with stenting is effective in preventing further thrombotic events.[1,2] Despite dual antiplatelet therapy with aspirin (acetylsalicylic acid) and clopidogrel, major cardiovascular events occur in about 9% of patients and up to 4.7% of patients develop stent thrombosis, suggesting response variability or resistance to antiplatelet agents.[3,4] Stent thrombosis could be considered as a serious adverse drug reaction related to clopidogrel inefficacy.

Currently, clopidogrel is administered to the vast majority of patients without any systematic assessment of platelet inhibition. Several studies have shown an increased risk of post-PCI thrombotic events in patients with clopidogrel resistance.[5-10] A recent meta-analysis of 25 studies found an overall prevalence of 21% (95% CI 17%, 25%) of laboratory-defined clopidogrel resistance.[11] This meta-analysis also indicated that patients *ex vivo* labeled as being clopidogrel-resistant have an increased risk of stent thrombosis and other cardiovascular outcomes.

Recommendations from the scientific community suggest that an increase in the clopidogrel maintenance dose could prevent coronary events. Recent American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for PCI recommend platelet aggregation studies in patients in whom subacute thrombosis may be catastrophic or lethal (for example, in those with an unprotected left main coronary artery, a bifurcating left main coronary artery, or one remaining patent coronary vessel) and an increase in the clopidogrel maintenance dosage to 150 mg/day when antiplatelet resistance is suspected (Level of Evidence C).[12] Some studies have shown that a higher clopidogrel maintenance dosage is associated with reduced platelet reactivity and enhanced platelet inhibition in clopidogrel-resistant patients, which testifies to a dose-effect relationship.[13-16] In a recent observational study, Lemesle et al. showed for the first time an association between a 150 mg/day maintenance dosage of clopidogrel within the first 15 days after PCI and a decrease in the composite primary endpoint (death, myocardial infarction, and stent thrombosis).[17] No test of aggregation was performed in this study to determine patients' response to clopidogrel but it could be hypothesized that the benefit was confined to the clopidogrel-resistant patients. Assessing the benefit-risk profile of high clopidogrel maintenance dosages is necessary to define the best strategy for treating patients according to their response to clopidogrel.[18,19]

Thus, the goal of the present study was to investigate the association between a high maintenance dosage of clopidogrel in clopidogrel-resistant patients and the risk of stent thrombosis. We hypothesized that patients resistant to clopidogrel who receive the standard maintenance clopidogrel dosage (75 mg/day) are at increased risk for stent thrombosis and that consequently those who receive a high maintenance dosage (150 mg/day) will display less stent thrombosis. We also attempted to evaluate the hemorrhagic accidents that could be associated with a high maintenance dosage of clopidogrel.

Methods

Study Design and Population

An observational study was undertaken at Toulouse University Hospital, a tertiary referral center in the Midi-Pyrenees region in the Southwest of France, over 3 years (from 1 January 2004 to 31 December 2006). All consecutive patients with an adenosine diphosphate (ADP)-induced platelet aggregation assessment that defined them as 'clopidogrel resistant' were selected. Following identification of these patients, hospital medical records were consulted for complementary data. We included patients who underwent a PCI with stenting and were treated with double antiplatelet therapy comprising clopidogrel and aspirin after PCI. All patients included in the study received a clopidogrel loading dose of 300 mg. Double antiplatelet therapy with clopidogrel and aspirin was continued for at least 3 months after bare-metal stent implantation and for at least 6 months after drug-eluting stent implantation, and ideally for up to 12 months in patients who were not at high risk of bleeding, according to the French Society of Cardiology recommendations.[20] In our study we focused on events occurring while patients were still receiving dual antiplatelet therapy. Follow-up was for a minimum of 3 months and always until clopidogrel withdrawal. For follow-up data for patients attending our center, we used the patients' medical records. For patients followed up in another institution, we directly called the general practitioner or cardiologist involved to identify events.

ADP-induced platelet aggregation assessment is not a compulsory test before PCI.[12] Since 2004, the cardiologists of Toulouse University Hospital have been performing this test before PCI and 4–12 hours after a loading dose of clopidogrel in patients considered to be at very high cardiovascular risk referred to this center by other hospitals of the Midi-Pyrenees region. From 2004 to 2005, patients were treated with the standard maintenance clopidogrel dosage of 75 mg/day. Since 2006, clopidogrel-resistant patients without evident hemorrhagic risk received a clopidogrel maintenance dosage of

150 mg/day after PCI in the cardiology department of Toulouse University Hospital, according to the American College of Cardiology/American Heart Association guidelines for PCI.[12] Therefore, the resistant patients could be divided into two groups: patients who received a maintenance dosage of 75 mg/day and those who received 150 mg/day.

Our principal objective was to compare the rates of definite stent thrombosis (defined according to the Academic Research Consortium [ARC] designations of definite, probable, or possible)[21] in patients treated with a clopidogrel maintenance dosage of 75 mg/day (2004–5) and those treated with 150 mg/day (2006). We also compared clinical characteristics, concomitant medication, rate of major adverse cardiac events (MACE) and hemorrhagic accidents, and stent characteristics between the two groups.

Platelet Aggregation Test: Conventional Optical Platelet Aggregometry

Fasting blood samples were collected using a 19- or 22-gauge needle and citrated tubes containing sodium citrate solution (0.109 mol/L) as an anticoagulant, 4–12 hours after the clopidogrel loading dose. The blood-citrate mixture was centrifuged at 150 *g* for 10 minutes at 20°C. The resulting platelet-rich plasma was stimulated with 10 µmol of ADP, and aggregation was assessed using a Laser 4M Servibio Bioart (BIO ART SA/NV, Sint-Katelijne-Waver, Belgium) aggregometer. Aggregation was expressed as the maximal percentage change in light transmittance from baseline, using platelet-poor plasma as a reference. Resistant patients were defined as having a platelet aggregation of ≥40%, intermediate responders were characterized by a platelet aggregation ranging between 30% and 40% that was slowly reversible, and normal responders were defined as having a reversible platelet aggregation of <30% at 5 minutes aggregation amplitude.[22]

Statistical Analysis

Continuous variables were expressed as median, first quartile, and third quartile values. Comparisons between groups were performed using the Wilcoxon rank sum test. Categorical variables were expressed as counts and percentage frequencies with the 95% confidence interval and were compared using the chi-square (χ^2) test; if the frequency was <5%, the Fisher exact test was performed. Logistic regression with statistical analyses performed using STATA® software (StataCorp LP, College Station, TX, USA) was used to estimate the odds ratios (ORs) of definite stent thrombosis, MACE, and hemorrhagic accidents with the clopidogrel maintenance dosage. A regression model was used to adjust for conventional thrombosis and cardiovascular risk factors (diabetes mellitus, hypertension, active smoking, excess weight, dyslipidemia, family history of coronary artery disease, proton pump inhibitor use, left ventricular ejection fraction, and creatinine value). Results were presented as relative risks (RRs) by applying the method of Zhang and Yu[23] when the incidence of the outcome of interest was >10% in the 150 mg/day treatment group. The significance threshold was fixed at 5%.

Results

During the study period, 65 consecutive patients had an ADP-induced platelet aggregation test that defined them as resistant. We excluded seven patients who did not undergo a PCI with stenting, four who were not treated with clopidogrel, and two because of lack of data. Hence, 52 patients underwent a PCI with stenting and were treated with double antiplatelet therapy (clopidogrel plus aspirin). The mean follow-up duration was 159 ± 106 (7–365) days, with a median of 104 days. MACE occurred in 35 patients (67.3%): cardiovascular death in four patients, myocardial infarction in six patients, and urgent revascularization in 25 patients. Among the included patients, 33 (63.5%) developed a definite stent thrombosis.

Comparison of the 32 patients treated with a clopidogrel maintenance dosage of 75 mg/day and the 20 patients who received 150 mg/day showed that the two treatment groups were approximately similar regarding baseline clinical characteristics. However, patients treated with clopidogrel 75 mg/day had a slightly higher body mass index, a greater incidence of diabetes, and a higher incidence of excess weight (table I). Some baseline angiographic characteristics differed between the two groups: maximal stent diameter was greater ($p = 0.004$), the left main coronary artery as the treated vessel was more frequent ($p = 0.008$), and ST elevation acute coronary syndrome was more frequent ($p = 0.008$) in the clopidogrel 150 mg/day group, and non-ST elevation acute coronary syndrome ($p = 0.002$) was more frequent in the clopidogrel 75 mg/day group. Other angiographic characteristics such as the number, type, and length of the implanted stents were similar between the two groups (table II).

The regression model, which adjusted for conventional thrombosis and cardiovascular risk factors, showed the incidence of stent thrombosis (adjusted RR 2.46; 95% CI 1.63, 2.76; $p = 0.002$) and MACE (adjusted RR 2.63; 95% CI 1.82, 2.82; $p = 0.001$) to occur in a significantly higher number of patients receiving clopidogrel 75 mg/day than in those receiving 150 mg/day (table III). The risk of urgent revascularization was also higher in the 75 mg/day treatment group (adjusted RR 2.61; 95% CI 1.25,

Table I. Baseline clinical characteristics of clopidogrel-resistant patients receiving a clopidogrel maintenance dosage of 75 mg/day (n = 32) compared with those receiving clopidogrel 150 mg/day (n = 20)

Characteristic	Maintenance dosage (mg/day)		p-Value
	75 (n = 32)	150 (n = 20)	
Age (y), median [Q1–Q3]	71.0 [65.0–75.5]	75.0 [61.0–80.0]	0.749
Gender (male), n [% (95% CI)]	26 [81.3 (67.8, 94.8)]	18 [90.0 (76.9, 103.1)]	0.463
BMI (kg/m^2), median [Q1–Q3]	27.5 [26.7–31.3]	25.9 [24.6–29.1]	0.260
Fibrinogen (g/L), median [Q1–Q3]	4.4 [3.0–5.9]	3.5 [3.1–3.8]	0.219
Creatinine (μmol/L), median [Q1–Q3]	105.0 [90.0–116.0]	99.0 [85.0–159.0]	0.682
Medication after PCI, n [% of patients (95% CI)]			
fibrates	2 [6.3 (–2.1, 14.7)]	0 [0.0 (NA)]	0.517
statins	28 [87.5 (76.0, 99.0)]	18 [90.0 (76.9, 103.1)]	1.000
ACE inhibitors	15 [46.9 (29.6, 64.2)]	10 [50.0 (28.1, 71.9)]	0.826
angiotensin II receptor antagonists	2 [6.3 (–2.1, 14.7)]	1 [5.0 (–4.6, 14.6)]	1.000
diuretics	7 [21.9 (7.6, 36.2)]	8 [40.0 (18.5, 61.5)]	0.160
potassium channel agonist	4 [12.5 (1.0, 24.0)]	2 [10.0 (–3.1, 23.1)]	1.000
β-receptor antagonist	20 [62.5 (45.7, 79.3)]	16 [80.0 (62.5, 97.5)]	0.183
calcium channel antagonist	2 [6.3 (–2.1, 14.7)]	0 [0.0 (NA)]	0.517
proton pump inhibitors	26 [81.3 (67.8, 94.8)]	14 [70.0 (49.9, 90.1)]	0.500
antidiabetics	5 [15.6 (3.0, 28.2)]	0 [0.0 (NA)]	0.143
insulin	5 [15.6 (3.0, 28.2)]	4 [20.0 (2.5, 37.5)]	1.000
GPIIb-IIIa antagonists	2 [6.7 (–2.2, 15.6)]	3 [15.0 (–0.6, 30.6)]	0.377
Risk factors for CAD, n [% of patients (95% CI)]			
diabetes mellitus	13 [40.6 (23.6, 57.6)]	5 [25.0 (6.0, 44.0)]	0.249
hypertension	14 [43.8 (26.6, 61.0)]	9 [45.0 (23.2, 66.8)]	0.930
active smoking	9 [28.1 (12.5, 43.7)]	5 [25.0 (6.0, 44.0)]	0.805
passive smoking	12 [37.5 (20.7, 54.3)]	9 [45.0 (23.2, 66.8)]	0.592
excess weight (BMI >27 kg/m^2)	17 [53.1 (35.8, 70.4)]	8 [40.0 (18.5, 61.5)]	0.357
dyslipidemia	15 [46.9 (29.6, 64.2)]	9 [45.0 (23.2, 66.8)]	0.895
family history of CAD	4 [12.5 (1.0, 24.0)]	4 [20.0 (2.5, 37.5)]	0.695
LVEF (%), median [Q1–Q3]	45.0 [35.0–60.0]	47.5 [30.0–60.0]	0.720

BMI = body mass index; **CAD** = coronary artery disease; **GP** = glycoprotein; **LVEF** = left ventricular ejection fraction; **NA** = not applicable; **PCI** = percutaneous coronary intervention; **Q1** = first quartile; **Q3** = third quartile.

3.55; p = 0.017). No significant difference was observed between the two groups regarding hemorrhagic accidents, cardiovascular death, and myocardial infarction. One patient receiving clopidogrel 150 mg/day developed a hematoma at the site of femoral puncture and another patient treated with 75 mg/day developed a hemorrhagic cerebrovascular accident with hemiplegia.

Discussion

This study shows that a high clopidogrel maintenance dosage is associated with a decreased risk of stent thrombosis and MACE in clopidogrel-resistant patients. To our knowledge, this is the first clinical study that has analyzed the effect of a high clopidogrel maintenance dosage on the occurrence of serious cardiovascular outcomes, especially stent thrombosis in clopidogrel-resistant patients.

Signal generation from laboratory data of hospitalized patients has shown efficacy in several studies in identifying adverse drug reactions.[24] Thus, we decided to use this method; we exploited hematology laboratory data to identify patients with resistance to clopidogrel and serious cardiovascular outcomes despite dual antiplatelet therapy with aspirin and clopidogrel.

Our data showed that MACE occurred in 67.3% of clopidogrel-resistant patients. Many studies have shown that patients resistant to clopidogrel (irrespective of the platelet aggregation test employed) have an increased risk of stent thrombosis and other adverse cardiovascular outcomes.[5-11,22,25-27] In a prospective study performed by Matetzky et al., 40% of patients in the clopidogrel-resistant group (ADP-induced platelet aggregation at day 6: 103 ± 8% of baseline) had a recurrent adverse cardiovascular event.[7] In another prospective study, performed by Buonamici et al., clopidogrel nonresponders had a nearly 4-fold increase in definite or probable stent thrombosis compared with clopidogrel responders.[5] The rate of MACE in our study is higher than that in these similar studies, since our center is a tertiary referral center and patients were at higher cardiovascular risk than those in these cited studies.[5,7] Moreover, the ADP-induced platelet aggregation assessment was performed in patients considered at very high cardiovascular risk referred to this center by other hospitals of the Midi-Pyrenees region.

Our data showed that clopidogrel-resistant patients using the conventional clopidogrel dosage of 75 mg/day developed significantly more stent thrombosis and MACE than those receiving 150 mg/day. This result could be explained by decreased platelet reactivity and enhanced platelet inhibition associated with a high clopidogrel maintenance dosage, as shown in several studies.[13-16] Fontana et al. showed that a clopidogrel maintenance dosage of 150 mg/day administered for 15 days to 'low responders' (using the phosphorylation state of the vasodilator phosphoprotein assay and ADP aggregation) was as-

Table II. Baseline angiographic characteristics of clopidogrel-resistant patients receiving a clopidogrel maintenance dosage of 75 mg/day (n = 32) compared with those receiving clopidogrel 150 mg/day (n = 20)

Characteristic	Maintenance dosage (mg/day)		p-Value
	75 (n = 32)	150 (n = 20)	
No. of implanted stents (n), median [Q1–Q3]	2 [1–3]	1.5[1–2.5]	0.316
Stent length (mm), median [Q1–Q3]	27.0 [18.0–44.0]	19.5 [12.0–44.0]	0.341
Maximal stent diameter (mm), median [Q1–Q3]	3.0 [2.8–3.5]	3.5 [3.0–4]	0.004*
Stent type, n [% of patients (95% CI)]			
DES only	10 [32.3 (15.8, 48.8)]	7 [38.9 (16.4, 61.4)]	0.638
BMS only	17 [54.8 (37.3, 72.3)]	8 [44.4 (21.4, 67.4)]	0.483
DES and BMS	4 [12.9 (1.1, 24.7)]	3 [16.7 (–0.5, 33.9)]	0.697
Stent thrombosis appearance time after PCI (days), median [Q1–Q3]	4.0 [2.0–6.0]	3.0 [2.0–7.0]	0.564
MACE appearance time after PCI (days), median [Q1–Q3]	4.0 [2.5–11.0]	3.0 [2.0–7.0]	0.430
Baseline angiographic characteristics			
Vessel treated, n [% (95% CI)]			
left main	2 [6.5 (–2.2, 15.2)]	8 [40.0 (18.5, 61.5)]	0.008*
RCA	9 [29.0 (13.0, 45.0)]	9 [45.0 (23.2, 66.8)]	0.244
LCx	14 [45.2 (27.7, 62.7)]	7 [35.0 (14.1, 55.9)]	0.472
LAD	17 [54.8 (37.3, 72.3)]	10 [50.0 (28.1, 71.9)]	0.735
Preprocedure troponine (ng/mL), median [Q1–Q3]	0.49 [0.10–4.05]	0.72 [0.10–17.64]	0.810
Type of procedure, n [% (95% CI)]			
elective PCI	21 [67.7 (51.2, 84.2)]	14 [70.0 (49.9, 90.1)]	0.865
bifurcation	8 [25.8 (10.4, 41.2)]	2 [10.0 (–3.1, 23.1)]	0.280
chronic occlusion	3 [9.7 (0.7, 20.1)]	3 [15.0 (–0.6, 30.6)]	0.668
Clinical presentation, n [% (95% CI)]			
ST ACS	12 [37.5 (20.7, 54.3)]	15 [75.0 (56.0, 94.0)]	0.008*
NST ACS	17 [53.1 (35.8, 70.4)]	2 [10.0 (–3.1, 23.1)]	0.002*
silent ischemia	2 [6.3 (–2.1, 14.7)]	0 [0.0 (NA)]	0.517

BMS = bare-metal stent; **DES** = drug-eluting stent; **LAD** = left anterior descending coronary artery; **LCx** = left circumflex coronary artery; **MACE** = major adverse cardiac events; **NA** = not applicable; **NST ACS** = non-ST elevation acute coronary syndrome; **PCI** = percutaneous coronary intervention; **Q1** = first quartile; **Q3** = third quartile; **RCA** = right coronary artery; **ST ACS** = ST elevation acute coronary syndrome; * indicates statistically significant.

Table III. Post-percutaneous coronary intervention major adverse cardiovascular events (MACE) and/or hemorrhagic events in clopidogrel-resistant patients

Characteristic	Maintenance clopidogrel dosage (mg/day)		p-Value	Crude OR	Adjusted OR (95% CI)[a]	Crude RR	Adjusted RR (95% CI)[b]
	75 (n = 32)	150 (n = 20)					
MACE, n (%)	28 (87.5)	7 (35.0)	0.001*	13.00	21.51 (3.26, 141.76)*	2.50	2.63 (1.82, 2.82)*
cardiovascular death	3 (9.4)	1 (5.0)	0.602	1.97	2.14 (0.12, 37.30)	1.88	NA
myocardial infarction	5 (15.6)	1 (5.0)	0.206	3.52	8.52 (0.31, 236.39)	3.13	NA
revascularization	20 (62.5)	5 (25.0)	0.017*	5.00	5.66 (1.36, 23.58)*	2.50	2.61 (1.25, 3.55)*
Stent thrombosis, n (%)	26 (81.3)	7 (35.0)	0.002*	8.05	11.54 (2.47, 53.97)*	2.32	2.46 (1.63, 2.76)*
cardiovascular death	3 (9.4)	1 (5.0)	0.602	1.97	2.14 (0.12, 37.30)	1.88	NA
myocardial infarction	4 (12.5)	1 (5.0)	0.252	2.71	12.71 (0.16, 986.24)	2.50	NA
revascularization	19 (59.4)	5 (25.0)	0.017*	4.38	5.66 (1.36, 23.58)*	2.38	2.61 (1.25, 3.55)*
Hemorrhagic accident, n (%)	1 (3.1)	1 (5.0)	0.374	0.61	0.10 (0.001, 16.09)	0.63	NA

a ORs adjusted for conventional thrombosis and cardiovascular risk factors (diabetes mellitus, hypertension, active smoking, excess weight, dyslipidemia, family history of coronary artery disease, proton pump inhibitor use, left ventricular ejection fraction, and creatinine value).

b Adjusted RRs were calculated by applying the method of Zhang and Yu[23] for outcomes of interest with an incidence >10% in the 150 mg/day treatment group.

NA = not applicable; **OR** = odds ratio; **RR** = relative risk; * indicates statistically significant.

sociated with a relative 20% increase in its biological effect.[15] Another randomized prospective study also showed that a high maintenance dosage of clopidogrel (150 mg/day) in a high-risk group of patients with type 2 diabetes mellitus and coronary artery disease was associated with enhanced platelet inhibition.[16] However, while these studies emphasized that a high clopidogrel maintenance dosage has an increased biological effect, the data were not translated into a clinical setting (i.e. the effect on stent thrombosis). Lemesle et al., in a recent observational study, showed that a 600 mg loading dose of clopidogrel followed by a 150 mg/day maintenance dosage of clopidogrel within the first 15 days after PCI was associated with a decrease (hazard ratio 0.694; 95% CI 0.485, 0.993; p = 0.046) in the composite primary endpoint (death, myocardial infarction, and ST) without an increase in hemorrhagic complications.[17] It seems that doubling the clopidogrel maintenance dosage could greatly reduce the risk of stent thrombosis through the mechanism depicted above, in clopidogrel-resistant patients. The most important risk that could threaten patients by doubling the clopidogrel maintenance dosage is hemorrhagic accident. In our study this risk was not significantly increased in the high-maintenance dosage group. Only one patient in each group had a hemorrhagic accident. However, given the small size of the study and the wide confidence intervals (table III), these data are not conclusive, and randomized, controlled trials are needed to confirm these results.

There are some limitations to our study. The observational cohort study design does not have the advantages of randomized, prospective studies. The difference in the occurrence of stent thrombosis found between the two treatment groups could be the result of systematic healthcare system differences between 2004–5 and 2005–6; it is possible that our results were influenced by other changes in care policy during that time and were not exclusively associated with the clopidogrel maintenance dosage. The regression model was used to adjust for known risk factors of stent thrombosis. However, many confounders may be unknown and therefore could not be adjusted for. Patients included in the study were complex cases; they had high cardiovascular risk and resistance to clopidogrel. This makes extrapolation of results difficult in the general population and in patients responding to clopidogrel who could be at higher risk of hemorrhage. The relatively small number of included patients limits the study power and does not allow consideration of all risk factors associated with stent thrombosis after PCI and hemorrhagic risk. Thus, randomized, controlled trials are needed to more precisely evaluate stent thrombosis risk factors in clopidogrel-resistant patients and hemorrhagic risk that would preclude patients from using a clopidogrel maintenance dosage of 150 mg/day.

Nevertheless, we emphasize that the present study was performed in a population of very high-risk patients with resistance to clopidogrel. These patients are the most difficult to treat in cardiology departments. Our results suggest that doubling the clopidogrel maintenance dosage in this population could be justified; the risk of definite stent thrombosis and MACE was significantly lower in patients treated with 150 mg/day.

Conclusions

To our knowledge, this study is the first to investigate the association between the clopidogrel maintenance dosage and the occurrence of stent thrombosis after PCI in clopidogrel-resistant patients. This observational cohort study showed a high-maintenance dosage of clopidogrel to decrease post-PCI stent thrombosis and MACE. These findings deserve confirmation in a prospective well conducted study.

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