JACC Vol. 30, No. 5
November 1, 1997:1181–6

Quantification of the Benefit of Earlier Thrombolytic Therapy: Five-Year Results of the Grampian Region Early Anistreplase Trial (GREAT)

JOHN M. RAWLES, BSc, MBBS, FRCP, FRCP(Edin)

Aberdeen, Scotland, United Kingdom

Objectives. **This report presents the 5-year results of the Grampian Region Early Anistreplase Trial (GREAT) and quantifies the benefit of earlier thrombolysis in terms that are generally applicable.**

Background. **Although it is accepted that the earlier thrombolytic therapy is given for acute myocardial infarction the greater the benefit, there are widely differing estimates of the magnitude of the time-related benefit of thrombolysis because of inappropriate trial design and analysis.**

Methods. **In a previously reported randomized trial, anistreplase (30 U) was given intravenously either before hospital admission or in the hospital, at a median time of 105 and 240 min, respectively, after onset of symptoms. Intention to treat and multivariate analyses of the 5-year results were performed.**

Results. **By 5 years, 41 (25%) of 163 patients had died in the prehospital treatment group compared with 53 (36%) of 148 in the hospital treatment group (log-rank test, $p < 0.025$). Delaying thrombolytic treatment by 1 h increases the hazard ratio of death by 20%, equivalent to the loss of 43/1,000 lives within the next 5 years (95% confidence interval 7 to 88, $p = 0.012$). Delaying thrombolytic treatment by 30 min reduces the average expectation of life by ~1 year.**

Conclusions. **The magnitude of the benefit from earlier thrombolysis is such that giving thrombolytic therapy to patients with acute myocardial infarction should be accorded the same degree of urgency as treatment of cardiac arrest. Policies should be developed for giving thrombolytic therapy on-site if practicable and by the first qualified person to see the patient.**

(Am J Coll Cardiol 1997;30:1181–6)

Although it is agreed that the earlier thrombolytic therapy is given for acute myocardial infarction the greater the benefit (1), there is no generally accepted figure for the magnitude of the time-related benefit of thrombolysis. Some placebo-controlled trials of thrombolytic therapy did not show any greater benefit with earlier treatment (2,3), whereas at the other extreme, it has been claimed that, in terms of its potential for saving life, giving thrombolytic therapy is as urgent as the treatment of cardiac arrest (4).

Much effort is required and is being expended to shorten delays to thrombolysis, so it is important to quantify the benefit of earlier thrombolysis to know whether the effort is likely to be worthwhile.

In assessing the time-related benefit of thrombolytic therapy, it is tempting to look only at the outcome of patients given thrombolytic therapy at different times (e.g., while participating in clinical trials comparing different thrombolytic agents). In such hospital-based trials of thrombolysis, treatment is initiated as soon as practicable after the patient is admitted to the hospital. The largest single component of the delay from onset of symptoms until commencement of treatment is delay by the patient in seeking medical assistance (5,6); but patient delay is influenced by severity of infarction, and there is a tendency for patients with poor left ventricular function and a higher mortality risk to seek help earlier (7,8). This behavior acts as a confounding factor, tending to mask the benefit of earlier thrombolytic therapy; the sickest patients get the earliest treatment.

To quantify the time-related benefit of thrombolysis, time of presentation has to be dissociated from time of initiating treatment. Patients must be randomly allotted treatment on presentation or after a deliberate delay. However, because it is generally agreed that earlier thrombolytic therapy is more beneficial, and only the magnitude of the time-related benefit is unknown, it is considered unethical to impose a deliberate delay in starting thrombolytic therapy. This ethical objection may be overcome by randomly allocating patients to receive thrombolysis before hospital admission or later, in the hospital. The late treatment group then receives the best available treatment, and the ethical objections are met. However, the trial design is still not ideal because the later times of administration of thrombolysis before hospital admission may over-

From the Medicines Assessment Research Unit, University of Aberdeen, Aberdeen, Scotland, United Kingdom. GREAT was supported by SmithKline Beecham, Wetwyn Garden City, Edinburg; long-term follow-up was funded by the Acute Healthcare Research Committee of the Scottish Office Department of Health, Edinburg, Scotland, United Kingdom.

Manuscript received May 14, 1997; revised manuscript received July 11, 1997, accepted July 16, 1997.

Address for correspondence: Dr. John M. Rawles, Medicines Assessment Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZN, Scotland, United Kingdom.

Published by Elsevier Science Inc.

0735-1097/97/$17.00
PII S0735-1097(97)00299-4

JACC Vol. 30, No. 5
November 1, 1997:1181–6

Abbreviations and Acronyms

CI = confidence interval
EMIP = European Myocardial Infarction Project
FTT = Fibrinolytic Therapy Trialists' Collaborative Group
GREAT = Grampian Region Early Anistreplase Trial
MITI = Myocardial Infarction Triage and Intervention trial
TIMI = Thrombolysis in Myocardial Infarction

lap with the earlier times of administration in hospital (9). If dose rather than time were being compared, an overlap of the doses actually received in low and high dose groups would vitiate the trial. The only way that a meaningful result could be salvaged would be to abandon the intention to treat analysis and construct a dose–response curve relating outcome to the dose actually received.

The Grampian Region Early Anistreplase Trial (GREAT) (10) was a randomized, double-blind, parallel-group trial of anistreplase given either at the first opportunity before hospital admission by general practitioners or later, in hospital in Aberdeen. Grampian is a rural area of northeast Scotland, and patients had to travel at least 30 min to reach the hospital. The trial was conducted in this region to maximize the time difference between prehospital and hospital administration. The trial has been fully described, and the 1-year results were reported by Rawles (11). In this report the 5-year results are presented. Besides an intention to treat analysis, other analyses are performed to construct the temporal equivalent of a dose–response curve. An attempt is made to quantify the benefit of earlier thrombolysis in terms that are generally applicable away from the setting of the trial, for example, in urban locations or in countries with different health care systems.

Methods

Trial entry was for patients of any age, seen by their general practitioners within 4 hours of symptom onset, with a strong clinical suspicion of acute myocardial infarction and none of the standard contraindications. The practices that participated in the trial were located 16 to 62 miles (26 to 100 km) from the hospital in Aberdeen to which all patients were referred (average distance 36 miles [58 km]). The doctors were supplied with paired ampoules of anistreplase (30 U) and matching placebo, the ampoules being randomly labeled "home injection" or "hospital injection." The home injection was given as a slow intravenous injection by the general practitioner, and the hospital injection was sent with the patient to the hospital, where it was given by the hospital staff. Patients were personally followed up for 1 year. Thereafter, we were notified of deaths of trial patients by the Scottish Registry Office. Follow-up is complete to 5 years; all data beyond 5 years are censored.

Statistical analyses. Statistical analyses were performed using SPSS release 6.1.3. Survival in the two groups is depicted using Kaplan-Meier curves and compared using the log-rank test.

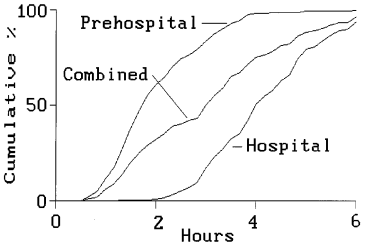


Figure 1. Cumulative percent of patients in the prehospital, hospital and combined groups who had received thrombolytic treatment at various times.

Using the Cox proportional hazards model, survival in the two groups combined was regressed stepwise against randomization assignment; age; gender; previous myocardial infarction; and patient delay in seeking help, time of randomization, time of administration of anistreplase and the logarithms of these three time delays. The logarithms were included because of the possibility that the effect of any of these delays might be nonlinear, with a greater effect sooner rather than later after start of symptoms. The stepwise analysis selects variables according to their significance, which was set at $p < 0.05$. Multiple logistic regression analysis was also used to regress death within 5 years against the same predictor variables.

Results

Intention to treat analysis. Three hundred eleven patients were recruited: 163 to the "prehospital" group, 148 to the "hospital" group. The two groups were similar in baseline comparisons; mean age was 63.4 years (range 32 to 93) (10).

Time of thrombolysis (Fig. 1). The median time after symptom onset to administration of anistreplase was 105 min (range 25 to 390) in the prehospital group and 240 min (range 80 to 540) in the hospital group. The cumulative percent of patients in each group who had received treatment by various times is shown in Figure 1. Although the medians are separated by 135 min, the times of administration of thrombolytic therapy in one group overlap those of the other group in 254 (82%) of 311 cases.

Mortality. By 5 years, 41 (25%) of 163 patients had died in the prehospital group compared with 53 (36%) of 148 in the hospital group. Kaplan-Meier survival curves for prehospital and hospital groups are shown in Figure 2, and these are separate throughout the 5-year follow-up period. Mean survival in the prehospital group was 1,517 days compared with 1,309 days in the hospital group (difference 208 days, 95% confidence interval [CI] 42 to 374, $p < 0.025$ [log-rank test]).

Multivariate analysis. The extent of overlap in the times of administration of thrombolytic therapy in prehospital and hospital groups, illustrated in Figure 1, diminishes the ability of the trial to demonstrate a difference in outcome between randomized groups. An alternative approach is to combine the

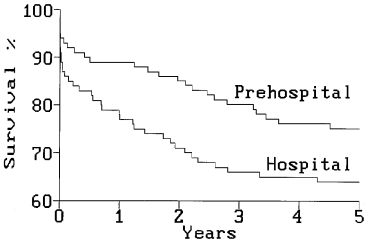


Figure 2. Kaplan-Meier survival curves for patients in the prehospital and hospital groups.

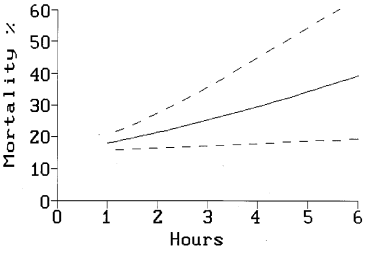


Figure 4. Relation between timing of anistreplase administration and probability of dying within 5 years. **Dashed lines** = 95% confidence intervals.

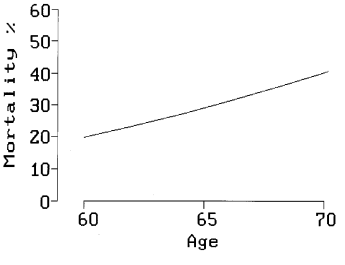
two groups and perform multivariate analysis to quantify the relation between time of thrombolysis, illustrated by the middle line in Figure 1, and outcome. The median and mean times of administration of anistreplase for the combined group of patients were 180 and 188 min, respectively.

Age (coefficient 0.0812, $p < 0.0001$) and time of anistreplase administration (coefficient 0.0030, $p = 0.0025$) were the two predictor variables selected for inclusion in the Cox proportional hazards model. The same two predictor variables were selected by multiple logistic regression analysis (coefficients: constant −8.0405, $p < 0.0001$; age 0.0995, $p < 0.0001$; thrombolysis time 0.0036, $p = 0.0119$). The selection of time of anistreplase administration rather than randomization assignment indicates that the essential difference between the prehospital and hospital groups is the timing of thrombolysis.

Age. The hazard ratio for age 60 years, less than the average of 63.4 years, is 0.755, whereas that for age 70 years is 1.701, an increase of 225% over the decade. The relation between age at trial entry and probability of dying within the next 5 years is illustrated in Figure 3.

Time of anistreplase administration. The hazard ratio for anistreplase given 30 min earlier than average is 0.914, whereas if given 30 min later than average, it is 1.094, an increase of 20% over the hour. By logistic regression, a 1-h delay in giving anistreplase is equivalent to 43/1,000 additional deaths within 5 years (95% CI 7/1,000 to 88/1,000, $p = 0.012$). This is the average gradient of the regression line in Figure 4 relating time of thrombolysis to the probability of death within 5 years. Comparison of Figures 3 and 4 shows that a delay in giving thrombolytic therapy of 5 h increases the probability of dying within 5 years by about the same amount as an increase in age from 60 to 70 years. Delay in giving thrombolytic treatment by 30 min is equivalent to aging by 1.11 years, or loss of life expectation of ~1 year (30 min × 0.0030 = 1.108 years × 0.0812).

Figure 3. Relation between age at trial entry and probability of dying within 5 years.



Discussion

In GREAT (10), two groups of patients with suspected acute myocardial infarction that were similar in all other respects were randomly allotted thrombolytic therapy before hospital admission, within 2 h of symptom onset, or in hospital, >2 h later. At 1 month, although there was a mortality difference of 6% in favor of prehospital thrombolysis, this did not reach conventional statistical significance ($p = 0.07$), but by 1 year it was 11% and was highly significant ($p = 0.007$) (11). The present analysis reports that the mortality difference has been maintained throughout the follow-up period, and is 11% at 5 years ($p = 0.025$).

GREAT, completed >5 years ago, was carried out in a rural location in the northeast of Scotland, where general practitioners still make home visits. Does it have any relevance for cardiologists practising in the United States? Are the results in any way applicable to urban areas or to hospitals with a fast-track system for dealing with patients with acute myocardial infarction?

In the present report the 5-year results of GREAT were used as the basis for multivariate analysis of the pooled data from both groups, enabling the general relation between time of thrombolysis and outcome to be quantified regardless of whether thrombolysis is given at home or in-hospital. The benefits of earlier thrombolysis derived from this analysis are calculated as hazard ratios, but more accessibly, as lives saved per hour of earlier treatment. Also calculated is the effect of thrombolysis delay on expectation of life. Expressed in these ways, the results should be widely relevant to current practice in any health care system.

Delay in giving anistreplase by 1 h increases the hazard ratio for death by 20%, equivalent to 43/1,000 additional deaths within the next 5 years. Delaying thrombolytic therapy by 5 h is equivalent to aging by 10 years. A delay of 30 min results in a reduction of life expectation of ~1 year. How do these estimates of time-related benefit compare with others?

The Fibrinolytic Therapy Trialists Collaborative Group (FTT) estimate of the benefit/time gradient. The most authoritative estimate of the time-related benefit of thrombolytic therapy comes from the FTT (12) overview of all nine randomized trials of >1,000 patients in which thrombolytic therapy is compared with placebo. The data are classified into five time periods from 0 to 24 h from onset. In each time period, the mortality rate in patients given thrombolytic therapy is less than that in those given placebo, and the absolute benefit is greater with earlier treatment. Regression of benefit by time of randomization yields a straight line with an intercept of 35/1,000 at time zero, and zero benefit at 21.5 h after onset; the gradient indicates a loss of benefit of 1.6/1,000 per h of delay.

The benefit/time gradient derived from the FTT overview is so low that many would consider that any great effort in expediting thrombolysis would not be justified, particularly the effort required to take thrombolytic therapy out of the hospital and into the community. However, the FTT estimate may be criticized on three grounds.

Thrombolytic therapy is beneficial by causing the thrombosed infarct-related artery to be reperfused—the "open artery hypothesis" (13); but the mechanism of benefit depends on how quickly reperfusion occurs. If within 2 h of onset, reperfusion results in myocardial salvage, which is steeply time dependent (14–16). By 6 h, myocardial salvage is all over (17), but an open artery confers electrical stability on the infarct (18,19) and reduces infarct expansion and remodeling (20–22). These late mechanisms are only weakly time dependent, if at all. It is therefore inherently unlikely that the mortality/time benefit of thrombolytic therapy would be best represented by a straight line. A nonlinear statistical model with a steeper gradient with earlier treatment is to be expected; a straight line that predicts a benefit of only 35/1,000 when thrombolytic therapy is given at time zero is almost certainly wrong.

In the FTT overview, the mean time of randomization was 6.7 h after onset; only 7% of patients were randomized, and even fewer received thrombolytic treatment, within 2 h. Prediction of benefit within 2 h, when myocardial salvage is the predominant mechanism of benefit, is therefore heavily weighted by what happens to the bulk of patients who are given thrombolytic therapy after 2 h and who benefit from a different mechanism. Moreover, the time periods are too wide to show important detail within them. For example, it is likely that the benefit in the first hour is higher than in the second hour, yet these two time periods are combined.

However, the most cogent criticism of the FTT estimate of the benefit/time gradient is that it is methodologically incorrect. It is a fundamental principle of clinical trial design that comparisons are made between groups that are determined by a random process; but the temporal groups in the FTT analysis were determined by the time of presentation of patients in hospital. It is as if, in a dose comparison trial, the patients themselves were to decide which dose to take; there is the possibility of bias from sicker patients choosing a higher dose. In a nonrandomized time-comparison study, there is the possibility that sicker patients may get earlier treatment; the time-related benefit would then be underestimated. Within the FTT data there is evidence that this is so. The mortality rate in patients given thrombolytic therapy at 2 to 4 h is 8.4%, but the mortality rate in those who are treated at 0 to 2 h is not lower, as expected, but slightly higher at 9.3%. The reason for this finding is seen in the mortality rates in the placebo group: There also the rate is higher at the earlier than at the later time (13.2% vs. 11.4%); patients with a higher mortality risk are treated earlier. Because of this bias, the benefit/time gradient cannot be calculated from these data, either by comparison of mortality rates in patients given thrombolytic therapy at different times or by reference to a control group: There is not one control group but several that are demonstrably different from each other. To determine the benefit/time gradient we have to know what the mortality rate would have been for patients presenting at one time and being treated at another. However, this experiment was not done, and time of presentation and time of treatment were always closely associated.

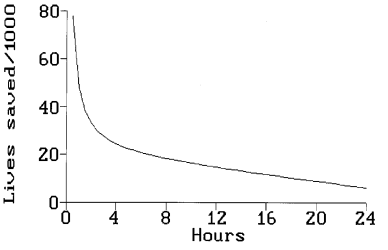


Figure 5. Relation between absolute mortality benefit and time of randomization to thrombolytic therapy. Data from Boersma et al. (25).

The criticisms of the FTT estimate of time-related benefit of thrombolytic therapy may be summarized as follows: a linear statistical model, underrepresentation of early-treated patients and nonrandom determination of time of treatment. Despite these criticisms having been voiced, members of the FTT have recently dismissed these objections and claimed that their estimate of the benefit/time gradient is correct (23).

Other estimates of the time-related benefit of thrombolysis. In the Thrombolysis in Myocardial Infarction (TIMI)-II trial (24) it was observed that for each hour of earlier treatment, the absolute mortality rate fell by 10/1,000. In that analysis (24) four treatment periods of 1 h were considered from 0 to 4 h after onset of symptoms. However, apart from the narrower time periods, the same criticisms apply here as are leveled at the FTT analysis: a linear model, underrepresentation of early patients and nonrandom determination of time of treatment.

Criticism of the FTT benefit/time gradient comes also from the Rotterdam group (25), who extended the FTT database to include all 22 randomized trials that compare thrombolytic therapy and placebo and have ≥100 patients. The results in all the temporal subgroups reported in these trials were kept separate for a benefit/time analysis. A nonlinear relation between benefit and time of randomization was demonstrated and was significantly better than a linear model; Figure 5 illustrates the benefit/time regression obtained. Initially the gradient is steep, but there is an inflection at ~2 h, after which

the benefit is much less time dependent. This shape of curve is what might be expected theoretically and reflects the different mechanisms of benefit at different times. The model uses a reciprocal term, so the predicted absolute benefit at time zero is infinite, but at 30 min it is 78/1,000. The benefit predicted at 1.5 h from onset is 38/1,000, and at 2.5 h 30/1,000. The mean benefit/time gradient at 2 h is therefore 8/1,000 per h, whereas at 4 h it is 3/1,000 per h. Although not guilty of forcing the data into a linear model, that analysis, like that of the FTT, is flawed by a nonrandom determination of time of treatment. If sicker patients receive earlier treatment, then the benefit of earlier treatment will be underestimated.

Randomized trials of prehospital thrombolysis. The only way in which the time-related benefit of thrombolysis may be properly quantified is with a trial in which the time of administration of therapy is randomly determined. To meet ethical objections to introducing any avoidable delay, the early group is given treatment before hospital admission and the late group in the hospital. Eight such trials have been reported, with a combined total of 6,607 patients; GREAT (10) is the third largest of these trials, being exceeded in size by the European Myocardial Infarction Project (EMIP) (26) (n = 5,469) and the Myocardial Infarction Triage and Intervention trial (MITI) (27) (n = 360); there are five other trials with 57 to 145 patients. All but one of these trials have shown a tendency toward a lower mortality with prehospital thrombolysis, but in none has this been significant at 1 month. However, a meta-analysis (25) gives an average benefit/time gradient of 21/1,000 per h (SE 6), with a highly significant ($p = 0.002$) mortality reduction in favor of prehospital thrombolysis (25). This, then, is the best available estimate of the time-related benefit of thrombolysis, being based on intention to treat analyses of appropriately designed trials using a variety of thrombolytic agents.

This estimate of the benefit/time gradient, 21/1,000 per h, is >10 times as great as that of the FTT and twice as great as that from TIMI-II. It is entirely consistent with that from GREAT, which, of course, contributed to it. The mortality difference at 1 month in GREAT was 6% for a 135-min difference between median times of administration of prehospital and hospital thrombolytic therapy. The crude benefit/time gradient is therefore 27/1,000 per h and by multivariate analysis 21/1,000 per h (4).

The benefit/time gradient of 43/1,000 per year calculated in the present report is based on 5-year results from GREAT. Between 1 month and 1 year, the difference in mortality between prehospital and hospital groups increased from 6% to 11%, and that difference is still present at 5 years. Late mortality benefit from thrombolytic therapy is not unexpected if thrombolysis is early enough to result in myocardial salvage. Death from heart failure or recurrent infarction is less likely if myocardial loss in the index event is minimized. The estimates of the time-related benefits of thrombolysis derived from GREAT and reported in the present analysis are plausible and entirely consistent with those from the meta-analysis of randomized trials of prehospital thrombolysis.

Implications of the benefit/time gradient. On the basis of an estimated benefit/time gradient of 10/1,000 per h derived from TIMI-II, Cannon et al. (24) concluded that "the treatment of patients with an acute MI [myocardial infarction] should take on the urgency of a cardiac arrest." The present study, based on a trial of appropriate design, and taking deferred mortality benefit into account, suggests that the benefit/time gradient may be four times as steep as that estimated from TIMI-II.

The saving of life by resuscitation in out of hospital cardiac arrest in patients with an acute myocardial infarction has been estimated at 10 to 30/1,000 (28). If the response of the emergency services to calls from patients with an acute myocardial infarction is delayed by 1 h, 10 to 30/1,000 additional patients will die before admission to hospital. However, if thrombolytic therapy is delayed by 1 h, 21/1,000 additional patients will die in the first month and at least as many again in the next few years. Thus, in terms of potential for saving life, giving thrombolytic therapy may justifiably be considered as urgent as the treatment of cardiac arrest. If this claim seems exaggerated, we should recall that, given early enough, reperfusion therapy is a radical treatment for acute myocardial infarction, whereas all other treatments, including defibrillation, are palliative.

If these arguments are accepted, then it follows that, as in cardiac arrest, treatment should be initiated at the first opportunity, on-site if practicable, and by the first qualified person to see the patient. Doctor to doctor referrals for thrombolytic therapy should be unacceptable, as they would be for initiating treatment for cardiac arrest. We require doctors to be competent at resuscitating patients in cardiac arrest; thus, it would not be unreasonable to expect all frontline doctors to be competent also at diagnosis and treatment of coronary thrombosis.

References

1. National Heart Attack Alert Program Coordinating Committee 60 Minutes to Treatment Working Group. Emergency department: rapid identification and treatment of patients with acute myocardial infarction. Bethesda (MD): Dept. of Health and Human Services (US), National Institutes of Health, 1993.
2. Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). Lancet 1988;2:525–30.
3. AIMS Trial Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. Lancet 1988;1:545–9.
4. Rawles J. Magnitude of benefit from earlier thrombolytic treatment in acute myocardial infarction: new evidence from Grampian Region Early Anistreplase Trial (GREAT). BMJ 1996;312:212–5.
5. Schmidt SB, Borsch MA. The prehospital phase of acute myocardial infarction in the era of thrombolysis. Am J Cardiol 1990;65:1411–5.
6. Hartford M, Herlitz J, Karlson BW, Risenfors M. Components of delay time in suspected acute myocardial infarction with particular emphasis on patient delay. J Intern Med 1990;228:519–23.
7. Maynard C, Althouse R, Olsufka M, Ritchie JL, Davis KB, Kennedy JW. Early versus late hospital arrival for acute myocardial infarction in the Western Washington thrombolytic therapy trials. Am J Cardiol 1989;63:1296–300.

8. Trent RJ, Rose EL, Adams JN, Jennings KP, Rawles JM. Delay between the onset of symptoms of acute myocardial infarction and seeking medical assistance is influenced by left ventricular function at presentation. Br Heart J 1995;73:125–8.
9. Rawles J. Problems in quantifying the benefit of earlier thrombolysis in acute myocardial infarction. Pharmaceutical Medicine 1995;9:105–13.
10. GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners. BMJ 1992;305:548–53.
11. Rawles J, on behalf of the GREAT Group. Halving of 1-year mortality from acute myocardial infarction by domiciliary thrombolysis in the Grampian Region Early Anistreplase Trial (GREAT). J Am Coll Cardiol 1994;23:1–5.
12. Fibrinolytic Therapy Trialists' Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311–22.
13. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–22.
14. Mathey DG, Sheehan FH, Schofer J, Dodge HT. Time from onset of symptoms to thrombolytic therapy: a major determinant of myocardial salvage in patients with acute transmural infarction. J Am Coll Cardiol 1985;6:518–25.
15. Linderer T, Schroder R, Arntz R, et al. Prehospital thrombolysis: beneficial effects of very early treatment on infarct size and left ventricular function. J Am Coll Cardiol 1993;22:1304–10.
16. Hermans WT, Willems GM, Nijssen KM, Simoons ML. Effect of thrombolytic treatment delay on myocardial infarct size [letter]. Lancet 1992;340: 1297.
17. Weaver WD. Time to thrombolytic treatment: factors affecting delay and their influence on outcome. J Am Coll Cardiol 1995;25 Suppl:3S–9S.
18. Gang ES, Lew AS, Hong M, Wang FZ, Siebert CA, Peter T. Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. N Engl J Med 1989;321:712–6.
19. Bourke JP, Young AA, Richards DA, Uther JB. Reduction in incidence of inducible ventricular tachycardia after myocardial infarction by treatment with streptokinase during infarct evolution. J Am Coll Cardiol 1990;16:1703–10.
20. Bonaduce D, Petretta M, Villari B, et al. Effects of late administration of tissue-type plasminogen activator on left ventricular remodeling and function after myocardial infarction. J Am Coll Cardiol 1990;16:1561–8.
21. Marino P, Zanolla I, Zardini P, on behalf of the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effect of streptokinase on left ventricular remodeling and function after myocardial infarction: the GISSI trial. J Am Coll Cardiol 1989;14:1149–58.
22. Hirayama A, Adachi T, Asada S, et al. Late reperfusion for acute myocardial infarction limits the dilatation of left ventricle without the reduction of infarct size. Circulation 1993;88:2565–74.
23. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. N Engl J Med 1997;336: 847–60.
24. Cannon CP, Antman EM, Walls R, Braunwald E. Time as an adjunctive agent to thrombolytic therapy. J Thromb Thrombol 1994;1:27–34.
25. Boersma E, Maas ACP, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348: 771–5.
26. The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. N Engl J Med 1993;329:383–9.
27. Weaver WD, Cerqueira M, Hallstrom AP, et al., for the Myocardial Infarction Triage and Intervention Project Group. Prehospital-initiated vs. hospital-initiated thrombolytic therapy. JAMA 1993;270:1211–6.
28. Trent J, Adams J, Jennings K, Rawles J. Impact of resuscitation and thrombolysis on mortality rate from acute myocardial infarction. Int J Cardiol 1995;49:33–7.