Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty

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ABSTRACT To test the hypothesis that pretreatment with adequate antiplatelet therapy reduces the likelihood of acute coronary thrombosis during routine percutaneous transluminal coronary angioplasty (PTCA), we reviewed, blinded to treatment group, the films and records of 300 consecutive initially successful PTCA. Films before PTCA, immediately after, and at least 30 min after the last balloon inflation were assessed for the presence of any thrombus at the PTCA site. We excluded 37 patients who received streptokinase before PTCA or who had 100% occlusion or thrombus on pre-PTCA films. New thrombi were classified as clinically significant (defined as causing 100% occlusion or requiring emergency surgery or streptokinase therapy) or as not significant (not causing an acute problem or requiring intervention). Patients were classified into three groups, based on the type and extent of antiplatelet therapy received. Group 1 (no aspirin, n = 121) consisted of patients who did not receive aspirin before admission or in hospital before PTCA (with or without dipyridamole). Group 2 (standard treatment, n = 110) received aspirin with or without dipyridamole but did not receive both drugs before admission and in hospital before PTCA. Group 3 (maximal treatment, n = 32) received both aspirin and dipyridamole before admission and in hospital before PTCA. New thrombi were detected at 39 (14.8%) PTCA sites, of which 15 (5.7% of all PTCA sites) were considered clinically significant. Group 1 had the highest incidence of both thrombus (21.5%) and clinically significant thrombus (10.7%). A reduction was seen in group 2 in thrombus (11.8%; p = .07) and in clinically significant thrombus (1.8%; p = .005). Group 3 had no thrombus (p = .001) and no clinically significant thrombus (p = .04). In addition to inadequate pretreatment with antiplatelet therapy, univariate analyses demonstrated several other risk factors for thrombus: higher percent diameter stenosis before PTCA (p < .008), higher platelet count (p = .013), and current smoking (p = .03). Only higher platelet count (p < .001) and inadequate pretreatment (p = .001) were associated with clinically significant thrombus. Stepwise logistic regression analysis demonstrated that for thrombus, the lack of effective antiplatelet therapy was the most discriminatory variable, followed by current smoking, higher percent diameter stenosis, and dissection. For clinically significant thrombus, once the lack of pretreatment with effective antiplatelet therapy was considered, no other factors added significant discriminatory information. Thus, antiplatelet therapy administered before PTCA is associated with a decreased incidence and significance of acute coronary thrombosis complicating PTCA. The lack of effective antiplatelet therapy before PTCA, as well as current smoking, higher percent diameter stenosis, and dissection, identify patients at risk for this complication.

mole or in man given aspirin alone. Other factors, such as smoking, may alter endothelial competence and promote platelet reactivity. We hypothesized that pretreatment with effective antiplatelet therapy would decrease the incidence or severity of thrombus formed at the angioplasty site. We designed the following retrospective study to assess the association of pretreatment with aspirin (with or without dipyridamole) with a decreased incidence of acute coronary thrombosis complicating routine PTCA. In addition, we attempted to identify those clinical and angiographic variables that were predictive of this complication and to develop a predictive model of acute thrombosis complicating PTCA using stepwise logistic regression analysis.

Methods

Patients. The study group was drawn from all PTCA procedures performed at the Hospital of the University of Pennsylvania between April 20, 1980, and April 20, 1985 (402 attempted dilations in 369 patients). During this 5 year period, there was no uniform policy regarding the use of antiplatelet therapy before PTCA. The decision to institute prophylactic antiplatelet therapy in these patients was left to the referring physician and the hospital-based cardiologist. Concerns over excess bleeding problems in the event of emergency bypass surgery caused several physicians to avoid antiplatelet pretreatment. More than 95% of PTCA patients received at least 10,000 U of heparin intravenously in the laboratory (mean dose 10,213 U). After 1981, all patients received additional heparin as needed to keep the activated clotting time over 300 sec.

For inclusion in this study, we required that (1) the stenosis be crossed and dilated at least once, (2) a detailed medication history and in hospital nursing medication records be available, and (3) that films before, immediately after, and at least 30 min after dilation be available for review. Our laboratory’s policy is to routinely obtain angiograms in all patients 30 min after the last balloon inflation.

Our major aim was to study the effect of aspirin (with or without dipyridamole) on balloon-induced new thrombus formation. Accordingly, a total of 139 sites from 139 different patients were excluded (figure 1). There were inadequate films or records for 57 patients (14%). No dilation was performed in 45 patients. Of the remaining 300 sites, 13 had visible thrombus before PTCA and were analyzed separately. Since there was no way to exclude thrombus in patients receiving streptokinase or having 100% occlusion before PTCA, 21 sites meeting either of these criteria also were excluded. In addition, three patients taking antiplatelet agents other than aspirin or dipyridamole were excluded, leaving 263 sites from 220 patients as our study group.

Antiplatelet therapy. Each patient’s medication history was taken from the hospital record. A patient was considered to have been taking aspirin or dipyridamole before admission if it was recorded in the admission history, regardless of the dose. A patient was considered to have taken aspirin or dipyridamole in the hospital if the medication record indicated administration of the drug before PTCA, regardless of the dose or administration frequency. Since these criteria include patients with minimal therapy in a treatment group, they would be expected to bias the results against the identification of a treatment effect if the effect correlates positively with size of dose and frequency of administration.

The 263 sites were divided into three groups representing three increasing levels of pretreatment with antiplatelet drugs (figure 1). Group 1 (“no aspirin,” 121 sites) consisted of 101 sites from 99 patients with no antiplatelet pretreatment and 20 sites from 19 patients treated with dipyridamole alone. Group 2 (“standard treatment,” 110 sites) comprised 106 patients treated with aspirin either before admission or in hospital before PTCA or both. Dipyridamole was also taken in 71% of these cases at either or both times. Group 3 (“maximal treatment,” 32 sites) was composed of 28 patients who were treated with both aspirin and dipyridamole both before admission and in hospital before PTCA. Group 3 was distinguished from group 2 by the requirement that the patients must have received both drugs over both periods. These and other clinical characteristics (table 1) were obtained from the medical record without knowledge of the angiographic results.

Film review. All films were reviewed by one reviewer (J. W. H.) blinded to patient identity and treatment group. Films were scored for the presence of thrombus before, immediately after, and at least 30 min after the last balloon inflation. All films were scored as either definite thrombus, no thrombus, or uncertain for thrombus. The same three-tiered scale was used for all angiographic findings. A PTCA site was considered to have developed a thrombus only if a postinflation film was scored as having a definite thrombus. The reviewer attempted to differentiate between dissection and thrombus and to score thrombus as definite only when this distinction seemed clear angiographically. Films also were scored for the presence or absence of the

<table>
<thead>
<tr>
<th>TOTAL SITES ATTEMPTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>402</td>
</tr>
<tr>
<td>Included</td>
</tr>
<tr>
<td>263</td>
</tr>
<tr>
<td>Excluded</td>
</tr>
<tr>
<td>139</td>
</tr>
<tr>
<td>Inadequate Data: 57</td>
</tr>
<tr>
<td>Not Dilated: 45</td>
</tr>
<tr>
<td>Thrombus Pre-PTCA: 13</td>
</tr>
<tr>
<td>Other Antiplatelet Rx:3</td>
</tr>
<tr>
<td>Streptokinase Pre-PTCA:12</td>
</tr>
<tr>
<td>100% Stenosis: 9</td>
</tr>
</tbody>
</table>

FIGURE 1. Selection of the study population.
following angiographic findings: ulcerated plaque, eccentric stenosis, dissection, luminal irregularity, sluggish flow, peri-
vascular haziness, and filling defect. The percent diameter ste-
nosis was measured before and after PTCA.

Thrombus was defined as any combination of the following
angiographic findings that the reviewer deemed secondary
to definite thrombus and not a result of dissection or spasm: (1) the
appearance of a new, nonlinear filling defect, (2) new peri-
vascular haziness, (3) sluggish flow, or (4) new luminal irregu-
larities. More than one thrombus at a single site was counted only
once, although two thrombi at two separate sites were counted
separately.

Routine laboratory procedure included angiography immediately
after the last balloon inflation and angiography 30 min
later. Angiography was performed between these two times if
 warranted by the patient's symptoms. A change in the angi-
ographic appearance of the angioplasty site between the immedi-
ate and 30 min postinflation angiogram was instrumental in
identifying thrombi. Only 15% of thrombi were identified on
the immediate postinflation angiogram, leaving 85% that were
identified only on the 30 min postinflation angiogram.

Angiographically detected thrombi were further subdivided
into those that were clinically significant and those that were
not. A clinically significant thrombus was defined as one caus-
ing 100% occlusion of the vessel or requiring emergency bypass
surgery or streptokinase therapy. Vascular occlusion caused by
dissection or spasm was not considered to represent thrombosis.
A nonsignificant thrombus was defined as any angiographically
detected thrombus that did not meet the criteria for clinically
significant thrombus. Thrombi discovered at subsequent cath-
ereterization or acute occlusions thought to be thrombotic occur-
rning after initially leaving the catheterization laboratory were
not included in this study. Therefore thrombus and clinically
significant thrombus refer to acute events only.

**Statistical analyses.** For dichotomous variables, chi-square
analysis was used unless the expected value for a cell was less
than 5, in which case Fisher's exact test was used. A two-tailed
Student's t test was used for continuous variables. A p value
< .05 was considered significant for the univariate analyses
without correction for multiple comparisons. The relative risk
of thrombosis was estimated from the odds ratio. For stepwise
logistic regression analyses, the BMDP statistical package
was used with the F to enter a criterion of p < .10 and the F to
remove a criterion of p > .15. Continuous variables were divid-
ed into four ranges for the purpose of the multivariate analyses.
Loosely associated variables (p <.15) from the univariate anal-
eses were entered into the stepwise logistic regression analyses.
The contribution of antiplatelet therapy was further assessed by
performing multivariate logistic regression analyses after con-
trolling for potentially confounding variables. Data were ana-
yzed with both the PTCA site and the patient as the units of
analysis. Results for both groups were comparable. Unless oth-
wise specified, the results reported refer to the data analysis
performed with PTCA site as the unit of analysis.

**Results**

**Overall.** Of 263 sites dilated, 39 (14.8%) were iden-
tified as having developed a definite thrombus. Of the 39
thrombi, 15 were considered clinically significant
(5.7% of total sites dilated). Six of these were treated
successfully with intracoronary streptokinase alone,
whereas eight required emergency bypass surgery.
One complete occlusion was treated conservatively
without immediate intervention (figure 2). Thus
thrombi were responsible for early failure of the PTCA
procedure at nine sites (3.4%).

**Clinical characteristics.** Clinical characteristics were
similar in all three groups (see table 1). Group 3 had a
disproportionately high number of bypass graft dilations, since most patients are treated with aspirin and dipyridamole after bypass surgery. There were more current smokers (p = .01) and patients with hypertension (p = .02) in groups 1 and 3 than in group 2. Because the use of antiplatelet pretreatment became more common during the time of the study, there was a greater proportion of patients from the 1980 to 1982 period in group 1 than in the 1983 to 1985 period (p = .02).

Univariate analysis. Figure 3 demonstrates the incidence of thrombus and clinically significant thrombus broken down by antiplatelet treatment groups. Compared with group 1 (10.7%), there were significant reductions in clinically significant thrombus for both group 2 (1.8%; p = .005) and group 3 (0%; p = .04). Group 1 had a 21.5% incidence of thrombus, whereas group 2 had a lower rate (11.8%; p = .07) and group 3 had no thrombus (vs group 2, p = .04; vs group 1, p = .001). Combining groups 2 and 3 yields a group that comprises all patients who received aspirin at some point before PTCA. When this group is compared with group 1 (no aspirin), the incidence of thrombus was reduced by more than half to 9.2% (p < .01), and the incidence of clinically significant thrombus was reduced sixfold to 1.4% (p = .001).

As seen in figure 4, the incidence of thrombus and clinically significant thrombus also were analyzed by strict categories of no treatment, dipyridamole alone, aspirin alone, and aspirin and dipyridamole, with any doses being acceptable. The results were similar to those reported above. The rates of thrombus were as follows: no treatment 21.8%, dipyridamole alone 20% (p = .56), aspirin alone 12.5% (p = .19), and aspirin and dipyridamole 8.2% (p = .01). When analyzed for clinically significant thrombus in this way the results also were similar: no treatment 11.9%, dipyridamole alone 0% (p = .10), aspirin alone 3.1% (p = .13), and aspirin and dipyridamole 0.9% (p = .001). All p values represent comparisons with the no treatment group.

Several other outcome variables in addition to thrombus and clinically significant thrombus also were assessed for the three treatment groups. These are summarized in table 2. Emergency bypass surgery for all reasons (p = .04) and streptokinase administration (p = .02), as well as luminal irregularity (p = .04), were negatively correlated with antiplatelet pretreatment. Importantly, the incidence of dissection was uniformly distributed in the groups, as would be expected if it occurred independently of antiplatelet therapy. The lack of significance of the correlation between filling defect and treatment group is probably because dissec-
tion-induced filling defects were included in this category.

Univariate analyses also were performed with all clinical and angiographic variables to assess their degree of association with thrombus and clinically significant thrombus. As seen in table 3, in addition to the lack of pretreatment with aspirin and/or dipyridamole, higher platelet count (p = .013), current smoking (p = .03), and higher percent diameter stenosis before PTCA (p = .008) were positively associated with

<table>
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<tr>
<th>Outcome variable</th>
<th>Group 1 &quot;No aspirin&quot; (n = 121)</th>
<th>Group 2 &quot;Standard Rx&quot; (n = 110)</th>
<th>Group 3 &quot;Maximal Rx&quot; (n = 32)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Dissection</td>
<td>33 (27.3)</td>
<td>35 (31.8)</td>
<td>9 (28.1)</td>
<td>.79</td>
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<tr>
<td>Staggish flow</td>
<td>12 (9.9)</td>
<td>8 (7.3)</td>
<td>1 (3.1)</td>
<td>.42</td>
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<tr>
<td>Luminal irregularity</td>
<td>63 (52.0)</td>
<td>39 (35.5)</td>
<td>14 (43.8)</td>
<td>.04</td>
</tr>
<tr>
<td>Filling defect — any cause</td>
<td>37 (30.6)</td>
<td>25 (22.7)</td>
<td>5 (15.6)</td>
<td>.15</td>
</tr>
<tr>
<td>Perivascular haziness</td>
<td>38 (31.4)</td>
<td>22 (20.0)</td>
<td>8 (25.0)</td>
<td>.14</td>
</tr>
<tr>
<td>Streptokinase administration — all causes</td>
<td>12 (9.9)</td>
<td>2 (1.8)</td>
<td>1 (3.1)</td>
<td>.02</td>
</tr>
<tr>
<td>Emergency bypass surgery — all causes</td>
<td>12 (9.9)</td>
<td>3 (2.7)</td>
<td>0 (0)</td>
<td>.04</td>
</tr>
<tr>
<td>Any thrombus</td>
<td>26 (21.5)</td>
<td>13 (11.8)</td>
<td>0 (0)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Clinically significant thrombus</td>
<td>13 (10.7)</td>
<td>2 (1.8)</td>
<td>0 (0)</td>
<td>&lt;.005</td>
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</table>

Data in parentheses are percentages.

### TABLE 3
Association of clinical and angiographic variables with any thrombus and clinically significant thrombus

<table>
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<th>Any thrombus</th>
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<td></td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Dichotomous variables</td>
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<tr>
<td>Drug pretreatment</td>
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<td>Aspirin before admission (%)</td>
<td>15</td>
<td>33</td>
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<td>Aspirin in hospital (%)</td>
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<td>45</td>
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<tr>
<td>Dipyridamole before admission (%)</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Dipyridamole in hospital (%)</td>
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<td>45</td>
</tr>
<tr>
<td>No aspirin (%)</td>
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<td>42</td>
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<tr>
<td>No dipyridamole (%)</td>
<td>67</td>
<td>48</td>
</tr>
<tr>
<td>No aspirin or dipyridamole (%)</td>
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<td>35</td>
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<tr>
<td>Calcium antagonist (%)</td>
<td>67</td>
<td>76</td>
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<td>β-Blocker (%)</td>
<td>85</td>
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<tr>
<td>Clinical</td>
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<tr>
<td>Sex (% M)</td>
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<tr>
<td>Year (% pre-1983)</td>
<td>23</td>
<td>17</td>
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<tr>
<td>Diabetes mellitus (%)</td>
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<td>Hyperlipidemia (%)</td>
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<td>Current smoking (%)</td>
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<td>Prior bypass surgery (%)</td>
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<td>Unstable angina (%)</td>
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<td>Dissection (%)</td>
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<td>Eccentric stenosis (%)</td>
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<td>Ulcerated plaque (%)</td>
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<td>22</td>
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<tr>
<td>Continuous variables</td>
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<tr>
<td>% Stenosis pre-PTCA</td>
<td>83±1&lt;sup&gt;B&lt;/sup&gt;</td>
<td>78±1</td>
</tr>
<tr>
<td>Platelet count (× 10&lt;sup&gt;11&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>293±16</td>
<td>260±5</td>
</tr>
</tbody>
</table>

MI = myocardial infarction.

<sup>A</sup>95% confidence limits in parentheses.

<sup>B</sup>Mean ± SEM.
thrombus. Only the lack of pretreatment with aspirin and/or dipyridamole and higher platelet count (p < .001) were associated with clinically significant thrombus. Trends toward association with thrombus were noted for ulcerated plaque (p = .05), eccentric stenosis (p = .06), and dissection (p = .12). For clinically significant thrombus, a trend was noted for current smoking (p = .06). A trend toward a negative association was noted with prior bypass surgery (p = .06), although virtually all of these patients were treated with aspirin and/or dipyridamole. There were only eight dilations in bypass grafts, and when these were excluded the results were unchanged.

The relative risk of developing a thrombus during PTCA was estimated by the odds ratio. Without aspirin pretreatment the relative risk for developing any thrombus was 2.7 (95% confidence limits = 1.5–5.9) (table 3). There was an eightfold increased risk of developing a clinically significant thrombus without aspirin and a 15-fold increased risk without dipyridamole. There was approximately a twofold increased risk of any thrombus for current smoking, ulcerated plaque, eccentric stenosis, and dissection.

The year the procedure was performed is a potential confounding variable. The fraction of pretreated patients increased in the later years. Additionally, experience was greater and technique improved in the latter half of the study period. If the lack of thrombus production was a function of operator experience and improved technique, an association between year of PTCA and thrombus formation would be expected. However, if the production of thrombi were instead related only to the balloon injury (which presumably has not appreciably changed), then the year of the procedure should not be associated with thrombus. As shown in figure 5, there was no significant difference between the early period (1980 to 1982) and the late period (1983 to 1985) in the incidence of either thrombus or clinically significant thrombus for the aspirin-treated or the untreated patients.

**Thrombus before PTCA.** We analyzed separately the data from the excluded group that had thrombus before PTCA. Of the 13 sites, nine still had visible thrombus after PTCA (69%) and three had a clinically significant thrombus (23%). Two of these three patients required emergency bypass surgery and one was treated with streptokinase. These three patients were among the five that received no aspirin or dipyridamole at any point before PTCA, thus yielding a clinically significant thrombus rate of 60% in patients with preexisting thrombus who were not pretreated with antiplatelet drugs.

**Multivariate analyses.** Using stepwise logistic regression analyses, we evaluated several models for predicting thrombus and clinically significant thrombus. Initially we evaluated the seven variables identified by the univariate analyses as being associated with thrombus or clinically significant thrombus: antiplatelet pretreatment status, platelet count, current smoking, percent diameter stenosis before PTCA, ulcerated plaque, eccentric stenosis, and dissection. The “lack of treatment” variable was entered as a graded treatment variable with no treatment = group 1, intermediate treatment = group 2, and maximal treatment = group 3. Platelet count was entered as four groups in relation to the mean: more than 1 SD below the mean, from 1 SD below to the mean, from the mean to 1 SD above, and over 1 SD above. The percent diameter stenosis was entered as four groups as well: under 70%, 70% to 79%, 80% to 89%, and 90% to 99%. All other variables were dichotomous.

For thrombus, “lack of treatment” entered first, with an improvement in the chi-square p value of .001, followed by current smoking (p = .06), percent diameter stenosis (p = .03), and dissection (p = .12). Eccentric stenosis, ulcerated plaque, and platelet count did not add any additional discriminating information. If “lack of treatment” was redefined as simply “no aspirin” and the rest of the model was kept the same, “lack of treatment” still entered first (p = .006), followed by eccentric stenosis (p = .06), dissection (p = .10), and current smoking (p = .06). For clinically significant thrombus, “lack of treatment” defined either way entered first (p = .001) with no other variable entering and staying in the model, suggesting that no other variable added any significant discriminatory in-

![Graph showing rates of thrombosis](https://via.placeholder.com/150)
formation after controlling for the lack of pretreatment with aspirin.

To address the question of nonrandomization of clinical characteristics in our treatment groups, we ran the stepwise logistic regression analysis with the nonrandomly distributed variables entered first, thus controlling for them. The year the procedure was performed was made into a dichotomous variable with the “early” period being 1980 to 1982 and the “late” period being 1983 to 1985. This variable, along with current smoking, hypertension, and prior bypass surgery, was forced into the regression model first. Then the remainder of the associated variables from the univariate analysis were allowed to move in or out. With thrombus as the dependent variable, percent diameter stenosis entered first (p = .01), followed by “lack of treatment” (p = .007) and ulcerated plaque (p = .10). No other variables entered the model. For clinically significant thrombus, “lack of treatment” entered first (p = .01), followed by platelet count (p = .12) and dissection (p = .16).

We attempted to control for nonrandomly distributed variables one last way by running nonstepwise logistic regression with all variables forced into the equation simultaneously. In this case, the size of the “F to remove” for a variable is a measure of its relative importance in the model. As shown in table 4 for both thrombus and clinically significant thrombus, the F to remove is highest for “lack of treatment.”

Discussion

This study demonstrates that in patients undergoing elective PTCA without angiographic evidence of thrombus before the procedure, the lack of pretreatment with effective antiplatelet therapy was the most powerful predictor of acute thrombosis complicating the procedure. Moreover, it was an even better predictor of clinically significant thrombosis. Increasing levels of antiplatelet therapy were associated with reduced streptokinase administration and, more importantly, with less emergency bypass surgery for all reasons.

The observation that thrombi can form during PTCA despite apparently adequate heparin therapy is not new. Heparin used alone in PTCA has theoretical reasons for being inadequate and possibly detrimental in terms of preventing platelet activation at the angioplasty site. It has several effects on platelets in vitro, some inhibitory, and others resulting in increased activation. Heparin has been shown to neutralize the antiaggregatory activity of prostacyclin. Platelet inhibitory drugs may overcome heparin-dependent aggregation. Thus aspirin may attenuate this potentially negative effect.

PTCA causes a pronounced, immediate, localized endothelial injury that has been demonstrated graphically by scanning electron microscopy. The vessel that is denuded of its endothelium exposes proaggregatory substances in the subendothelial layers such as collagen. Without the intact, functioning endothelium, a host of natural anticoagulant, fibrinolytic, and antiaggregatory mechanisms may be lost. In addition, endothelial injury may lead to the release of procoagulant substances such as tissue factor. Platelets have been shown in vitro to augment this response. Several investigators have shown in animals that, in the absence of antiplatelet therapy, platelets are rapidly deposited at an angioplasty site. This has been corroborated in man by indium-111 platelet scintigraphy. Pretreatment with aspirin in peripheral angioplasty in man has been shown to decrease platelet deposition at the angioplasty site with the same technique. Endothelial injury also may lead to decreased endogenous synthesis of tissue plasminogen activator (t-PA) and increased release of an inhibitor of plasminogen activators. These two effects tend to be additive in diminishing the natural fibrinolytic mechanisms, thereby impairing the vessel’s ability to lyse developing fibrin thrombi. Endothelial cells also have one or more receptors for t-PA that may modulate local fibrinolytic function. Balloon-induced endothelial injury may alter local t-PA binding. Actual fibrin strands have been seen shortly after PTCA by angiography. Recently, activated human platelets in vitro have been shown to release an inhibitor of t-PA. Thus local platelet activation also may help protect fibrin-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any thrombus (F to remove p value)</th>
<th>Clinically significant thrombus (F to remove p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate treatment</td>
<td>77.1 &lt;.0001</td>
<td>3.1 &lt;.05</td>
</tr>
<tr>
<td>Ulcerated plaque</td>
<td>3.2 .07</td>
<td>0.2 .63</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>2.2 .09</td>
<td>0.7 .58</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.4 .11</td>
<td>2.4 .13</td>
</tr>
<tr>
<td>Dissection</td>
<td>2.1 .14</td>
<td>1.5 .22</td>
</tr>
<tr>
<td>Year</td>
<td>1.7 .15</td>
<td>1.3 .26</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.0 .16</td>
<td>1.9 .17</td>
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<tr>
<td>Platelet count</td>
<td>1.5 .21</td>
<td>2.2 .09</td>
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<tr>
<td>Eccentric stenosis</td>
<td>0.6 .45</td>
<td>0.0 .95</td>
</tr>
<tr>
<td>Prior bypass surgery</td>
<td>0.1 .83</td>
<td>0.0 .85</td>
</tr>
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</table>
containing thrombi from the body’s natural fibrinolytic mechanisms. Although this is part of the normal hemo-
static process, it also may contribute to the pathogene-
sis of acute thrombosis complicating PTCA.

The finding that higher platelet counts before PTCA
were associated with a higher thrombosis rate is not
surprising. Platelet count has been shown to be directly
related to the size of a thrombus in a thrombus growth
model in vitro.31 That it failed to be an independent
predictor after controlling for antiplatelet therapy sug-
gests that the negative effect of having more platelets is
partially or completely ameliorated by rendering them
partially ineffective.

We demonstrated an association between current
smoking and thrombosis complicating PTCA. Nicot-
ine has been shown to inhibit vascular prostacyclin,
but not platelet thromboxane production.10 Platelet ag-
gregation is increased in chronic smokers, and smoking
makes platelets more responsive to various proag-
gregatory stimuli over the short term.8 In a rat
preparation, chronic smoking caused aortic endothelial
denumentation, subendothelial platelet adhesion, and
 altered endothelial ultrastructure.9 Thus a smoker who
already may be in a hypercoagulable state may require
aggressive antiplatelet and/or anticoagulant therapy to
prevent a thrombotic complication when subjected to
the prothrombotic stress of PTCA.

Clearly, dissections also produce powerful stimuli
for platelet adherence and thrombus formation.18 The
presence of an eccentric stenosis, an ulcerated plaque,
a very tight stenosis, or an intimal dissection may
increase the risk of developing small thrombi. Our
study suggests that in the face of adequate or maximal
antiplatelet therapy, these lesion characteristics are not
associated with an increased risk of major thrombus
formation. However, our group sizes are small and the
resulting power of not being able to demonstrate an
association is low. Correcting for nonrandomly dis-
tributed characteristics suggested a possible predictive
value for a higher percent diameter stenosis, dissec-
tion, and ulcerated plaque. Further evaluation of the
potential association of these characteristics with poor
outcomes is warranted.

Support for the contention that total occlusion fre-
quently may be related to platelet activation comes
from Peterson et al.,32 who demonstrated that there
was no rise in coronary sinus thromboxane B2 in seven
of seven uncomplicated PTCA. However, both pa-
tients with total occlusion requiring bypass surgery and
not responding to nitroglycerin had markedly elevated
levels of thromboxane B2. A patient with occlusion
secondary to spasm had no elevation. This suggests
that platelet activation is either a consequence of or a
contributing causative factor in acute occlusion.

Previous studies. Six large series of patients under-
going PTCA report an incidence of total occlusion be-
tween 1.6% and 12.2%.2, 4, 5, 33-35 Of these six series,
four reported their typical antiplatelet regimen. In
three series in which aspirin with or without dipirida-
mole was administered routinely before PTCA, the
mean total occlusion rate was 3% in 1394 patients.
In contrast, the remaining study in which dipiridamole
with or without aspirin was administered4 reported a
12.2% total occlusion rate in 238 patients. These fig-
ures do not represent thrombosis rates. Since total oc-
closure may be a result of spasm, dissection, thrombo-
sis, or a combination of these, it is hard to compare
these results directly with ours. Nevertheless, our
overall emergency surgery rates are comparable to
those series in which patients were treated with similar
regimens.

Limitations. There are several caveats to be consid-
ered when interpreting our data. The angiographic
method of detecting thrombi is neither very sensitive
nor entirely specific. Filling defects may be caused by
factors other than thrombi (e.g., dissection). Never-
theless, preliminary angioscopic results suggest that
angiography underestimates the incidence of throm-
bus, being more specific than it is sensitive.36, 37 When
a vessel becomes totally occluded, it is often difficult
to be sure whether the cause is purely thrombotic,
purely secondary to dissection, or a combination of
both factors. In one series, all six patients whose
PTCAs failed, who required emergency surgery, and
who underwent angioscopy had thrombus, although
only two were recognized angiographically.37 We re-
garded all sites scored as “uncertain” for thrombus as
having no thrombus, thereby probably underestimat-
ing the true incidence of thrombus. This was true for
dissection as well. Thrombi that are layered uniformly
against the vessel wall likely will be missed, as will be
those microthrombi that are too small to be seen on an
angiogram.

The overall incidence of thrombi detected in our
laboratory is greater than that reported in other se-
ries.2, 4 We believe this difference is in part due to our
laboratory’s policy to routinely perform angiograms
on all patients at least 30 min after the last balloon
inflation. Only 15% of the 39 thrombi detected were
seen on the immediate postinflation films. Thus, if a
patient leaves the laboratory shortly after the last bal-
loon inflation, most thrombi will not be detected and
the incidence of thrombus formation will be
underestimated.
This study was retrospective with no randomization relative to treatment groups. We attempted to correct for this by forcing those nonrandomly distributed variables into the multivariate analysis first, thereby controlling for them. When doing so, our results were essentially unchanged in that the lack of adequate antiplatelet pretreatment was still a powerful predictor of both any thrombus and clinically significant thrombus. Similarly, it was the most important variable when all independent variables were forced into a regression with either thrombus or clinically significant thrombus as the dependent variable.

There was marked heterogeneity within our drug treatment groups, due in part to changes in the ways these drugs have been used over the past 5 years. To qualify for the maximal treatment group, one only had to take both drugs before admission (any dose qualified for entry) and to receive at least one dose of each in the hospital. For dipyridamole, one dose likely would represent a suboptimal regimen, and this was often the case. Thus we do not believe that our study suggests an optimal regimen. Arguments could be made for less aspirin (to minimize the effects on endothelial prostacyclin production) or for more aspirin (to reduce total thromboxane A2 production as much as possible). Even the timing of the dose relative to the time of the procedure theoretically could matter, with a longer interval between aspirin administration and PTCA allowing for more complete return of vascular prostacyclin production.

Our data suggest that some aspirin is probably better than none and that long-term as well as short-term dipyridamole before the procedure may add additional benefit in terms of reducing the incidence of any thrombus at the PTCA site. This needs to be investigated further by prospective controlled trials before further conclusions can be drawn.

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