Economic evaluation of treatment strategies for patients suffering acute myocardial infarction in Greece

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Tenecteplase was compared with alteplase and reteplase for the treatment of acute myocardial infarction (AMI). Tenecteplase was administered by an intravenous (IV) bolus injection over 5 minutes. Alteplase 100 mg was given as a 50-mg bolus followed by a 50-mg IV infusion over 90 minutes. Reteplase was given as two bolus doses of 5 units each, with a 30-minute interval between doses. Aspirin and heparin were co-administered.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients presenting with AMI and with no contraindications to thrombolysis. The reference population in the current study was based on the GUSTO III trial (GUSTO III Investigators 1997, see ‘Other Publications of Related Interest’ below for bibliographic details).

Setting
The setting was tertiary care. The economic study was conducted in Greece.

Dates to which data relate
The effectiveness evidence and resource use data were gathered from two studies published in 1995 and 1996 (GUSTO III Investigators 1997 and Van de Werf et al. 1999, see ‘Other Publications of Related Interest’ below for bibliographic details). The resource use and cost data were derived from hospital records from 1996 to 2002. In addition, some of the costs were estimated on the basis of expert opinion. The costs were reported in 2003 prices.

Source of effectiveness data
The estimates for the final outcomes were derived from a synthesis of published studies.

Modelling
A decision analysis model was constructed to determine the expected lifetime costs and effectiveness of tenecteplase versus alteplase and reteplase. A deterministic model was used and the structure of the tree was presented. The time horizon of the analysis was the remaining life expectancy of the individual patient, although an additional analysis was limited to one year. The model assumed that aspirin and heparin were co-administered with the thrombolytic agent.
Outcomes assessed in the review
A systematic review was undertaken to identify the effectiveness parameters of the model. The occurrence of the following events due to thrombolytic therapy was assessed:

death;
stroke;
bleeding;
anaphylaxis;
congestive heart failure;
reinfarction;
cardiogenic shock;
tamponade or cardiac rupture;
pericarditis;
acute mitral regurgitation;
ventricular septal rupture;
pulmonary embolism;
second- and third-degree atrioventricular block;
asystole; and
electromechanical dissociation.

Study designs and other criteria for inclusion in the review
No specific criteria for inclusion in the review were stated. However, the authors described focusing on large Phase III randomised controlled trials, hospital settings, the three specified drugs and the health outcomes of interest.

Sources searched to identify primary studies
It was stated that the studies were identified from a review of MEDLINE, EMBASE, the Science Citation Index, the Cochrane Controlled Trials Register, HTA, NHS EED, DARE, and internet sites such as the UK National Institute of Clinical Excellence. The search terms used included "myocardial infarction", "heart infarction", "thrombolysis" and other unspecified related terms, combined with the specific drugs.

Criteria used to ensure the validity of primary studies
The authors reported that the studies were assessed for the acceptability of randomisation, baseline comparability, inclusion and exclusion criteria, blinding, and management of withdrawals.

Methods used to judge relevance and validity, and for extracting data
Two researchers working independently extracted the data using a common questionnaire. No further details were given.
Number of primary studies included
Two primary studies were included in the review.

Methods of combining primary studies
One of the trials compared alteplase with reteplase and the other alteplase with tenecteplase. The results were combined by calculating the probability of the occurrence of each event when alteplase was administered, and also the relative risk (RR) in relation to alteplase with reteplase and tenecteplase. The authors assumed that the RR observed in one population would be the same in the other trial population.

Investigation of differences between primary studies
The two primary studies included were both large multinational trials. In addition, the population demographics and main clinical characteristics were compared and found to be similar.

Results of the review
The following probabilities of an event occurring after administration of alteplase, and the RR (in relation to alteplase) with tenecteplase and with reteplase, respectively, were used in the model.

The probability of death associated with alteplase was 6.15 (standard deviation, SD=0.34), with RRs of 0.992 (SD=0.05) and 1.032 (SD=0.07) for tenecteplase and reteplase, respectively.

The probability of stroke associated with alteplase was 1.66 (SD=0.16), with RRs of 1.074 (SD=0.14) and 0.916 (SD=0.14) for tenecteplase and reteplase, respectively.

The probability of bleeding associated with alteplase was 5.94 (SD=0.48), with RRs of 0.784 (SD=0.15) and 1.015 (SD=0.10) for tenecteplase and reteplase, respectively.

The probability of anaphylaxis associated with alteplase was 0.2 (SD=0.02), with RR of 0.376 (SD=0.04) and 0.833 (SD=0.01) for tenecteplase and reteplase, respectively.

The probability of congestive heart failure associated with alteplase was 17.5 (SD=1.36), with RRs of 0.872 (SD=0.08) and 0.983 (SD=0.09) for tenecteplase and reteplase, respectively.

The probability of reinfarction associated with alteplase was 3.81 (SD=0.29), with RRs of 1.078 (SD=0.09) and 1.000 (SD=0.09) for tenecteplase and reteplase, respectively.

The probability of cardiogenic shock associated with alteplase was 4.00 (SD=0.31), with RRs of 0.965 (SD=0.07) and 1.045 (SD=0.10) for tenecteplase and reteplase, respectively.

The probability of tamponade or cardiac rupture associated with alteplase was 7.00 (SD=0.05), with RRs of 0.816 (SD=0.19) and 0.889 (SD=0.08) for tenecteplase and reteplase, respectively.

The probability of pericarditis associated with alteplase was 2.60 (SD=0.20), with RRs of 1.124 (SD=0.11) and 1.000 (SD=0.10) for tenecteplase and reteplase, respectively.

The probability of acute mitral regurgitation associated with alteplase was 0.7 (SD=0.05), with RRs of 0.886 (SD=0.20) and 1.500 (SD=0.15) for tenecteplase and reteplase, respectively.

The probability of ventricular septal rupture associated with alteplase was 3.00 (SD=0.02), with RRs of 0.817 (SD=0.03) and 0.667 (SD=0.06) for tenecteplase and reteplase, respectively.

The probability of pulmonary embolism associated with alteplase was 0.04 (SD=0.00), with RRs of 2.750 (SD=0.20) and 1.000 (SD=0.10) for tenecteplase and reteplase, respectively.
The probability of second-degree atrioventricular block associated with alteplase was 2.20 (SD=0.17), with RRs of 1.000 (SD=0.10) and 1.273 (SD=0.12) for tenecteplase and reteplase, respectively.

The probability of third-degree atrioventricular block associated with alteplase was 3.1 (SD=0.24), with RRs of 1.000 (SD=0.10) and 1.129 (SD=0.11) for tenecteplase and reteplase, respectively.

The probability of asystole associated with alteplase was 4.2 (SD=0.03), with RRs of 1.000 (SD=0.10) and 1.000 (SD=0.1) for tenecteplase and reteplase, respectively.

The probability of electromechanical dissociation associated with alteplase was 2.2 (SD=0.17), with RRs of 1.000 (SD=0.04) and 1.091 (SD=0.11) for tenecteplase and reteplase, respectively.

Methods used to derive estimates of effectiveness
This analysis was also based on authors' assumptions.

Estimates of effectiveness and key assumptions
For the reference group containing patients with an average age of 63 who survived an AMI without any further complications, the authors assumed that they would live, on average, for another 10 years, whilst if they experienced complications such as stroke, reinfarction or bleeding, they would live on average for 8 more years.

Measure of benefits used in the economic analysis
The measure of health benefit was the life-years of patient survival. This was obtained from the decision model. A discount rate of 3.5% was applied to the health benefits.

Direct costs
The direct costs to the health service were considered in the analysis. These included both in-hospital and post-discharge costs. In-hospital costs comprised hospitalisation for 7 days, additional aggregate costs for adverse events due to thrombolytic treatment, coronary angiography and angioplasty procedures, and drug costs. Maintenance costs after discharge were for drugs, doctor visits and rehabilitation for stroke patients, and were estimated on the basis of expert advice. Resource use and the cost of in-hospital treatment were derived from hospital records relating from 1996 to 2002. Post-discharge costs were estimated on the basis of expert opinion. The cost estimates were reported separately from other model parameters. Discounting was applied at a rate of 3.5%. The costs were reported in 2003 prices. The total expected cost per patient was derived by modelling.

Statistical analysis of costs
To explore uncertainty in the cost estimates, a Monte Carlo simulation was undertaken, assuming a normal distribution, with 5,000 iterations. The average expected cost per patient was reported with the SD and 95% confidence intervals (CIs).

Indirect Costs
The indirect costs were not included, which was appropriate given the study perspective.

Currency
Euros (Euro).

Sensitivity analysis
A sensitivity analysis was carried out to investigate the robustness of the results under the uncertainty surrounding the
parameters of the model. One-way sensitivity analyses were undertaken by varying the values of all model parameters, including costs, by +/- 10%. The discount rates were also varied, but the range over which they were examined was not reported.

A probabilistic sensitivity analysis was conducted to investigate uncertainty in the baseline probability and RR estimates. Normal distributions were assigned to the variables and 5,000 simulations were carried out. The authors did not justify their assumption of normal distributions.

Sub-group analyses were also undertaken for patients aged over 75 years, and for treatment initiated more than 4 hours after symptom onset. Cost-effectiveness acceptability curves were presented. A further analysis used a 1-year time horizon.

**Estimated benefits used in the economic analysis**

The estimated life expectancy per patient following thrombolysis was 8.472 years (mean 7.122, 95% CI: 6.408 - 7.836) with tenecteplase, 8.402 years (mean 7.096, 95% CI: 6.386 - 7.806) with alteplase, and 8.359 years (mean 7.096, 95% CI: 6.249 - 7.944) with reteplase. These values were discounted at 3.5%.

**Cost results**

The estimated total cost of treatment per patient was Euro 18,990 (mean Euro 18,144, 95% CI: 17,273 - 19,015) with tenecteplase, Euro 18,896 (mean 17,984, 95% CI: 17,091 - 18,877) with alteplase, and Euro 18,947 (mean 18,075, 95% CI: 17,114 - 19,036) with reteplase. The costs were discounted at 3.5%. The costs were estimated over the patient's lifetime.

**Synthesis of costs and benefits**

The authors reported that none of the differences in survival or costs between the three thrombolytic agents was statistically significant in the base-case. Consequently, they could not reject the hypothesis that the three treatments had equal effectiveness, equal lifetime patient costs and equal cost-effectiveness.

The sensitivity analysis showed statistically significant differences between the outcomes and costs of treatment between the three drugs within the sub-groups. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the incremental costs by the incremental life-years saved. For patients aged over 75 years, the ICER of tenecteplase compared with alteplase was Euro 2,205 (mean 3,043), whereas reteplase was dominated by alteplase. For thrombolysis initiated more than 4 hours after symptom onset, the ICER of tenecteplase compared with alteplase was Euro 868 (mean 1,073) per year of survival, whereas reteplase was again dominated by alteplase. When the analysis was limited to 1 year, no statistical difference was observed in survival and in the total treatment costs of the three therapies.

The one-way sensitivity analysis showed that 10% changes in each of the parameters had no impact on the study conclusions.

**Authors’ conclusions**

Decisions on whether to reimburse new therapies should be based on cost-effectiveness rather than simple price comparisons. From the perspective of the Greek National Health Service (NHS), tenecteplase is a cost-effective treatment for acute myocardial infarction (AMI) and is comparable with two thrombolytic agents, alteplase and reteplase, which are already approved for reimbursement. In addition, it has advantages among older patients and those who receive treatment late.

**CRD COMMENTARY - Selection of comparators**

A justification was given for the comparators used. Both of the thrombolytic drugs were approved for reimbursement in the Greek NHS. You should decide if these comparators are representative of current practice for AMI in your own setting.
Validity of estimate of measure of effectiveness
The authors described a systematic identification, selection and synthesis of evidence to form the estimates of effectiveness. In general, the methodology and conduct of the review were satisfactory, although clear inclusion and exclusion criteria were not stated. The use of a systematic review strengthens the validity of the estimates of the model input parameters. In addition, all parameters were varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The decision analysis model used to estimate the benefits was appropriate, as it incorporated a range of potential events related to thrombolytic therapy with transition probabilities taken from published literature. The effectiveness analysis did not disprove the hypothesis that the three treatments had equal effectiveness.

Validity of estimate of costs
The analysis of the costs was performed from the perspective of the Greek NHS. It appears that all the relevant categories of costs and costs have been included in the analysis. The costs were reported separately to other model parameters, but the resource use quantities were not specified. In addition, many of the costs, particularly those for adverse events associated with thrombolysis, were presented in an aggregated manner. This will limit the reproducibility of the study in other settings. A sensitivity analysis was conducted on all of the model input parameters, including the costs, but no justification was given for the ranges used. The costs were treated stochastically. A probabilistic sensitivity analysis was also undertaken, although the authors did not justify their assumptions of the distributions. Cost-effectiveness acceptability curves were presented for the sub-group analyses. The in-hospital resource use and cost data were derived from electronic patient records. However, the cost of post-discharge treatment was based on expert opinion and it was unclear whether the values used were appropriate. Discounting was applied at an appropriate rate to the costs and the benefits, which was correct given the time horizon of the analysis. The cost data were reported for a single specified price year.

Other issues
The authors did not compare their findings with those from other studies, so it is not known how far their results agreed with those of published studies. They commented that a direct comparison of the three drugs in a randomised controlled trial was not available. In terms of the issue of the generalisability of the results to other settings, the authors emphasised that their findings related to the Greek NHS hospital setting only. In general, the authors do not appear to have presented their results selectively. However, they failed to report the statistical tests used and the values of the significant differences observed between the therapies for the cost and health outcome variables in the sub-group analysis. The authors’ conclusions reflected the scope of the analysis. They reported as limitations of their analysis, general issues with modelling studies, the lack of quality of life adjustments to benefits, and lack of a societal perspective. However, they followed standard recommendations to limit bias, and argued that the three treatments were unlikely to differ in terms of quality of life.

Implications of the study
The authors stated that, on the basis of the demonstrated cost-effectiveness, tenecteplase should be added to the positive drug list and reimbursed in the Greek NHS. They recommended that further research adopts a societal perspective for the analysis, and that a comparison be undertaken between thrombolysis and angioplasty.

Source of funding
Funded by Boehringer Ingelheim Greece (the manufacturer of tenecteplase).

Bibliographic details
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Clinical Trials as Topic /economics; Cost-Benefit Analysis; Drug Costs /statistics & numerical data /trends; Female; Fibrinolytic Agents /economics /therapeutic use; Greece /epidemiology; Humans; Male; Middle Aged; Models, Economic; Myocardial Infarction /drug therapy /economics /mortality; Plasminogen Activators /economics /therapeutic use; Recombinant Proteins /economics /therapeutic use; Survival Rate /trends; Tissue Plasminogen Activator /economics /therapeutic use; Treatment Outcome

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