The role of antiplatelet agents in modifying the extent of restenosis following percutaneous transluminal coronary angioplasty

We previously reported that a combination of aspirin and dipyridamole given before, during, and for 6 months following percutaneous transluminal coronary angioplasty (PTCA) did not reduce the incidence of restenosis. In that trial, a total of 272 successfully dilated segments in 243 patients reached final quantitative angiography and of these, 86 segments (31.6%) had restenosed (46 of 130 segments in the group of patients given placebo and 40 of 142 segments in the aspirin-dipyridamole group). A secondary analysis of these 86 segments revealed that at follow-up angiography the severity of restenosis was greater in the 46 segments in the placebo group than in the 40 segments in the active treatment group (mean minimal luminal diameter at the stenosis = 0.76 ± 0.52 and 1.03 ± 0.45 mm, respectively, $p = 0.01$). The frequency of total or subtotal occlusions was higher in the placebo group (17.4%) than in the active treatment group (5.0%), but this observation did not reach statistical significance ($p = 0.07$). Although long-term treatment with aspirin and dipyridamole after successful PTCA does not reduce the incidence of recurrence, this secondary analysis suggests that it is associated with a decreased likelihood of severe restenosis. (AM HEART J 1990;119:232.)

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A combination of aspirin and dipyridamole begun 24 hours before percutaneous transluminal coronary angioplasty (PTCA) and continued up to 6 months following PTCA does not decrease the incidence of restenosis.[1] This conclusion was based on the definition of restenosis as a dichotomous outcome, namely, restenosis versus no restenosis. Such an approach does not take into account the possibility that antiplatelet agents might modify the severity of restenosis while not affecting its frequency. Accordingly, we relate in this report the findings of a secondary analysis on the subset of restenosed lesions with regard to drug effect on the severity of restenosis, defined as a continuous variable.

METHODS

The methodology has been described in detail elsewhere.[1] Briefly, the trial was a randomized, double-blind, placebo-controlled study to evaluate the role of an aspirin-dipyridamole combination in the prevention of restenosis. A secondary objective was a comparison between the placebo and active drug treatment groups on the incidence of periprocedural events, defined as Q wave myocardial infarction and/or coronary bypass surgery and/or a second PTCA within 48 hours of the index PTCA. There were two participating centers, the Montreal Heart Institute and the Toronto General Hospital. Recruitment spanned 3 years (1983 to 1986) with 1895 patients screened and 1519 excluded. Patients randomized to receive active drug ($n = 187$)received an oral aspirin-dipyridamole combination (330 mg and 75 mg) three times daily beginning 24 hours before PTCA. Eight hours before PTCA, to ensure acceptable blood levels for the procedure, the oral dipyridamole was replaced with intravenous dipyridamole at a dosage of 10 mg per hour for 24 hours and the oral aspirin was continued. Sixteen hours after PTCA, the initial combination was reinstituted and continued with follow-up angiography performed 4 to 7 months after PTCA or earlier if symptoms dictated. Patients randomized to the placebo group ($n = 189$) received matching oral and intravenous preparations. Compliance as determined by capsule count was found to be equivalent and good in both treatment arms.

All angiograms were analyzed in a blinded fashion by experienced technicians under the supervision of radiologists not associated with the angioplasty procedure, using

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Table I. Demographic, clinical, and angiographic characteristics of the patients with restenosed segments

Characteristics	*Aspirin-dipyridamole group*	*Placebo group*	*p Value*
Patients restenosed	37	42	
Segments restenosed	40	46	
Age (yr)	53.3 ± 8.1	53.1 ± 10.0	0.95
Female (%)	10.8	19.0	0.31
Current smoker (%)	24.3	26.2	0.98
History of hypertension (%)	24.3	14.3	0.26
LDL cholesterol (mmol/L)	3.6 ± 1.1	3.7 ± 0.9	0.40
Diabetes (%)	2.7	9.5	0.21
Angina class (%)			
I	11.4	7.9	
II	37.1	34.2	0.91
III	40.0	42.1	
IV	11.4	15.8	
Unstable angina (%)	24.3	23.8	0.96
Previous myocardial infarction (%)	27.0	23.8	0.74
Extent of coronary artery disease (%)			
1 vessel	62.2	71.4	
2 vessels	37.8	26.2	0.37
3 vessels	0.0	2.4	
Segments in which PTCA was performed			
LAD/RCA/CCA (% distribution)	72/23/5	54/28/18	0.12
Patients in whom PTCA was performed			
Single lesion angioplasty (%)	62.2	61.9	0.98
Multiple lesion angioplasty (%)	37.8	38.1	

Plus-minus values are means ± SD.
LDL, Serum low-density lipoproteins; LAD, left anterior artery; RCA, right coronary artery; CCA, circumflex artery. Multiple-lesion angioplasty refers to either single-vessel multiple-lesion angioplasty or to multiple-vessel angioplasty.
Coronary artery disease was defined as stenosis of 50% or more by visual examination.
p Values refer to the difference in prevalence between the two groups.

the computer-assisted quantitative coronary angiographic analysis system (CAAS) of Reiber et al.[2] Measurements were made in the single projection showing the most severe stenosis and whenever possible all three measurements (pre-PTCA, immediately post-PTCA, and final) were performed in the same projection. Intravenous nitroglycerin (200 μg) was given at the time of PTCA and at final angiography to minimize differences in vascular tone. Biplane orthogonal views were available in all cases but were not always adequate because of vessel foreshortening or branch overlap. This, in addition to the fact that there is only a small and consistent difference between the single and biplane measurements,[3] justified our decision to choose the single best projection approach. The intrinsic reproducibility of this system in our hands is 0.12 mm for absolute measurements and 3.3% for percent diameter stenosis (i.e., 1 standard deviation of same cine frame analysis at two separate times).

The severity and extent of angiographic restenosis was determined by two approaches, namely percent diameter stenosis and absolute minimal luminal diameter.

1. Percent diameter stenosis (%DS). This is the minimum diameter at the stenosis as a percent of the reference diameter (the diameter of the undiseased vessel). The Reiber system[4] permits the measurement of this reference diameter by either a user-defined or an interpolated method. The interpolated method consists of a computer estimate of the original diameter over the obstructed segment. Using proximal and distal center line segments and the computer reference diameter function, the contours over the obstructed region can be reconstructed. This method was chosen for analysis because it is less variable than the user-defined approach, which depends on a subjective visual selection of the nearest normal-appearing coronary segment. Successfully dilated segments were those that were ≥ 50 %DS before PTCA and were reduced to < 50 %DS excluding those segments with < 10 %DS change.[5] Restenosed segments were those successfully dilated segments that were ≥ 50% diameter stenosed at final angiography, again excluding those segments with a less than 10% change. The restenosed segments were displayed graphically in the form of a histogram by drug group, using final %DS from 50% to 100% (in 5% groups). The severity of restenosis was analyzed in the two treatment groups using %DS as an isolated variable and also adjusting for pre- and immediately post-PTCA diameter stenosis.

2. Absolute minimal luminal diameters. There is now evidence suggesting that the reference diameter diminishes in the months following angioplasty, potentially resulting in an underestimation of the restenotic process as defined by %DS.[6] Therefore we analyzed the restenosed segments in absolute terms by comparing the mean minimum diam-

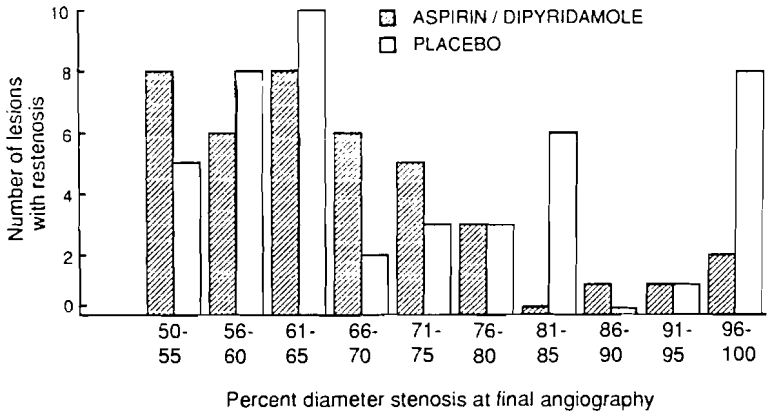

Fig. 1. A frequency- distribution histogram by percent diameter stenosis at final angiography of restenosed segments in patients in the aspirin-dipyridamole group *(hatched bars)* and the placebo group *(open bars)*.

eter of the stenosis at final angiography in the two treatment groups as an isolated variable and also adjusting for pre- and immediately post-PTCA stenosis diameters.

Statistical analysis. The data presented and summarized in this secondary analysis were recorded as part of a previously reported prospective double-blind trial[1] and were therefore assessed in a blinded fashion. Differences between treatment groups in the distribution of baseline characteristics and outcome variables were tested by the chi square test or t test statistic for categorical or continuous data, respectively. All tests for significance were two-sided and statistical significance was assessed at the conventional level of 0.05.

RESULTS

Of 313 patients discharged from the hospital with a successful angioplasty of at least one segment, 243 with 272 segments had final quantitative angiography in the 4- to 7-month post-PTCA window and 86 of these 272 segments (31.6%) were restenosed. Of 130 segments in the aspirin-dipyridamole group, 40 were restenosed (30.8%) compared with 46 of 142 (32.4%) in the placebo group ($p = 0.77$).

Table I summarizes, by treatment group, the demographic, clinical, and angiographic characteristics of the patients who had at least one lesion restenosed at final angiography. There were no statistically significant differences in any of those factors that have been shown to predict restenosis.[7, 8]

Extent and severity of restenosis by %DS. Fig. 1 is a histogram of lesion severity by percent diameter stenosis at final angiography in the active treatment and placebo groups. The distribution is skewed toward more severe lesions in the placebo group. There was a trend toward more total or subtotal occlusion (i.e., ≥96% DS) in the placebo group (8 of 46 or 17.4%) than in the active treatment patients (2 of 40 or 5.0%), although this did not reach significance ($p = 0.07$). Table II shows a further analysis of the data. Before and immediately after PTCA, there were no differences in percent diameter stenosis between the aspirin-dipyridamole and placebo segments. At final angiography, there was a trend toward greater lesion severity in the placebo group, although this did not reach significance ($p = 0.07$). Moreover, the extent of restenosis as reflected by the mean difference of the final and immediate post-PTCA percent diameter stenosis was significantly greater for the placebo patients than for the actively treated patients (42.2 ± 18.7 versus 33.9 ± 13.3, $p = 0.02$).

Severity of restenosis by absolute minimal luminal diameter (Table III). The mean minimal luminal diameter at the stenosis immediately following PTCA of those segments destined to restenose was no different in the two treatment groups, but at final angiography the mean absolute diameter was significantly lower in the placebo group. The serial reference diameter measurements showed the same pattern so that the mean reference diameter in the placebo group decreased from that immediately following PTCA to the follow-up study and at that time was significantly less than the mean reference diameter of the active treatment group.

DISCUSSION

There has been considerable research and several publications on the incidence of restenosis, both from the standpoint of pathophysiology and prevention.[8-10] However, there has been little attention given to the issue of the severity of restenosis in spite of the well-known observation that recurrence may vary from mild and clinically insignificant to extremely severe and so extensive as to even preclude

Table II. Percent diameter stenosis and derived values on serial quantitative coronary angiography in restenosed segments in the two study groups

	Aspirin-dipyridamole	*Placebo*	*p Value*
1. Restenosed lesions	40	46	
2. Mean ± SD			
Pre PTCA	71.9 ± 12.9	71.9 ± 11.1	0.99
Immediately post PTCA	32.7 ± 9.3	30.0 ± 10.8	0.20
At final angiography	66.5 ± 12.4	72.2 ± 16.4	0.07
At final angiography–immediately post PTCA	33.9 ± 13.3	42.2 ± 18.7	0.02

Table III. Serial absolute diameter measurements in the two study groups

	*Aspirin-dipyridamole**	*Placebo**	*p Value*
Minimal luminal diameter (mm)			
Pre PTCA	0.85 ± 0.38	0.79 ± 0.38	0.48
Immediately post PTCA	2.08 ± 0.37	2.07 ± 0.50	0.99
At final angiography	1.03 ± 0.45	0.76 ± 0.52	0.01
Reference diameter (mm)			
Pre PTCA	3.08 ± 0.73 (n = 37)	2.81 ± 0.55 (n = 44)	0.08
Immediately post PTCA	3.12 ± 0.61	2.98 ± 0.06	0.26
At final angiography	3.09 ± 0.68 (n = 38)	2.71 ± 0.67 (n = 37)	0.02

*Unless otherwise stated, aspirin-dipyridamole (n = 40) and placebo (n = 46).

repeat angioplasty.[11] In our study, using a prospective, double-blind, placebo control design and end point evaluation by quantitative angiography, the incidence of restenosis within 6 months following successful angioplasty was not different between patients taking placebo and those receiving a comprehensive antiplatelet regimen.

However, the analysis described in this present report, performed on only those segments that had restenosed, suggests that the extent and severity of restenosis is less in patients taking an aspirin-dipyridamole combination than it is in patients receiving placebo. The mean minimal luminal diameter of placebo segments at follow-up was significantly less than that of active treatment segments in spite of almost identical diameters attained by angioplasty in both treatment groups. Adding further support to this observation was the finding that the reference diameters behaved in a similar fashion, with a deterioration occurring at final angiography in the placebo group but not in the patients taking the aspirin-dipyridamole combination. These results are in agreement with those of Beatt et al.,[6] who have shown that the reference diameter is involved in both the dilation and restenosis process. Since this phenomenon leads to an underestimation of stenosis when defined by percent diameter measurements, it is not surprising that the difference between placebo and aspirin-dipyridamole segments at final angiography, as measured by percent diameter stenosis, did not quite reach statistical significance. Still, even using this latter approach, the extent of restenosis defined as the difference between the final and immediate post-PTCA measurements was greater in placebo segments than it was in active treatment segments.

It should be emphasized that a possible antiplatelet drug effect on the severity of restenosis was not one of the primary objectives of this study at its inception, and a secondary approach such as this should always be viewed as a preliminary observation requiring further confirmation. Nonetheless, this analysis does suggest that the modification of restenosis severity might at least partially be attributed to the administration of platelet-active drugs. The two groups of patients were comparable with respect to several demographic, clinical, angiographic, and procedural variables that have been implicated in restenosis. The difference persisted after taking into account other possible confounding factors such as the pre-PTCA stenosis severity and the immediate post-PTCA residual stenosis. Finally, this observation is not inconsistent with other clinical and experimental data on the pathophysiology of restenosis. There is now little question that antiplatelet agents

decrease the incidence of procedural complications within 48 hours of PTCA.[1, 12, 13] Angiographic findings at PTCA in patients not receiving antiplatelet agents periprocedurally have shown a relatively high frequency of significant and insignificant thrombi at the angioplasty site when compared with patients who are optimally covered.[12] Faxon et al.[14] have shown that in the New Zealand rabbit atherosclerotic model unprotected with antiplatelet agents during PTCA, restenosis is primarily due to intraluminal thrombosis, and in almost all animals with organized thrombus the vessel was totally occluded. This is in agreement with a trend we noted, namely that 17.4% of restenosed placebo segments were totally or subtotally occluded, compared with only 5.0% of restenosed active drug treatment segments.

How can these discordant results on the same patients be reconciled, namely a positive active drug effect on restenosis severity but a negative effect on incidence? An answer may be found in the almost certain multifactorial pathogenesis of restenosis in humans. These factors include accelerated atherosclerosis,[15] vasospasm,[16-18] smooth muscle proliferation and migration,[19] and organized intraluminal thrombus at the dilated site. Not all of these processes are platelet-dependent, and this might explain why certain antiplatelet regimens such as the one we administered do not alter the overall incidence of restenosis. However, platelets almost certainly play a central role in the fibrocellular proliferative and the thrombogenic responses, and there is experimental evidence that these, particularly the latter,[14] produce a more severe restenosis process that platelet-active agents have been shown to interrupt.[21]

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