Randomized Evaluation of Anticoagulation Versus Antiplatelet Therapy After Coronary Stent Implantation in High-Risk Patients

The Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS)

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Background—Although the association of ticlopidine and aspirin has been shown to be superior to anti–vitamin K agents and aspirin after coronary stent implantation in low-risk patients, the latter combination has remained an unproven reference regimen for high-risk patients until recently.

Methods and Results—We randomized 350 high-risk patients within 6 hours after stent implantation to receive during 30 days either aspirin 250 mg and ticlopidine 500 mg/d (A+T group) or aspirin 250 mg/d and oral anticoagulation (A+OAC group) targeted at an international normalized ratio of 2.5 to 3. The primary composite end point was defined as the occurrence of cardiovascular death, myocardial infarction, or repeated revascularization at 30 days. Patients were eligible if (1) the stent(s) were implanted to treat abrupt closure after PTCA; (2) the angiographic result after implantation was suboptimal; (3) a long segment was stented (>45 mm and/or ≥3 stents); or (4) the largest balloon inflated in the stent had a nominal diameter of ≤2.5 mm. The primary cardiac end point was reached for 10 patients (5.6%) in the A+T group and 19 (11%) in the A+OAC group (relative risk [RR], 1.9; 95% CI, 0.9 to 4.1; P=0.07).

Major vascular and bleeding complications were less frequent in the A+T group (3 patients, 1.7%) than in the A+OAC group (12 patients, 6.9%) (RR, 4.1; 95% CI, 1.2 to 14.3; P=0.02).

Conclusions—High-risk patients should be treated with A+T rather than A+OAC after coronary stenting because the bleeding and vascular complications are significantly reduced and there is a marked trend suggesting a decrease in cardiac events. (Circulation. 1998;98:2126-2132.)

Key Words: angioplasty ■ antiplatelet agents ■ stents ■ thrombosis
A+T combination with the current standard of A+OAC in the prevention of subacute (<1 month) cardiac events in high-risk situations after coronary stent implantation. The secondary objective was to assess the safety of both regimens in terms of vascular and bleeding complications.

Study Design
Thirty-one centers in 9 European countries (see the “Appendix”) included patients between February 1996 and January 1997. The study was designed as a multicenter, randomized, controlled, open-label study conducted in 2 parallel groups of patients considered at high risk of subacute occlusion after intracoronary stenting. Patients were assigned to a 1-month treatment period with either A+T or A+OAC. Each patient gave written informed consent. The study was approved by the local ethical review board in each participating center and was carried out according to the principles of the Helsinki declaration and the European Guidelines for Good Clinical Practice.

Randomization Procedure
Randomization was carried out by contacting a central randomization service by telephone within the first 6 hours after completion of the procedure. It was stratified into 4 stent categories on the basis of the procedure. It was stratified into 4 stent categories on the basis of the principles of the Helsinki declaration and the European Guidelines for Good Clinical Practice.

Inclusion and Exclusion Criteria
Patients were candidates for the study if they satisfied ≥1 of the following conditions at the end of the implantation procedure (Figure 1): bailout situations if the stent(s) were implanted because of abrupt closure (TIMI grade 0 or 1 flow) or because of coronary dissection type C, D, E, or F after balloon angioplasty; suboptimal result of stenting with residual stenosis within the deployed stent estimated of >20% diameter stenosis, angiographically documented residual dissection or >30% diameter stenosis immediately proximal or distal to the deployed stent, or slow flow (less than TIMI grade 3) through the stented segment at the end of the procedure; multiple stent implantations in the same vessel if ≥3 stents were implanted or if the total stented length was ≥45 mm; and nominal diameter of the largest balloon inflated in the stent ≤2.5 mm. Patients were excluded from randomization if any of the following conditions were met: recent myocardial infarction with total serum creatinine phosphokinase levels still above the upper limit of normal; persistent ischemia determined by 12-lead ECG recordings and/or chest pain at the time of randomization; age <18 years; pregnancy; anticipated difficulties with follow-up; administration of GP IIb/IIIa antagonists either before or during the procedure or planned administration during the 30-day follow-up period; ongoing OAC treatment or contraindication to either aspirin, ticlopidine, OAC, or heparin; coronary re-intervention (percutaneous or surgical) planned within the 30-day follow-up period; and previous participation in any other study involving an investigational drug or device within the past 30 days.

Study Drugs and Procedures
All study medication was open labeled. For patients in the A+T group, ticlopidine 250 mg BID and aspirin 250 mg/d were started immediately after randomization. The whole daily dose (500 mg) of ticlopidine was given in 1 intake on the first day. Intravenous heparin was discontinued 6 hours before sheath removal and was not to be administered for >36 hours. Patients in the A+OAC group received aspirin 250 mg immediately after randomization, and OAC was started on the day of the procedure. The OACs were targeted at an international normalized ratio (INR) of 2.5 to 3.0. Heparin was discontinued when a stable INR was achieved (2 measurements of >2.5 separated by ≥24 hours). All other treatments except GP IIb/IIIa antagonists (see exclusion criteria above) were at the discretion of the attending physicians, whether before, during, or after the procedure. Creatine kinase (CK) and CK-MB levels were obtained at least once on the day after the procedure and more often if clinically indicated. Activated partial thromboplastin time and INR were monitored at least daily in the A+OAC group during the hospital stay. After hospital discharge, blood cells and platelet counts were checked on day 15 in both groups, and INR was monitored at least weekly in the A+OAC group. At the time of the 30-day follow-up visit, a physical examination, an ECG, and hematological

### TABLE 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=350)</th>
<th>A+T Group (n=177)</th>
<th>A+OAC Group (n=173)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>60.4±9.9</td>
<td>60.2±9.3</td>
<td>60.7±10.5</td>
<td>NS</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>69 (19.7)</td>
<td>27 (15.3)</td>
<td>42 (24.3)</td>
<td>0.035</td>
</tr>
<tr>
<td>Mean body mass index</td>
<td>26.6±3.3</td>
<td>26.4±3.1</td>
<td>26.8±3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>172 (49.1)</td>
<td>88 (49.7)</td>
<td>84 (48.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>31 (8.9)</td>
<td>13 (7.3)</td>
<td>18 (10.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous PTCA, n (%)</td>
<td>81 (23.1)</td>
<td>41 (23.2)</td>
<td>40 (23.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>9 (2.6)</td>
<td>4 (2.3)</td>
<td>5 (2.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous cerebral TIA, n (%)</td>
<td>7 (2.0)</td>
<td>5 (2.8)</td>
<td>2 (1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>37 (10.6)</td>
<td>14 (7.9)</td>
<td>23 (13.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>51 (14.6)</td>
<td>25 (14.1)</td>
<td>26 (15.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>128 (36.6)</td>
<td>61 (34.5)</td>
<td>67 (38.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>167 (47.7)</td>
<td>87 (49.2)</td>
<td>80 (46.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>70 (20.0)</td>
<td>32 (18.1)</td>
<td>38 (22.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
counts were again obtained. In the A+T group, hematological counts were repeated 5 to 6 weeks after the index procedure. All patients in both groups were then followed up clinically for 6 to 8 months.

Definitions
The primary efficacy end point was defined as the occurrence of 1 of the following critical cardiac events, whichever occurred first:

1. Cardiovascular death.
2. Any myocardial infarction in the territory of the stented vessel. Myocardial infarction was counted as an end point whether it occurred spontaneously or in association with angioplasty or surgery. A diagnosis of myocardial infarction was made if new Q waves not occurring spontaneously or in association with angioplasty or surgery. A diagnosis of myocardial infarction was made if new Q waves not present at baseline developed on the ECG and/or if the creatinine phosphokinase levels increased beyond the upper limit of normal together with a CK-MB increase above the upper limit of normal.
3. Repeated percutaneous intervention or CABG involving the previously stented segment because of recurrent ischemia, arrhythmia, or hemodynamic failure.

The secondary safety end point of major vascular and/or bleeding complications was defined as the occurrence of ≥1 of the following:

1. Vascular access site requiring surgical repair.
2. Any bleeding leading to a decrease of hemoglobin of ≥4 g/dL and/or requiring transfusion of ≥2 U of blood.
3. Documented intracranial or retroperitoneal bleeding.

Adequate compliance was defined for the A+T group as the intake of at least half of the tablets of ticlopidine and sachets of aspirin and for the A+OAC group as the intake of at least half of the sachets of aspirin and no evidence of premature permanent discontinuation of OAC. All events of both efficacy and safety end points were blindly validated by an independent Critical Adverse Event Committee.

Statistical Methods

Study Power
According to the literature available at the time of study design, the incidence of subacute stent thrombosis in high-risk situations after coronary stent implantation ranged from 12% to 20% with conventional anticoagulant and aspirin therapy. Results in similar patients treated with A+T suggested a risk of subacute occlusion of 3% to 7%. Considering the improvements in stent implantation techniques being made at the time, the lower incidence of both ranges was used for sample size calculation. With an α risk of 5% and a β risk of 15% in a bilateral test, the number of patients required per group was 175. A total of 350 patients was therefore chosen.

Primary End Point
The data were first analyzed according to the intention-to-treat principle. We used χ² tests to compare the 2 groups. A Mantel-Haenszel χ² test was computed to adjust the statistic on the stratification variable. The Breslow-Day test was used to assess the interaction between strata and judgment criteria. The relative risk and its 95% CI were computed by the Taylor method. Survival curves were computed using the Kaplan-Meier analysis. Log rank and Wilcoxon’s statistics were used to test the global homogeneity of the 2 curves. Similar analyses were carried out on a per-protocol basis for only those patients documented as compliant with the study drug regimen.

Secondary End Point
The incidence of major vascular and bleeding complications within 1 month after stenting in the 2 groups was compared with a χ² test, and the 95% CIs of percentages were calculated in each group.

Results
Three hundred fifty patients were enrolled in 31 centers from 9 European countries (see the “Appendix”). Baseline clinical and angiographic characteristics are given in Table 1. Index angioplasty and stenting procedures are summarized in Table 2. Sixty-six patients (33 in each group) received 1 or several Palmaz-Schatz stents, 16 (10 in the A+T group and 6 in the A+OAC group) received only Wiktor stents, 15 (8 in the A+T group and 7 in the A+OAC group) received only Gianturo-Roubin stents, and 253 (126 in the A+T group and 127 in the A+OAC group) received other types of stents (114 Microstents [AVE], 61 NIR [Scimed], 34 Multilink [ACS], 20 Pura [Devon], 16 Wallstent [Schneider], and 12 various) or a combination of several stent types.
A1 OAC group (95% CI, 6.7% to 16.6%). The relative risk of reaching the main end point was therefore 1.94 (95% CI, 0.93 to 4.06) (P=0.07). The same probability value was obtained with the Mantel-Haenszel test after the homogeneity of the randomization strata had been checked (Breslow-Day test, P=0.301). Individual end points are depicted in Figure 2, and cardiac event-free survival curves are shown in Figure 3. There were 3 deaths in the A+T group (1 cardiac tamponade on day 1, 1 closure of a nonstented vessel on day 3, and 1 pulmonary edema on day 6) and 2 in the A+OAC group (both caused by subacute stent thrombosis and unsuccessful reintervention on days 3 and 6, respectively). The secondary end point of major vascular access site and/or bleeding complications was reached by 3 of 177 patients (1.7%) in the A+T group (95% CI, 0.4 to 4.9) and by 12 of 173 patients (6.9%) in the A+OAC group (95% CI, 3.6 to 11.8) (P=0.02). In the A+T group, 1 patient developed access site pseudoaneurysm, 1 had vascular access site surgery, and 1 suffered gastrointestinal bleeding. Among the 12 patients with ≥1 secondary end points in the A+OAC group, 5 suffered retroperitoneal bleeding, 5 had access site bleeding, 2 developed femoral pseudoaneurysm, and 2 had significant bleeding from other sources (1 gastrointestinal and 1 pleural). No patient in either group developed intracerebral bleeding. The mean duration of hospital stay after the index stenting procedure was 4.6±4.5 days (range, 2 to 33 days) in the A+T group and 7.7±4.1 days (range, 2 to 32 days) in the A+OAC group (P<0.0001).

When the main end-point evaluation was repeated with a per-protocol analysis at 30 days, 10 of 172 patients (5.8%) in the A+T group and 17 of 157 patients (10.8%) in the A+OAC group (P=0.1) developed critical cardiac events. During the extended follow-up period (2nd to 6th month after stent implantation), a similar number of cardiac events were reported in both groups (Table 3).

### Patient Compliance and Potential Drug Side Effects

One hundred sixty-eight patients (95%) in the A+T group and 147 (85%) in the A+OAC group completed the 30-day treatment as scheduled. Reasons for premature discontinuation of treatment in the A+T and A+OAC groups were critical cardiac end point reached (5 and 7 patients, respectively), adverse event (2 and 13 patients), or a combination of both (1 and 5 patients). One additional patient in the A+T group was given OAC instead of the study drug because of the onset of atrial fibrillation during the follow-up period. Overall, noncompliance (insufficient adhesion to the prescribed drug regimen) was 1.7% in the A+T group and 3.5% in the A+OAC group.

Three patients (1.7%) in the A+T group developed asymptomatic granulocytopenia 27, 29, and 32 days, respectively, after ticlopidine was first given. Because of the late onset of this side effect, it did not lead to premature treatment cessation and resolved spontaneously without any clinically apparent consequences. Nadir values for white blood cell and neutrophil counts were 2000 and 200 cells/mm³, 3500 and 1500 cells/mm³, and 3000 and 900 cells/mm³, respectively. A skin rash or cutaneous allergic reaction developed in 6 patients (3.4%) in the A+T group, led to permanent premature treatment cessation in 3 (1.7%), and was considered drug related in 3 (1.7%). In 1 of these 3 patients, a Stevens-Johnson syndrome required the patient to be hospitalized but resolved over 6 days after interruption of A+T. The patient developed a cardiac event during the 4th week after stenting while taking no antithrombotic medication. In the A+OAC group, a rash or allergic reaction was observed in 10 patients (5.8%); it was thought to be drug related in 1 (0.6%), but treatment was continued. In the A+T group, 3 patients (1.7%) developed hepatitis, and 3 others (1.7%) had mild to moderate transient serum hepatic enzyme rises a median of 32 days after study onset (range, 0 to 45 days). Resolution occurred in all cases and did not require the study drugs to be

### TABLE 3. Cardiac Events Between 30 Days and 6 Months

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>A+T Group (n=167), n (%)</th>
<th>A+OAC Group (n=154), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Non-Q-wave myocardial infarction</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>CABG</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Repeated PTCA</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Composite (any of the above)</td>
<td>28 (16.8)</td>
<td>25 (16.2)</td>
</tr>
</tbody>
</table>
interrupted. In the A+OAC group, 1 patient (0.6%) developed cholecystitis after 18 days, and OAC was discontinued. Minor gastrointestinal complaints were noted in 16 patients (9.0%) in the A+T group and 7 patients (4.0%) in the A+OAC group but led to treatment adjustment in only 1 patient in the A+OAC group and none in the A+T group.

There were no significant differences in the incidence of cardiac events between both groups for the period extending beyond the 30-day period to 6 months (Table 3).

Discussion

The recent exponential development of coronary stenting was made possible by the conjunction of major improvements in implantation techniques, availability of new designs, and use of combined antiplatelet regimens using aspirin and ticlopidine. For high-risk situations, however, a course of OAC is still often recommended after coronary stent implantation. The present study suggests that this should no longer be considered optimal because treatment is greatly simplified by the use of an A+T combination, duration of hospital stay is reduced, and bleeding and/or vascular complications are clearly less frequent than with A+OAC. Although the main end point of MATTIS just failed to reach statistical significance (relative risk of A+OAC versus A+T, 1.94; 95% CI, 0.93 to 4.1; \( P = 0.07 \)), there was also a marked trend in favor of the antiplatelet regimen for preventing cardiac events during the 30-day follow-up. When the present results are analyzed in conjunction with the available information from other workers, it appears that combined antiplatelet therapy should now be considered as the preferred mode of treatment for all patients after coronary stent implantation, regardless of their risk stratification.

In the first randomized controlled evaluation of adjunctive therapy in a group of 517 patients following implantation of Palmaz-Schatz stents (ISAR trial), Schömig et al showed that a regimen of A+T compared with conventional management with A+OAC was associated with a significantly lower incidence of cardiac events at 1 month (1.6% versus 6.2%, respectively). The occurrence of major vascular and/or bleeding complications was also reduced (0% versus 6.5%). Furthermore, a subgroup of patients at high risk in the ISAR study was reported separately, and the benefit of A+T over A+OAC was greater in those patients than in the intermediate- and low-risk groups. Bertrand et al evaluated the Wiktor stent in a similar fashion in an intermediate-risk group of 485 patients (FANTASTIC trial), and their results suggested that the benefit of combined antiplatelet therapy is not limited to slotted-tube stents but also exists for tantalum coil stents. Leon et al evaluated A+OAC versus A+T versus aspirin alone in 1652 patients with an optimal result after implantation of a single Palmaz-Schatz coronary stent in a native vessel (STARS trial). The incidence of major cardiac events was significantly lower with combined antiplatelet therapy (0.6%) than with either A+OAC (2.4%) or aspirin alone (3.6%). In this low-risk population with a target INR of 2.0 to 2.5, the overall bleeding and/or vascular complication rate was low, and the differences between groups were less important (2.2% for A+T, 2.4% for A+OAC, and 1.3% for aspirin alone; \( P = \text{NS} \)). Finally, Hall et al compared aspirin alone to A+T after coronary stenting. A trend was observed in favor of the combination therapy (cardiac events, 3.9% versus 0.8%; bleeding/vascular complications, 1.0% versus 0% respectively), further suggesting the superiority of combined antiplatelet therapy over aspirin alone.

Most of the differences in overall clinical outcome between MATTIS and the previously reported evaluations discussed above can most likely be attributed to the patients’ risk profiles because these differed markedly by design and ranged from low (STARS) to intermediate or mixed (Hall et al, ISAR, FANTASTIC) to high (MATTIS) (Figure 4). The composite end points also varied between studies (in STARS, only Q-wave infarction, not isolated CK elevation, was considered a major adverse event) and may further explain some of the differences. Stent type could also have influenced the incidence of cardiac events after implantation, but this was not apparent from the present study because a large number of different stents was used by the investigators and the 4 predefined stent categories were associated with similar rates of cardiac events.

Neutropenia was noted in 3 patients (1.7%) in the A+T group. It occurred late (at the end of the 1-month treatment course), did not lead to any clinical manifestations, and resolved spontaneously. This clearly underlines the need for full blood count monitoring in routine clinical practice, once every 2 weeks for as long as ticlopidine is given during the first 3 months. Clopidogrel is an ADP receptor antagonist that inhibits platelet aggregation. The CAPRIE study has shown that clopidogrel provides additional benefit in preventing stroke, myocardial infarction, and vascular death in patients at high risk of thrombotic events compared with aspirin, with no increase in the neutropenia rate. It is likely that clopidogrel will become a preferable alternative to ticlopidine after stent implantation.

Study Limitations

The MATTIS trial was designed to evaluate clinical and not angiographic end points. The incidence of subacute stent thrombosis is thus not precisely known. Systematic repeated coronary angiography after all nonfatal cardiac events would not have been practical or indeed ethically acceptable. The clinical end points, which are also more meaningful to the patient, were therefore used alone. They were all validated by an independent Critical Adverse Event Committee that was blinded to treatment assignment.

![Figure 4. Randomized controlled trials of pharmacological treatment after coronary stent implantation (definitions of cardiac events are not identical in each study; see text).](image-url)
Platelet IIb/IIIa receptor blocking agents were, by design, not used in the present study. We chose to exclude patients already receiving such agents before randomization because this would most probably have decreased our ability to detect significant differences between the 2 study arms. After randomization, patients would have been potential candidates only for “rescue” administration of IIb/IIIa agents,14 a still unresolved mode of therapy.

We attempted to stratify patients in both groups according to the type of stents implanted. There were no significant differences between the 4 predefined groups in terms of cardiac events, but because a great variety of new designs became available and have been widely used in Europe since 1995, the actual stratification was heavily skewed toward the “multiple and other types” stent group. This somewhat limits the ability of the study to totally eliminate the confounding effect of stent design on the occurrence of cardiac events after implantation. However, whereas most previous studies only concerned 1 stent type,18,20,22,23,30 8 different types of stents were used by the investigators in the present series, and the benefits of A+T were broadly similar to those discussed in previous reports. It would thus appear that a combined antiplatelet regimen is appropriate therapy after implantation of a variety of metallic coronary stents and is not limited to any particular design or composition.

Conclusions
The present data confirm the good benefit/risk ratio of A+T over A+OAC observed in other randomized controlled trials and allow extension of the indication for the combined antiplatelet therapy to individuals at high risk of stent thrombosis and cardiac events and to a wide variety of metallic stents currently used in daily practice.

Appendix
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Critical Adverse Event Committee
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References


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