Myocardial Infarction in the Elderly
Benefits and Risks of Thrombolytics

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Abstract

    Patients aged 75 years and older comprise 36% of all patients with myocardial infarction and 60% of all deaths from myocardial infarction in the US. Data from randomised, placebo-controlled clinical trials and observational data demonstrated a beneficial effect of thrombolytic therapy in eligible patients with acute myocardial infarction younger than 75 years of age. The overall data support the use of thrombolytic therapy in eligible patients with acute myocardial infarction aged 75 years and older. There is an urgent need to conduct a large-scale, prospective, double-blind, randomised, placebo-controlled trial investigating the effect of thrombolytic therapy on the combined endpoint of all-cause mortality plus cerebral bleeding at hospital discharge and at long-term follow-up in eligible patients aged 75 years and older with acute myocardial infarction. Current guidelines for the care of patients with acute myocardial infarction from the American College of Cardiology/American Heart Association support the use of thrombolytic therapy in eligible patients aged 75 years and older who present within 12 hours of symptom onset of acute myocardial infarction as a Class IIa indication, that is, one for which the weight of evidence/opinion is in favour of usefulness/ efficacy. Absolute contraindications to thrombolytic therapy include prior haemorrhagic stroke, other cerebrovascular events within 1 year, active internal bleeding, known intracranial neoplasm, suspected aortic dissection, and acute pericarditis. Stroke is a potential risk of the use of thrombolytics.

Persons aged 75 years and older comprise 6% of the population in the US, but 36% of all myocardial infarctions and 60% of all deaths from myocardial infarction.[1,2] This trend is reflected in other countries in the Western world. Mortality and complication rates are especially high in patients aged 75 years and older with acute myocardial infarction because of frequent co-morbidities, later presentation after the onset of acute myocardial infarction, and diagnostic uncertainty because of atypical presentations of acute myocardial infarction. Reperfusion therapy including thrombolytic therapy and primary percutaneous transluminal coronary angioplasty (PTCA) is also under-utilised among eligible elderly patients with acute myocardial infarction.

Persons aged 75 years and older also comprise the fastest growing segment of the US population and in the Western world. Despite these data, there is a paucity of data from randomised, placebo-controlled clinical trials investigating the efficacy and risks of thrombolytic therapy in persons aged 75 years and older with acute myocardial infarction. This article will discuss the available data on the use of thrombolytic therapy in eligible persons aged 75 years and older with acute myocardial infarction.

1. Thrombolytic Therapy

Substantial data from randomised, placebo-controlled clinical trials and observational studies clearly demonstrate that thrombolytic therapy is efficacious in reducing mortality in patients at least up to the age of 75 years who present within 12 hours of symptom onset of acute myocardial infarction with ST-segment elevation (equal to or greater than 1mV) in contiguous leads of a 12-lead electrocardiogram or with left bundle branch block.[3] Except for the Intravenous Streptokinase in Acute Myocardial Infarction Trial,[4] which enrolled a small number of elderly persons and showed no significant change in mortality, randomised, placebo-controlled studies have demonstrated that thrombolytic therapy decreases mortality in older persons with acute myocardial infarction.[5-8] Pooling long-term data following thrombolytic therapy for acute myocardial infarction from three of these studies[9-11] showed that thrombolytic therapy caused a significant 18% reduction in mortality in younger persons versus a significant 10% reduction in mortality in older persons with a significant 2% absolute reduction in mortality in younger persons versus a significant 3% absolute reduction in mortality in older persons.[9-11]

1.1 Randomised, Placebo-Controlled Studies in Patients Aged ≥75 Years

In the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI-1) study, 1215 patients older than 75 years of age with acute myocardial infarction were randomised in a double-blind manner to streptokinase therapy or to placebo.[5] At 21-day follow-up, mortality was 28.9% in patients treated with streptokinase versus 33.1% in persons treated with placebo (p = 0.11).[5] Streptokinase was associated with a reduction in 42 deaths per 1000 patients older than 75 years of age with acute myocardial infarction in this study.[5]

Forman and Wei[12] reported data from the Second International Study of Infarct Survival (ISIS-2)[7] on 401 patients aged 80 years and older with acute myocardial infarction who were randomised in a double-blind manner to either streptokinase therapy or to placebo. At 5-week follow-up, mortality was 20.1% in patients randomised to streptokinase and 34.2% in patients randomised to placebo (p = 0.002), a significant 41% reduction in mortality by streptokinase.[12] Streptokinase saved 141 lives per 1000 patients aged 80 years and older with acute myocardial infarction in this study.[12] However, subset analyses in most randomised trials should be interpreted with great caution.

The Fibrinolytic Therapy Trialists' Collaborative Group summarised randomised, placebo-controlled data in 5754 patients with acute myocardial infarction aged 75 years and older treated with thrombolytic therapy.[13] These data demonstrated an insignificant reduction in mortality at 35-day follow-up in patients treated with thrombolytic therapy (24.3%) versus placebo (25.3%).[13] However, the absolute benefit of thrombolytic therapy was associated with a reduction in 10 deaths per 1000 patients aged 75 years and older with acute myocardial infarction treated with thrombolytic therapy.[13] This study also showed that the incidence of stroke was 2% in persons aged 75 years and older receiving thrombolytic therapy for acute myocardial infarction versus 1.2% in the control group.[13] Subset analyses with adequate numbers as in this study are more reliable.

1.2 Observational Data in Patients Aged ≥75 Years

Berger et al.[14] analysed data from the Cooperative Cardiovascular Project. Of 37 983 patients aged 65 years and older who presented within 12 hours of symptom onset of acute myocardial infarction with ST-segment elevation or left bundle branch block, 14 341 patients (38%) were treated with thrombolytic therapy, and 1599 patients (4%) underwent primary PTCA within 6 hours of hospital arrival. Compared with no reperfusion therapy, thrombolytic therapy caused no significant effect on 30-day mortality, whereas primary PTCA significantly reduced 30-day mortality by 21%.[14] Thrombolytic therapy had no significant effect on

30-day mortality in patients aged 75 years and older in this study.[14]

At 1-year follow-up, compared with no reperfusion therapy, thrombolytic therapy significantly reduced mortality by 15%, whereas primary PTCA significantly reduced mortality by 37%.[14] Both thrombolytic therapy and primary PTCA were effective in significantly reducing 1-year mortality in patients aged 65 to 74 years, 75 to 84 years, and 85 years and older with acute myocardial infarction.[14] Although thrombolytic therapy was associated with a reduction in 1-year mortality, a cause and effect relationship cannot be inferred from observational data.

Thiemann et al.[15] performed a retrospective cohort study of 7864 patients aged 65 to 86 years with acute myocardial infarction who were eligible for thrombolytic therapy. Of 5191 patients aged 65 to 74 years, 1330 patients (26%) were treated with thrombolytic therapy.[15] Complete data were available for 5113 of these 5191 patients (98%). Of 2673 patients aged 76 to 86 years, 1066 patients (40%) were treated with thrombolytic therapy.[15] Complete data were available for 2634 of these 2673 patients (99%).

Compared with no thrombolytic therapy, thrombolytic therapy caused a 12% reduction in 30-day mortality in patients aged 65 to 75 years with acute myocardial infarction ($p = 0.02$).[15] However, compared with no thrombolytic therapy, thrombolytic therapy caused a 38% significant increase in 30-day mortality in patients aged 76 to 86 years with acute myocardial infarction.[15] Long-term follow-up data were not provided in this observational study.[15]

Gitt et al.[16] analysed the prospective data on 6815 unselected patients aged 75 years and older with acute myocardial infarction from the Maximal Individual Therapy of Acute Myocardial Infarction Registry and the Myocardial Infarction Registry. Of these patients, 1782 patients (27%) were treated with thrombolytic therapy, and 367 patients (5%) were treated with primary PTCA.[16]

In patients aged 75 years and older with acute myocardial infarction, compared with no reperfusion therapy, thrombolytic therapy insignificantly reduced hospital mortality by 5% but significantly reduced 18-month mortality by 42%.[16] Compared with no reperfusion therapy, primary PTCA significantly reduced hospital mortality by 61% and significantly reduced 18-month mortality by 57%.[16]

Stenestrand et al.[17] analysed data from 5428 patients aged 75 years and older with acute myocardial infarction from the Swedish Register of Cardiac Intensive Care. Thrombolytic therapy was administered to 2445 of 5428 patients (45%) in this study.[17] The combined endpoint of cerebral bleeding or all-cause mortality within 1 year was significantly reduced from 48% in patients with acute myocardial infarction treated with no thrombolytic therapy to 38% in patients with acute myocardial infarction treated with thrombolytic therapy ($p < 0.001$).[17]

2. Stroke

Thrombolytic therapy is associated with an increased risk of developing stroke.[13] Age over 75 years is an independent risk factor for developing haemorrhagic stroke in patients with acute myocardial infarction treated with a thrombolytic agent.[18] The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) I investigators reported that patients over 75 years of age with acute myocardial infarction had a 2.1% incidence of intracranial haemorrhage if they were treated with alteplase versus a 1.2% incidence of intracranial haemorrhage if they were treated with streptokinase.[19] In the GUSTO III study, there was a tendency for patients over 75 years of age with acute myocardial infarction to develop more haemorrhagic strokes if they were treated with reteplase than if they were treated with alteplase.[20] In studies using reteplase, there was likely to be an overuse of the amount of heparin used as concomitant therapy. At the time the studies were done, the investigators did not know that the dose of heparin used needed to be reduced in patients receiving reteplase.

The Fibrinolytic Therapy Trialists' Collaborative Group reported no excess strokes in patients

younger than 55 years of age with acute myocardial infarction receiving thrombolytic therapy.[13] However, there was an excess of five strokes for each 1000 patients (0.5%) aged 55 to 74 years with acute myocardial infarction treated with thrombolytic drugs and an excess of eight strokes for each 1000 patients (0.8%) aged 75 years and older with acute myocardial infarction treated with thrombolytic drugs.[13] The incidence of stroke was 2% in patients aged 75 years and older receiving thrombolytic therapy for acute myocardial infarction versus 1.2% in the control group.[13]

3. Recommendations for Use of Thrombolytic Therapy

The data discussed clearly demonstrate a beneficial effect of thrombolytic therapy in eligible patients with acute myocardial infarction younger than 75 years of age. The overall data support the use of thrombolytic therapy in eligible patients with acute myocardial infarction aged 75 years and older.

Although short-term mortality was not reduced by thrombolytic therapy in patients aged 75 years and older with acute myocardial infarction in the observational studies reported by Berger et al.[14] and Gitt et al.,[16] these studies showed that thrombolytic therapy caused a significant reduction in 1-year mortality[14] and in 18-month mortality.[16] However, the observational data by Thiemann et al.[15] showed that thrombolytic therapy significantly increased 30-day mortality in patients aged 76 to 86 years with acute myocardial infarction. This study did not analyse long-term mortality in patients treated with and without thrombolytic therapy.

Since patients aged 75 years and older currently comprise 36% of all patients with acute myocardial infarctions and 60% of all deaths from acute myocardial infarction in the US[1,2] and also comprise the fastest growing segment of the US population, there is an urgent need to conduct a large-scale, prospective, double-blind, randomised, placebo-controlled trial investigating the effect of thrombolytic therapy on the combined endpoint of all cause

mortality plus cerebral bleeding at hospital discharge and at long-term follow-up in eligible patients aged 75 years and older with acute myocardial infarction. This study is especially important since primary PTCA is not available at numerous hospitals to which elderly patients with acute myocardial infarction are admitted. This study should include high-risk elderly patients who have not traditionally been considered suitable candidates for clinical trials or aggressive therapy. Unfortunately, a randomised, placebo-controlled trial to assess the benefit and risk of thrombolytic therapy in patients over 75 years of age with acute myocardial infarction was prematurely stopped because of slow patient recruitment.[21]

Until the data from such a study are available so that evidence-based medical care may be provided, the author agrees with the current guidelines for the care of patients with acute myocardial infarction from the American College of Cardiology/ American Heart Association.[3] These guidelines support the use of thrombolytic therapy in eligible patients aged 75 years and older who present within 12 hours of symptom onset of acute ST-segment elevation myocardial infarction as a Class IIa indication, that is, one for which the weight of evidence/ opinion is in favour of usefulness/efficacy.[3]

4. Choice of Thrombolytic Agent

Streptokinase (1.5MU administered intravenously over 1 hour) may be preferable to recombinant human tissue plasminogen activators for elderly persons because it causes fewer episodes of stroke and cerebral haemorrhage. Streptokinase is also much less expensive. The choice of thrombolytic drug, however, is controversial. Minimisation of delays in thrombolytic therapy is more important than the choice of thrombolytic drug.

5. Contraindications to Thrombolytic Therapy

Absolute contraindications to thrombolytic therapy include prior haemorrhagic stroke, other cerebrovascular events within 1 year, active internal bleeding, known intracranial neoplasm, sus-

pected aortic dissection, and acute pericarditis.[3] Relative contraindications to thrombolytic therapy include uncontrolled hypertension with a blood pressure greater than 180/110mm Hg, recent major surgery or trauma within 2 to 4 weeks, a known bleeding disorder, active peptic ulcer disease, a remote stroke or other intracerebral pathology, and noncompressible vascular puncture.[3]

In patients aged 75 years and older with relative contraindications to thrombolytic therapy, the decision to administer thrombolytic therapy must be based on an assessment of potential benefit versus risk. The potential benefit is increased in patients with large anterior myocardial infarctions and limited in haemodynamically stable patients with small inferior myocardial infarctions. Elderly patients with acute myocardial infarction and with contraindications to thrombolytic therapy may benefit from reperfusion by primary PTCA with or without stenting if available.[22]

6. Conclusions

There is an urgent need to conduct a large-scale, prospective, double-blind, randomised, placebo-controlled trial investigating the effect of thrombolytic therapy on the combined endpoint of all-cause mortality plus cerebral bleeding at hospital discharge and at long-term follow-up in eligible patients aged 75 years and older with acute myocardial infarction. This study should include high-risk elderly patients who have not traditionally been considered suitable candidates for clinical trials or aggressive therapy. Reperfusion therapy including thrombolytic therapy and primary PTCA is under-utilised among eligible elderly patients with acute myocardial infarction.[23,24]

Acknowledgements

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