

Long-Term Beneficial Effect of Late Reperfusion for Acute Anterior Myocardial Infarction With Percutaneous Transluminal Coronary Angioplasty

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Background—Although the short-term and long-term beneficial effects of early coronary revascularization by primary PTCA or thrombolytic therapy have been established for acute myocardial infarction, thrombolytic therapy >24 hours after the onset of acute myocardial infarction has not been shown to improve clinical outcome. The purpose of this study was to assess the effect of late revascularization by primary PTCA over a 5-year period.

Methods and Results—Eighty-three patients with initial Q-wave anterior myocardial infarction >24 hours after onset were randomized into a PTCA group (n=44) and a no-PTCA group (n=39). Long-term follow-up was conducted with regard to end points, which included cardiac death, nonfatal recurrence of myocardial infarction, and development of congestive heart failure. Left ventricular ejection fraction and regional wall motion at 6 months after myocardial infarction were similar in the 2 groups. Left ventricular end-diastolic and end-systolic volume indexes were significantly smaller in the PTCA group than in the no-PTCA group ($P<0.0001$). With cardiac events as end points, a 5-year Kaplan-Meier event-free survival analysis revealed that the no-PTCA group had a worse prognosis than the PTCA group ($P<0.0001$). Patency of the infarct-related artery, left ventricular ejection fraction, end-diastolic volume index, and end-systolic volume index were significantly associated with cardiac events by a Cox proportional hazards analysis (hazard ratios 0.120, 0.845, 1.065, and 1.164, respectively).

Conclusions—In initial Q-wave anterior myocardial infarction, we conclude that even with late reperfusion, PTCA had beneficial effects on cardiac events over the 5-year period after myocardial infarction, with the prevention of left ventricular dilation after myocardial infarction being a possible mechanism. (*Circulation*. 1998;98:2377-2382.)

Key Words: myocardial infarction ■ angioplasty ■ reperfusion ■ prognosis

Early reperfusion in acute myocardial infarction (AMI) by thrombolytic therapy has been shown to reduce infarct size, preserve left ventricular function, and improve both the short- and long-term prognoses.^{1,2} Several studies of thrombolytic therapy for the late treatment of patients with AMI (late reperfusion) have shown that such treatment confers a survival benefit, although late reperfusion did not reduce the infarct size or preserve left ventricular function.³ Recently, the open-artery theory has been proposed, which suggests that even if patency of the infarct-related artery (IRA) is achieved late, after AMI is complete, the long-term outcome of such patients is still better than that in patients in whom patency was not achieved.⁴ Nevertheless, thrombolytic therapy beyond 12 hours after the onset of symptoms did not improve the clinical

outcome, probably because it was ineffective in establishing coronary patency.⁵ The failure of earlier studies may be due to the lower initial success rates of emergency PTCA and high reocclusion rates as reported in some randomized trials in which late PTCA was performed for occluded IRA beyond 12 hours after the onset of AMI.^{6,7} Recently, Sabri et al⁸ demonstrated a high initial success rate, a low complication rate, and a low incidence of reocclusion by late PTCA in a nonrandomized trial. In addition, Pizzeti et al⁹ reported beneficial effects of “very late” (2 weeks after myocardial infarction [MI]) mechanical reperfusion of the IRA on left ventricular (LV) remodeling. Hochman,¹⁰ in an editorial comment on the Pizzeti report, evaluated the beneficial effects of late PTCA for occluded IRA after anterior MI but stated that a randomized trial was necessary.

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We conducted this randomized trial study to assess the effect of late mechanical reperfusion by primary PTCA and to assess any long-term beneficial effect over a 5-year period.

Methods

Patient Selection

The study population was selected from 101 consecutive patients who were admitted to the coronary care unit of Okamura Memorial Hospital, with initial Q-wave anteroseptal MI from January 1990 to December 1992 >24 hours (ranging from 24 hours to 3 weeks) after the onset of symptoms. Inclusion criteria were a history of persistent ST-segment elevation of >0.2 mV in ≥ 2 leads on standard 12-lead ECG. Only patients with total occlusion of the IRA (Thrombolysis in Myocardial Infarction [TIMI] grade 0 or 1) were eligible for this study. Patients were excluded for the following reasons: (1) age >80 years; (2) history of MI or cardiomyopathy; (3) history of stroke within the previous 6 months; (4) severe valvular disease; (5) left bundle branch block or permanent pacemaker; (6) chronic renal failure; (7) ventricular septal defect; (8) perfusion state of the infarct-related artery exceeded TIMI grade >1 at the initial angiography; (9) $\geq 50\%$ stenosis in the left main coronary artery; (10) uncertain time of reperfusion; and (11) change in medications during the follow-up. After exclusion, 83 patients were enrolled in this study.

Acute Catheterization and Angiography

After administering intravenous heparin (5000 U), coronary angiography (CAG) and left ventriculography (LVG) were performed with the use of standard techniques. After baseline hemodynamic measurements, CAG was recorded in multiple angulated projections to visualize the IRA and to evaluate the extent of collateral circulation. Collaterals to the IRA were evaluated before intervention according to the definition of Rentrop et al¹¹: grade 0 to grade 3. Forty-nine patients underwent LVG, and LV ejection fraction (LVEF), end-diastolic volume index (EDVI), and end-systolic volume index (ESVI) were calculated by the area-length method.¹² Percent regional wall motion of the anterior wall was calculated by the centerline method¹³ with correction for the 30° right anterior oblique projection.

Randomization

After informed consent was obtained and TIMI grade (0 or 1 flow at the proximal portion of the left descending artery) was confirmed, patients were randomized into a primary angioplasty group (PTCA group) and a no-angioplasty group (no-PTCA group). One of a group of consecutively numbered, sealed envelopes containing a card generated at the biostatistical core laboratory was pulled for random selection of the patient to undergo angioplasty at the same sitting or not at all.

Angioplasty Procedure

Primary angioplasty was performed according to the standard technique. In patients randomized into the PTCA group, an attempt at dilatation of the IRA was required. All of the patients received another 5000 U of heparin before angioplasty, and additional heparin (3000 U) was administered each hour during the procedure. Angiographic success was defined as TIMI grade 2 or 3 flow and <50% diameter narrowing after angioplasty with the use of computer-assisted quantitative coronary angiographic evaluations with an on-line analysis system¹⁴ and digital images (ACA-DCI, Phillips).

Medical Treatment After Randomization

All of the patients were monitored for 24 hours and maintained on heparin infusion for 24 hours, which was titrated to maintain an activated clotting time of ≥ 200 seconds. All of the patients received intravenous nitroglycerin for ≈ 24 hours after admission. Nitrates and aspirin were administered orally followed by the infusion of nitroglycerin. Other cardioactive agents (calcium channel blockers, β -blockers, and angiotensin-converting enzyme [ACE] inhibitors)

were administered at the discretion of the physician. Medications were not changed after randomization, and the dosage was kept constant throughout the study period, except for warfarin.

Measurement of Cardiac Enzymes

We measured the peak creatinine kinase (CK) activity and myosin light chain 1 (MLC1) to estimate the infarct size. Blood samples were drawn from the femoral or antecubital vein for measurement of CK and MLC1 at admission, every 3 hours until 2 days, and then twice daily until 10 days after the onset of AMI. CK activity was determined according to the method of Rosalki.¹⁵ MLC1 was measured by ELISA.¹⁶

Follow-Up Catheterization and Angiography

Follow-up cardiac catheterization and angiography were performed 6 months after AMI in the chronic phase. All of the patients underwent CAG to assess the occurrence of restenosis. Restenosis was defined by quantitative coronary angiography as the recurrence of >50% luminal narrowing in the coronary segment that had previously been dilated. In the case of restenosis, repeat PTCA was performed to avoid stenosis of the IRA in patients who had been randomized into the PTCA group. In patients who were randomized into the no-PTCA group, we did not perform additional revascularization procedures on the IRA. Revascularization procedures were performed on other vessels if angina had occurred or if the patient had positive results in exercise testing. All of the patients also underwent LVG, and LVEF, percent regional wall motion, EDVI, and ESVI were determined. Angiographic data were assessed by independent observers who were blinded to this study.

Long-Term Follow-Up

Long-term follow-up was conducted with regard to cardiac events as end points, including cardiac death, recurrent nonfatal MI, and the development of congestive heart failure (CHF). Long-term follow-up was based on a systematic review of all of the hospital and outpatient charts to assess rehospitalization during the follow-up period and a final telephone interview with regard to end points.

Statistical Analysis

Data are presented as mean \pm SD. Differences in baseline characteristics were evaluated by Student's *t* test and by the χ^2 test. A *P* value of <0.05 was considered significant. Differences in survival and event-free survival between the groups were evaluated by the Kaplan-Meier method. Comparisons were made with the use of the log-rank test.

For clinical and angiographic variables, a multivariate analysis was performed with the Cox proportional hazards model, run in a stepwise manner, to assess the association with cardiac events (cardiac death, recurrence of MI, CHF).

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the PTCA and no-PTCA groups. The mean time to reperfusion from the onset of symptoms was 8.29 ± 9.68 days (range 24 hours to 3 weeks) in the PTCA group. There were no significant differences in the baseline characteristics between the groups. The degree of heart failure as measured by the Killip classification was similar in the 2 groups. The number of patients taking ACE inhibitors (5 [11%] in the PTCA group, 9 [23%] in the no-PTCA group), which have been reported to affect the long-term outcome,¹⁷ was also similar in the 2 groups. Likewise, the number of patients taking β -blockers was also similar in the 2 groups.

TABLE 1. Baseline Characteristics

	PTCA (n=44)	No PTCA (n=39)	P
Age, y	61.8±11.9	61.6±8.8	0.106
Male sex, n (%)	34 (77)	29 (74)	0.561
Hypertension, n (%)	19 (43)	16 (41)	0.486
Hyperlipidemia, n (%)	16 (36)	14 (36)	0.965
Diabetes, n (%)	15 (34)	16 (41)	0.122
Current smoker, n (%)	20 (45)	21 (53)	0.104
Preinfarction angina, n (%)	14 (32)	12 (31)	0.948
Cardiogenic shock, n (%)	2 (4.5)	3 (7.6)	0.166
Anticoagulant agents, n (%)	32 (73)	29 (74)	0.866
Antiplatelets, n (%)	28 (64)	18 (47)	0.110
β-Blockers, n (%)	12 (27)	11 (28)	0.889
Calcium blockers, n (%)	30 (68)	28 (72)	0.633
Diuretics, n (%)	11 (25)	14 (36)	0.214
ACE inhibitors, n (%)	5 (11)	9 (23)	0.155
On admission			
Pulmonary capillary wedge pressure, mm Hg	12.7±6.68	14.4±6.65	0.175
Cardiac index	3.17±0.61	3.08±0.88	0.334
Maximum CK	2957±2985	2235±1215	0.248
Maximum MLC1	23.2±17.9	26.1±14.7	0.493
Killip class, n (%)			0.511
I	35 (79)	28 (72)	
II	7 (16)	10 (25)	
III	2 (4.5)	1 (2.5)	
IV	0 (0)	0 (0)	

Values are mean±SD.

Baseline Angiographic Characteristics

The baseline angiographic characteristics of the 2 groups are shown in Table 2. The 2 groups were similar with respect to the initial TIMI flow grades, number of diseased vessels, and the collaterals. The reference diameters of the occluded IRA were also similar in the 2 groups.

Results of Angioplasty

The results of angioplasty are also shown in Table 2. Primary PTCA for the occluded IRA was performed in 44 patients. TIMI grade 3 flow was achieved in 38 patients and TIMI grade 2 flow was achieved in 3 of 44 patients after angioplasty. The minimal lumen diameter of the IRA increased from 0 to 2.41±0.57 mm, and residual stenosis was 14.5±11.8% after angioplasty. Successful reperfusion was achieved in 41 (93%) patients. The remaining 3 patients who failed to achieve ≥2 flow after balloon dilatation were considered unsuccessful.

Follow-Up Angiography

CAG was performed for all of the patients 6 months after the onset of AMI. Reocclusion was recognized in 2 patients, and restenosis was recognized in 12 patients in the PTCA group. Repeat angioplasty was performed in 14 restenosed patients, and all of the procedures attempted were successful. Sponta-

neous recanalization was recognized in 5 patients in the no-PTCA group. Revascularization procedures were performed on other vessels in 4 (9%) of the 44 in the PTCA group and in 4 (10%) of the 39 in the no-PTCA group. The treated vessels were 3 right coronary artery (RCA) and 1 left circumflex (LCx) in the PTCA group, and 2 RCA and 2 LCx in the no-PTCA group. All of these procedures were successful without major complications.

Acute and Follow-Up LV Functions

Thirty-two of the 44 (73%) patients in the PTCA group and 17 (44%) of the 39 patients in the no-PTCA group underwent LVG in the acute phase, and all of the study patients underwent LVG 6 months after the onset of AMI. As shown in Table 3, there were no significant differences between the 2 groups with respect to acute LVEF, percent regional wall motion, EDVI, and ESVI. In the follow-up LVG, although LVEF and percent wall motion were similar in the 2 groups, EDVI and ESVI in the PTCA group were significantly smaller than those in the no-PTCA group.

Long-Term Follow-Up

We were able to follow up all of the patients. During the mean follow-up period of 50±24 months, 1 patient in the PTCA group died from CHF, and 4 patients in the no-PTCA group died (1 reoccurrence of MI and 3 CHF). The incidence of cardiac death was higher in the no-PTCA group, but this difference was not statistically significant. The incidence of other cardiac events was significantly higher in the no-PTCA group (Table 4). The Figure shows the 5-year Kaplan-Meier actuarial event-free survival curves for cardiac death and the combined end points of cardiac death, CHF, and reoccurrence of MI. Considering all of the events, the no-PTCA group had a worse prognosis than the PTCA group.

Factors Associated With Cardiac Events During Follow-Up

A Cox proportional hazards analysis was performed to determine which factors were associated with cardiac events during the follow-up period. The following were considered independent variables: age, sex, smoking, hypertension, diabetes mellitus, hyperlipidemia, preinfarction angina, cardiogenic shock, patency of the IRA, TIMI flow grade at the initial angiography, collateral flow (present or none), peak CK, peak MLC1, warfarin, aspirin, β-blockers, ACE inhibitors, and LVEF, percent wall motion, EDVI, and ESVI on follow-up LVG. As a result, the patency of the IRA, LVEF, EDVI, and ESVI and were significantly associated with cardiac events ($P=0.0074$; hazard ratio 0.120, $P=0.0002$; 0.845, $P=0.0111$; 1.065, and $P=0.0152$; 1.164, respectively).

Discussion

Our results indicate that late, including very late (from 24 hours to 3 weeks after MI), PTCA for an occluded IRA after initial Q-wave anterior MI provides a high initial success rate and has a beneficial effect on cardiac events over a 5-year period compared with persistent occlusion of the IRA, with the prevention of LV dilation after AMI being a possible mechanism. This is the first report of a randomized trial for patients with initial

TABLE 2. Angiographic Characteristics

	PTCA (n=44)	No PTCA (n=39)	P
Extent of coronary artery disease, n (3%)			0.421
1 vessel	2 (62)	27 (59)	
2 vessels	6 (22)	8 (23)	
3 vessels	6 (16)	4 (18)	
Grade of collaterals, n (%)			0.367
0	22 (50)	24 (61)	
1	13 (29)	10 (26)	
2	7 (16)	2 (5.2)	
3	2 (4.5)	3 (7.6)	
TIMI flow grade (before randomization), n (%)			0.699
0	37 (84)	34 (87)	
1	7 (14)	5 (13)	
Reference diameter, mm	2.80±0.56	2.77±0.55	0.808
TIMI flow grade (after randomization), n (%)			
0	0 (0)	34 (87)	
1	3 (7)	5 (13)	
2	3 (7)	0 (0)	
3	38 (86)	0 (0)	
Minimal lumen diameter after PTCA, mm	2.41±0.57		
Residual stenosis after PTCA, %	14.5±11.8		

Values are mean±SD.

Q-wave anterior MI to demonstrate both a high initial success rate and long-term clinical benefits after MI.

Previous studies of both primary PTCA and thrombolytic therapy of the IRA within 6 hours of AMI demonstrated lower mortality and reinfarction rates as the result of an improvement of LV function and a reduction in infarct size.¹⁸ However, thrombolytic therapy for late-entry patients did not have a beneficial effect after a 1-year follow-up.^{5,19} In the LATE study,⁵ thrombolytic therapy >12 hours from the onset of symptoms did not have a beneficial effect in patients with AMI. Possible causes of the unfavorable outcome after thrombolytic therapy for late-entry patients may be the

relatively low rate of successful reperfusion, which was reported to be 60% to 65%,^{5,6} and the high rate of reocclusion late after successful thrombolytic therapy.^{6,20} The patency of the IRA has been reported to be one of the strongest predictors of late survival.^{19,21} Therefore, late-entry patients are often not candidates for thrombolytic therapy. If primary PTCA could give a high rate of initial successful reperfusion and could maintain long-term patency, PTCA would be a good strategy for treating late-entry patients.

Primary PTCA for late-entry patients with AMI has been reported to provide a higher initial recanalization success rate (81% to 98%)²² than thrombolytic therapy. However, in 2 small randomized trials, late PTCA was associated with low patency rates several months after onset.^{6,7} In patients with initial anterior Q-wave MI >24 hours after the onset of AMI, we demonstrated that the success rate of primary PTCA was 93% in patients randomized into the PTCA group, and a high patency rate (94%: 37 of 39 successful reperfusion) was seen at 6 months after primary PTCA. We expected that primary PTCA would have a beneficial effect even for late-entry

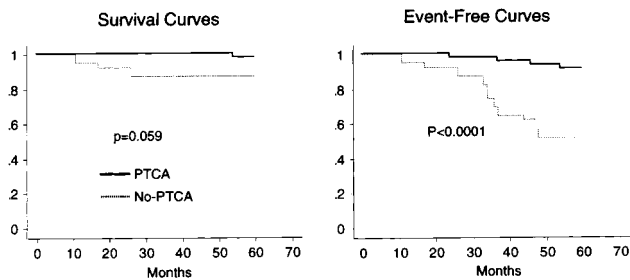
TABLE 3. Acute and Follow-Up LV Function

	PTCA	No PTCA	P
LVEF, %			
Acute	48.5±8.65 (n=32)	47.9±11.8 (n=17)	0.950
Follow-up	53.9±8.96 (n=44)	49.5±8.07 (n=39)	0.059
% Wall motion			
Acute	10.9±5.32 (n=32)	10.6±7.60 (n=17)	0.798
Follow-up	11.2±4.63 (n=44)	9.39±4.53 (n=39)	0.063
EDVI, mL/mm ²			
Acute	66.7±11.1 (n=32)	69.0±15.5 (n=17)	0.557
Follow-up	66.4±11.6 (n=44)	78.0±13.2 (n=39)	<0.0001
ESVI, mL/mm ²			
Acute	34.6±10.6 (n=32)	36.0±14.0 (n=17)	0.676
Follow-up	31.1±11.2 (n=44)	39.8±11.4 (n=39)	0.0004

Values are mean±SD.

TABLE 4. Cardiac Events During Long-Term Follow-Up Between PTCA and No-PTCA Groups

	PTCA (n=44)	No PTCA (n=39)	P
Total cardiac events	4	19	<0.0001
Death	1	5	0.064
Development of CHF	1	10	0.0017
Recurrent AMI	3	7	0.121



Five-year Kaplan-Meier actuarial cardiac survival and event-free curves for the PTCA ($n=44$) and no-PTCA ($n=39$) groups. With regard to cardiac survival, no significant difference was observed between the 2 groups. However, the no-PTCA group had worse prognosis. With regard to cardiac events (including cardiac death, nonfatal reoccurrence of MI, and development of CHF), the PTCA group had better prognosis than the no-PTCA group during the 5-year period.

patients. A previous report⁹ demonstrated that late mechanical opening of the IRA had beneficial effects on LV remodeling. However, no previous studies had demonstrated long-term beneficial clinical effects. We demonstrated that EDVI and ESVI at 6 months after onset were significantly smaller in the PTCA group, whereas they were equivalent between the groups at the onset of anterior MI. In addition, primary PTCA had long-term beneficial effects over the 5-year period after anterior MI despite a similar LVEF and percent wall motion of the infarct area at ≥ 6 months after onset.

Possible Mechanisms of Beneficial Effects of Late Reperfusion

LV volumes were significantly smaller in the PTCA (late reperfusion) group than in the no-PTCA group, whereas LVEF was similar in the 2 groups in our study. The peak MLC1 level was also similar in the 2 groups. The MLC1 level has been reported to reflect the infarct size, and reaches its peak 5 to 8 days after the onset of AMI.²³ We estimated the infarct size, even for late-entry patients, by peak MLC1. The infarct sizes estimated from the peak MLC1 level were similar between the groups. These results are consistent with previous reports²⁴ of the open artery hypothesis that late reperfusion could prevent LV remodeling after the onset of AMI, whereas infarct size is not preserved.

If residual persistent ischemia (viable or hibernating myocardium) is present near the risk region of the occluded IRA, late reperfusion could restore LV function, independent of the time after onset. Sabia et al²⁵ showed that regional wall motion in patients with collateral flow can be improved after successful angioplasty a mean of 12 days after MI, and Welty et al²⁶ reported that an open artery after coronary angioplasty for post-MI ischemia is associated with significantly lower mortality rates, particularly in patients with LVEF $<50\%$. In our study, none of the patients complained of chest pain on admission, and none of the patients had antegrade flow at the initial angiography. However, 22 (50%) patients in the PTCA group and 24 (61%) patients in the no-PTCA group had collateral flow at the initial angiography. Although they were similar between the 2 groups in the grade or the presence of collaterals, CAG is insufficient for assessing residual myocardial perfusion. There-

fore, one possible mechanism is that primary PTCA might relieve residual ischemia after Q-wave MI.

Importance of Patency of the IRA for Late Cardiac Survival

The open artery theory was suggested by the fact that patients with a patent IRA after thrombolytic or spontaneous recanalization had a markedly lower mortality rate at long-term follow-up than patients with an occluded IRA.²¹ However, no previous randomized studies have assessed whether a patent IRA by primary PTCA provides long-term beneficial effects even for late-entry patients. In patients with initial anterior Q-wave MI, we demonstrated that late PTCA provided a high vessel patency rate and had beneficial effects on the incidence of cardiac death, reoccurrence of MI, and CHF over a 5-year period. We also showed that patency of the IRA achieved by late PTCA was an independent predictor of improved long-term survival. Previous studies^{27,28} that have demonstrated an association between IRA patency and long-term outcome after MI included not only patients who underwent PTCA but also those with spontaneous recanalization and those who underwent thrombolytic therapy. In patients in whom the IRA has already been reperfused at the initial angiography, salvage of myocardium within the risk region might have already occurred, caused not only by the beneficial effect of the open artery but also by ordinary early reperfusion. The purpose of this study was to evaluate the time-independent beneficial effects of late mechanical reperfusion, isolated from other possible beneficial effects. Therefore, we enrolled a homogeneous group of patients with a similar infarct location and no antegrade flow, who were admitted late and treated only with primary PTCA.

Accordingly, we conclude that primary PTCA could achieve IRA patency and provides long-term beneficial effects in patients even with late-entry Q-wave anterior MI.

Study Limitations

Our study has several limitations. First, serial ventriculograms of sufficient technical quality for analysis were obtained in 73% of the patients in the PTCA group and in 44% of those in the no-PTCA group. Thus we may have insufficient data for an evaluation in the acute stage. Although we randomized the study patients and no significant differences were apparent between the baseline characteristics of the groups, we cannot rule out the possibility of a selection bias. Second, because of the small sample size, we cannot rule out the possibility of a type II error on the basis of our selection criteria to evaluate the beneficial effects of late perfusion. Third, we assessed myocardial perfusion only by the degree of collateral flow. However, contrast ultrasound measurement and reversible 201-thallium uptake defect may provide results superior to those obtained by angiography. Therefore, we cannot rule out the possibility that residual ischemia, hibernating myocardium, or stunned myocardium within the infarct area varied between the groups.

Finally, we performed CAG 6 months after the onset of AMI to assess late vessel patency. Therefore, we cannot evaluate sustained vessel patency throughout the follow-up period.

Clinical Implications

Patency of the IRA has beneficial effects on LV function and on the prognosis after MI. Although very late-entry patients are not candidates for thrombolytic therapy, primary PTCA can provide revascularization of the IRA with a high success rate. Although the rate of reocclusion has been relatively high in previous studies, this aggressive mechanical revascularization procedure may contribute to a lower late cardiac mortality rates, and the use of stents and/or anti-platelet therapy may help to reduce the rate of reocclusion.

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