Commentary

Debate: Should the elderly receive thrombolytic therapy, or primary angioplasty?

Harvey D White

Green Lane Hospital, Auckland, New Zealand

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Abstract

Thrombolysis and primary angioplasty are both recommended reperfusion strategies for elderly patients presenting with myocardial infarction (MI). Primary angioplasty is most beneficial in high-risk patients. While the elderly have a high absolute risk of dying or developing complications after MI, they also have an increased risk of intracranial haemorrhage if they are given thrombolytic therapy. It could therefore be reasonably argued that primary angioplasty is the reperfusion strategy of choice in the elderly. However, primary angioplasty has not been shown to have a greater relative benefit than thrombolytic therapy in the elderly. Recent data from the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group show that thrombolytic therapy significantly reduces mortality compared with control treatment in patients over 75 years of age presenting within 12 h of symptom onset, with ST-segment elevation or bundle branch block. Future advances in adjunctive therapies may improve myocyte perfusion and hence the outcomes achieved by both invasive and noninvasive reperfusion strategies. Better thrombolytic regimens incorporating adjunctive agents such as bivalirudin may reduce the risk of intracranial haemorrhage. Few hospitals can provide a 24-h primary angioplasty service with door-to-balloon times consistently less than 90 min, and thrombolytic therapy is therefore a far more practical option in most instances.

Keywords: angioplasty, elderly, thrombolysis

Introduction

Primary angioplasty and thrombolytic therapy have both been recommended as appropriate reperfusion therapies for patients presenting with either ST-segment elevation or new-onset left bundle branch block, within 12 h of the onset of ischaemic symptoms [1]. Certain caveats apply to the recommendations for primary angioplasty, including the prior experience of the operator (who must perform at least 75 procedures per year) and the throughput of the centre (which must perform at least 200 procedures per year). The procedure must also be performed in a timely fashion, ie balloon dilation must occur within 60 to 90 min of the diagnosis of acute MI.

ASSENT-2 = Second Assessment of the Safety and Efficacy of a New Thrombolytic trial; FTT = Fibrinolytic Therapy Trialists; GISSI-1 = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico trial; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries trials; ISIS-2 = Second International Study of Infarct Survival; MI = myocardial infarction; PAMI = Primary Angioplasty in Myocardial Infarction trials; TIMI = Thrombolysis in Myocardial Infarction trials; TPA = tissue plasminogen activator.

The evidence for thrombolytic therapy is based on randomised comparisons with placebo or control treatment in over 100,000 patients [2]. The evidence for primary angioplasty is based on comparisons with thrombolytic therapy in a total of 2745 patients, of whom 1348 underwent primary angioplasty. The FTT collaborative overview of all large thrombolytic trials included data from 5788 patients aged ≥75 years, whereas the recent systematic overview of primary angioplasty trials included data from only 199 patients aged ≥75 years, 149 of whom underwent primary angioplasty [3].

The FTT overview did not specifically report the outcomes of elderly patients presenting with ST-segment elevation or bundle branch block within 12 h of symptom onset, and did not include data on gender or infarct site. It did, however, include all patients randomised up to 24 h after symptom onset, regardless of electrocardiographic findings (eg normal electrocardiograms, T-wave inversion, ST-segment depression, etc). In the 5788 patients ≥75 years of age presenting with any electrocardiographic changes within 24 h of symptom onset, thrombolytic therapy reduced mortality nonsignificantly from 25.3% to 24.3% (95% confidence interval −16 to 36).

New thrombolytic data

New data from the FTT Collaborative Group show that in patients over 75 presenting with ST-segment elevation or bundle branch block within 12 h of symptom onset, thrombolytic therapy reduced the mortality rate significantly by 15% (from 29.4% with control treatment to 26.0%, $P = 0.03$). This represents 34 lives saved per 1000 patients treated, twice the benefit seen in patients aged <55 years (16 lives saved per 1000 treated) (personal communication from the FTT Secretariat, dated 4 August 2000).

These results can be generalised to community hospitals as the bulk of the data in the FTT overview came from the Second International Study of Infarct Survival (ISIS-2) and Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-1) trials, which were conducted predominantly in non-academic centres. Unlike primary angioplasty, thrombolytic therapy requires no specialised skills. In a study of 516 United States (US) hospitals, there was no significant association between the volume of thrombolytic treatments given and in-hospital mortality [4], whereas the in-hospital mortality rates associated with primary angioplasty were 28% lower in high-volume centres (>33 procedures/year) than in low-volume centres (5 to 11 procedures/year).

Registry studies

Several registry studies [5,6] have recently concluded that thrombolytic therapy worsens outcomes in the elderly. In a US Medicare observational study, the 30-day mortality rates among 7864 patients aged between 76 and 86 years presenting within 4 h of symptom onset were 15.4% with thrombolytic therapy and 18% with control treatment ($P = 0.003$). The authors concluded that thrombolytic therapy was 'unlikely to confer survival benefit and may have significant disadvantage' [5]. It should be noted, however, that a large proportion of the patients given thrombolytic therapy had contraindications, for example 12% had a systolic blood pressure of >180 mmHg, and 18% had a recent history of trauma, peptic ulcer or internal bleeding.

The Cooperative Cardiovascular Project [6], which studied 16,305 patients considered 'ideal' for reperfusion therapy, reported that 30-day mortality rates were reduced by primary angioplasty, but not by thrombolytic therapy. At 1 year, however, both treatment modalities were associated with lower mortality rates than control treatment (odds ratios for mortality 0.85 [95% confidence interval 0.77 to 0.94] with thrombolytic therapy and 0.63 [95% confidence interval 0.49 to 0.81] with primary angioplasty, after adjustment for baseline characteristics). Patients who received thrombolytic therapy within 30 min had lower mortality rates at both 30 days and 1 year than those who received it later. In patients over 65, the mean time to thrombolytic therapy was 62 ± 48 min and the mean time to primary angioplasty was 131 ± 60 min. Only 42% of eligible patients with no absolute contraindications against thrombolytic therapy received reperfusion therapy (4.2% underwent primary angioplasty) [6].

Although adjustments were made for known variables in both of these studies, observational studies can sometimes be confounded by the influence of unforeseen factors. For this reason, randomised trial data are usually considered more reliable because randomisation helps to ensure that unforeseen factors are balanced between the different treatment groups. It is inappropriate to rely upon registry data as a basis for clinical management, as illustrated by various large registry studies that have subsequently been shown to be wrong [7,8].

In most instances the relative benefits of treatment are similar across different risk groups, unless there is an a priori reason why a particular subgroup should differ in its response to treatment. Thus, patients at higher risk will gain a greater absolute benefit from treatment. Following MI the elderly have a much higher mortality rate and a higher incidence of complications such as heart failure and cardiogenic shock. They are also more prone to the haemorrhagic complications of thrombolytic therapy, such as intracranial haemorrhage, and one would therefore expect primary angioplasty to have its greatest benefit in the elderly.

Angioplasty in the elderly

There are, however, few data specifically concerning primary angioplasty in the elderly. In the Primary Angio-

plasty in Myocardial Infarction (PAMI) study, which compared angioplasty with the older 3-h tissue plasminogen activator (TPA) infusion regimen, the greatest benefit was observed in patients over 65. There was no significant reduction in the combined endpoint of death/MI in patients under 65 (0.8% mortality in both groups), but there was a marked reduction in the same endpoint in patients ≥65 (death/MI was 8.6% with angioplasty versus 20.0% with TPA, $P = 0.048$) [9]. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-IIB trial, the largest randomised trial comparing angioplasty with thrombolytic therapy, 1138 patients were randomised to receive either accelerated TPA or primary angioplasty. Although primary angioplasty resulted in better 30-day outcomes (death/MI/stroke occurred in 9.6% versus 13.7% with TPA, $P = 0.03$), there was no significant difference in death/MI at 6 months (13.3% versus 15.0%, respectively, odds ratio 0.87 [95% confidence interval 0.62 to 1.23]). While the absolute benefit of angioplasty was greater with each decade of life, the relative benefit was no greater in older than in younger patients [10]. Although the numbers were small ($n = 90$) there was no difference in mortality for patients ≥80 years (27.3% with angioplasty versus 26.7% with TPA). Likewise, a recent systematic overview of all trials comparing primary angioplasty with thrombolytic therapy reported that there was no difference in the relative benefit in the elderly, although the absolute benefit was greater [3].

Why aren't the advantages of angioplasty over thrombolytic therapy greater in the elderly than in younger patients? One reason is that elderly patients tend to delay longer before presenting for treatment, thus reducing the window of opportunity for myocardial salvage. This is particularly disadvantageous in patients treated with primary angioplasty, who already face a longer wait for reperfusion once they arrive at hospital, compared with those treated with thrombolytic therapy, which can be initiated sooner [11]. The elderly also tend to have more severe coronary stenoses and greater impairment of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow at baseline. In GUSTO-IIB, for instance, TIMI grade 3 flow was present in 19% of patients aged <40 versus 6% of those aged 70 to 79 [10].

There is evidence that thrombolytic therapy lyses coronary artery thrombi just as well in the elderly as it does in younger patients [12]. In the GUSTO-I angiographic substudy, univariate and multivariate analysis showed that age was not a predictor of TIMI flow grades at 90 min, with similar proportions of patients under and over the age of 75 achieving TIMI grade 3 flow (38% versus 37%) [13]. Although the elderly are more prone to bleeding (particularly intracranial haemorrhage) following thrombolytic therapy [14], most patients suffering intracranial haemorrhage die (60% in GUSTO-I) rather than survive with a disability (20% in GUSTO-I), and so the benefit:risk ratio of thrombolytic therapy is largely already accounted for in the mortality statistics.

The recent systematic overview of all trials comparing primary angioplasty with thrombolytic therapy [3] showed that the mortality benefits were maintained at 6 months, but with borderline statistical significance ($P = 0.04$). Some of the trials had missing data, and if one extra death had occurred in the angioplasty limb of one of these trials, or if two studies had reported equal outcomes, there would have been no significant overall mortality advantage associated with primary angioplasty. In this overview, there was a trend showing that longer door-to-balloon times tended to be associated with lesser benefits of primary angioplasty.

In the recent Stent-PAMI study, the mean door-to-balloon time was 112 min [15]. Some researchers have suggested that the time to treatment may be less important with primary angioplasty than with thrombolytic therapy [16]. The scientific rationale for this is uncertain as myocardial salvage is clearly time-dependent, and patency of the infarct-related artery has other long-term advantages that are independent of salvage, such as decreased left ventricular remodelling, improved electrical stability, and the capacity for collateral supply to other coronary territories in the event of reinfarction [17]. Although thrombolytic therapy is less effective at lysing old clots [18], patency does improve with time. In GUSTO-I, for instance, streptokinase achieved patency (TIMI grade 2 or 3) in 57% of patients by 90 min and 73% by 180 min, while accelerated TPA achieved patency in 76% by 180 min. In the Second US National Registry of Myocardial Infarction, 27,080 patients were treated with primary angioplasty between June 1994 and March 1998, and it was found that the mortality rate was significantly related to the door-to-balloon time (median 116 min) [19]. The adjusted mortality rates were 41% higher in patients with door-balloon times of >2 h and 62% higher in those with door-to-balloon times of >3 h ($P < 0.001$). It should be noted that the timing of angioplasty was not randomised in these studies.

The quest for more effective pharmacological reperfusion strategies must be balanced against the risk of increasing intracranial haemorrhage rates [20]. The percentage of patients suffering intracranial haemorrhage has risen with the introduction of the newer thrombolytic agents, partly because more elderly patients are now being included in clinical trials, and possibly also because the ability to detect haemorrhagic complications has improved. However, the increase in intracranial haemorrhage cannot be entirely explained by changing demographics [21]. Tenecteplase is a new, relatively fibrin-specific bolus thrombolytic agent. In the Second Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) trial [22], the rates of major bleeding (ie life-threatening, resulting in death or requiring transfusion) in the over-75

age group were 8.12% with tenecteplase and 11.62% with TPA. The rates of intracranial haemorrhage in the same age group were 1.72% and 2.62%, respectively. These results suggest that tenecteplase may be particularly suitable for use in the elderly, as may newer thrombolytic regimens incorporating either a half-dose thrombolytic plus a IIb/IIIa inhibitor or a full-dose thrombolytic plus the direct thrombin inhibitor, bivalirudin, which have been shown to cause less bleeding than unfractionated heparin [23].

Angioplasty with stenting has been shown to achieve TIMI grade 3 flow in a very high proportion of patients, for example 86% in Stent-PAMI [15]. However, this figure does not apply to all patients. In Stent-PAMI the trial registry showed that of the 1458 patients with acute MI who were screened, only 900 (62%) were randomised. Of those not randomised, 38% did not undergo angioplasty. The reasons why angioplasty is sometimes not performed include poor vascular access, renal failure and other comorbid conditions. If a 'rule of ninety-fives' is applied to all patients with acute MI who are eligible for reperfusion (ie 95% of patients are eligible for angioplasty ± stenting, 95% of these procedures are successful, and 95% of patients whose procedures are successful achieve TIMI grade 3 flow), then the actual incidence of TIMI grade 3 flow for all comers is 86% (ie 95% × 95% × 95%). This incidence of TIMI grade 3 flow is no better than that achieved with half-dose TPA plus abciximab in the TIMI-14 trial [24]. It is also important to remember that in the real world, primary angioplasty takes considerably longer to perform than thrombolysis. The interventionist performing the procedure may well be less experienced than those participating in clinical trials, which tend to be conducted in centres of excellence. The patency rates achieved by primary angioplasty in the real world may therefore be nearer those seen with thrombolytic therapy than those achieved under optimal clinical trial conditions [11]. It is likely that advances in adjunctive therapies will enhance the reperfusion rates achieved by both approaches, and hence patient outcomes should also improve.

Conclusion

Primary angioplasty has its greatest benefit in high-risk patients and in the elderly, for whom thrombolysis carries an increased risk of stroke (particularly haemorrhagic stroke). Although there is potential to develop chest pain units where patients with acute MI could be triaged for transfer to centres of excellence with expertise in angioplasty, the costs and logistical difficulties of such an approach would be considerable. Only about 25% of hospitals in the US have the capacity to perform angioplasty, and so it is unlikely that this procedure will be readily available to the majority of patients presenting with acute MI in the near future. Prompt administration of a thrombolytic regimen, with facilitated angioplasty reserved for patients identified as high-risk (such as the elderly and patients with evidence of reperfusion failure), is likely to result in the greatest good for the greatest number of patients.

Regardless of the reperfusion strategy used, event rates in the elderly remain high, and so further research is needed to develop better treatments. Meanwhile, it is vital that as many patients as possible receive reperfusion therapy as soon as possible by whichever means is available.

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Author's affiliation: Cardiology Department, Green Lane Hospital, Private Bag 92 189, Auckland 1030, New Zealand

Correspondence: Professor Harvey White, Cardiology Department, Green Lane Hospital, Private Bag 92 189, Auckland 1030, New Zealand. Tel: +64 9 630 9992; fax: +64 9 630 9915; e-mail: harveyw@ahsl.co.nz