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Glycoprotein IIb/IIIa Receptor Inhibition with Abciximab during Percutaneous Coronary Interventions Increases the Risk of Bleeding in Patients with Impaired Renal Function

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Key Words
Abciximab · Bleeding · Clopidogrel · Mortality · Percutaneous coronary intervention · Renal insufficiency

Abstract
Objective: Whether patients with renal insufficiency (RI) undergoing percutaneous coronary interventions (PCI) benefit from abciximab added to clopidogrel plus aspirin is unknown. ***Methods:*** The study included 2,159 patients with coronary artery disease undergoing elective PCI. RI was assessed using glomerular filtration rate (GFR) cutoff values: moderate-to-severe RI (GFR ≤60 ml/min), mild RI (GFR >60 to ≤90 ml/min) and no RI (GFR >90 ml/min). The 30-day incidence of major adverse cardiac events (MACE) and bleeding were the primary outcome analyses. ***Results:*** In patients with moderate-to-severe RI, mild RI and no RI, MACE occurred in 5.2, 5 and 2.9%, respectively, in the abciximab group (p = 0.14) and in 4.2, 3.8 and 4.0%, respectively, in the placebo group (p = 0.96). In the abciximab group, bleeding complications occurred in 8.9% of patients with moderate-to-severe RI, in 2.0% with mild RI and in 2.1% with no RI (p < 0.001). Multivariable analysis identified GFR as an independent correlate of MACE (p = 0.03) and bleeding (p = 0.001) with a trend for an interaction between GFR and abciximab regarding major bleeding (p = 0.22). ***Conclusions:*** In patients with RI undergoing PCI, adding abciximab to clopidogrel plus aspirin increases the risk of bleeding without benefit in reducing the risk of ischemic complications within the first 30 days.

Introduction

The combination of aspirin and clopidogrel is the standard antiplatelet therapy for coronary stenting [1–4]. Although patients with renal insufficiency (RI) benefit from percutaneous coronary interventions (PCI), they exhibit a higher mortality and morbidity after coronary intervention and RI has been reported to be an independent correlate of mortality [5, 6]. The increased risk of thrombotic events may result from multiple platelet abnormalities and coagulation disorders associated with RI [7]. RI creates a prothrombotic state due to increased concentrations of fibrinogen and von Willebrand factor associated with the severity of impaired renal function [8–10], enhanced activity of tissue factor and reduced ac-

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tivities of antithrombin III and the fibrinolytic system [9, 10]. Hemostatic disorder associated with RI, however, is diverse and an increased risk of bleeding has been well documented and attributed mainly to reduced platelet aggregation due to decreased releasable ATP, decreased serotonin content in dense granules, reduced production of prothrombotic thromboxane A_2 and reduced cell surface expression of glycoprotein IIb/IIIa receptors due to masking the receptor surface by fibrinogen, von Willebrand factor or their fragments [8, 11–13]. Therefore, bleeding complications as well are expectable in patients with RI treated with antiplatelet therapy in the setting of PCI.

Recently we showed that therapy with abciximab after pretreatment with a high loading dose of clopidogrel was not associated with a clinical benefit within the first 30 days in low-risk patients undergoing elective PCI [14]. The aim of this study was to investigate whether patients with RI would benefit from abciximab added to a high loading dose of clopidogrel and aspirin during elective PCI.

Methods

Patients

This study presents a post hoc analysis of 2,159 patients with coronary artery disease who underwent PCI between May 2000 and February 2003 in the setting of the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) trial [14]. This trial was a randomized, double-blind, placebo-controlled study in which patients with coronary artery disease underwent elective PCI after being randomly assigned to abciximab (n = 1,079) or placebo (n = 1,080). The complete study protocol can be found in the primary publication [14]. Angina was graded according to the Canadian Cardiovascular Society classification system [15]. Exclusion criteria were: myocardial infarction within the prior 14 days; unstable angina with ST-segment changes of at least 0.1 mV in at least 2 electrocardiographic leads at rest, a troponin T level of more than 0.03 ng/ml, or both; target lesion in a venous bypass graft; chronic occlusion (present for longer than 3 months); target lesion with angiographically visible thrombus; left ventricular ejection fraction of less than 30%; hemodynamic instability; insulin-dependent diabetes mellitus; pericarditis; cancer; stroke in the prior 3 months; active bleeding or bleeding diathesis; trauma or major surgery in the preceding month; suspected aortic dissection; ongoing oral anticoagulation therapy or glycoprotein IIb/IIIa inhibitors within the preceding 14 days; severe, uncontrolled hypertension (systolic blood pressure of more than 180 mm Hg); hemoglobin level of less than 10.0 g/dl or a hematocrit below 34%; platelet count of less than 100,000 per mm^3 or more than 600,000 mm^3; known allergic reaction to the study medication; pregnancy. All patients gave informed consent for the intervention.

Renal Evaluation

Venous blood samples were collected on admission prior to angioplasty/stenting procedure for each patient and analyzed by routine tests. Glomerular filtration rate (GFR) was calculated using the Cockroft-Gault formula [16]: GFR (ml/min) = [(140 – age) × weight (kg)]/[72 × serum creatinine (mg/dl)] for men, multiplied with 0.85 for women. Moderate-to-severe RI was defined as a GFR ≤60 ml/min, a cutoff value previously proposed by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative Advisory Board [17] and the American Heart Association's Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention [18]. Patients with a GFR >60 ml/min and ≤90 ml/min were defined as patients with mild RI and patients with a GFR >90 ml/min as those with no RI.

Pharmacological Therapy

All patients received 600 mg clopidogrel as a loading dose at least 2 h before the PCI; aspirin 325–500 mg was also given before the intervention. Patients in the abciximab group received abciximab as a bolus of 0.25 mg/kg body weight, followed by an infusion of 0.125 μg/kg/min for 12 h (maximum 10 μg/min) along with 70 U of heparin/kg. Patients in the placebo group received a bolus of placebo followed by 12 h infusion and a bolus of heparin of 140 U of heparin/kg. After the procedure, all patients received 75 mg clopidogrel twice a day for 3 days followed by a dose of 75 mg clopidogrel daily for at least 4 weeks in combination with 100–325 mg aspirin daily as indefinite therapy.

Angiographic Evaluation

Complexity of lesions was defined according to the modified American College of Cardiology/American Heart Association grading system [19]. Class B2 and C lesions were considered complex. Global left ventricular ejection fraction was determined by using the area-length method. Digital coronary angiograms were analyzed offline with the automated edge detection system CMS (Medis Medical Imaging Systems, Nuenen, The Netherlands).

Follow-Up, Definitions and Outcomes

Patients were interviewed by telephone at 30 days, and those with cardiac symptoms were seen in the outpatient clinic for a complete clinical, electrocardiographic and laboratory checkup. The primary outcome analyses of this study were major adverse cardiac events (MACE; death from any cause, myocardial infarction and target vessel revascularization within 30 days) and bleeding complications. Myocardial infarction was diagnosed when typical, prolonged chest pain was associated with either an increase of 3 times or more of creatine kinase or its MB isoenzyme or development of new pathological Q-waves on surface electrocardiogram. A bleeding complication was defined as major if it was intracranial or if clinically significant overt signs of hemorrhage were associated with a drop in hemoglobin of more than 5 g/dl. Minor bleeding was defined as clinically overt hemorrhage, associated with a drop in hemoglobin between 3 and 5 g/dl.

Statistical Analysis

Data are expressed as means ± standard deviation or counts (with percentages in parentheses). Continuous data were compared with analysis of variance. Categorical data were compared

Table 1. Baseline clinical characteristics

Characteristic	GFR ≤60 (n = 507 patients)	60< GFR ≤90 (n = 914 patients)	GFR >90 (n = 738 patients)	p value
Age, years	74.8 ± 7.5	66.9 ± 7.8	58.2 ± 8.6	<0.001
Women	243 (48)	176 (19)	90 (12)	<0.001
Diabetes	121 (24)	173 (19)	147 (20)	0.08
Current smoker	53 (11)	141 (15)	181 (25)	<0.001
Cholesterol level, mg/dl	197.8 ± 48.5	201.8 ± 46.4	204.3 ± 50.5	0.21
Hypertension	312 (62)	531 (58)	329 (45)	<0.001
Previous myocardial infarction	183 (36)	281 (31)	239 (32)	0.12
Previous PCI	208 (41)	365 (40)	271 (37)	0.23
Previous bypass surgery	70 (14)	91 (10)	46 (7)	<0.001
Angina class III and IV	209 (41)	363 (40)	297 (40)	0.86
Left ventricular ejection fraction, %	57.8 ± 13.7	60.3 ± 12.0	58.7 ± 11.6	<0.001
Multivessel disease	397 (78.3)	704 (77.0)	501 (67.9)	<0.001

Data are means ± SD or number of patients (with percentages in parentheses).

with the χ^2 test or Fisher's exact test, as appropriate. Multiple logistic regression analysis model was used to identify independent factors of MACE or bleeding complications while adjusting for other clinical variables. The following variables were entered into the model: age, sex, diabetes, smoking, arterial hypertension, prior coronary artery bypass surgery, multivessel disease, left ventricular ejection fraction, GFR, treatment group (abciximab or placebo) and the interaction term 'low GFR*abciximab'. All analyses were performed with the S-Plus statistical package (Insightful Corp., Seattle, Wash., USA). $p < 0.05$ was considered to indicate statistical significance.

Results

Characteristics of the Patients

Of the total study population, 507 patients (23.5%) had a GFR ≤60 ml/min and thus were considered to have moderate-to-severe RI, 914 patients (42.3%) had a GFR >60 ml/min and ≤90 ml/min and therefore were considered to have mild RI and 738 patients (34.2%) had a GFR >90 ml/min. Demographic and baseline clinical data are shown in table 1. In comparison to patients with a normal GFR >90 ml/min, patients with RI were older and more likely to be female. They more often had a history of arterial hypertension and previous bypass surgery and were smokers less often. Left ventricular ejection fraction differed significantly between groups. Patients with moderate-to-severe RI more often had multivessel disease than patients in the other 2 groups. Creatinine was 1.35 ± 0.82 mg/dl in patients with moderate-to-severe RI, 1.06 ± 0.18 mg/dl in patients with mild RI and 0.88 ± 0.18 mg/dl in patients with no RI. GFR was 47.1 ± 10.2 ml/min in patients with moderate-to-severe RI, 74.7 ± 8.4 ml/min in patients with mild RI and 114.0 ± 22.7 ml/min in patients with no RI (table 1).

Angiographic and procedural data are shown in table 2. Patients in the group with GFR ≤60 ml/min had smaller vessel size and slightly shorter lesions than patients in the other 2 groups. The remaining data did not appear to differ significantly among the patients of different groups.

Ischemic Events

Table 3 shows the incidence of adverse events within 30 days after procedure. During the first 30 days, 3 deaths (1.2%) were observed in the group with GFR ≤60 ml/min who received abciximab. No deaths occurred in the groups with mild or no RI. In patients who received placebo, there were 2 deaths in the group with mild RI and 1 death in the group with no RI. No differences in the recurrent myocardial infarction were observed (table 3; fig. 1). In subgroups with moderate-to-severe, mild and no RI, target vessel revascularization within the first 30 days was needed in 1 patient (0.4%), 8 patients (1.8%) and 1 patient (0.3%), respectively, in patients who received abciximab ($p < 0.04$). In patients who received placebo, target vessel revascularization was needed in none of the patients with moderate-to-severe RI, in 3 patients (0.6%) with mild RI and in 4 patients (1.1%) with no RI ($p = 0.22$). MACE did not differ significantly among patients with moderate-to-severe, mild or no RI, either in the abciximab or placebo groups (table 3).

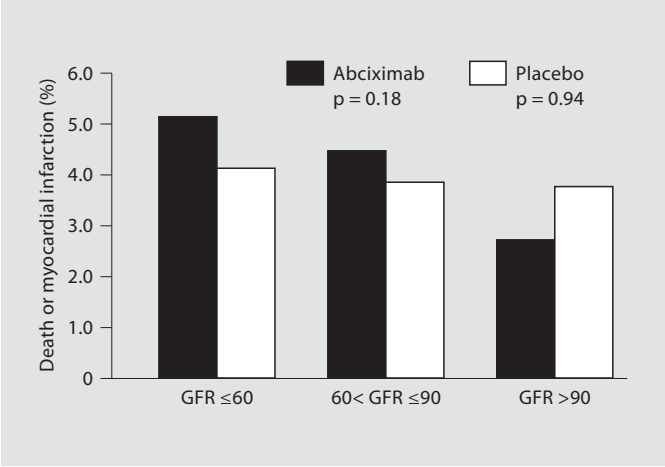

Fig. 1. Combined incidence of death or myocardial infarction in patients receiving abciximab or placebo within 30 days after coronary intervention.

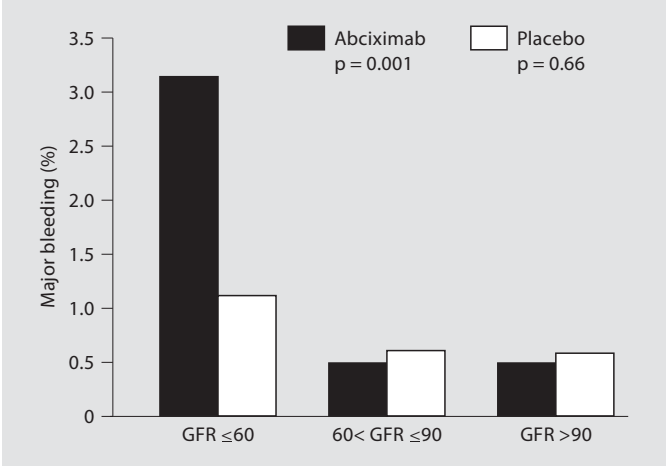

Fig. 2. Major bleeding in patients who received abciximab or placebo.

Table 2. Angiographic and procedural characteristics

Characteristic	GFR ≤60 (n = 682 lesions)	60< GFR ≤90 (n = 1,211 lesions)	GFR >90 (n = 918 lesions)	p value
Location of treated lesion				0.36
Left main artery	17 (2.5)	31 (2.6)	12 (1.3)	
Left anterior descending artery	261 (38.2)	491 (40.5)	388 (42.2)	
Left circumflex artery	186 (27.3)	325 (26.8)	243 (26.6)	
Right coronary artery	214 (31.4)	356 (29.4)	273 (29.7)	
Bypass vessel	4 (0.6)	8 (0.7)	2 (0.2)	
Complex lesions (B2/C)	438 (64.2)	809 (66.7)	590 (64.4)	0.34
Chronic occlusions	28 (4.1)	56 (4.6)	48 (5.2)	0.57
Restenotic lesions	42 (6.2)	71 (5.9)	50 (5.4)	0.82
Lesion length, mm	11.9 ± 6.5	12.7 ± 7.2	12.8 ± 6.7	0.01
Vessel size, mm	2.77 ± 0.55	2.81 ± 0.57	2.84 ± 0.53	0.008
Mean lumen diameter before, mm	1.06 ± 0.50	1.07 ± 0.51	1.05 ± 0.50	0.84
Mean lumen diameter after, mm	2.71 ± 0.64	2.72 ± 0.66	2.77 ± 0.62	0.06
Type of intervention				0.92
Balloon angioplasty	67 (9.8)	113 (9.3)	85 (9.2)	
Stent	615 (90.2)	1,097 (90.7)	834 (90.8)	

Data are means ± SD or number of patients (with percentages in parentheses).

Hemorrhagic Events

In patients with moderate-to-severe, mild and no RI, bleeding occurred in 8.9% (n = 22), 2% (n = 9) and 2.1% (n = 8), respectively, in the abciximab group ($p < 0.001$) and in 5.0% (n = 13), 2.1% (n = 10) and 1.7% (n = 6), respectively, in the placebo group (p = 0.03). With respect to major bleeding, significant differences between groups were observed only in patients who received abciximab (table 3, fig. 2). On the other hand, minor bleeding occurred more often in groups with RI, irrespective of treatment with abciximab or placebo. There were significant differences with regard to need for blood transfusion with the decline in renal function only in patients who received abciximab but not in those who received placebo. There were no significant differences regarding thrombocytopenia according to renal status in groups

Table 3. Adverse events during the first 30 days

Parameter	GFR ≤60 (n = 507 patients)	60< GFR ≤90 (n = 914 patients)	GFR >90 (n = 738 patients)	p value
Treatment received				0.23
Abciximab	248 (49)	443 (49.0)	388 (53)	
Placebo	259 (51.0)	470 (51)	351 (47.0)	
Death				
With abciximab	3 (1.2)	0	0	0.006
With placebo	0	2 (0.4)	1 (0.3)	0.58
Myocardial infarction				
With abciximab	10 (4.0)	20 (4.5)	10 (2.6)	0.32
With placebo	11 (4.2)	18 (3.8)	12 (3.4)	0.87
Target vessel revascularization				
With abciximab	1 (0.4)	8 (1.8)	1 (0.3)	0.04
With placebo	0	3 (0.6)	4 (1.1)	0.22
MACE				
With abciximab	13 (5.2)	22 (5.0)	10 (2.9)	0.14
With placebo	11 (4.2)	18 (3.8)	14 (4.0)	0.96
Major bleeding				
With abciximab	8 (3.2)	2 (0.5)	2 (0.5)	0.001
With placebo	3 (1.2)	3 (0.6)	2 (0.6)	0.66
Minor bleeding				
With abciximab	14 (5.7)	7 (1.6)	6 (1.5)	0.001
With placebo	10 (3.9)	7 (1.5)	4 (1.1)	0.035
Any bleeding				
With abciximab	22 (8.9)	9 (2.0)	8 (2.1)	<0.001
With placebo	13 (5.0)	10 (2.1)	6 (1.7)	0.03
Blood transfusion				
With abciximab	10 (4.0)	5 (1.1)	2 (0.5)	0.001
With placebo	4 (1.5)	4 (0.9)	1 (0.3)	0.24
Thrombocytopenia <20,000				
With abciximab	2 (0.8)	7 (1.5)	1 (0.3)	0.14
With placebo	0	0	0	0

Data are number of patients (with percentages in parentheses). Percentages are related to treatment received.

who received abciximab or placebo (table 3). However, profound thrombocytopenias (<20,000 mm^3) were found only in patients receiving abciximab.

Results of Multivariable Analysis

Multiple logistic regression analysis was used to identify independent correlates of MACE and bleeding (see Methods for variables entered into the analysis). The model showed that GFR was an independent correlate of increased risk of 30-day MACE [odds ratio (OR) 2.27, 95% confidence interval (CI) 1.06–4.89; p = 0.03 comparing the group with GFR ≤60 ml/min with the group with GFR >90 ml/min]. Abciximab therapy was not an independent correlate of 30-day MACE (OR 1.14, 95% CI 0.73–1.77; p = 0.56 for abciximab vs. placebo). No interaction between GFR and abciximab was observed regarding increased risk of MACE (p = 0.73). When applied to identify the independent correlates of bleeding, the model showed that GFR was again an independent correlate of increased risk of any bleeding (OR 5.75, 95% CI 2.25–14.65; p < 0.001 comparing the group with GFR ≤60 ml/min with the group with GFR >90 ml/min) and of major bleeding (OR 10.91, 95% CI 2.00–60.00; p = 0.006 comparing the group with GFR ≤60 ml/min with the group with GFR >90 ml/min). There was an increased risk of major bleeding with abciximab (OR = 1.87, 95% CI 0.73–4.81; p = 0.10), but the level of statistical significance was not achieved due to the limited number of events. There was a trend for interaction between GFR and abciximab regarding increased risk of major bleeding (p = 0.22).

Discussion

This study demonstrated that impaired renal function is an important predictor of MACE and bleeding complications within the first 30 days in low-risk patients with coronary artery disease undergoing elective PCI. However, the most important finding of this study is that in patients with RI and coronary artery disease undergoing PCI, glycoprotein IIb/IIIa receptor blockade with abciximab added to a regimen of 600 mg of clopidogrel plus aspirin increased the risk of bleeding with no benefit in reducing the risk of ischemic complications within the first 30 days after coronary intervention.

With regard to bleeding complications following therapy with abciximab, previous studies yielded conflicting results. In patients with severe RI, Jeremias et al. [20] found no significant differences in major bleeding complications between patients with and without abciximab therapy. Conversely, another prior study showed an association between abciximab therapy and increased bleeding risk in patients with RI and coronary heart disease [21]. A recent study by Freeman et al. [22] showed that the use of glycoprotein IIb/IIIa receptor antagonists in patients with acute coronary syndromes and RI resulted in a significant increase in the bleeding rates. However, the use of glycoprotein IIb/IIIa antagonists was associated with a decreased risk of in-hospital mortality [22]. Other studies have also demonstrated a higher incidence of major bleeding after abciximab therapy in patients with RI [23, 24]. In the present study, even though patients were not randomized according to renal function status, abciximab was given on a randomized basis. Our results showed that the use of abciximab was associated with an increase in the risk of bleeding in patients with RI. This conclusion is supported by finding increased rates of major and minor bleeding and a greater need for blood transfusion in patients with RI treated with abciximab (in univariate analysis) and by observing a trend for an interaction between low GFR and abciximab regarding the increased risk of major bleeding (in multivariable analysis). Furthermore, profound thrombocytopenia, another marker of increased risk of bleeding, occurred only in patients who received abciximab. Interestingly, however, an increased risk of minor bleeding was also associated with RI even in patients who did not receive abciximab. This finding is in agreement with a previous study investigating patients undergoing balloon angioplasty or stenting for acute myocardial infarction, which has reported an association of RI with higher rates of major bleeding and increased need of blood transfusion independent of abciximab use [5]. Furthermore, a retrospective analysis of patients with acute coronary syndromes found that coadministration of clopidogrel and enoxaparin was an independent risk factor for major bleeding in patients with RI [25]. Thus, these studies and the present one show that RI per se and/or the use of antithrombotic therapy in patients with RI pose an increased risk of hemorrhagic complications in patients undergoing PCI. Considering the magnitude of risk related with minor bleedings observed in our study, it seems that an antiplatelet therapy with aspirin and clopidogrel with a loading dose is relatively safe even in patients with advanced RI.

We recognize that the limited number of adverse events and in particular of bleeding complications is an important limitation of this study. Furthermore, a relatively large list of exclusion criteria may imply that findings of this study are not applicable to all patients with coronary artery disease undergoing PCI. In particular, these findings may not be extrapolated to high-risk patients with acute coronary syndromes undergoing a PCI procedure.

Conclusions

In patients with RI undergoing elective PCI, abciximab added to a regimen of loading dose of clopidogrel plus aspirin does not reduce the incidence of ischemic complications but increases the risk of bleeding within the first 30 days following coronary intervention. Based on the results of this study, in patients with RI undergoing elective PCI, the use of abciximab additive to a regimen of loading-dose clopidogrel plus aspirin is not recommended.

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