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Pre-hospital thrombolytic therapy with either alteplase or streptokinase

Practical applications, complications and long-term results in 529 patients

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KEY WORDS: Myocardial infarction, thrombolysis, long-term results.

Objective: *To assess the practical application, safety and long-term outcome of pre-hospital thrombolytic intervention with either alteplase or streptokinase in patients with extensive myocardial infarction.*

Design: *Prospective study.*

Subjects: *Patients with chest pain of more than 30 min duration, presenting within 6 h of symptom onset and with electrocardiographic evidence of extensive evolving myocardial infarction.*

Methods: *Eligibility of patients was established by the general practitioner or the ambulance nurse using a standardized questionnaire with (contra-) indications for thrombolytic therapy. Computerized ECG was recorded by ambulance nurses. In the presence of extensive ST segment elevation (sum ST deviation of at least 1·0 mV), eligible patients received either 100 mg alteplase (n=246) or 50 mg alteplase in the ambulance followed by 0·75 × 10^6 IE streptokinase in hospital (n=90), or 1·5 × 10^6 IE streptokinase intravenously (n=193).*

Main outcome measurements: *Death and life-threatening complications (ventricular fibrillation, cardiac arrest) and side effects (hypotension, allergic reactions) during transportation to hospital and in the first 24 h following hospitalization, and survival up to 5 years follow-up.*

Results: *From 1988–1993, 529 patients received thrombolytic treatment initiated pre-hospital. The time gained by pre-hospital administration of thrombolysis amounted to 50 min. The rate of complications during transportation and during the first 24 h after hospitalization was low. Hospital mortality was 2% and 1-year mortality 3%. Cumulative survival at 5 years was 92%. This was superior to the 84% 5-year survival observed in a matched group of 239 patients with similar baseline characteristics treated with alteplase in hospital.*

Conclusions: *Pre-hospital administration of either alteplase or streptokinase is feasible and safe and results in significant time gain. The long-term prognosis is excellent in spite of extensive evolving myocardial infarction upon admission.*

Introduction

The value of thrombolytic therapy in patients with evolving myocardial infarction is well documented, but gains diminish if such therapy is started late after the onset of symptoms. The earlier thrombolytic therapy is initiated, the greater its benefits[1–6]. In clinical practice, only a small minority of patients receive treatment within the first hour of onset of symptoms. Many patients wait several hours before alerting the general practitioner or the ambulance service and it takes additional time for the general practitioner to respond and establish the diagnosis[7–9]. Ambulance transport and in-hospital delivery of thrombolytic therapy also carry inherent delays[10].

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Efficient strategies have been developed to ensure rapid pre-hospital initiation of thrombolytic therapy[11–24]. In The Netherlands, the REPAIR study (REPerfusion in Acute Infarction Rotterdam) was designed to evaluate the feasibility of pre-hospital thrombolytic intervention by general practitioners and ambulance nurses[11,13,18]. Here, we report the practical application and complications associated with pre-hospital thrombolytic therapy with either alteplase or streptokinase in 529 patients during the 5-year period of the REPAIR study. The long-term outcome of patients treated pre-hospital is compared with the outcome of a matched group of patients with similar baseline characteristics treated in hospital.

Patients and methods

The REPAIR study was initiated in June 1988. After extensive field testing, pre-hospital thrombolytic

Table 1 Indications and contra-indication for REPAIR eligibility

Indications for pre-hospital thrombolytic therapy
Chest pain of more than 30 min duration
No relief by nitroglycerin
Onset of symptoms <6 h
Age <75 years
ECG: sum ST elevation of at least 1·0 mV in the absence of conduction defects*
Contra-indications for prehospital thrombolytic therapy
Cardiac massage
Artificial respiration
Systolic blood pressure >200 mmHg
Known bleeding disorder
History of cerebrovascular accident
In the previous 3 months:
Major trauma
Surgery
Haemoptysis
Gastroduodenal ulcer or blood loss
Urological bleeding
Pregnancy/menstruation
Paresis or paralysis
Previous thrombolysis

*Bundle branch block, or QRS complex duration longer than 130 ms. A more detailed description of ECG algorithms has been provided[11,13,18]. Patient selection for pre-hospital therapy was more strict than in hospital to allow for the limited time available for assessment and the limited experience of general practitioners and ambulance nurses.

treatment, the indications for which have been described previously[11,13,18] was accepted as routine management in the Rotterdam Ambulance Service in January 1991. Briefly, the referring general practitioner or, in his/her absence, the ambulance nurse, checked the criteria for eligibility in all patients with chest pain suggestive of myocardial infarction using a short questionnaire (Table 1). These selection criteria were more restricted than those used in hospitals to minimize the risk of inappropriate selection of patients for thrombolytic therapy or inclusion of patients at high risk of bleeding. A small portable ECG system (Sicard P, Siemens, Sweden) with special easy application electrodes and a diagnostic computer program (Mortara Inc, Milwaukee, U.S.A.) was used to confirm the presence of an evolving myocardial infarction with extensive myocardial ischaemia (defined as a summed ST segment deviation of more than 1·0 mV in the absence of conduction defects)[13,18].

All patients received basic medical care, provided by the general practitioner or the ambulance nurse, including, when necessary, pain relief with opiates, oxygen, nitrates, and rhythm monitoring. Eligible patients were subsequently treated with alteplase or streptokinase intravenously, before they were transferred to hospital. Until 1991, patients received 100 mg alteplase, but this was then changed, for economic reasons, to 1 500 000 Units of streptokinase. In the transition period, a group of patients received alteplase prior to hospital admission (one vial of 50 mg), followed by 750 000 IE of streptokinase in hospital.

Complications and side-effects were recorded during transportation in the ambulance as well as in the first 24 h following hospitalization. Long-term outcome was determined using information from the hospital and from the municipal registries.

To compare the time to treatment and the long-term outcome, two non-randomized control groups were selected. To estimate the time gained by pre-hospital administration of thrombolytic therapy, treated patients were compared to a control group of patients transferred to hospital, who were not eligible for pre-hospital thrombolysis at that moment, but who received thrombolytic treatment immediately after clinical evaluation in hospital[13,18]. Long-term survival in REPAIR was compared with survival in patients treated in hospital. To obtain such a control group, 491 patients were selected from a database of a previous study with alteplase[26], using the same selection criteria as applied in REPAIR.

Group differences were assessed with Student t, analysis of variance using Kruskal–Wallis and chi-square tests where appropriate. Two-tailed P values <0·05 were considered statistically significant. Survival curves were generated using the Kaplan–Meier method.

Results

Between June 1988 and June 1994, 529 patients received pre-hospital thrombolytic therapy: 246 patients were treated with alteplase only, 90 patients with alteplase in the ambulance followed by streptokinase in hospital, and 193 patients with streptokinase. Four patients died before treatment could be initiated and were excluded. Baseline characteristics are shown in Table 2. Patients were younger, and more frequently male during the first 3 years in comparison to the group treated after 1991. This was related to the extension of the age limit from 70 during the initial programme to 75 years from 1991 onward. In the initial phase of the study, 11% of the intravenous lines could not be inserted at the patient's home or in the ambulance. This decreased significantly in the course of the study as a result of increased experience of the ambulance nurses. During the 5-year study period, seven patients without myocardial infarction were erroneously included (false-positive rate 1%) as a result of noisy electrocardiographic signals, leading to a false-positive computer interpretation. One patient was treated based upon a previous electrocardiogram, recalled from the computer memory.

Pre-hospital complications were rare (Table 3). Ventricular fibrillation occurred in 3% and was successfully treated by defibrillation in all patients. There were no bleedings or deaths outside hospital. During the first 24 h after hospitalization, 2% of the patients died. No significant differences were observed between the thrombolytic agents, although symptomatic hypotension and allergic reactions occurred more often in patients treated with streptokinase. The main source of minor bleeding was the intravenous access site. Only 2% of the patients

Table 2 Characteristics of patients with thrombolytic agents before hospitalization over 6 consecutive years

	1988*	1989	1990	1991	1992	1993†	Total
Number	36	65	126	116	103	83	529
Male gender	32 (89%)	62 (95%)	105 (83%)	98 (84%)	79 (77%)	64 (77%)*	440 (83%)
Mean age (years)	59·3	56·7	57·7	59·4	60·9	60·4*	59·1
Treatment with alteplase (%)	36 (100%)	65 (100%)	120 (95%)	21 (18%)	2 (2%)	—	244 (46%)
Treatment with streptokinase (%)	—	—	6 (5%)	95 (82%)	101 (98%)	83 (100%)	285 (54%)
Anterior infarction (%)	11 (30%)	25 (38%)	48 (38%)	41 (35%)	35 (34%)	25 (30%)	185 (35%)
Infusion in ambulance (%)	32 (89%)	63 (97%)	124 (98%)	114 (98%)	101 (98%)	83 (100%)*	517 (98%)
False-positive ECG (%)	1 (3%)	3 (5%)	—	2	1 (1%)	—	7 (1%)
Treated <1 h (%)	7 (19%)	12 (18%)	36 (29%)	29 (25%)	32 (31%)	33 (40%)*	149 (28%)

*$P<0·05$.
*Second half of 1988 only.
†First half of 1993 only.

Table 3 Complications pre-hospital and in the first 24 h after hospitalization

Complications	rt-PA* n=246	rt-PA, SK† n=90	SK‡ n=193	Total n=529
Pre-hospital				
Mortality	—	—	—	—
Ventricular tachycardia	—	—	1 (1)	1 (1)
CPR/ventricular fibrillation	8 (3)	3 (3)	5 (2)	16 (3)
Hypotension	—	—	2 (1)	2 (1)
Allergic reaction	—	—	2 (1)	2 (1)
In hospital				
Mortality	4 (2)	1 (1)	5 (3)	10 (2)
Ventricular tachycardia	23 (9)	6 (7)	5 (3)	34 (6)
CPR/ventricular fibrillation	26 (11)	8 (9)	21 (11)	55 (10)
Hypotension	4 (2)	3 (3)	23 (12)	30 (6)
Allergic reaction	—	—	3 (2)	3 (1)
Major bleeding§	8 (3)	1 (1)	3 (2)	12 (2)
Minor bleeding	29 (12)	7 (8)	27 (14)	63 (12)
Additional thrombolytics	9 (4)	4 (4)	12 (6)	25 (5)

*100 mg alteplase.
†50 mg alteplase in the ambulance, followed by $0·75 \times 10^6$ IE streptokinase in hospital.
‡$1·5 \times 10^6$ IE streptokinase.
§Cerebrovascular accidents or severe bleedings requiring blood transfusion.
CPR=cardiac pulmonary resuscitation.

required blood transfusions. Overall, 5% of the patients received additional thrombolytic therapy for recurrent infarction in hospital.

The median delay between onset of symptoms and ambulance call was 55 min. After arrival of the ambulance, evaluation of patient eligibility until initiation of thrombolytic treatment required a median interval of 18 min. In the course of the project, this time gradually shortened from a median of 24 min in 1988 to 17 min in 1993 (Fig. 1). The P value associated with this decrease was <0·001. Median time to administration of thrombolytic agents in the control group was 68 min after arrival of the ambulance. This group consisted of 220 patients, treated in 1988. In this control group, 75% were men, the mean age was 60 years and 47% had anterior myocardial infarction. Since thrombolytic therapy in the pre-hospital study population was initiated within 18 min after arrival of the ambulance, the time gained with pre-hospital treatment was approximately 50 min. Initially, 19% of the patients were treated within the first

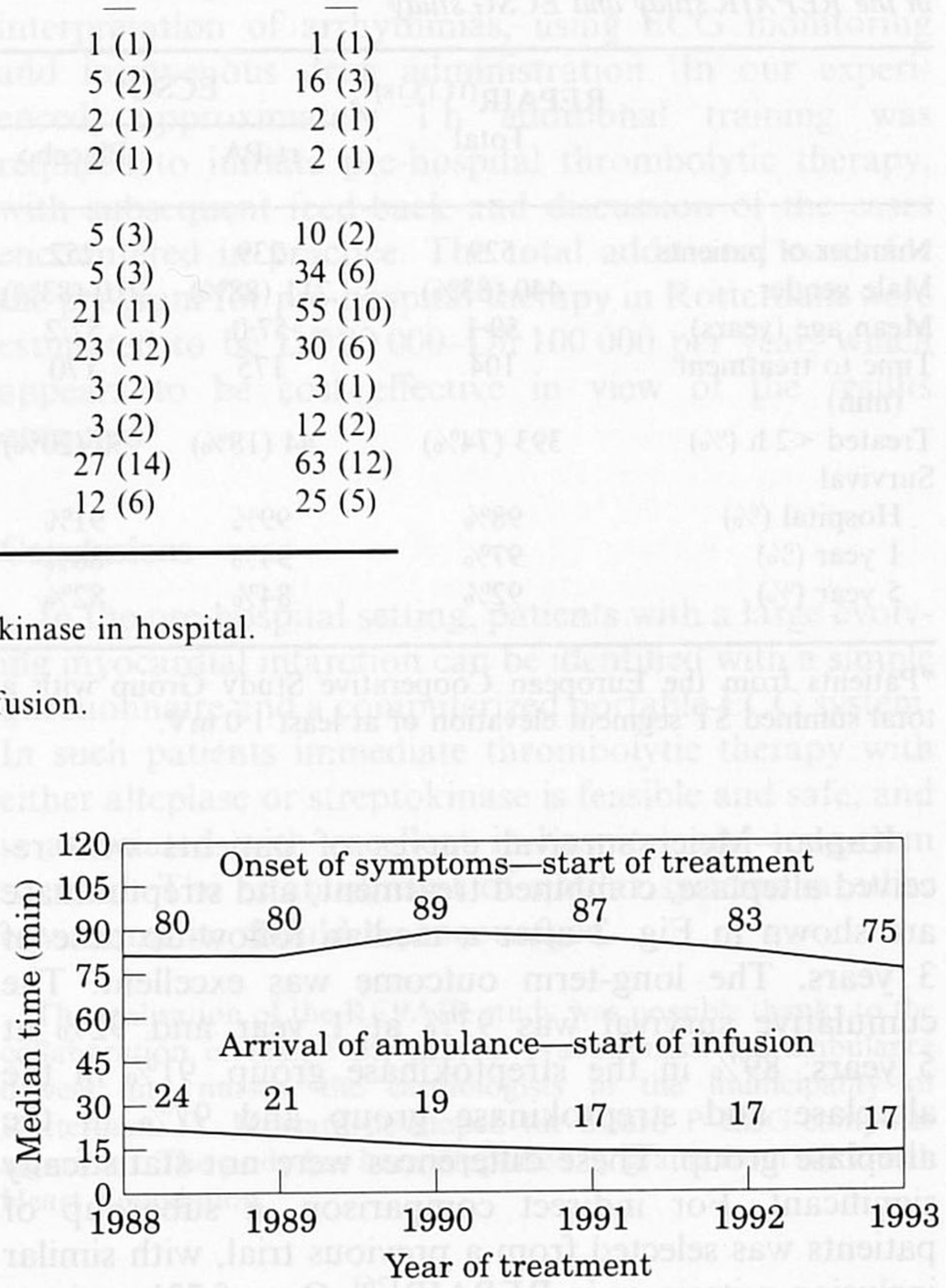

Figure 1 Time (medians) between the onset of symptoms and initiation of pre-hospital thrombolytic treatment and the time elapsed between arrival of the ambulance and start of infusion over 6 consecutive years.

hour of the onset of symptoms, but this number increased to 40% in the course of the project. In contrast, only 1% of the patients in the control group had thrombolytic treatment initiated within the first hour after the onset of symptoms.

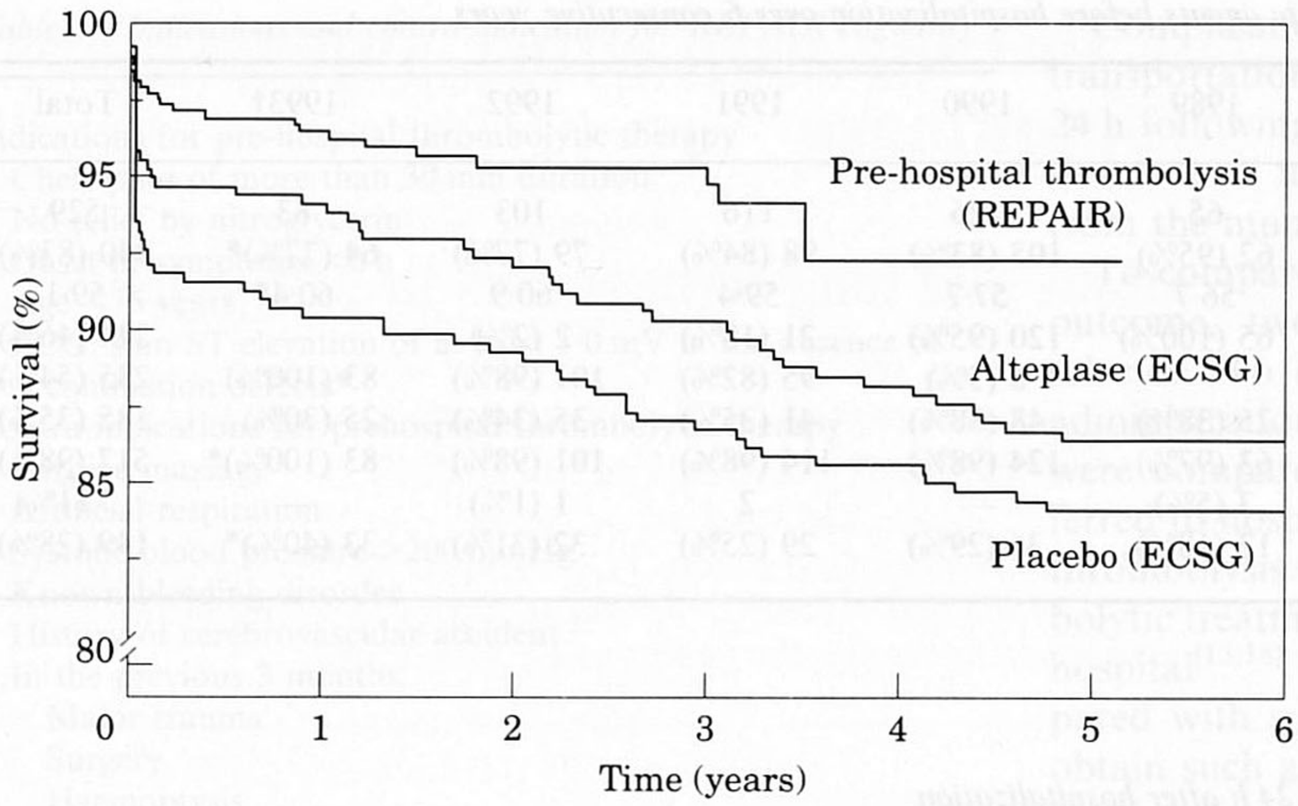

Figure 2 Kaplan–Meier survival curves of patients who received thrombolytic therapy before hospital admission in the REPAIR study, and in patients receiving alteplase or placebo in the ECSG study.

Table 4 Comparison of patients treated with thrombolytic therapy in the REPAIR study and ECSG study

	REPAIR[11,13,18]	ECSG*	
	Total	rt-PA	Placebo
Number of patients	529	239	252
Male gender	440 (83%)	211 (88%)	210 (83%)
Mean age (years)	59·1	57·0	57·2
Time to treatment (min)	104	175	170
Treated <2 h (%)	393 (74%)	44 (18%)	50 (20%)
Survival			
Hospital (%)	98%	99%	91%
1 year (%)	97%	94%	88%
5 year (%)	92%	84%	82%

*Patients from the European Cooperative Study Group with a total summed ST segment elevation of at least 1·0 mV.

Kaplan–Meier survival curves of patients who received alteplase, combined treatment, and streptokinase are shown in Fig. 2 after a median follow-up time of 3 years. The long-term outcome was excellent. The cumulative survival was 97% at 1 year and 92% at 5 years: 89% in the streptokinase group, 91% in the alteplase and streptokinase group and 97% in the alteplase group. These differences were not statistically significant. For indirect comparison, a subgroup of patients was selected from a previous trial, with similar inclusion criteria as in REPAIR[26]. Out of 721 patients in that study, 491 had ECG evidence of extensive evolving myocardial infarction with a sum of ST segment deviation exceeding 1·0 mV. In this series, treatment was initiated approximately 3 h after symptom onset. Other patient characteristics were similar to REPAIR (Table 4). Two hundred and thirty-nine patients had been treated with alteplase and 252 received placebo. At 1 year, survival was 97% in REPAIR, compared to 94% in patients receiving alteplase in hospital and 88% in the hospital placebo group. At 5 years, these figures were 92%, 84%, and 82% respectively.

Discussion

The REPAIR experience since 1988 confirms that identification of candidates for thrombolytic therapy in the pre-hospital setting is feasible. Pre-hospital therapy with either alteplase or streptokinase appeared to be safe and resulted in a significant time gain when compared to in-hospital therapy after ambulance transport. Competent organization of the ambulance service, skilled ambulance nurses and good cooperation with general practitioners were of major importance for the success of the study. A unique feature of the REPAIR program is the initiation of therapy by experienced ambulance nurses, even when no physician (general practitioner) is present. Even before initiation of the REPAIR project, the level of education of the ambulance nurses was high. All completed 6 years education in basic somatic and psychiatric nursing, with advanced education in Coronary Care and Intensive Care. The diagnosis of myocardial infarction was confirmed in hospital in 98% of the patients, who received pre-hospital thrombolytic intervention. The false-positive rate was low, and appeared related to technical problems which have since been resolved.

The MITI (Myocardial Infarction Triage and Intervention) project in Seattle was also conducted by ambulance paramedics using telephone transmission of the ECG for immediate review and interpretation by a physician[23]. All other pre-hospital programmes were conducted by physicians in the ambulances using standard electrocardiography[14–17,20–24]. In many communities, however, ambulances are manned by paramedics instead of physicians. The combined REPAIR and MITI experience have confirmed that thrombolytic therapy can be given safely and effectively in such a setting.

The time gain by pre-hospital thrombolytic therapy in Rotterdam was approximately 50 min. In other series the time gain ranged from 33–130 min[14–20]. The time between arrival of the ambulance and initiation of thrombolytic therapy in our project decreased significantly and was only 17 min in 1993, as a result of improved routine of the ambulance nurses. In REPAIR, 74% of patients were treated within 2 h of symptom onset. Such early therapy was associated with very low morality figures in spite of pre-hospital selection of patients with electrocardiographic evidence of large evolving myocardial infarction. One year survival was 97%, and 5-year survival 92%. In a non-randomized but otherwise comparable group of patients treated in hospital with thrombolytic therapy, 5-year survival was 84%.

The EMIP (European Myocardial Infarction Project) study was a randomized comparison of pre-hospital and in-hospital therapy. Treatment in EMIP was initiated approximately 0·5 h later than in REPAIR, averaging 130 and 190 min after onset of symptoms, respectively. However, hospital mortality was reduced by pre-hospital therapy to 9·7% compared with 11·1% for hospital therapy ($P=0·08$). The EMIP report included a combined analysis of all randomized trials comparing pre-hospital and in-hospital therapy. The outcome of that analysis indicated that pre-hospital treatment was associated with a significant 17% reduction in mortality (95% confidence interval, 2–29%, $P=0·03$)[22]. The additional value of very early therapy was also shown in an analysis of the MITI study, where mortality was only 1·2% in patients treated within 70 min of symptom onset and 8·7% in those treated later ($P=0·04$). A recent meta-analysis of large randomized trials reported a loss of benefit of thrombolytic therapy of $1·6 \pm 0·6$ per 1000 for an additional delay of 1 h, or an additional benefit of 1·6 per 1000 for earlier therapy by 1 h[6]. It should be appreciated that most patients in these trials were treated more than 2 h after the onset of symptoms. Furthermore, patients were not randomized to receive earlier or later therapy, thus characteristics of patients treated at different intervals were probably not the same. The benefit of pre-hospital therapy in EMIP and other randomized trials was almost ten-fold higher: 14 per 1000 patients. Together with MITI and the very low mortality in REPAIR this supports the concept that the additional benefit is considerably greater if very early treatment can be achieved. Thus, pre-hospital therapy is particularly effective when a large proportion of patients can be treated within 1 or 2 h.

There is no doubt that pre-hospital thrombolytic therapy should be a preferred mode of treatment, provided that a cost effective system can be established. Both the additional costs and the effectiveness of systems for pre-hospital thrombolytic therapy will depend on the setting in which such a system is introduced. The benefit will be greater if patients can be reached very early[11,13,16,18], and in settings where transportation time is long[19]. In other environments, intermediate benefit will be achieved such as those participating in the large multicentre EMIP study.

Electrocardiography is required to establish a diagnosis of evolving myocardial infarction with sufficient certainty to initiate thrombolytic therapy. Thus an electrocardiograph must be added to the ambulance equipment. Currently computer ECG systems such as used in REPAIR can be obtained at acceptable low prices, in the range of Dfl 10 000–15 000. Furthermore integrated systems, designed especially for the ambulance environment, are available which include in a single portable unit: a defibrillator, ECG monitor (1–2 channels), and a diagnostic 12-lead ECG recorder. Costs will increase if telephone transmission of the ECG is required for physician review and time gain will diminish[16]. However, the REPAIR experience indicated that such review is not necessary, while it would also cause additional delay since transmission is not always reliable, and since the physician at the central receiving station may be occupied by other tasks.

Additional training of ambulance nurses or paramedics will require some costs, depending on the level of expertise which is present. A first requirement for ambulance personnel is basic life support including interpretation of arrhythmias, using ECG monitoring and intravenous drug administration. In our experienced, approximately 1 h additional training was required to initiate pre-hospital thrombolytic therapy, with subsequent feed-back and discussion of the cases encountered in practice. The total additional costs for the program for pre-hospital therapy in Rotterdam were estimated to be Dfl 70 000–Dfl 100 000 per year, which appears to be cost effective in view of the results obtained.

Conclusions

In the pre-hospital setting, patients with a large evolving myocardial infarction can be identified with a simple questionnaire and a computerized portable ECG system. In such patients immediate thrombolytic therapy with either alteplase or streptokinase is feasible and safe, and is associated with excellent in-hospital and long-term survival. The establishment of similar systems in other environments should be encouraged.

The realisation of the REPAIR study was possible thanks to the collaboration of many: the general practitioners, the ambulance drivers and nurses, the cardiologists in the municipality of Rotterdam. D. Mortara developed the Sicard P ECG-computer algorithm. The study has been supported by grants from the Dutch Heart Foundation.

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