zidovudine or pentamidine had a causal role in the initial development of symptomatic disease in these patients.

Finally, though there may be some beneficial effect of high purity clotting factor concentrates on the immune systems of patients with haemophilia,[8] there is little evidence that this has translated into clinical benefit for these patients.[7] Conversely, a recent paper has suggested that increased usage of intermediate purity clotting factor concentrates may be beneficial for HIV positive haemophilic patients.[9]

Despite the provision of new data which support the HIV hypothesis for the development of AIDS, the arguments proposed by Duesberg in his commentary remain unchanged and contradict the "foreign protein-zidovudine" hypothesis. For the benefit of patients infected with HIV it must now be time to move on to enable researchers to devote time to the real issues at hand.

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Magnitude of benefit from earlier thrombolytic treatment in acute myocardial infarction: new evidence from Grampian region early anistreplase trial (GREAT)

John Rawles

Abstract

***Objective*—To generalise from the results of the Grampian region early anistreplase trial (GREAT) and to express the benefit of earlier thrombolysis in terms of lives saved per hour of earlier treatment.**

***Design*—Multivariate analysis of a randomised double blind trial.**

***Setting*—29 rural practices in Grampian region and teaching hospitals in Aberdeen.**

***Subjects*—311 patients with suspected acute myocardial infarction and without contraindications to thrombolysis who were seen by their general practitioners within four hours of the start of symptoms.**

***Interventions*—Anistreplase 30 units given intravenously, either by general practitioners before hospitalisation or later in hospital.**

***Main outcome measure*—Death within 30 months of entry into trial.**

***Results*—Death within 30 months was positively related to age ($P<0.0001$) and to delay between start of symptoms and thrombolytic treatment ($P=0.0004$). However, the probability of dying rose exponentially with earlier presentation, so death within 30 months was negatively related to the logarithm of the time of randomisation ($P=0.0163$). In patients presenting two hours after start of symptoms each hour's delay in receiving thrombolysis led to the loss of 21 lives per 1000 within 30 days (95% confidence interval 1 to 94 lives per 1000) ($P=0.03$) and 69 lives per 1000 within 30 months (16 to 141 lives per 1000) ($P=0.0004$).**

***Conclusions*—The magnitude of the benefit from earlier thrombolysis is such that giving thrombolytic treatment to patients with acute myocardial infarction should be accorded the same degree of urgency as the treatment of cardiac arrest.**

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BMJ 1996;312:212-6

Introduction

It is generally accepted that the earlier thrombolytic treatment is given for acute myocardial infarction, the greater the benefit. Guidelines have been developed and published recommending that thrombolysis should be given expeditiously.[1] But in developing policies for the speedy provision of thrombolytic treatment it is essential to know the magnitude of the benefit from earlier thrombolysis in relation to the difficulties experienced in expediting treatment. The benefit needs to be expressed as lives saved per hour of earlier treatment. The magnitude of the benefit of earlier thrombolysis can be determined ethically only with a trial in which patients are randomly allotted to receiving treatment on presentation, in the community, or later, after admission to hospital. Trials of this design are few and small in size; the three largest are the European myocardial infarction project (EMIP),[2] the myocardial infarction triage and intervention study (MITI),[3] and the Grampian region early anistreplase trial (GREAT).[4] Mortality after one month was not significantly reduced in any of these trials.

The objectives of GREAT were to assess the feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners. As this was a small trial, prehospital thrombolysis was not expected to show a significant reduction in mortality, and surrogate measures of efficacy were used. In order to maximise the time saving by domiciliary thrombolysis, and the likelihood of demonstrating its greater efficacy over hospital thrombolysis, participation was restricted to rural practices ≥ 26 km from the teaching hospital to which all cases were referred. Because the prehospital phase of the trial was conducted by general practitioners, delays in hospital were little affected by the conduct of the trial and were estimated at 87 minutes. As a consequence of this and the rural setting, the time saving by domiciliary thrombolysis in GREAT was substantial, at over two hours. As expected, prehospital thrombolysis did not result in a significant reduction in mortality at one month, but the mortality curves of home treated and hospital treated groups diverged during follow up, and the difference between them reached statistical significance by three months.[4] At one year the absolute difference between mortality in home treated and

hospital treated groups was 11% (95% confidence interval 3% to 19%) (P=0·007).[5] GREAT is thus the only trial to show a significant reduction in mortality with prehospital thrombolysis.

No further trials of prehospital thrombolysis are in progress or planned, so it is important that as much information as possible is obtained from this trial. One objection to GREAT is that the results are not applicable to urban areas or to hospitals with a fast track system for dealing with patients with acute myocardial infarction. In this paper, follow up of GREAT is extended to 30 months from entry into the trial. These results are used as a basis for a 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 lives saved per hour of earlier treatment. Expressed in this way, the results should be widely applicable.

Patients and methods

The trial has been described in detail previously.[4] Entry into the trial was based on strong clinical suspicion of acute myocardial infarction by the general practitioner. Symptoms characteristic of myocardial infarction had to have been present for ⩾20 minutes but ⩽4 hours; this narrow time window was chosen so that patients allotted thrombolytic treatment in hospital should receive it there within six hours of the start of symptoms. The exclusion criteria included the standard contraindications to thrombolytic treatment.

Of the 311 patients recruited, 163 were treated at home and 148 in hospital. Their mean age was 63 years, 216 were men, and 67 had had previous myocardial infarction. The median delay between start of symptoms and a patient calling his or her general practitioner was 45 minutes. The median (mean) time of randomisation to home or hospital treatment was 105 (122) minutes after start of symptoms. Anistreplase 30 units was given intravenously at median times of 180 minutes after start of symptoms, 101 minutes in the home treated group and 240 minutes in the hospital treated group.

Follow up was by direct contact of patients during the first year. Thereafter, deaths among the patients were flagged by the Scottish Registry Office.

STATISTICAL ANALYSIS

Stepwise multiple logistic regression analysis was used (SPSS, release 4·0) to regress death within 30 months against age, sex, previous myocardial infarction, patient's delay in seeking help, time of randomisation, 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 the delays might be non-linear, with a greater effect sooner rather than later after start of symptoms. The stepwise analysis selects predictor variables according to their significance, which was set at $P<0·05$. Age, log transformation of time of randomisation, and time of giving anistreplase were the three predictor variables selected for inclusion in the regression equation. Death within 30 days was then regressed against the same three predictor variables; both models were highly significant overall ($P<0·0001$).

Results

Follow up was complete for all patients up to 30 months from entry into trial and showed a divergence of the mortality curves for home and hospital groups (fig 1). At 30 months the difference was 15% absolute (17% *v* 32%, difference 15% (95% confidence intervals 6% to 25%, P=0·0014).

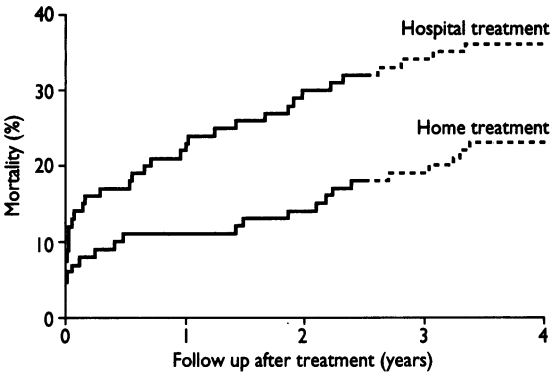

Fig 1—*Cumulative percentage mortality in patients with suspected acute myocardial infarction who were given thrombolytic treatment at home or later in hospital. Follow up after 30 months is incomplete, indicated by dotted line*

TIME OF TREATMENT

Figure 2 shows a plot from the logistic regression equation of the predicted probability of dying within 30 months for patients with a mean age of 63, presenting at a mean of 122 minutes after start of symptoms, and given thrombolytic treatment 1-6 hours after start of symptoms. For comparison, the actual mortalities in the home treated and hospital treated groups are shown for each of six periods of one hour.

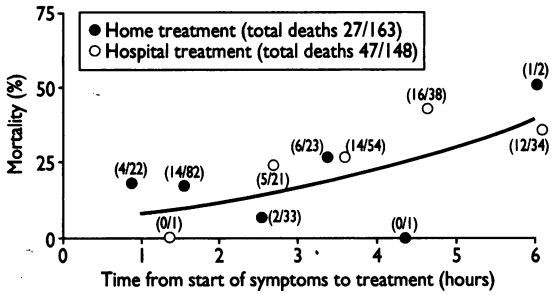

Fig 2—*Percentage mortality in patients with suspected acute myocardial infarction who were given thrombolytic treatment at different times after start of symptoms. Line represents predicted probability of dying within 30 months for patients with same mean age (63 years) and time of presentation (122 minutes) as those in the trial*

Figure 3 shows a plot of the predicted probability of dying within 30 months for patients with a mean age of 63, presenting two hours after start of symptoms, and given thrombolytic treatment 0-4 hours after presentation. The average gradient of the plotted line was calculated by linear regression. For each hour's delay in thrombolysis, 69 lives per 1000 would be lost within 30 months (95% confidence interval 16 to 141

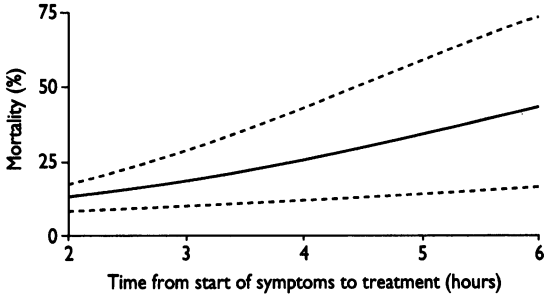

Fig 3—*Predicted probability of dying within 30 months for patients with suspected acute myocardial infarction presenting two hours after start of symptoms and given thrombolytic treatment 0-4 hours later (95% confidence intervals shown as dashed lines)*

lives per 1000) (P=0·0004), and 21 lives per 1000 would be lost within 30 days (1 to 94 lives per 1000) (P=0·03).

TIME OF PRESENTATION

Figure 4 shows a plot of the predicted probability of dying within 30 months for patients given thrombolytic treatment six hours after the start of symptoms but who presented 0-5 hours earlier. For the same time of thrombolysis, the risk of death rose exponentially with earlier presentation.

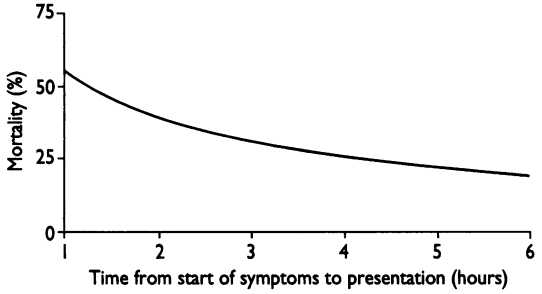

Fig 4—*Predicted probability of dying within 30 months for patients with suspected acute myocardial infarction given thrombolytic therapy six hours after start of symptoms but presenting 0-5 hours earlier*

Discussion

PATIENT DELAY IN SEEKING HELP AND SEVERITY OF MYOCARDIAL INFARCTION

Quantification of the benefit of earlier thrombolysis is confounded by the way patients with acute myocardial infarction behave. The time taken by a patient to call for help after the start of symptoms is a large part of the total delay to thrombolysis. But patients with more severe infarction tend to call sooner[6-9] so that the outcome from acute myocardial infarction treated at different times depends on the balance between the greater severity of infarctions presented earlier and the greater efficacy of thrombolytic treatment when given earlier. In the large placebo controlled clinical trials of thrombolytic treatment patients were treated in hospital as soon as they presented there, and the tendency for patients with more severe infarction to present earlier masks the increased benefit of earlier treatment. It is therefore not possible to measure the time related benefit of thrombolysis by retrospective subgroup analysis of such trials, and attempts to do so lead to a gross underestimate.[10]

INTENTION TO TREAT ANALYSES OF RANDOMISED TRIALS OF PREHOSPITAL THROMBOLYSIS

The magnitude of the time related benefit of thrombolysis can be determined only with a trial in which patients are randomly allotted treatment on presentation or after a delay, such as the European myocardial infarction project,[2] the myocardial infarction triage and intervention study,[3] and GREAT.[4] Although mortality after one month was not significantly reduced in any one of these trials, when the results of all three trials are combined prehospital thrombolysis reduced one mortality by 1·7% absolute (P=0·03); over the period of 1-4 hours from the start of symptoms, 23 more lives would be saved per 1000 patients treated per hour of earlier treatment. Although tentative, this is the best estimate of the time related benefit of thrombolysis based on intention to treat analyses of appropriately designed trials.[11]

FOLLOW UP OF GRAMPIAN TRIAL

Throughout the follow up of GREAT, the mortality in those patients given thrombolysis at home was about half that of those given thrombolysis in hospital.[5] The mortality curves diverged so that the difference between them, while not significant at one month, reached significance by three months and was highly significant at the end of a year. Between then and 30 months there was a further divergence of the mortality curves (fig 1) so that the mortality benefit was three times as great at 30 months as at 30 days from entry to the trial. This substantial deferred mortality benefit associated with prehospital thrombolysis is likely to result from the index infarct being smaller with earlier thrombolysis: patients with small first infarcts are less likely to develop heart failure and are better able to survive reinfarction months later.

By contrast, follow up of placebo controlled trials of thrombolytic treatment given in hospital 4-5 hours after start of symptoms has shown parallel survival curves with no additional mortality benefit beyond the first month or so.[12-16] Thrombolytic treatment given at that time does not lead to myocardial salvage, but opening an affected artery may confer electrical stability and prevent expansion of the infarct and cardiac failure.

MULTIVARIATE ANALYSIS OF GRAMPIAN TRIAL

The trial design used in GREAT resulted in dissociation of the times of presentation and randomisation from those of administration of thrombolytic treatment. This permits the separate quantification of the increased benefit of thrombolytic treatment with earlier administration (fig 3) and its confounding factor, the increased severity of infarction with earlier presentation (fig 4). In GREAT these two effects are of similar magnitude but opposite sign.

After age at entry into the trial, the next most important influence on the occurrence of death within the next 30 months was the time of administration of thrombolytic treatment—the earlier treatment was given the lower the mortality. Because the trial was small the confidence intervals are wide, but the change in benefit with time is steep and gets steeper with earlier presentation. For patients who could receive thrombolysis two hours after the start of symptoms, each hour's delay increases the mortality risk by 21 lives per 1000 within 30 days and 69 lives per 1000 within 30 months. For patients who could present one hour after start of symptoms, the comparable figures are 29 and 83 respectively. For patients given throm-

Key messages

- It is generally accepted that the earlier thrombolytic treatment is given for acute myocardial infarction, the greater the benefit
- However, studies comparing treatment in the community with later treatment in hospital showed that earlier treatment did not significantly reduce mortality in the following month
- Continued follow up of Grampian region early anistreplase trial showed that mortality benefit of prehospital thrombolysis trebled between 30 days and 30 months after entry into trial
- Patients who sought medical help quickly after start of symptoms had more severe infarction, and thus a higher mortality risk, than those seeking help later, which can mask greater efficacy of earlier thrombolysis
- Giving thrombolytic treatment at the first opportunity should be considered as urgent as treatment of cardiac arrest

bolytic treatment in hospital at a median time of about four hours after start of symptoms, each hour's delay increased the mortality risk by 30 lives per 1000 within five weeks.[10] Thus the additional benefit of starting thrombolysis at the first opportunity in the community may exceed the absolute benefit of giving it later in hospital.

Resuscitation from cardiac arrest in hospital saves about 50 lives per 1000 patients with acute myocardial infarction; 10-30 per 1000 may be saved by prehospital resuscitation.[17] From every 1000 patients with acute myocardial infarction, as many lives may be lost by an hour's delay in giving thrombolytic treatment as would be lost by a similar delay in treating cardiac arrest.

CONCLUSIONS

Between 30 days and 30 months after acute myocardial infarction there was a substantial additional mortality benefit associated with prehospital thrombolysis. The magnitude of the benefit from earlier thrombolysis is such that giving thrombolytic treatment at the first opportunity is a matter of the utmost clinical importance; in terms of potential lives saved it is as urgent as the treatment of cardiac arrest.

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Conflict of interest: None.

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Benefit from earlier thrombolytic therapy is certain, but what is the magnitude of benefit?

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Abundant evidence exists to confirm that fibrinolytic treatment saves lives in patients with acute myocardial infarction and that the earlier the treatment the higher the benefit obtained.[1] There is also evidence to suggest that administration of fibrinolytic treatment, under certain conditions, before hospital admission may lead to further improvement in patients' prognosis with no significant additional risk.[2-4]

John Rawles attempts to quantify the benefit of earlier fibrinolytic treatment using the data from the 311 patients included in the GREAT trial, which evaluated the feasibility, safety, and efficacy of domiciliary fibrinolysis by general practitioners.[5] Such quantification is essential if providers of health care are to make an informed decision on whether to allocate resources to domiciliary fibrinolysis. The magnitude of the benefit is controversial, and the trial that could fully resolve this will never be performed for obvious ethical reasons. This trial would require randomising patients to, say, four or five groups, each group having a predetermined delay from diagnosis of acute myocardial infarction to fibrinolytic treatment. Thus, the only available way to assess the magnitude of benefit of earlier fibrinolytic treatment compared with later treatment is to retrospectively analyse data from fibrinolytic studies, performing indirect comparisons of the randomised groups or using an epidemiological approach.

In the systematic overview by the Fibrinolytic Therapy Trialists' Collaborative Group an unadjusted, indirect comparison showed that a one hour delay in the time to treatment would lead to an increased mortality of 1·6 (SD 0·6) lives per 1000 within 35 days.[1] The underlying assumption in this analysis was that the patients in the different subgroups defined by the time to treatment were comparable, which is, of course, not the case. Dr Rawles presents a classic epidemiological approach with a model using multivariate analysis of the effect of the time gained in the delay to treatment on mortality at 30 days and 30 months. The outcome of the analysis of data combined from both treatment groups is, not surprisingly, in favour of earlier fibrinolytic treatment, and the results are impressive: "In patients presenting two hours after start of symptoms each hour's delay in receiving thrombolysis led to the loss of 21 lives per 1000 within 30 days (95% confidence interval 1 to 94 lives per 1000) (P=0·03) and 69 lives per 1000 within 30 months (16 to 141 lives per 1000) (P=0·0004)."

However, these results, though significant, should be moderated by the considerable width of the 95% confidence intervals (1 to 94 for 30 day mortality and 16 to 141 for 30 month mortality), which make the results equally compatible with more favourable and less favourable results. Although the point estimator at 30 days is much greater than that reported by the Fibrinolytic Therapy Trialists' Collaborative Group