European Heart Journal (1988) **9**, 346–353

Immediate PTCA after successful thrombolysis with intracoronary streptokinase, three years follow-up

A matched pair analysis of the effect of PTCA in the randomized multicentre trial of intracoronary streptokinase, conducted by the Interuniversity Cardiology Institute of the Netherlands*

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KEY WORDS: Coronary angioplasty, intracoronary thrombolysis, streptokinase, prognosis after myocardial infarction.

Immediate PTCA following thrombolysis with streptokinase was performed in 46 out of 533 patients enrolled in a multicentre randomized trial of early reperfusion in patients with acute myocardial infarction. Additional effects of PTCA in patients with a residual diameter stenosis in the infarct-related coronary artery of 70% or more after thrombolysis were compared with successful thrombolysis alone in a matched pair analysis. Thirty six pairs of patients were formed identical with respect to the infarct related coronary artery, presence or absence of previous myocardial infarction, total ST segment elevation on the ECG at admission to the trial, and delay between onset of symptoms and hospital admission. PTCA after thrombolysis did not lead to additional limitation of infarct size, nor to further preservation of left ventricular function. Infarction rate during the three-year follow-up was 14% after PTCA versus 30% after thrombolysis alone (P=0·05). Similarly, patients had less angina or heart failure after PTCA, since on average 128 out of 156 weeks follow-up were symptom free, while this was only 102 weeks after thrombolysis alone (P=0·03). Immediate PTCA after thrombolysis with intracoronary streptokinase seems to prevent recurrent ischemia and reinfarction. Further studies should address the proper indication and timing of PTCA after thrombolysis.

Introduction

Several recent studies have shown that a strategy aimed at early recanalization of an infarct related coronary artery with intracoronary streptokinase[1–3] will result in salvage of myocardial tissue, preservation of left ventricular function and improved survival[4–8]. However, in many patients a severe stenosis of the infarct related artery remains after successful thrombolysis. This artery may reocclude in some of the patients and thus abolish the initial beneficial effects of thrombolytic therapy. Indeed, non-fatal reinfarction occurred more frequently in patients allocated to thrombolytic therapy than in conventionally treated patients[3,8]. In order to prevent reocclusion, but also to optimize coronary flow to the jeopardized myocardium, immediate PTCA following thrombolysis has been advocated by several authors[9–12]. In a group of patients in the randomized trial conducted by the Interuniversity Cardiology Institute of the Netherlands (ICIN) PTCA was performed as part of the reperfusion procedure. The purpose of the present analysis was to evaluate the influence of PTCA performed immediately after successful thrombolysis on infarct size, left ventricular function, reinfarction, reocclusion, and on the necessity for sub-

Submitted for publication on 13 July 1987 and in revised form 28 September 1987.

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0195–668X/88/040346+08 $02.00/0

sequent revascularization procedures. In order to eliminate a possible selection bias, patients who underwent immediate PTCA were compared with a matched group of patients with similar baseline characteristics in whom the lesion in the infarct related coronary artery was suitable for PTCA but who were admitted to those hospitals where immediate PTCA could not be performed.

Patient selection and methods

Patient selection and methods of the trial have been described extensively before[3]. Thrombolytic therapy was given after informed consent and consisted of intracoronary administration of streptokinase in the catheterization laboratory, usually 250 000 U. In patients admitted since January 1984 this was preceded by intravenous administration of 500 000 U streptokinase given upon hospital admission, in order to reduce treatment delay. Immediate PTCA was performed in two out of the five participating hospitals. The indication for PTCA was a residual diameter stenosis in the infarct related coronary artery of 70% or more after successful thrombolysis as visualized during catheterization.

Total ST segment elevation was calculated as the sum of ST segment elevation in standard and precordial leads, as described before[7]. Infarct size was estimated from serial determination of α-hydroxybutyrate dehydrogenase levels (HBDH)[5]. Global left ventricular ejection fraction was measured by radionuclide angiography 10–20 days after admission. All patients were followed at the outpatient clinic for 20–60 months. Hospital admissions were recorded and functional class was assessed according to the criteria of the New York Heart Association (NYHA). From these data the functional status was defined for each patient at weekly intervals as the lowest of the following five mutually exclusive classifications:

Class I (NYHA), not hospitalized
Class II (NYHA), not hospitalized
Class III or IV (NYHA), not hospitalized
Hospitalized
Deceased

The mean number of weeks spent in each category was calculated for all patients. Mean survival was calculated as the mean time elapsed between admission to the study and death or end of follow-up[8]. Follow-up was either completed till three years after admission to the study or till May 1987.

The patients in whom immediate PTCA was attempted (PTCA group) were matched with patients allocated to thrombolytic therapy in those centres where PTCA could not be performed as part of the recanalization procedure (Sk-only group). The matching procedure was performed only once by investigators who were at that time blinded to the follow-up data, according to the following rules:

(1) coronary angiograms of all patients successfully treated with streptokinase and admitted to those centres where acute PTCA was not performed were reviewed by three cardiologists to assess whether the lesion in the infarct related coronary artery had been suitable for PTCA;

(2) all patients were grouped with regard to the infarct related coronary artery and the presence or absence of previous myocardial infarction;

(3) within each group pairs of patients were selected with least difference in admission delay (maximum difference 30 min) and secondly least difference in total ST segment elevation (maximum difference 0·6 mV) on the admission ECG.

In order to ascertain that differences between the PTCA group and the Sk-only group were not due to differences between the various hospitals, two matched control groups of patients allocated to conventional therapy were constructed. One control group was formed from patients allocated to conventional therapy in the hospitals where immediate PTCA was performed (matched control group I), and the other from patients allocated to conventional therapy in hospitals without immediate PTCA (matched control group II).

Results

A total of 533 patients were admitted to the trial. Acute angiography was performed in 234 out of 269 patients allocated to thrombolytic therapy. PTCA was performed as part of the recanalization procedure in 46 patients admitted to two of the five participating centres.

Patency of the infarct related coronary artery as shown at angiography was achieved in 98 patients admitted to one of the three centres where acute PTCA was not performed. The lesion in the infarct related coronary artery was on review judged to be suitable for PTCA in 62 patients. These 62 patients

Table 1 Baseline characteristics

	C	T	All PTCA	Matched groups		Matched control groups	
				PTCA	Sk-only	CI	CII
No. of patients	264	269	46	36	36	36	36
Males	224	217	39	29	29	28	26
Previous infarction	60	56	12	4	4	4	4
Anterior infarction	116	130	29	22	22	22	22
Age (median)	56	57	59	59	56	52	55
Admission delay (median; min)	90	90	90	90	105	90	100
ΣST (median; mV)	1·2	1·1	1·3	1·2	1·1	1·2	1·3

C, control group; T, allocated to thrombolysis; Sk, streptokinase; PTCA, percutaneous transluminal coronary angioplasty; CI, matched control group from hospitals with acute PTCA; CII, matched control group from hospitals with Sk-only; ΣST, total ST segment elevation on the electrocardiogram made on admission to the trial.

were matched with the 46 patients in whom immediate PTCA was carried out. Thirty six pairs of patients were formed following the matching rules as described in the methods section. Ten patients in whom immediate PTCA was performed could not be matched because no pairs of patients could be formed which were identical with regard to the infarct related coronary artery and the presence or absence of previous myocardial infarction. In addition, two matched control groups of 36 patients each were formed. Baseline characteristics were distributed evenly between the four matched groups (Table 1).

Acute PTCA was performed more often when the lesion was located in the left anterior descending artery (29 out of 55 patients with such a lesion in the two hospitals with acute PTCA, 53%) than in the right coronary artery (15 out of 40 patients, 38%) or the left circumflex artery (two out of 19 patients, 11%). Acute PTCA led to a significant decrease in residual stenosis ($P=0{\cdot}001$), although immediate reocclusion was observed in two patients (Table 2). Reocclusion, defined as an occluded infarct related coronary artery at second angiography in patients with successful thrombolysis, was observed in nine out of 57 patients with a second angiogram (16%) in the matched groups (Table 3). Reocclusion rates were similar in the PTCA group and the Sk-only group (18% versus 14%), but higher when the lesion was located in the right coronary artery or left circumflex artery (six out of 21 patients, 28%) and lower in case of a lesion in the left anterior descending artery (three out of 36 patients, 8%).

Enzymatic infarct size, measured by cumulative HBDH release, did not differ in the PTCA group (median 760 U l^{-1}) from that in the Sk-only group (median 740 U l^{-1}). Left ventricular ejection fraction (LVEF), measured by radionuclide angiography after 10–20 days, also did not differ between the PTCA and the Sk-only group (median 49% *vs.* 50%).

Follow-up ranged from 20 to 60 months (mean 38 months). Three-year follow-up was complete for more than 90% in the matched groups. Three-year mortality was low in patients allocated to thrombolytic therapy: 6% in the PTCA group and 11% in the Sk-only group respectively.

Reinfarction rate within three years was considerably lower in the PTCA group (14%) than in the Sk-only group (30%, $P=0{\cdot}05$). Furthermore, immediate PTCA decreased the need for late PTCA or coronary artery bypass surgery, performed when signs of ischaemia returned. No significant differences in reinfarction rate of late revascularization were observed between the two matched control groups (Table 4).

In order to obtain a complete picture of total mortality and morbidity in the PTCA group and the Sk-only group, the proportion of patients in each functional class was calculated at weekly intervals during three-year follow-up and is presented in Fig. 1. From these data the mean number of weeks spent in a functional class or in hospital were derived (Table 5). Patients in the PTCA group had less symptoms of angina pectoris or heart failure (16 *vs.* 37 weeks in the Sk-only group, $P=0{\cdot}04$). Consequently, in the PTCA group more weeks were spent without symptoms (128 *vs.* 102 weeks in the Sk-only

Table 2 Results of coronary angiography (N = 234)

	All patients		Matched groups	
	PTCA	Sk-only	PTCA	Sk-only
Number of patients	46	188	36	36
Infarct related artery				
LAD	29	74	22	22
RCA	15	74	14	14
LCX	2	38	0	0
Bypass	0	2	0	0
Patency at the end of the procedure				
Occluded	2	34	2	0
91–99%	4	89	4	27
50–90%	4	54	4	8
< 50%	36	11	26	1
Patency at second angiography				
Occluded	6	27	4	5
91–99%	0	30	0	6
50–90%	9	54	9	12
< 50%	22	29	16	5
Unknown	9	48	7	8

PTCA, percutaneous transluminal coronary angioplasty; Sk, streptokinase; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.

Table 3 Patency of the infarct related coronary artery at second angiography (10–40 days) in patients with successful thrombolysis (N = 198)

	All patients		Matched groups	
	PTCA	Sk-only	PTCA	Sk-only
Number of patients	44	154	36	36
LAD				
Patent	22	45	16	17
Occluded	1	5	1	2
Unknown	4	12	5	3
RCA or LCX				
Patent	9	57	7	8
Occluded	5	14	4	2
Unknown	3	21	3	4

For abbreviations see Table 2.

group, $P = 0{\cdot}03$). Mean survival during three-year follow-up and mean time spent in hospital did not differ between the PTCA group and the Sk-only group. Similar effects of PTCA were observed in patients with anterior and with inferior infarction. In patients with anterior infarction, 122 weeks were, on average, symptom free in the PTCA group versus 97 weeks in the Sk-only group. In patients with inferior infarction these figures were 139 and 111 weeks, respectively.

Table 4 Three-year follow-up

	Matched groups		Matched control groups	
	PTCA	Sk-only	CI	CII
No. of patients	36	36	36	36
Deceased	2	4	5	8
Reinfarction	5*	11	3	2
Bypass surgery	6	4	5	3
(Re-)PTCA	1†	10	1	0
No complications	23‡	14	22	23

*$P=0{\cdot}05$, †$P=0{\cdot}003$, ‡$P=0{\cdot}03$: Fisher exact test.
For abbreviations see Table 1.

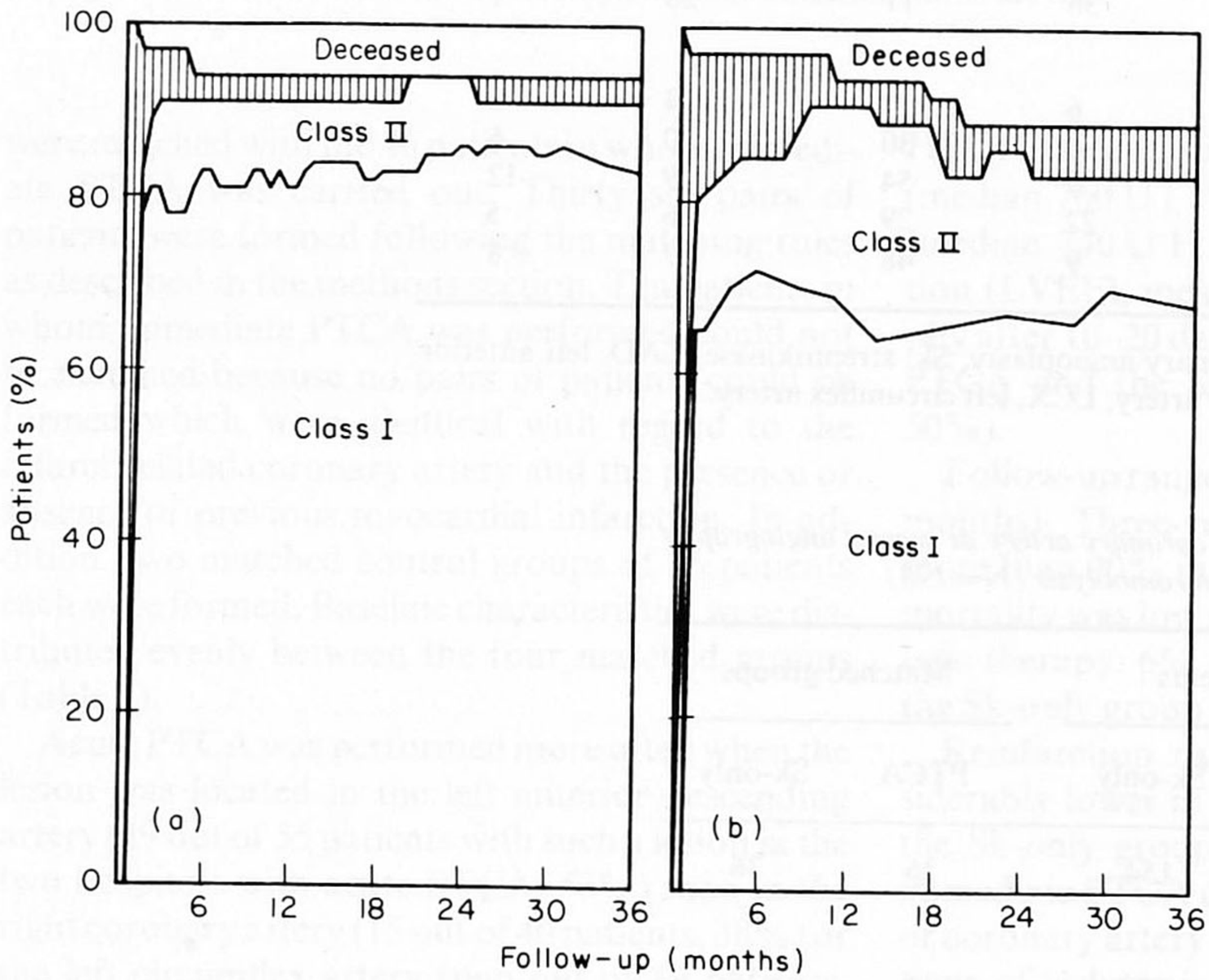

Figure 1 Proportion of patients in each functional class during the first three years after myocardial infarction. NYHA class III or IV and in hospital are combined and are indicated by the shaded area. (a) Sk + PTCA group. (b) Sk-only group.

The largest benefit of PTCA after thrombolysis was observed in the subgroup of patients admitted to hospital within two hours after the onset of myocardial infarction with high ST segment elevation on the ECG recorded on hospital admission. These patients were, on average, 128 weeks without symptoms in the PTCA group versus 87 weeks in the Sk-only group ($P=0{\cdot}04$). On the other hand, little benefit was observed in patients with low ST segment elevation or longer treatment delay.

Discussion

Immediate PTCA after thrombolytic therapy has been introduced as a means to enhance reperfusion of the ischaemic myocardium and to prevent reocclusion and recurrent ischaemia. However, in the present analysis immediate PTCA did not further limit infarct size, nor did it prevent reocclusion. On the other hand, reinfarction during three-year follow-up and the need for late revascularization

Table 5 Mean number of weeks spent in the different functional classes or in hospital

	Matched groups	
	PTCA	Sk-only
Class I	128	102
Class II	15	29
Class III–IV	1	8
In hospital	4	5
Mean survival (weeks)	148	144

procedures were reduced by immediate PTCA in comparison with successful thrombolysis with streptokinase alone.

The PTCA and Sk-only groups were constructed using those baseline characteristics which have been shown to determine the effect of thrombolytic therapy: the delay between onset of symptoms and treatment, and the extent of myocardial ischaemia as reflected by the total ST segment elevation on the admission ECG[7]. Patients were matched with the same infarct related coronary artery and either with or without a history of previous myocardial infarction. Nevertheless, the matched pair analysis might be criticized because the two groups of patients (PTCA and Sk-only) were treated in different hospitals. However, all patients in the study were treated according to the same guidelines[3]. In order to ascertain that treatment was similar in the different hospitals, two matched control groups were constructed with the same baseline characteristics as the PTCA and Sk-only groups (Table 1). No significant differences appeared between these control groups at three-year follow-up (Table 4), which supports the validity of the present analysis. Furthermore, the data are in close agreement with other studies of immediate PTCA after thrombolytic therapy[13–15]. Infarct size and left ventricular function were not altered by immediate PTCA. Similarly, Erbel *et al.*[14] observed no differences in left ventricular end-diastolic volume, end-systolic volume or ejection fraction in a randomized study comparing intracoronary streptokinase with and without immediate PTCA. In the TAMI study, also, no differences were reported in left ventricular ejection fraction between patients treated with recombinant tissue-type plasminogen activator (rt-PA) alone and patients with immediate PTCA after thrombolysis with rt-PA[13].

Regional wall motion was not analyzed in the present report because the groups were too small to obtain meaningful results. Erbel *et al.*[14] reported improvement in regional wall motion in anterior infarction after PTCA compared with intracoronary streptokinase alone, but not in inferior infarction. On the other hand, Topol *et al.*[13] did not observe a beneficial effect on regional wall motion comparing rt-PA with immediate PTCA to rt-PA alone.

Early reocclusion was observed in four out of 29 patients with PTCA (14%) and in five out of 28 patients with Sk-only (18%), who underwent late angiography. These data are similar to those reported by Erbel *et al.*[14] from a prospective randomized trial with reocclusion during PTCA in two and late reocclusion in 10 out of 71 patients (14%), and to the results of smaller non-randomized studies[9,12,16,17]. The reocclusion figures are considerably greater than after PTCA out of the setting of acute myocardial infarction. The high reocclusion rate associated with immediate PTCA after thrombolytic therapy may be related to the extent of vascular injury from both plaque rupture which caused the infarction[18,19], bleeding in the plaque after thrombolytic therapy, and intimal splitting and dissection after PTCA[20–23]. Furthermore, residual mural thrombi in spite of thrombolysis may contribute to early reocclusion.

Long-term follow-up after successful thrombolysis followed by immediate PTCA compared favourably with successful thrombolysis alone, in that more patients were symptom-free during three-year follow-up while fewer patients suffered from reinfarction or required re-PTCA or bypass surgery (Tables 4 and 5). Total morbidity was also lower in the PTCA group (Fig. 1). In the subgroup of patients with high ST segment elevation, admitted to the hospital within two hours after onset of symptoms, thrombolytic therapy resulted in the largest reduction in three-month mortality (7% *vs.* 16% in the control group) and, in this particular subgroup, immediate PTCA resulted also in the largest improvement in quality of life (128 weeks without symptoms *vs.* 87 in the Sk-only group), making these patients the ones who benefited most from thrombolytic therapy and from immediate PTCA.

From the data presented here and in other studies, the proper role of PTCA after thrombolysis remains uncertain. Immediate PTCA adds little, if anything, to the early salutary effects of thrombolysis, i.e limitation of infarct size and preservation of left

ventricular function[4–6], but PTCA does reduce the incidence of recurrent ischaemia and reinfarction. It is yet to be defined whether the observed long-term benefits, particularly the reduction of reinfarction, requires early PTCA or bypass surgery in all or most patients after thrombolytic therapy. Therefore, future studies should address the question whether angiography should be performed in all patients after thrombolytic therapy in order to assess indications for PTCA or bypass surgery, or whether angiography and further interventions should be deferred and performed only in patients with signs of recurrent ischaemia after thrombolysis.

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Appendix

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