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Guidelines to Reducing Delays in Administration of Thrombolytic Therapy in Acute Myocardial Infarction

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Summary

The thrombotic coronary accident that triggers a myocardial infarction initiates a 'wavefront' of ischaemic cell death that can be aborted by timely restoration of blood flow. Myocardium destined for necrosis can be salvaged by quick lysis of the culprit clot to restore perfusion, reduce infarct size and save lives. While a number of useful thrombolytic regimens have been investigated, the greatest barrier to optimising efficacy is reducing the delay between the onset of symptoms and administration of thrombolytic therapy.

Clinical experience has confirmed laboratory evidence that prompt restoration of coronary blood flow can salvage more than 50% of ischaemic myocardium if achieved within 2 hours. However, after 6 hours of sustained ischaemia, the opportunity to achieve meaningful salvage is largely lost. Analysis of pooled data estimates that for each hour of delay 1.6 fewer lives are saved per 1000 patients treated. Other investigators have estimated 60 to 80 lives saved per 1000 patients treated within 1 hour of symptom onset.

More realistically, the time from symptom onset to treatment averages 2.5 to 5 hours in various studies. Reluctance to seek medical help results in a delay of more than 4 hours in at least 40% of patients. There may be some benefits of late, time-independent reperfusion from 12 to 24 hours after symptoms. Some hiber-

nating myocardium may be salvaged resulting in less adverse late ventricular remodelling, reduced infarction expansion and improved electrical stability.

Barriers to timely thrombolytic treatment may be classified as presentation delay or treatment delay. Strategies to optimise timely treatment have included pre-hospital administration of thrombolytics. This achieves greatest benefit when used in a more rural setting where transportation times tend to be longer. In this setting, as much as 140 minutes has been shaved off the symptom-to-needle time with a 50% reduction in 3-month mortality sustained as a 30% reduction in 5-year mortality.

Most hospitals can improve their treatment (door-to-needle) time by focusing on chronic sources of delay. An emergency room culture of quick, coordinated response to chest pain must involve registration clerks, triage nurses, ECG technicians and emergency physicians. The authority to decide thrombolytic therapy must reside with the primary care physicians in any emergency room that encounters an acute infarction. The profound, life-saving benefits of thrombolytic therapy when used in a timely way should evoke a new sense of urgency in medical personnel when encountering the individual with a potential myocardial infarction.

1. The Relevance of Delay

The sense of urgency to attain early reperfusion flows from our understanding of the inexorable 'wavefront' of ischaemic cell death that follows acute myocardial infarction (AMI). Modern reperfusion techniques with thrombolysis and angioplasty have made the attainment of early coronary patency practical. This early restoration of flow aborts the infarct process, salvages threatened myocardium, reduces infarct size, and lowers morbidity and mortality in the months and years to follow (fig. 1).

This brief review focuses on the time-sensitive aspects of AMI as related to pathophysiology, prognosis and benefits of therapy, and on ways to optimise clinical outcome.

2. Rationale for Early Reperfusion

2.1 Laboratory Evidence

In a satisfying confirmation of laboratory evidence by clinical experience, it has been abundantly demonstrated that early restoration of coronary flow after AMI aborts the infarction with important clinical benefit. Reimer et al.[1] rigorously illustrated the time-sensitive relation between the duration of interrupted coronary flow and the degree to which necrosis replaces ischaemic myocardium. By ligating a canine coronary artery for various intervals, the proportion of ischaemic muscle in the vascular bed that became necrotic could be determined morphologically. A 'wavefront phenomenon' of cell death began in the subendocardium and expanded outwards to occupy ischaemic but viable myocardium. The volume of potentially viable tissue rapidly diminished with prolonged ischaemia as necrosis usurped a larger proportion of the territory at risk. After early reperfusion (within 40 minutes) 55% of ischaemic myocardium was salvaged, while less than 17% remained viable after 6 hours. This time frame has held remarkably constant in studies with experimental thrombolytic occlusion in dogs[2] as well as with clinical thrombolysis in humans[3-5] (fig. 2).

2.2 Clinical Evidence

We now fantasise about the 'golden first hour' of opportunity *post* infarction that represents the potential for reaping enormous rewards from early reperfusion.[6] However, it is only a fortunate 5% who actually receive treatment within 1 hour of the onset of symptoms.[4,7] Timely lytic therapy within

this first hour of symptoms will not only reduce mortality dramatically, but will also abort the infarction completely in 40% of patients.[6,8]

In the GISSI-1 trial[4] the most striking 30-day mortality reduction was 47% among those randomised within the first hour, compared with no measurable salvage for randomisation after 6 hours. The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group[7] analysed large, randomised trials involving 46 000 patients. Greatest benefit was attained among those treated with least delay (fig. 3). It was estimated that for each hour of delay, 1.6 fewer lives were saved per 1000 patients treated. The FTT meta-analysis involved patients treated in hospital, with only 34% being treated less than 3 hours after onset and a mean time to randomisation of 6.7 hours after onset. This generated a linear regression model with a consistent delay/benefit relation extending into the first 1 to 2 hours from symptom onset (fig. 3).

However, a nonlinear delay/benefit relationship best describes the exaggerated benefits of very early thrombolytic treatment[9] (fig. 4). Boersma et al.[9] submitted all randomised trials with at least 100 patients that compared fibrinolytic therapy with control to a meta-analysis, including a number with early prehospital therapy. They found a much larger benefit of very early treatment than the FTT group. This was better represented by a nonlinear regression model, with a large reduction in mortality detected among those randomised to treatment within 1 hour of the start of symptoms (fig. 4). Approximately 60 to 80 lives were saved per 1000 patients treated within 1 hour in the Boersma meta-analysis, compared with 39 per 1000 in the FTT overview.[7,9]

Large, randomised trials tend to have underrepresentation of patients treated very early when benefits are maximised. The proportional effect of fibrinolytic therapy on 35-day mortality according to treatment delay is illustrated in figure 5. Given that sicker patients tend to present earlier for postinfarction therapy, the greater benefit of very early thrombolysis in this group of patients emphasises the large potential for very real myocardial salvage.

The great promise of treatment benefit within the first hour is not reflected by all individual stud-

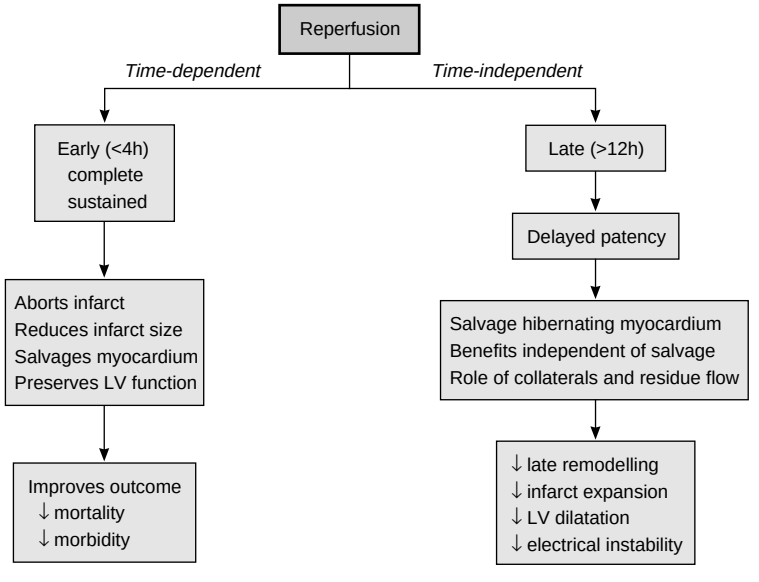

Fig. 1. The benefits of early restoration of myocardial reperfusion. *Abbreviation:* LV = left ventricular.

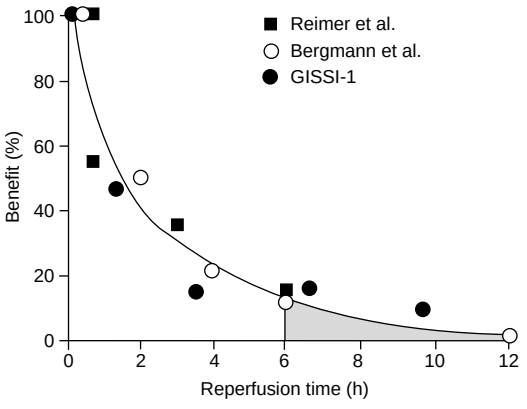

Fig. 2. Reperfusion time-benefit curve depicts combined data representing the time-dependent benefit anticipated depending on the interval between coronary artery occlusion and reperfusion; data from Reimer et al.,[1] Bergmann et al.[2] and GISSI.[4] The shaded area represents an estimate of the portion of total benefit that is not time-dependent (reproduced from Tiefenbrunn & Sobel,[14] with permission). 'Benefit (%)' indicates percentage of myocardial salvage[1,2] and percentage reduction in mortality.[4]

ies. In GUSTO-I, mortality for patients treated within the first hour did not appear to be lower than those treated between 1 and 2 hours after onset.[5,10] However, too few patients were treated within an hour in GUSTO-I and the 95% confidence limits (CI) were wide.[5,10] Despite these inconsistencies, overwhelming evidence supports the principle that delayed treatment condemns potentially salvageable myocardium to death. The idealised relationship between mortality reduction, extent of salvage and time to reperfusion is illustrated in figure 6.[11]

Unfortunate reality prevails for most infarction patients, with only a small proportion deriving full benefit from thrombolytic therapy due to delays in seeking or receiving prompt treatment. The median time from symptoms to therapy was 3 hours among Canadian patients enrolled in GUSTO-I, with 75% of patients receiving therapy more than 1 hour after arrival at hospital.[12] In most trials, 40% of patients will get thrombolytic attention more than 4 hours after the onset of symptoms. Consequently, in the messy confusion of the real world, few patients are treated within the 'golden first hour' and receive the full advantage of the potential for early reperfusion, myocardial salvage and a better outcome.

Establishing the temporal outer limits of thrombolytic treatment efficacy is justified by the 30% of AMI patients who are treated 6 or more hours after symptom onset.[13] The large prototype thrombolytic trials offered conflicting results with respect to benefits derived for those where treatment was delayed to between 12 and 24 hours after symptoms. While the GISSI trial showed a striking reduction of benefit when treatment was delayed beyond 6 hours, the ISIS-2 trial revealed a significant 19% survival benefit for treatment delayed to 12 hours, with a trend to benefit at 12 to 24 hours.[3,4] The FTT Group overview documented a highly significant mortality reduction of 14 ± 5% (2p = 0.005) among the 13 000 patients presenting at 7 to 12 hours. There was a nonsignificant benefit trend for the 9000 who presented after 12 hours.[7]

The Late Assessment of Thrombolytic Efficacy (LATE) study randomised patients to alteplase (tissue plasminogen activator) or placebo between 6

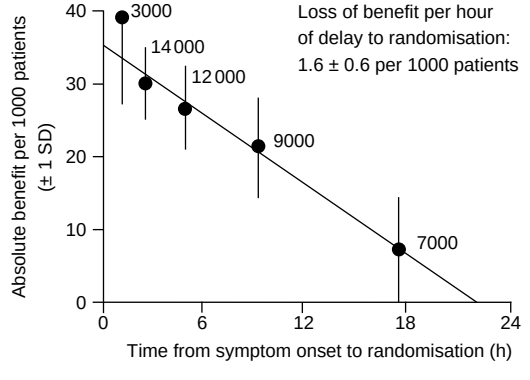

Fig. 3. Absolute reduction in 35-day mortality versus delay from symptom onset to randomisation for fibrinolytic therapy among 45 000 patients with ST elevation or bundle branch block. Absolute benefit (± 50) is plotted against mean recorded delay time (reproduced from the Fibrinolytic Therapy Trialists' Collaborative Group,[8] with permission). 'Benefit' refers to mortality reduction in this figure. The numbers above the line indicate the number of patients analysed at each interval.

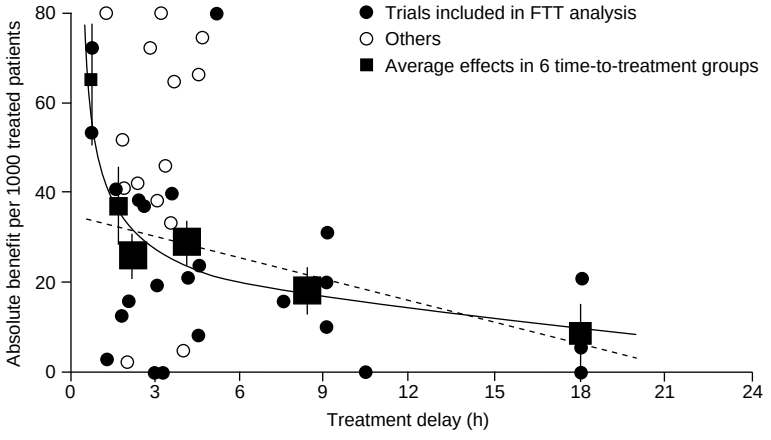

Fig. 4. Absolute 35-day mortality reduction versus treatment delay. The linear and nonlinear regression lines are fitted within the data from trials included in the Firbrinolytic Therapy Trialists (FTT) analysis and from additional trials. The areas of the black squares are inversely proportional to the variance of absolute benefit described (note the higher estimates of 1- to 2-hour treatment delay benefit for the nonlinear regression compared with the linear regression) [reproduced from Boersma et al.,[9] with permission]. In this figure, 'absolute benefit' refers to 35-day mortality reduction.

and 24 hours from symptom onset.[13] Compared with placebo, treatment within 12 hours reduced 35-day mortality from 11.97 to 8.90%, a relative reduction of 25.6% (p = 0.0229, 95% CI 6.3-45.0%). Mortality rates were 8.7 and 9.2%, respectively, for those treated at 12 to 24 hours. Designed to meet the needs of latecomers, this study suggested that the time window for benefit with alteplase extends to 12 hours from symptom onset, but not beyond. Moreover, among those whose therapy is delayed, the stroke/benefit ratio becomes increasingly adverse.

In an ironic twist, an 'early hazard' limitation has been described in randomised trials comparing a thrombolytic agent with placebo. In the elderly in particular, an increased mortality rate of 0.5% in the first 24 to 48 hours was documented among those treated with thrombolytics. However, this 'early hazard' was fully compensated by the subsequent and sustained absolute reduction in mortality among those individuals 75 years of age or older who received thrombolytic therapy. Moreover, the 'early hazard' phenomenon seems to be associated with streptokinase more than with t-PA. This may reflect improved survival benefits correlated with the more efficient Thrombolysis in Myocardial Infarction (TIMI) III brisk normal flow attained with t-PA.[5] While the mechanisms for possible early differences in mortality are speculative, early and sustained reperfusion with fibrinolytic therapy improves long term survival.

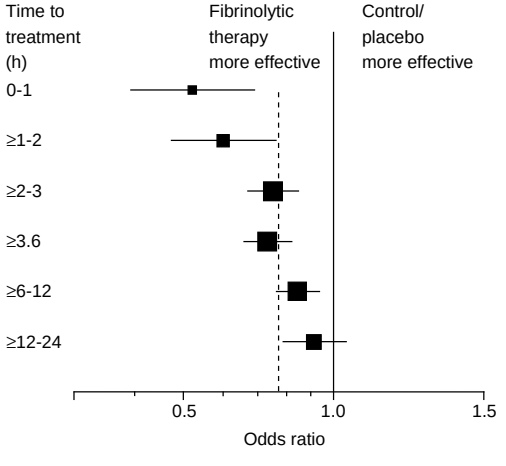

Fig. 5. Proportional effect of fibrinolytic therapy on 35-day mortality according to treatment delay. Odds ratios, plotted with 95% confidence intervals (CI) on a log scale, are significantly different over the 6 groups (Breslow-Day test, p = 0.001). The areas of the black squares are proportional to the amount of statistical information (reproduced from Boersma et al.,[9] with permission).

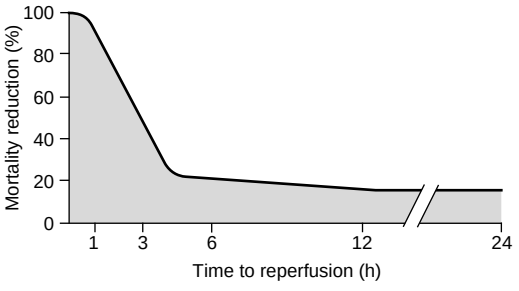

Fig. 6. Curve of hypothetical relation among mortality reduction, the extent of salvage (shaded area under the curve), and the time to reperfusion. In this construct, mortality reduction within the first 1 to 2 hours is primarily due to myocardial salvage. Later reperfusion results in lesser salvage, although mortality is still reduced, perhaps mediated in part through less 'time-dependent' mechanisms (reproduced from Gersh & Anderson,[11] with permission).

3. Time-Independent Benefits of Reperfusion

The windows of opportunity to achieve myocardial salvage may be extended if some residual flow persists after the infarction. Initially, there may be intermittent or occult flow through the freshly thrombosed stenosis as the vessel winks opened and closed.[14] Collateral vessels may provide some muscle-saving flow to the area in jeopardy, while myocardium may be hibernating to await the arrival of fresh circulation that rejuvenates some measure of function. The rate of necrosis will also be determined by factors influencing myocardial oxygen demands.

Patients who do not receive early reperfusion may derive more modest benefit from the time-insensitive advantages of an open infarct-related vessel (fig. 6). The 'open-artery' hypothesis implies prognostic benefit from late reperfusion in the absence of any myocardial salvage. Putative benefits include less adverse remodelling of the infarct region with reduction in ventricular dilatation and aneurysm formation, reduced electrical instability and improved collateral development to protect adjacent healthy muscle[15] (fig. 1)

4. Sources of Delay

As with so many aspects of life, a heart attack is what happens when you are making other plans. Human response to a worrisome symptom is never simple, frequently irrational and always individual. Barriers to early thrombolytic treatment may be classed as (a) presentation delay or (b) treatment delay, the so-called 'door-to-needle' time (fig. 7).

4.1 Presentation Delay

Presentation delay represents the time from symptom onset to hospital arrival. This is the largest barrier to quick treatment, and includes patient delay in seeking medical help and the transport time to the hospital. Intensively studied by Weaver et al.[8] in Seattle, the median time from symptom onset to appealing for help is 4 hours, and among the subset eligible for thrombolytics the median delay is 2 to 3 hours. This delay relates in part to patient nonawareness of cardiac symptoms, or to denial ('it's only indigestion'), which could prove fatal.

Patient delay is increased by the onset of symptoms at night, the severity of pain and its lack of typicality.[10] Taking time to contact the family GP can be a barrier to quick attention, as can a failure to immediately access the most readily available emergency ambulance service.[16,17] Only 50% of AMI patients call an emergency telephone number which prompts an earlier response, and these individuals are more likely to interpret their cardiac symptoms correctly. Ironically, the most vulnerable are more likely to delay seeking help, such as the older woman, individuals with diabetes, low-income earners and those with a history of angina, hypertension or heart failure.[10]

Another component of presentation delay is the time for paramedic assessment and transportation to hospital. Patients who do not come by ambulance tend to arrive 1 to 2 hours later than those who do. In the US, the total prehospital time averages 45 to 100 minutes from the summons for help by the 911 (emergency service) telephone call.[18,19] There may be great variation according

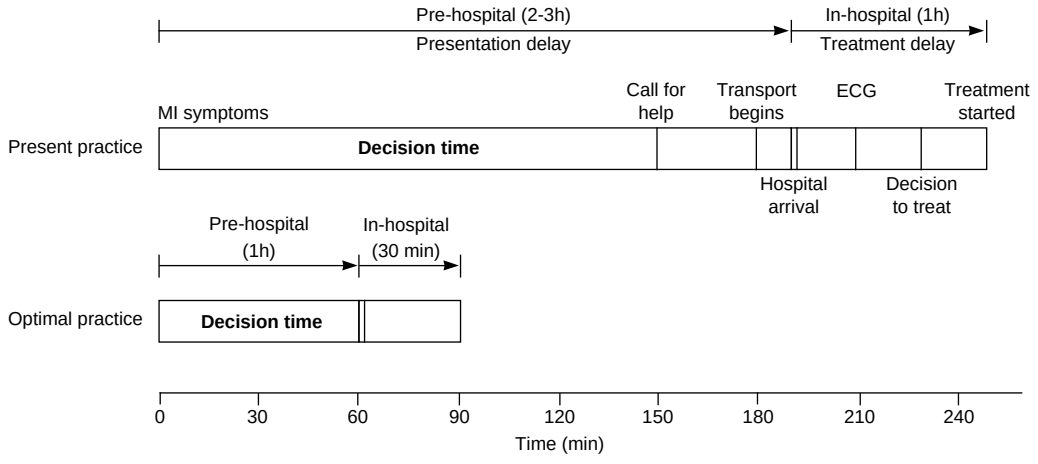

Fig. 7. Critical path illustrating the components of delay from symptoms to thrombolytic treatment. The timeline for a suboptimal 3- to 4-hour delay (above) contrasts with the recommended 60 to 90 minutes (below).

to local demographics. In rural settings, where transportation times are long, the advantage of prehospital administration of thrombolytics holds some promise. Average delay to reperfusion as experienced in present practice compared with optimal treatment is illustrated in figure 7.

4.2 Treatment Delay

An expert panel has recommended that hospital treatment time (the 'door-to-needle' time) not exceed 30 minutes.[20] This is half the median time of 57 minutes documented as current American practice.[19] In the GUSTO-I trial, Canadian centres had a median door-to-needle time of 85 minutes compared with 66 minutes among US hospitals.[12] This represents half of the total delay in time to treatment and is most amenable to improvement. There are 3 rate-limiting steps before thrombolytic therapy is given in hospital: (1) time to electrocardiogram (ECG) acquisition, (2) time to decision to treat, and (3) time to get treatment started. Each of these steps occupies 20 minutes of the hour most hospitals take to get the thrombolytic agent started.[21]

Treatment delay is exacerbated by policies that specify consultation with a cardiologist or specialist before drug infusion. Transfer to the coronary care unit (CCU) before treatment increased delay by 36 minutes.[21] Hospitals need to stock drugs in the emergency department to reduce as much as possible the time required to initiate therapy. Acquisition of a prehospital ECG with transmission to a site for interpretation has reduced hospital triage time by 30 minutes,[18,22] but most communities do not have this capability. The modern era of reperfusion has witnessed dramatic drops in treatment delay as emergency room habits reflect an appropriate sense of urgency concerning an infarct in evolution.

5. Strategies to Optimise Timely Treatment

Given the many factors determining delay in reperfusion therapy after AMI, a multifaceted solution appears most realistic.

5.1 Reducing Presentation Delay

This largely patient-centred barrier to prompt treatment has defied simple solution. Public education campaigns have failed to evoke earlier presentation of the target audience, those with ischaemic heart disease.[6,23] Often, a higher proportion of sensitised patients with atypical noncoronary symptoms will seek assessment while many pa-

tients with known coronary disease ignore worsening symptoms. Weaver[6] has expressed pessimism that patient behaviour in this area can be influenced by mass media campaigns.

5.2 Prehospital Treatment

The prehospital phase after the appeal for help tends to be a small component of overall delay and the most refractory to improvement. Attempts to abbreviate this aspect of delay have inspired investigation of prehospital treatment with thrombolytic agents. An important prerequisite is the ability to acquire and interpret a high-quality 12-lead ECG in the field. In this endeavour, many are screened but few are chosen: less than 5% of patients triaged in the field met the ECG and clinical criteria for thrombolytic treatment.[17] The amount of time saved by prehospital treatment is contingent upon a longer transportation time to hospital, generally more than 90 minutes.[8,24,25]

Complex and expensive trials of prehospital lytic therapy demonstrated a 30- to 140-minute reduction in treatment delay, but were usually underpowered to detect a statistical difference in clinical outcome. An exception was the Grampian Region Early Anistreplase Trial (GREAT), conducted by general practitioners in a rural setting near Aberdeen, where transportation time tended to be longer.[25] Among the 311 randomised patients, the median difference between the prehospital and in-hospital treatment groups was 140 minutes. This resulted in a significant 50% reduction in 3-month mortality (10.4 *vs* 21.6%, $p = 0.007$) which persisted to 30 months.[26]

The recently published GREAT 5-year results show a sustained improvement in survival (25 *vs* 36%, $p < 0.025$). In this trial, a delay in thrombolytic treatment by 1 hour increases the hazard of death by 20%, equivalent to the loss of 43/1000 lives within the next 5 years (95% CI 7 to 88, $p = 0.0125$).[27] Defined by its rural demographics, the astounding reduction in treatment delay achieved by the GREAT trial cannot be extrapolated to an urban milieu with ready access to efficient hospital care. Regardless of the setting, patients treated early in the course of their infarct showed about 50% reduction in mortality.[3,4,8,24] Given its logistical complexity, it is doubtful that prehospital thrombolytic therapy will catch on in the urban environment where most infarcts take place.

5.3 Posthospital Treatment

Many hospitals have considerable room for improvement to attain the recommended 30-minute 'door-to-needle' time. Attention must focus on the potential delays encountered in initial emergency room triage, decisions to acquire and interpret the first ECG and to initiate therapy (table I). An emergency room culture of rapid response to the chest pain patient must involve the registration clerks, triage nurses, ECG technicians and decision-making physicians. Quality assurance procedures with periodic audit and helpful feedback to uncork bottle-necks must be put in place.[28,29]

Substantial time savings have been achieved by the simple expedient of moving the treatment venue from the CCU to the emergency room, and by empowering the emergency physician with the authority to treat.[30] Specialists and cardiologists requiring time for evaluation prior to initiating treatment should not be necessary for the detailed management of the typical infarct patient in the emergency department.

Emergency department nurses and other staff in the ER need to be taught the typical presenting features of AMI. They should be sensitised to the potential for saving lives among high-risk groups that

Table I. Strategies to reduce treatment delay

Recognise acute myocardial infarction for the emergency it is
Train emergency room staff to expedite registration, triage, electrocardiogram acquisition and the decision to treat
Use inclusion/exclusion check lists and treatment protocols
Authorise therapy by the primary care individual in the emergency department
Promote effective communication between clerks, nurses and physicians
Periodically audit 'door-to-needle' time and rectify recurring sources of unnecessary delay
Have in-service training for emergency staff to reiterate the relevant features of safe and expedient reperfusion therapy

tend to be overlooked, such as the elderly and individuals with diabetes. Protocols, procedures and standing orders should be in place so that patients with chest pain are expedited to early attention with a 12-lead ECG, oxygen administration, intravenous access, blood tests obtained, monitoring established and analgesia with nitroglycerin (glyceryl trinitrate) and morphine initiated. Unessential time wasters such as getting a chest x-ray or summoning the cardiology staff should be postponed. An efficient, directed clinical assessment by the emergency physician supported by ECG evidence for infarction should result in a quick decision for starting reperfusion therapy with aspirin, heparin and the thrombolytic of choice in eligible patients. Drugs must be available in the emergency department. Atypical features, lack of early ECG criteria for infarction or potential contraindications may prompt consultation with a specialist. Judging from the numerous elements involved in attaining timely hospital-based therapy, efficient communication and rapid decision-making are essential. These principles are applicable wherever AMI is treated.[31]

More recently, decision-making for reperfusion therapy in AMI has become more interesting with the introduction of direct percutaneous transluminal coronary angioplasty (PTCA) and stenting, adjuvant therapy with glycoprotein IIB/IIIA inhibitors and the development of faster, more effective and easier-to-use thrombolytic agents.

6. Conclusions

The early and complete restoration of flow remains a vital principle for reducing postinfarction morbidity and mortality. The importance of the choice of thrombolytic agent or mode of revascularisation pales in comparison to the imperative of avoiding unnecessary delay in getting the treatment started. For the AMI patient, the simple equation holds that delays in initiating treatment plus damaged myocardium equals loss of lives. While more tidy, an AMI is no less a medical emergency than a gunshot wound or multiple trauma. It should be accorded the same status. The potential benefits of thrombolytics in myocardial infarction have given new meaning to the term ‘emergency’. The prognostic promise of reperfusion therapy requires that AMI be accorded the sense of urgency it so richly deserves.

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