Commentary

Debate: Should the elderly receive thrombolytic therapy, or primary angioplasty, for acute myocardial infarction? The case for primary angioplasty

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Abstract

As the population ages the number of elderly patients presenting with acute myocardial infarction (AMI) will continue to increase. There has been no head-to-head trial of thrombolytic therapy versus primary percutaneous coronary intervention (PCI) in this patient cohort, but there is evidence that favors primary PCI. Most elderly patients are candidates for primary PCI, but many have contraindications to thrombolytic therapy. Hemorrhagic complications are more common in the elderly, and many of these patients present with conditions in which thrombolytic agents have decreased efficacy, such as heart failure or prior bypass surgery. PCI can also obviate the need for further risk stratification in most patients.

Keywords: elderly, myocardial infarction, primary angioplasty

Introduction

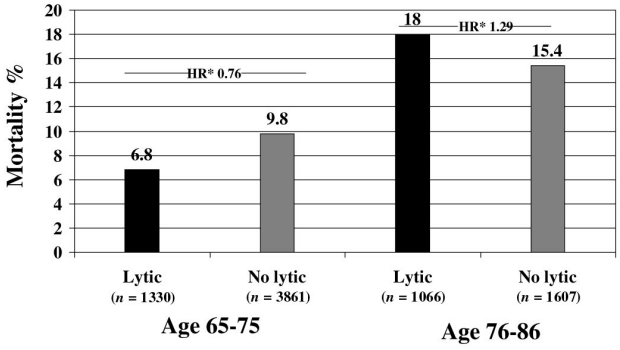
Patients older than 70 years remain one of the fastest growing populations. In the USA alone this group increased from 21.1 million in 1990 to over 25 million in 1999, and is projected to reach nearly 36 million people by the year 2020. With this in mind, the number of elderly patients presenting with an ST-segment elevation AMI will continue to increase. Despite this, there have been no head-to-head trials of thrombolytic therapy versus PCI that are specifically designed for this patient population. However, there are indications from previous trials that primary PCI is likely to be the superior therapy.

Elderly patients have a documented increase in bleeding (including intracranial hemorrhage) with thrombolytic therapy. In fact, age greater than 65 years has been associated with an odds ratio of 2.2 (95% confidence interval 1.4–3.5) for intracranial hemorrhage as compared with younger patients [1–3]. The percentage of women is higher than that of men among elderly patients, and hemorrhagic complications are known to be higher in women (and even greater if their weight is <70 kg). Also, any previous hemorrhagic stroke, which is more common in elderly patients, is a very strong contraindication to thrombolytic therapy [4].

AMI = acute myocardial infarction; GISSI = Gruppo Italiano per lo Studio della Streptokinasi nell'Infarcto Miocardico; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; PAMI = Primary Angioplasty in Myocardial Infarction; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; t-PA = tissue-type plasminogen activator.

Elderly patients are likely to have more contraindications to thrombolytic therapy, more comorbid conditions, and more adverse hemodynamic and angiographic predictors of poor outcome than younger patients. A recent pooled analysis of 3032 patients enroled in primary PCI trials [5] revealed that patients older than 75 years were more likely to have a history of hypertension, diabetes mellitus, congestive heart failure, previous coronary revascularization (PCI or bypass surgery), peripheral vascular disease, stroke, or chronic obstructive lung disease. At angiography they had lower left ventricular ejection fraction, higher left ventricular end-diastolic pressure, and more two-vessel or three-vessel coronary disease. In addition, these patients were significantly more likely to present with an infarction of Killip class II or higher.

Figure 1



Effect of treatment with thrombolytic therapy for ST-segment elevation AMI by age group. HR, hazard ratio. Data from Thiemann *et al* [17].

Studies including elderly acute myocardial infarction patients

Many of the early trials of thrombolytic therapy intentionally excluded patients aged 75 years or older because of a perceived increase in bleeding and overall mortality [6–12]. Later trials began to include these patients, and especially those that compared thrombolytic therapy with primary PCI, but the average age in many of these trials remained approximately 60 years. In the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) 1 trial of four regimens of thrombolytic therapy [13], the overall mortality rate was 7.0%. However, the 30-day mortality rates for patients aged 65–74, 74–85 and >85 years were 9.5, 19.6 and 30.3%, respectively [14]. In an analysis of the GUSTO IIb trial, Holmes *et al* [15] showed that, for each 10-year patient group (50–59 years, 60–69 years, etc), outcome was always superior with angioplasty as compared with tissue-type plasminogen activator (t-PA). In the Primary Angioplasty in Myocardial Infarction (PAMI)-1 trial [16], the benefit of percutaneous transluminal coronary angioplasty (PTCA) over t-PA was marked in patients aged more than 65 years, with a reduction in the 6-month composite endpoint of in-hospital death or reinfarction being reduced from 20 to 8.6% ($P<0.05$).

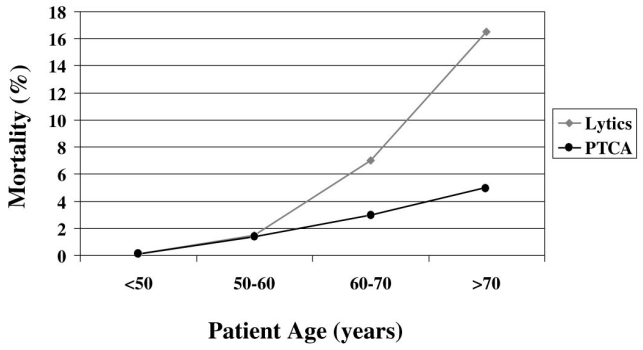
Recently, Thiemann *et al* [17] reported an analysis of 7864 patients (aged 65–86 years) who were eligible for thrombolytic therapy (presentation <12 h from symptom onset, ST-segment elevation ≥1.5 mm [limb leads] or ≥2 mm [precordial leads] in two or more contiguous leads; left bundle branch block was excluded). That study was designed to compare the risks and benefits of intravenous thrombolysis in patients aged 65–75 years with those in patients aged 76–86 years. Of note, over 50% of the patients in each group who met initial electrocardiographic criteria were excluded for various reasons, with 12% of the younger patients and 17% of the older patients having absolute contraindications to thrombolytic therapy. Intravenous thrombolysis was administered in 3861 out of 5191 (74%) of patients in the 65–75 years age group and in 1607 out of 2673 (60%) of the 76–86 years age group. At 30 days there was a survival benefit in the younger patients (hazard ratio 0.76, 95% confidence interval 0.61–0.95) and worsened survival in the older group (hazard ratio 1.29, 95% confidence interval 1.06–1.58), with mortality rates reduced from 9.8 to 6.8% in the younger group but increased from 15.4 to 18% in the older group (Fig. 1). On further analysis, death began to increase with thrombolysis after age 74.3 years. Thiemann *et al* speculated that increased rates of intracranial hemorrhage and cardiac rupture in the older patients may explain the lack of benefit of thrombolytic therapy in these persons.

Selected patient subsets

With regard to prior coronary bypass surgery, several studies have shown that thrombotic occlusion of a saphenous vein graft is the primary mechanism of AMI in these patients. Thrombolytic therapy is often ineffective because of poor flow in the graft (preventing delivery of the thrombolytic agent) as well as the presence of giant thrombus. Primary PCI is successful in up to 90% of these patients because the obstructing thrombus can be mechanically disrupted [18,19].

As mentioned above, older patients are more likely to present with congestive heart failure. Systemic thrombolytic therapy has not been shown to provide a survival benefit in these patients. In the Gruppo Italiano per lo Studio della Streptokinasi nell'Infarcto Miocardico (GISSI)-1 [20] and International Study Group (ISG) [21] trials, 17–23% of patients presented in Killip class II and 2–4% in class III. At 6-month follow-up in the GISSI-1 trial, mortality rates were 27% versus 29% for placebo in class II patients, and 50% versus 53% for placebo in class III patients (class IV patients were excluded). Likewise, no survival benefit for either group was seen in the ISG trial. It is theorized that poor cardiac pump function

Figure 2



Mortality by age group in selected trials of PTCA versus thrombolytic therapy. Modified from O'Neill *et al* [22].

results in decreased coronary perfusion, making the thrombolytic agents unable to penetrate the occlusive thrombus.

Advantages of primary percutaneous coronary intervention

In a pooled analysis of the PAMI-1, Zwolle and Mayo Clinic trials, O'Neill *et al* [22] showed an increasing benefit of primary PTCA over t-PA with increasing patient age (Fig. 2). This is probably due to the fact that primary PCI can restore Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in over 90% of patients, as opposed to 60–70% of patients treated with thrombolytic therapy. Data from primary PCI trials [5] revealed a mortality rate of approximately 10% in patients older than 75 years, which is lower than that in the thrombolytic trials.

Emergent catheterization not only defines the status of the infarct-related artery (patent or not, TIMI flow grade), but is extremely useful for risk stratification. Significant left main and multivessel disease can be delineated and hemodynamics can be assessed. An intra-aortic balloon pump can be inserted immediately if required. Noninvasive testing can usually be averted and hospital discharge can be accelerated, resulting in significant cost savings.

As a result of perceived or real contraindications, fewer than 10% of elderly patients with ST-segment elevation AMI receive thrombolytic therapy [23]. Primary PCI is not as readily available as thrombolytic therapy in all locations, but there are emerging data [24] that show that primary PCI can be performed safely in hospitals without on-site cardiac surgery. This may allow many more patients access to immediate catheter-based reperfusion.

Future insights

Of course, what is most needed is a head-to-head, prospective study of thrombolytic therapy versus primary PCI in elderly patients. The Senior PAMI trial will enrol 530 elderly AMI patients, who will be randomized to primary PCI or thrombolytic therapy (t-PA or rPA) with a primary composite end-point of death or disabling stroke at 30 days. Multiple secondary end-points will be measured at 1, 6, and 12 months.

There may also be a role for combination therapy, in which reduced-dose thrombolytic therapy (with or without a glycoprotein IIb/IIIa receptor antagonist) is administered in the field or in the receiving emergency room, with subsequent transfer for PCI ('facilitated angioplasty') [25].

Conclusion

As the population increases worldwide, the number of elderly patients who present with an ST-segment elevation AMI will continue to grow. There are no head-to-head trials of primary PCI versus thrombolytic therapy in elderly patients. However, data from previous trials that have included elderly patients suggest that primary PCI is safer and is probably more effective in such cohorts. The bleeding risk associated with PCI is lower, and PCI appears to be more effective in patients with prior coronary artery bypass grafting and those with congestive heart failure, groups that are more common among elderly patients. Primary PCI allows those patients who are not eligible for thrombolytic therapy to receive reperfusion therapy, is useful for early risk stratification, and usually obviates the need for noninvasive testing. Early discharge, with resultant lower hospital charges, is also possible in many cases. Access to primary PCI is expanding, and continued technical and therapeutic advances will allow for increased distribution and utilization of this therapy among elderly patients. The ongoing Senior PAMI trial will provide the first randomized, controlled trial evidence of thrombolytic therapy versus PCI in elderly patients.

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