Abciximab Reduces Monocyte Tissue Factor in Carotid Angioplasty and Stenting

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Background and Purpose—Abciximab, a nonselective glycoprotein IIb/IIIa inhibitor, was shown to reduce peri-interventional stroke rate in carotid stenting. We evaluated the effect of adjunct abciximab therapy on monocyte-platelet cross talk and neurological deficit in unprotected carotid stenting and compared its efficacy with distal filter protection.

Methods—Fifty patients were randomized to either standard antithrombotic therapy (n=30) consisting of aspirin, clopidogrel, and heparin or adjunct bolus (0.25 mg/kg) and 12-hour infusion (0.125 μg · kg⁻¹ · min⁻¹) of abciximab (n=20). A third cohort of patients was stented with filter protection (n=30). Monocyte-platelet aggregate formation and monocyte tissue factor expression were determined by whole blood flow cytometry, and F1.2 generation and soluble CD40 ligand (sCD40L) were determined by immunoassay.

Results—The incidence of peri-interventional ischemic episodes (23% versus 10%; P=0.2) and the number of de novo ischemic lesions detected by diffusion-weighted MRI (47% versus 30%; P=0.17) were not significantly different between standard antithrombotic therapy and adjunct abciximab but were reduced with filter protection (P=0.023). However, the number of transient ischemic attacks was lower (P=0.05) and the National Institutes of Health Stroke Score rapidly decreased in patients with adjunct abciximab. This clinical improvement was paralleled by a reduction in the postinterventional percentage of activated monocyte-platelet aggregates (CD62P+/CD14+; P=0.018) and the number of tissue factor–positive monocytes (TF+/CD14+; P=0.005). Both abciximab and filter protection suppressed F1.2 generation and significantly reduced sCD40L.

Conclusions—Abciximab limits thrombus propagation and thrombus stabilization after carotid stenting by reducing monocyte-platelet cross talk and in patients who do not allow placement of protection devices. (Stroke. 2003; 34:2560-2567.)

Key Words: antibodies, monoclonal ■ carotid stenosis ■ procoagulant ■ stents

Recently, several clinical studies reported reduced periprocedural ischemic events in patients undergoing carotid stenting with abciximab, a glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonist, as adjunct antiplatelet therapy in addition to the standard antithrombotic regimen. 1–3 However, the beneficial effect of adjunct abciximab was lost when continuous intravenous infusion was omitted after single bolus administration. 4 Today, filter devices catching thromboembolic debris during intervention are considered the gold standard in distal cerebral protection. 5

Platelet activation is immanent to symptomatic cerebrovascular disease (CVD), 6 and circulating monocyte-platelet aggregates (MPA) were recognized as a more sensitive marker of in vivo platelet activation than platelet surface P-selectin. 7 In ex vivo experiments, activated platelets were shown to induce monocyte tissue factor (TF), the major physiological trigger of coagulation in vivo, 8 via cross talk between P-selectin/PSGL-1 and CD40/CD40 ligand. 9 This procoagulant mechanism may be relevant in thrombus propagation after vascular injury in vivo.

Abciximab, a potent inhibitor of GPIIb/IIIa-mediated platelet aggregation, was shown to interfere with platelet-induced monocyte activation 10 and soluble CD40 ligand (sCD40L)–mediated cross-link of platelets. 11 Thus, we hypothesized that the beneficial effect of abciximab in carotid stenting may be due to limited thrombus propagation mediated by reduced MPA formation associated with less induction of monocyte TF and due to diminished thrombus stabilization by decreased sCD40L. To investigate the role of abciximab on monocyte-platelet cross talk in vivo, we deter-

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mined MPA and monocyte TF by whole blood flow cytometry in a cohort of 50 patients randomized to either standard antithrombotic therapy or adjunct bolus and 12-hour infusion of abciximab and in 30 consecutive patients with standard antithrombotic therapy and filter protection in the clinical setting of carotid stenting. We further recorded and quantified clinical symptoms of neurological deficit according to the National Institutes of Health Stroke Scale (NIHSS) score and the number of cerebral ischemic lesions by diffusion-weighted (DW) MRI.

Subjects and Methods

Study Population

The local ethics committee approved the study, and written informed consent was obtained from all patients. Fifty patients were enrolled in the study on an intention-to-treat basis between June 2001 and October 2002 and were assigned to either standard peri-interventional antithrombotic therapy consisting of aspirin, clopidogrel, and heparin or to adjunct bolus and 12-hour infusion of abciximab by adaptive randomization, a form of sequential treatment assignment balanced for prognostic factors. Since November 2002, all patients were stented with distal filter protection, of which 30 consecutive patients were enrolled in the study. Symptomatic CVD was defined as any sign of neurological ischemic deficit within the last 6 months. Indication for the procedure was ≥70% stenosis of the extracranial internal carotid artery (ICA) in symptomatic patients or ≥80% stenosis of the ICA in asymptomatic patients and with 1 of the following criteria: rapid progression during the last 12 months, contralateral ICA occlusion, carotid stenting required preoperatively, clinically silent cerebral infarction detected by cranial CT, and an ipsilateral lesion type consistent with the assumption of thromboembolism from the carotid plaque. The degree of stenosis was estimated according to duplex velocity criteria, and clinical indication for intervention was obtained from an independent neurologist. The final decision to treat was based on the angiographic degree of stenosis according to North American Symptomatic Carotid Artery Trial criteria. Impax DS3000 software (Agfa) was used for quantification according to North American Symptomatic Carotid Artery Trial criteria. Since November 2002, all patients were stented with distal filter protection, of which 30 consecutive patients were enrolled in the study. Symptomatic CVD was defined as any sign of neurological ischemic deficit within the last 6 months. Indication for the procedure was ≥70% stenosis of the extracranial internal carotid artery (ICA) in symptomatic patients or ≥80% stenosis of the ICA in asymptomatic patients and with 1 of the following criteria: rapid progression during the last 12 months, contralateral ICA occlusion, carotid stenting required preoperatively, clinically silent cerebral infarction detected by cranial CT, and an ipsilateral lesion type consistent with the assumption of thromboembolism from the carotid plaque. The degree of stenosis was estimated according to duplex velocity criteria, and clinical indication for intervention was obtained from an independent neurologist. The final decision to treat was based on the angiographic degree of stenosis according to North American Symptomatic Carotid Artery Trial criteria. Impax DS3000 software (Agfa) was used for quantification according to North American Symptomatic Carotid Artery Trial criteria.

Study Protocol

Premedication consisted of aspirin (100 mg/d) for at least 7 days and clopidogrel (75 mg/d; 4×75-mg loading dose) for at least 2 days before intervention. After vascular access, weight-adjusted heparin (70 U/kg) was given as an intra-arterial bolus, followed by diagnostic angiography in 2 planes and intravenous bolus of abciximab (0.25 mg/kg). We aimed for an activated clotting time of 250 to 270 seconds and made adjustments by weight-dependent coadministration of additional heparin. No adjunct abciximab was administered in the control and the filter protection groups.

Intervention

A single operator (R.A.) performed all interventions as described elsewhere. In brief, after administration of antithrombotic therapy, the guidewire was navigated through the stenosis. Predilatation was performed in all but 4 lesions with the use of a 3-3.5/30-mm balloon catheter, and self-expanding stents (Wallstent, Boston Scientific; Acculink-stent, Guidant) were deployed in all patients either over the wire or in monorail technique with distal filter protection (FilterWire EX, Boston Scientific). Single, short-term postdilatation was performed to deflate the stent with a 5-6/40-mm balloon catheter. The vascular access sheath was removed immediately after intervention, and the puncture site was sealed (Angioseal, St Jude Medical).

Diffusion-Weighted MRI

Baseline and postinterventional DW MRI was an obligation in this study according to the ethics committee and was performed on a 1.5-T high-field scanner (Philips) with a single-shot, spin-echo, echo-planar imaging sequence (echo time = 125 ms/repetition time = 1784 ms/b = 1000). A volume of 20 slices with field of view of 240 mm, scan matrix of 128×128 voxels (reconstruction matrix: 256×256 voxels), and slice thickness of 6 mm (0.1-mm gap) was examined. Diffusion was measured in 3 orthogonal planes, and isotropic images were calculated. Acute ischemic affections were evaluated on isotropic b1000 DW images.

Clinical End Points

The primary clinical end point was the occurrence of any peri-interventional neurological event classified as transient ischemic attack (TIA) or minor or major stroke according to Wholey et al. All patients were examined before and after intervention by on-call neurologists who were not aware of the patients’ treatment group and were reexamined 30 days after the procedure for residual neurological disability. Predefined secondary clinical end points were bleeding complications, classified as major when hemoglobin decrease was >2 g/dL and minor when hemoglobin decrease was ≥2 g/dL, and thrombocytopenia, classified as moderate when platelet count ranged from 50 000 to <100 000/µL with ≥25% decrease from the baseline count and as severe when platelet count was <50 000/µL. Pseudothrombocytopenia was defined as a 20% difference of the platelet count in 2 anticoagulants.

Blood Sampling

Peripheral venous blood was drawn in 1/10 volume of 3.8% sodium citrate (1.29 mol/L) on admission to the hospital, 1 and 24 hours after intervention. Plasma samples were centrifuged (1500 g) and stored at −80°C until analysis. Whole blood used for flow cytometric analysis was processed immediately.

Whole Blood Flow Cytometry

One hundred microliters of anticoagulated whole blood was incubated with pretitrated fluorescence-labeled monoclonal antibody anti–CD14-Cy5, anti–CD42b-APC, and anti–CD62P-PE (ImmunoTech) and monoclonal antibody anti-human TF-FITC (American Diagnostica) for 10 minutes at room temperature. Cells were fixed by adding 100 µL of Optilyse B (Instrumentation Laboratories), subjected to erythrolysis in 1 mL of distilled water, and analyzed by flow cytometry (FACScalibur with CellQuest software; Becton Dickinson) with the use of a standard 4-color filter configuration.

Definition of MPA

Gating CD14+ events on a 2-parameter dot plot displaying side scatter (SSC) versus CD14-Cy5 (FL-3) identified monocytes in whole blood. A total of 50 000 counts with 3000 CD14+ events were acquired. Expression of TF (CD142), gp1bα (CD42b), P-selectin (CD62P), and CD40L (CD154) was identified on single-parameter histograms. Respective isotype control antibody fluorescence was used to delineate a negative from the positive population with allowance for a 2% overlap. Data are given as percentage of positive events, which describes the proportion of CD14+ monocytes adherent to either constitutive (CD42b) and activated (CD62P, CD154) platelet markers or expressing TF.

Immuonassay

Prothrombin fragment F1.2 (Behring) and sCD40L (Bender, Med Systems) were determined by immunoassay at absorbance of A590 and A450 nm, respectively, with the use of a sandwich-type enzyme-linked immunoassorbent assay system according to the manufacturer’s instructions.
TABLE 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control n=30</th>
<th>Abciximab n=20</th>
<th>Protection n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72±8</td>
<td>73±9</td>
<td>71±10</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (37)</td>
<td>8 (40)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17 (57)</td>
<td>14 (70)</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (10)</td>
<td>2 (10)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (20)</td>
<td>3 (15)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Cardiovascular risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (97)</td>
<td>19 (95)</td>
<td>25 (83)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (23)</td>
<td>7 (35)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27 (90)</td>
<td>19 (95)</td>
<td>26 (87)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>17 (57)</td>
<td>12 (60)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Symptomatic CVD within last 6 months, n (%)</td>
<td>4 (13)</td>
<td>2 (10)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>History of transient ischemic attack, n (%)</td>
<td>9 (30)</td>
<td>4 (20)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>4 (13)</td>
<td>1 (5)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Contralateral occlusion, n (%)</td>
<td>4 (13)</td>
<td>1 (5)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

CVD indicates cerebrovascular disease.

TF Activity
TF activity of debris captured in filter devices was determined by chromogenic assay after 3 freeze-thaw cycles of samples eluted in assay buffer and incubation with factor VIIa (3.5 mmol/L) and factor X (165 mmol/L) at 37°C for 30 minutes. Amidolytic activity on Spectrozyme Xa (0.5 mmol/L) was determined at A405 nm with the use of a kinetic plate reader (DIAS, Dynatech CA) and compared with a standard curve created by serial dilutions of relipidated TF (2 to 312 pg/mL) complexed to factor VIIa (3.5 mmol/L).

Statistical Analysis
Epidemiological data are given as mean±SD unless otherwise stated. Numerical data for flow cytometry and immunoassay are given as median and interquartile range (Q1/Q3). Differences between groups for numerical parameters were calculated by Friedman ANOVA and were corrected for multiple comparisons according to Bonferroni. Differences for the same variable within the group were calculated by 1-way ANOVA and were corrected for multiple comparisons according to Bonferroni. Differences between groups for numerical parameters were calculated by Friedman ANOVA. Categorical variables were compared by χ² test. A value of P<0.05 was considered significant. SPSS version 10 for Macintosh was used as statistical software.

Results
Baseline Patient Characteristics
Study groups and controls were not different with respect to age, sex distribution, or cardiovascular risk factors (Table 1). Less than 25% of patients had symptomatic CVD within the last 6 months. However, as a result of comorbidities and individual lesion characteristics (Table 2), all patients enrolled were considered at high surgical risk.

Interventional Outcome and Ischemic Complications
Interventional success with residual stenosis of <30% was achieved in all patients. All ischemic episodes occurred within 24 hours of intervention, and the incidence of any peri-interventional neurological deficit (PND) was not statistically different between abciximab and control groups (P=0.2), although TIAs were less frequent with adjunct abciximab (P=0.05). Filter protection significantly lowered the rate of PND compared with control (P=0.001) and abciximab (P=0.04). No intervention-related death was registered within 30 days of follow-up. The NIHSS score of patients with major stroke in the abciximab group declined rapidly within 48 hours (Table 4).

Ischemic Lesion Formation After Carotid Stenting
All patients with clinical PND showed de novo cerebral lesion formation by DW MRI. However, 4 of 6 (66%), 2 of 3 (66%), and 7 of 14 (50%) MRI-defined de novo lesions remained clinically asymptomatic with adjunct abciximab, with filter protection, and in the control group, respectively (Tables 3 and 4).

Bleeding Complications and Thrombocytopenia
No major bleeding or intracranial hemorrhage was observed. One minor bleeding at the sheath implantation site in the control group caused subcutaneous hematoma. Moderate thrombocytopenia in 1 case in the control group was associated with TIA. One case of “severe thrombocytopenia” in the abciximab group was due to pseudothrombocytopenia (Tables 3 and 4).

MPA Formation and Monocyte TF Expression
The percentage of MPA, detected by constitutive (CD42b) and platelet activation markers (CD62P, CD40L), significantly correlated with the percentage of TF-expressing monocytes (TF+/CD14+; Figure 1) at baseline.
In patients with symptomatic CVD within the last 6 months, the percentage of activated MPA (CD62P/CD14+/CD14+) was 53% [interquartile range, 45% to 67%] versus 36% [range, 24% to 48%]; P = 0.001) was higher than in asymptomatic patients. In patients with PND, formation of activated MPA (CD62P/CD14+/CD14+) was increased on day 1 after intervention compared with patients without PND (47% [interquartile range, 37% to 68%] versus 34% [interquartile range, 23% to 39%]; P = 0.041; Figure 2B). No significant difference was observed for monocyte TF expression (Figure 2E) or F1.2 (Figure 2F) between PND and no-PND groups with pooled antithrombotic treatment. F1.2 significantly increased after intervention in both groups (P = 0.001; Figure 2F). In patients without PND, sCD40L decreased 1 hour after intervention (post: P = 0.001) to a level significantly lower than that of the PND group (1 [interquartile range, 0 to 5] versus 7 [interquartile range, 0 to 11] ng/mL; P = 0.001; Figure 2D). In the PND group, CD40L coexpressed in MPA (CD40L+/CD14+) was significantly lowered after intervention compared with the no-PND group (82% [interquartile range, 75% to 84%]) versus 68% [interquartile range, 63% to 71%]; P = 0.025; Figure 2C).

Effect of Abciximab and Filter Protection on Monocyte-Platelet Cross Talk
Platelet activation as measured by the percentage of (CD62P+/CD14+)-MPA was significantly reduced by adjunct abciximab (Figure 3B) 1 hour after intervention, associated with early reduction of monocyte TF (Figure 3E). A significant early periprocedural decrease of sCD40L (Figure 3D), but not of (CD40L+/CD14+)-MPA (Figure 3C), was observed with adjunct GPIIb/IIIa inhibition and filter protection (Figure 3D). On day 1 after intervention, both filter protection and adjunct abciximab resulted in reduced MPA, monocyte TF, and F1.2 generation (Figure 3A, 3B, 3E, 3F).

TF Activity in Filter Devices
Debris retrieved from filter devices contained a median TF activity of 28 [interquartile range, 9 to 87] pg/mL.

Discussion
Carotid angioplasty and stenting became an alternative to surgical endarterectomy for treatment of patients with carotid

![Figure 1](http://stroke.ahajournals.org/) Percentages of TF+ monocytes (Mo) and MPA as defined by platelet markers CD42b (A), CD62P (B), and CD40L (C) were correlated at baseline according to Pearson.
Patients with (PND) and without (no PND) symptoms of peri-interventional neurological deficit after carotid stenting were compared before (pre), 1 hour (post), and 24 hours (day 1) after intervention for percentage of MPA (A to C), plasma level of sCD40L (D), percentage of TF+ monocytes (Mo) (E), and plasma level of F1.2 (F) by ANOVA.

Figure 2.
artery stenosis and high surgical risk. However, symptomatic and asymptomatic microembolization are frequent complications in unprotected carotid stenting. Emboli of particulate matter derived from the atherosclerotic plaque consist of cholesterol clefts, calcium precipitates, fibrotic tissue fragments, thrombotic material, and activated platelets. In addition to the balloon-injured site of intervention, microemboli cause significant platelet activation, thrombus propa-

Figure 3. Percentage of MPA (A to C), plasma level of sCD40L (D), percentage of TF+ monocytes (Mo) (E), and plasma level of F1.2 (F) were compared before (pre) and 1 hour (post) and 24 hours (day 1) after intervention between the control, abciximab, and protection groups by ANOVA.
gation, and ischemia within the distal microvascular circulation. In parallel with the standardization of distal protection devices, optimal antithrombotic therapy is required during carotid stenting.

Encouraged by effective dethrombosis and reduction of ischemic complications in percutaneous coronary interventions, the safety and efficacy of abciximab were evaluated in carotid stenting as adjunct to the standard antithrombotic regimen, showing a trend for reduced periprocedural ischemic episodes.

Abciximab was shown to facilitate dispersal of newly formed platelet aggregates in vitro, displacing fibrinogen from activated GPIIb/IIIa receptors. However, the disaggregation effectiveness of abciximab decreased as the time between platelet activation and the addition of abciximab widened, indicating that abciximab is most effective at an early stage of thrombus formation. In analogy, bolus abciximab alone did not reduce periprocedural ischemic events since the process of platelet activation and thromboembolism continues for hours after carotid angioplasty.

We studied the effect of bolus and 12-hour infusion of abciximab as adjunct to the standard antithrombotic regimen versus filter protection on immediate clinical outcome and platelet-leukocyte cross talk in carotid stenting. In accordance with a previous study, the incidence of any PND was not significantly different between abciximab and control groups but was reduced with filter protection. However, the number of TIAs was reduced with adjunct abciximab (P=0.05), and the symptoms of major stroke in 1 patient of the abciximab group resolved almost completely within 48 hours. Although abciximab may cause hemorrhage in the setting of chronic and acute ischemia, no cerebral hemorrhage was detected with adjunct GPIIb/IIIa inhibition in our study.

Our data obtained by whole blood flow cytometry showed a higher number of activated MPA (CD62P+/CD14+) in patients with symptomatic CVD on admission and demonstrated correlative evidence for the increased expression of monocyte TF as a consequence of platelet-leukocyte cross talk in vivo. Abciximab reduced early MPA formation, resulting in limited leukocyte activation with lower monocyte TF expression. Consequently, decreased in vivo thrombin generation (reflected by reduced F1.2) may have diminished thrombus propagation and microembolic ischemia in the abciximab group. Although the protection device failed to reduce early peri-interventional MPA formation or TF expression, it captured microembolic debris expressing significant amounts of TF activity, which led to reduced platelet and leukocyte activation as detected on day 1 after intervention, suggesting that capture and elimination of embolic debris additionally diminished platelet activation. sCD40L was generally decreased 1 hour after intervention but was more pronounced with adjunct antithrombotic therapy and filter protection, suggesting reduced thrombus stabilization and diminished microembolic ischemia in the 2 study groups. Activated platelets engaged in heterotypic aggregates with monocytes may have provided a source for sCD40L since the percentage of activated MPA defined by CD40L+/CD14+ decreased in patients with PND.

In summary, distal filter protection appears superior to adjunct GPIIb/IIIa inhibition in prevention of PND during carotid stenting. However, peri-interventional use of abciximab may be considered during carotid stenting in patients who do not allow positioning of distal or flow reversal protection devices and in patients with periprocedural TIA despite filter protection. The combination of both distal protection and adjunct abciximab in carotid stenting remains to be studied.

Acknowledgments
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References
We read with great interest the article by Kopp et al in this issue of Stroke. In this article, patients undergoing carotid stenting were randomized to receive either aspirin, clopidogrel, and heparin therapy, or adjunct therapy with an abciximab bolus and infusion for 12 hours. A third cohort of 30 patients underwent stenting with filter protection using the same regimen (without adjunctive abciximab). Filter protection resulted in the greatest protection from de novo ischemic lesions demonstrated on MRI and was associated with the fewest periprocedural transient ischemic attacks and total ischemic events.

The authors use flow cytometry and immunoassays to convincingly demonstrate the utility of abciximab in reducing postintervention activated monocyte-platelet aggregates and TF-positive monocytes, thus limiting the potential for thrombus propagation. Nonetheless, the benefit of abciximab was still inferior to that of filter distal protection. Additionally, the potential for bleeding complications, especially in the setting of chronically ischemic brain, is greater with the use of abciximab. Thus, filter protection provides greater benefit with less bleeding risk, suggesting that distal protection should be considered for all patients requiring carotid stenting.

Although recent data exist in which the utility of distal protection devices in high-risk carotid patients is shown, this article provides evidence for the use of filter protection in all patients undergoing carotid stenting. Perhaps the benefit of filter protection is the ability to prevent ischemia resulting from embolic debris (directly) and from early periprocedural decrease of soluble CD40 ligand. Reduced MPA, monocyte TF, and Fl.2 generation was also seen with filter protection, as well as with abciximab administration. In those patients in whom the internal carotid artery is not compatible with the delivery of protection devices because of anatomical constraints (small diameter or excessive tortuosity), abciximab administration may be a good “second-line” defense against periprocedural stroke in patients.

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