

Thrombolytics and aspirin in the treatment of acute myocardial infarction: towards an understanding of factors limiting their use and consequences for overall benefit

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SUMMARY

After clinical trials had overwhelmingly demonstrated that treatment with thrombolytics and aspirin reduce mortality in acute myocardial infarction (AMI), the use of these agents in AMI, in particular thrombolytics, was lower than expected. This issue is reviewed with special emphasis on a series of studies undertaken by the European Secondary Prevention Study Group that was formed by researchers from 11 countries. The objective was to understand the fundamentals of the limited uptake and analyse the consequences for the overall benefit in clinical practice.

It was found that 36% of the AMI patients received thrombolytics, and that the calculated maximum rate was 55%, showing that about 1/5 of the patients despite no contraindications did not receive the treatment. Altogether 72% of the patients received aspirin. Thus, failure of the physicians to act on the evidence from clinical trials was not the main factor for the low use of thrombolytics; the major reasons were ECG findings not being indications for thrombolysis and late admission in hospital after onset of symptoms.

In the Norwegian cohort it was found that the patients receiving neither thrombolytics nor aspirin was a particular high-risk group with high mortality, contributing substantially to overall mortality. The total mortality was 18.1% and thus far higher than mortality reported in clinical trials. It was estimated what the mortality would have been had neither aspirin nor thrombolytics been given. The calculated mortality was 20.6%, implying an overall mortality reduction of 12% for the whole AMI cohort. Thus, the effects observed in clinical trials can not be translated into epidemiologically documented reduction in mortality, as optimal conditions for treatment with thrombolytics and aspirin are found only in a proportion of the patient groups constituting an unselected AMI population.

NORSK SAMMENDRAG

I kliniske forsøk er det vist at behandling med trombolytika og acetylsalicylsyre gir betydelig reduksjon av mortaliteten ved akutt hjerteinfarkt. I årene etter at dette ble fastslått var bruken av trombolytika lavere enn forventet. Dette temaet drøftes med utgangspunkt i en serie studier som ble gjennomført av European Secondary Prevention Study Group som ble dannet av forskere fra 11 land. Ett av målene var å få kunnskap om årsakene til den begrensede bruken og analysere konsekvensene for samlet mortalitetsgeviest av trombolytika og acetylsalicylsyre ved akutt hjerteinfarkt.

Det ble funnet at 36% av hjerteinfarktpasientene fikk trombolytisk behandling og deretter estimert at den maksimale andelen som var kandidater for slik behandling var 55%, noe som innebærer at 1/5 av pasientene ikke fikk behandlingen til tross for at det ikke forelå kontraindikasjoner. Hovedgrunnene til den begrensede bruken av trombolytika var at en høy andel enten manglet EKG-forandringer som kreves for slik behandling, eller at det hadde gått lang tid fra symptomdebut til ankomst i sykehus. Manglende evne til å implementere ny kunnskap i klinisk praksis var således ikke en vesentlig årsak til den relativt lave bruken. Andelen som fikk acetylsalicylsyre var 72%.

Spesiell analyse av den norske kohorten viste at pasientene som fikk verken trombolytika eller acetylsalicylsyre utgjorde en spesiell høyrisikogruppe med høy mortalitet, og som dermed bidro betydelig til den totale dødeligheten ved akutt hjerteinfarkt. Total mortalitet var 18,1% og dermed klart høyere enn det som er funnet i kliniske studier. Det ble beregnet hva mortaliteten ville ha vært dersom trombolytika og acetylsalicylsyre ikke hadde vært brukt. Den beregnede mortalitet var da 20,6%, noe som innebærer at samlet mortalitet var redusert med 12% for hele infarktgruppen. Således vil den gevinst som påvises i kliniske studier ikke gjenspeiles i epidemiologisk dokumentert reduksjon i mortalitet fordi de optimale betingelsene for behandling med trombolytika og acetylsalicylsyre bare er til stede hos en viss andel av pasientene som utgjør den samlede gruppen av infarktpasienter.

Substantial progress has been made in the treatment of acute myocardial infarction (AMI) in the past 15 years. The advent of thrombolytics and aspirin represent the major achievements, and is often described as a milestone.

EVIDENCE FROM CLINICAL TRIALS

Several large, randomised clinical trials of thrombolytic therapy have reported significant reductions in AMI mortality (1-5), and a meta-analysis of 9 major trials showed an 18% (95% confidence interval 13-23%) proportional reduction in 35-day mortality (6). The benefit of thrombolytic treatment declines with increasing delay before start of treatment. The exact nature of this relationship is debatable. The Fibrinolytic Therapy Trialists' Collaborative Group depicted a linear relationship (6), but it has been argued that it might be exponential, with a stronger effect during the first hours after symptom onset and a corresponding weaker effect after longer delays (7).

In the case of aspirin current practice is based on the results from one single clinical trial, the International Study of Infarct Survival (ISIS)-2 study (2). In that study aspirin treatment was started soon after the admission to hospital, and before thrombolytics were given. The ISIS-2 study, which had a 2x2 factorial design, showed mortality reductions of 23% and 25% for patients treated with aspirin and streptokinase, respectively. When combined, the two treatment regimens had an additive effect. In the ISIS-2 trial aspirin produced a similar-sized mortality reduction among patients treated early and among those treated late after onset of symptoms, and the effect was of the same magnitude in different age groups.

UPTAKE OF THROMBOLYTIC THERAPY

Soon after the appearance of the convincing trial results, expectations were high that thrombolytic therapy would become universally translated into clinical practice. It was thought that most of the patients with acute myocardial infarction would be candidates for the treatment, and furthermore that a mortality benefit corresponding to that observed in clinical trials could be obtained.

However, it turned out that the uptake of thrombolytic therapy did not take place to the extent expected. Population based data from the first half of the 1990s showed that half or less than half of the patients were treated with thrombolytics (8-11).

WHY LIMITED USE?

The reason for the limited use of these agents was not obvious. It might be that the doctors had failed to apply new knowledge fully or that there were widespread doubts about the evidence. Alternatively, the

applicability of thrombolytic therapy in clinical practice might be restricted by frequent presence of contraindications or absence of clear indications for therapy.

THE EUROPEAN SECONDARY PREVENTION STUDY GROUP

Researchers from eleven European countries formed the European Secondary Prevention Study Group (members of the group listed at the end of the paper), with one of the objectives being to investigate the reasons for the limited uptake of thrombolytic therapy. Study design and main results are summarised below while details are given elsewhere (12).

Methods

In order to obtain representative samples one geographically defined region within each country (median population 1.6 million) was selected. By drawing each sample from all hospitals admitting patients with AMI in a regional population, a mix of urban and rural settings and of teaching and non-teaching hospitals was included. In Norway the study population was Health region I comprising the counties of Oslo, Hedmark and Oppland in Eastern Norway. All ten hospitals treating emergency patients in the region participated.

Data were collected from all hospitals on all patients with the discharge diagnosis of acute myocardial infarction (International Classification of Diseases 9, 410) during a selected period within the years 1993 to 1994. Patients who died in hospital and received the same diagnosis were also included. From the medical records the rate of thrombolytic use was found. A shortfall of thrombolytic use was defined as the proportion of patients with no contraindications but who did not receive a thrombolytic.

Main results – thrombolytics

A total of 4035 patients were included in the study. The samples ranged from 200 to 520 patients in the eleven countries and were recruited from a mean of eleven hospitals. The mean age was 68 years, but female patients (33%) were on average 8 years older than males (mean 73 versus 65).

Use of thrombolytic treatment in AMI patients varied from 13% to 52% (median 36%) in the participating countries. Among the untreated (64%) three different groups of about similar size of patients were identified:

1. Patients whose symptom onset was more than 12 hours or unknown before the presentation in hospital, and accordingly were not obvious candidates for thrombolysis.
2. Patients causing diagnostic difficulty at presentation and/or lacking electrocardiogram (ECG) criteria for treatment. The ECGs did not show ST elevation or bundle branch block.

3. Patients with no apparent reason for withholding thrombolytic treatment. This is the shortfall, which accordingly was about one fifth of the whole study sample.

The investigators concluded that slightly more than one third of the AMI patients received thrombolytics and that the maximum proportion of patients eligible for thrombolytics was about 55%. For the Norwegian sample the observed rate of use of thrombolytics was 32% and the maximum rate approximately 50%.

CLINICAL TRIAL VERSUS CLINICAL PRACTICE PATIENTS

The results from the European Secondary Prevention Study Group were in keeping with other observations of low use of thrombolytics. In addition, we offered explanations for these observations. The low proportion of patients treated with thrombolytics could not be explained by a failure of the clinicians to act on the evidence provided by the randomised trials. Instead, the limited use could mainly be attributed to the presenting features of the patients. Two fifths of the patients presented late after onset of symptoms or did not have ECG criteria that were recognised as conditions for initiating thrombolysis.

This led us to the general issue of how representative the patients recruited to clinical trials of thrombolytics are for the unselected group of AMI patients.

Patients enrolled in trials frequently are selected and may differ from typical patients with regard to characteristic features and suitability for treatment. The Norwegian and the UK researchers in the European Secondary Prevention Group investigated this topic further on the basis of the patient samples from these two countries (13). Table 1 (not published before) summarises how these patients differed from those of four major trials with regard to some characteristics being crucial for thrombolytic therapy. These clinical trials have been the most important ones in establishing thrombolysis as a cornerstone treatment in AMI.

In the European Secondary Prevention Study it was shown that 1/5 of the patients were admitted later than 12 hours after start of symptoms, while several clinical trials excluded patients presenting later than 6 hours after symptom onset (3-5). The efficacy of thrombolytics is greatest when the treatment is started within a few hours. Most often presentation within 12 hours, and preferably within 6 hours, is a condition for treatment with these agents.

The range of ECG findings also differs markedly between clinical trial patients and patients observed in clinical practice. The classic ECG finding of ST elevation, in addition to bundle branch block, has been the main focus for trials of thrombolytic agents, and has turned out to be those for which mortality reduction has been documented. However, it is quite common for other abnormalities to be seen on the initial ECG.

Table 1. Comparison of AMI patients in population samples from Norway (n = 487) and the UK (n = 420) with four major placebo-controlled thrombolytic clinical trials (references 1-4). Size of source population: 0.9 million in Norway and 4.7 million in the UK.

| | Population sample | | Thrombolytic trial | | | |
|---|-------------------|----|--------------------|------------|----------|-----------|
| | Norway | UK | GISSI-1 (1) | ISIS-2 (2) | AIMS (3) | ASSET (4) |
| Presenting ECG, % | | | | | | |
| ST elevation | 52 | 57 | 91 | 61 | 99 | { |
| ST depression | 23 | 15 | 4 | 7 | 1 | {82 |
| | | | | | | abnormal |
| BBB | 7 | 7 | 1 | 4 | 0 | { |
| Other findings | 18 | 21 | 5 | 27 | 0 | 18 |
| Symptom onset to admission/randomisation (hrs) | | | | | | |
| Cumulative % | | | | | | |
| □ 3 | 35 | 50 | 52 | 30 | 46 | 55 |
| □ 6 | 61 | 72 | 83 | 63 | 100 | 100 |
| □ 12 | 79 | 85 | 100 | 86 | 100 | 100 |
| □ 24 | 90 | 93 | 100 | 100 | 100 | 100 |
| Age (years), Cumulative % | | | | | | |
| < 55 | 12 | 13 | 29 | 29 | 39 | 27 |
| < 65 | 26 | 35 | 64 | 64 | 82 | 63 |
| < 75 | 63 | 67 | 88 | 92 | 100 | 100 |

BBB: bundle branch block
 ECG: electrocardiogram
 UK: United Kingdom

For example, in the Norwegian cohort of the European Secondary Prevention Study 23% of the patients presented with ST depression, and these patients were excluded from thrombolytic treatment solely on the basis of the ECG criteria (13,14).

AGE AND THROMBOLYSIS

Furthermore, our study also clarified that age is a significant factor influencing the extent to which thrombolytics get to be used. This observational study had an age distribution that differed considerably from that in the clinical trials. In the Norwegian sample approximately 40% of the patients were over 74 years (table 1) compared to only 10% in the meta-analysis of clinical trials (6,13). Among clinicians it is a general understanding that older age alone should not be considered as a contraindication to thrombolysis in AMI. However, the finding that thrombolytics were withheld in a high proportion of older patients presenting early with ST elevation and without obvious contraindications, demonstrated that older age in fact acted as a contraindication. The shortfall was considerably higher in the older age groups than among the younger patients, and accordingly contributed most substantially to the overall shortfall (12,13).

Based on these observations there is a potential for some increased use of thrombolytics, particularly in the older patients with AMI. However, it should be kept in mind that in the meta-analysis of clinical trials the relative mortality reduction from thrombolytic treatment was lower among the oldest age group (above 75 years) (6). This might have had some influence on the physicians' perception of the benefits and/or risks of thrombolysis in older patients. However, the meta-analysis might have underestimated the effect of thrombolytics in older patients due to a particular selection of high-age patients in some of the large trials included in the meta-analysis. This matter has been discussed at greater length (15). In addition to these factors a broader definition of contraindications by treating clinicians is one possible explanation for the limited use in the older patients.

FEMALE SEX AND THROMBOLYSIS

In the European study female sex was identified as a factor negatively associated with thrombolytic therapy, independently of age (12). Odds ratio for females with regard to likelihood to receive thrombolytic therapy was 0.69 (95% CI 0.53–0.89) after adjusting for age and presence of generally accepted contraindications (12). We could not offer any explanation for this observation. No trial has given evidence that thrombolytic treatment is less effective or more hazardous in women. However, one could speculate that the difficulties in diagnosing myocardial infarction and selecting patients suitable for thrombolysis are more

pronounced in women than in men. This would tend towards lower use in females. It should be noted that apparent sex differences also have been reported for other interventions, such as coronary-artery bypass grafting and coronary angioplasty (16).

UPTAKE AND DIFFUSION OF ASPIRIN IN AMI

The ISIS-2 trial results were presented in March 1988 at the Congress of the American College of Cardiology (2). A few months thereafter, the convincing results from this simple treatment with aspirin were implemented into clinical practice worldwide. In the Norwegian cohort of the European Second Prevention Study 72% of patients were treated with aspirin (13,14). Thus, the use of aspirin was more than the double of the use of thrombolytics. The anticoagulant warfarin was used to some extent, implying that 87% of patients used aspirin or warfarin. In some patients anti-thrombotic therapy was contraindicated. It can be concluded from our studies, together with reports from other investigators (9,11,17), that the diffusion of aspirin treatment for AMI has been far more extensive than thrombolytic therapy, and possibly close to the feasible maximum.

CONTRIBUTION TO HOSPITAL MORTALITY FROM DIFFERENT SUBGROUPS OF AMI PATIENTS

Introduction of treatment regimens with thrombolytics and aspirin into clinical practice raised the interesting question of how this would impact overall hospital mortality (case fatality) from AMI. Epidemiological studies undertaken after uptake of thrombolytic therapy revealed a striking feature. They showed consistently high hospital mortality from myocardial infarction (18-24). The 30-day mortality in the treatment groups of clinical trials was in the range of 6-10%, which contrasted with much higher mortality rates in observational studies. Thus, the epidemiological data did not seem to fit in with the results from clinical trials. In an attempt to understand the fundamentals of the apparently conflicting findings we undertook additional analysis of the Norwegian cohort of the European Secondary Prevention Study (25). We assessed how patients allocated to different treatment groups contributed to overall mortality. Of the 487 patients, 32% received thrombolytics, 72% aspirin and 22% none of the treatments. Average hospital mortality was 18% while mortality within the different groups was as follows: no thrombolytic nor aspirin group 35%, aspirin group 14%, thrombolytic plus aspirin group 11% (25).

The characteristics of the group receiving neither thrombolytics nor aspirin revealed that the patients in this group were older, had increased frequency of

previous AMI, left ventricular failure, cardiopulmonary resuscitation, history of stroke and peptic ulcers, and ECG findings other than ST elevation. Consequently, the no treatment group was a high-risk group with inherent high hospital mortality. Thus, this group contributed substantially to the overall AMI mortality. We do not know whether or not mortality has changed in this subset over the years, but as the new agents have not come to use, and there is no information of other improvements, the evidence is that the mortality for this specific group has remained unchanged. So far, our findings clearly indicated that the introduction of the new therapies could only produce a modest reduction of hospital mortality from AMI.

Contrary to the patients receiving neither thrombolytics nor aspirin, patients treated with these agents had mortality rates only slightly higher than those observed in clinical trials that evaluated these drugs against placebo. These findings indicated that much of the same patient selection that had been undertaken in the recruitment to clinical trials of pharmacotherapies was applied when patients were found eligible for these therapies in clinical practice.

Furthermore, our analysis showed that the potential for increased use of thrombolytics and aspirin in the high mortality group, i.e. the patients receiving neither thrombolytics nor aspirin, was limited when standard indications for therapy were to be followed (25).

HOW MUCH HAS HOSPITAL MORTALITY BEEN REDUCED?

We elaborated further on the mortality issue in a study where we estimated what the hospital mortality of the Norwegian cohort would have been if thrombolytics and aspirin had not been used for any group of patients (26). The study design was the application of the therapeutic effects found in different subgroups of the meta-analysis of the clinical trials on this unselected group of AMI patients. The observed hospital mortality was 18.1% compared to an estimated mortality rate of 20.6% had neither of the treatments been administered. This implies that the two regimens had reduced overall mortality by 12%, of which aspirin contributed about 4/5 and thrombolysis 1/5. This is an important and worthwhile reduction of mortality, but much lower than reported from clinical trials. By com-

parison, the ISIS-2 study confirmed an additive effect of aspirin and streptokinase, showing a combined mortality reduction of 53% in patients with delays 0-4 hours before treatment, and 32% with delays 5-12 hours.

CONCLUSIONS

Through these series of studies it became clear that the effects observed in clinical trials could not be translated into epidemiologically documented reduction in mortality. The main reason for this was that the optimal conditions for treatment were found only in a proportion of the patient groups constituting an unselected myocardial infarction population. This should not, though, be interpreted in the way that thrombolytic therapy has not fulfilled its promise. Each day large numbers of patients' lives are saved worldwide owing to the treatment. The benefit of thrombolytics and aspirin could be enhanced by improvement of admission speed and increased prehospital treatment. Furthermore, in recent years the use of angioplasty in some subsets of AMI patients has become an important therapeutic modality, and combinations of established therapy with new pharmacotherapeutics, particularly glycoprotein IIb/IIIa antagonists, offer promise for improvement. Just more than a decade after the advent of thrombolytics and aspirin in the treatment of AMI, with the limitations described, their introduction into clinical practice still deserves to be referred to as a milestone. Smaller steps of improvement are continuously being taken, suggesting that new treatment regimens will come into use for more AMI patients, and with the hope that case fatality can still be lowered.

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