Costs and effects of c7E3 in high risk PTCA patients: an indirect analysis for the Netherlands

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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
Use of a monoclonal antibody Fab fragment (c7E3), a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor, in patients with unstable angina or high risk percutaneous coronary angioplasty (PTCA) in order to reduce the frequency of clinical restenosis.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with unstable angina, recent or evolving myocardial infarction, or high-risk angiographic morphology.

Setting
Hospital. The economic study was carried out in Rotterdam, The Netherlands using effectiveness data from the EPIC study in the USA.

Dates to which data relate
The effectiveness data corresponded to the EPIC study enrolment which began on 26 November 1991, and ended on 18 November 1992 with a 6-month follow-up period. The resource use data corresponded to patients treated between 1992 and 1994. The price year was not clearly reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken on a different patient sample from that used in the effectiveness analysis, employing the volume of events from the EPIC study.

Study sample
No power calculations were reported. A total of 2,099 patients was included in the study, and were randomized to receive c7E3 bolus and a 12 hour infusion (bolus plus infusion) (n=708); c7E3 bolus and placebo infusion (bolus) (n=695); or placebo bolus and placebo infusion (placebo) (n=696).
Study design
A multicentre, double-blind, randomized controlled trial, carried out in 56 participating centres. The duration of follow-up was 6 months. All but 21 of the 2,099 patients had their follow-up survival status determined (99% of complete follow-up). Randomisation was conducted by a telephone call to a coordinating centre and was stratified by study site and whether the patient was having an acute myocardial infarction. All events were reviewed by an independent clinical endpoints committee, which remained blinded to treatment and required consensus of at least two reviewers for classification.

Analysis of effectiveness
It was reported that most comparisons were made based on intention to treat. The primary endpoint was the 30-day composite incidence of death from any cause, MI, coronary artery bypass surgery, repeat percutaneous coronary angioplasty (PTCA), or need for an endoluminal stent or insertion of an intra-aortic balloon pump to treat ischaemia. The primary endpoint for 6 month outcome was the composite of death, nonfatal MI, or the need for a repeat revascularisation (PTCA, coronary artery bypass surgery, or both). The risk of bleeding was also considered. There were no significant differences by treatment assignment in terms of the baseline features of the patients who had a successful initial procedure.

Effectiveness results
By 30 days, 12.8% of placebo bolus/placebo infusion patients had experienced a major ischaemic event (death, MI, urgent revascularisation), compared with 8.3% of c7E3 bolus/c7E3 infusion patients, yielding a 4.5% difference (35% reduction, p=0.008). At 6 months, the absolute difference in patients with a major ischaemic event or elective revascularisation was 8.1% between placebo bolus/placebo infusion and c7E3 bolus/c7E3 infusion patients (35.1% versus 27.0%; 23% reduction p=0.001). The c7E3 bolus/placebo infusion group had an intermediate outcome which was not significantly better than that of the placebo bolus infusion group. Patients receiving c7E3 bolus only, or c7E3 bolus/c7E3 infusion, had a significant increase in bleeding complications in the first 48 hours, with an approximate doubling of packed red-blood-cell transfusion rate (placebo bolus/placebo infusion 7%, c7E3 bolus/placebo infusion 14%, c7E3 bolus/c7E3 infusion 17%, p<0.001).

Clinical conclusions
These results extend the benefit of c7E3 bolus/c7E3 infusion from reducing abrupt closure and acute-phase adverse outcome to a diminished need for subsequent coronary revascularisation procedures.

Measure of benefits used in the economic analysis
The benefit measures were patients without ischaemic events and patients without ischaemic events and major bleeding.

Direct costs
Discounting of costs was not carried out due to the short time frame of the study. Quantities of resource use were not reported separately from the costs. The costs measured were those associated with inpatient care, laboratory tests, therapeutic and diagnostic procedures both within the cardiology department and other areas of the hospital, for events occurring during a 6-month post-treatment period. The boundary adopted was the hospital. A group of 119 patients who had previously participated in the HELVETICA trial or in the CAPTURE study (both studies having selection criteria and complications similar to the EPIC study) was used to estimate the marginal costs per event. Costs were computed by linking the various events to estimates of costs. Unit costs were mainly based on the internal cost information of a university hospital in the Netherlands. The Dutch tariffs were used for some diagnostic and therapeutic procedures. The price year was not clearly reported.

Indirect Costs
Not considered.
Sensitivity analysis
A set of one-way sensitivity analyses was performed by altering cost and effect parameters. Cost-effectiveness ratios were also calculated for different patient subgroups.

Estimated benefits used in the economic analysis
The rate of survival without ischaemic events at 6 months was 73.02% for the intervention (bolus plus infusion c7E3), and 64.94% for the control group (the placebo group). The rate of survival with neither ischaemic events nor bleeding was 65.49% for the intervention versus 62.80% for the control. The option of using bolus c7E3 only was not considered in the economic analysis since the main effectiveness results for this group were not significantly different from the placebo group.

Cost results
The average cost per patient was Dfl 23,036 for the intervention (bolus plus infusion c7E3) versus Dfl 22,613 for the placebo.

Synthesis of costs and benefits
The average cost per (surviving) patient without incidence of ischaemic events at 6-month follow-up and the incremental cost per additional (surviving) patient without incidence of ischaemic events at 6-month follow-up, relative to the placebo, were the cost-effectiveness measures used in the synthesis of costs and benefits. These outcomes were also calculated taking into account the incidence of bleeding complications. The average cost-effectiveness for survivors without any ischaemic events was Dfl 31,547 for the intervention versus Dfl 34,821 for the placebo. The incremental cost-effectiveness ratio was Dfl 5,235. The average cost effectiveness ratios for patients surviving without ischaemic events or bleeding were Dfl 35,174 (intervention) and Dfl 36,011 (placebo). The corresponding incremental cost-effectiveness ratio of the intervention was Dfl 15,685. The sensitivity analysis showed the relative robustness of the study results to changes in cost and effect parameters. The sensitivity analysis performed in terms of patient subgroups suggested that, by careful choice of patients, and by a better understanding or by better taking account of the interactions between body weight and heparin, an even better cost-effectiveness profile of c7E3 could be achieved.

Authors' conclusions
c7E3 can be recommended as a cost-effective therapy to reduce ischaemic events in patients undergoing high risk PTCA, particularly in patients with unstable angina or evolving infarction (rescue or direct PTCA).

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparator (placebo in the absence of an established yardstick) is clear.

Validity of estimate of measure of benefit
The study results are likely to be internally valid given the fact that the benefit results were based on a large multicentre, double-blind, randomized clinical trial.

Validity of estimate of costs
The quantities of resource use were not clearly reported, although, with the exception of the price year, adequate details of cost estimation were given. No important direct medical cost items appear to have been omitted although the authors noted the importance of measuring indirect costs and costs related to other areas of health care.
**Other issues**
The conclusions reached by the authors appear justified given the uncertainties in the data. It should be noted that the study evaluated costs by applying prices in The Netherlands to resource use data from a US trial, while the generalisability of the results to the former and to other countries needs to be further discussed. Regarding the generalisability of the effectiveness results from the USA to the Netherlands, the authors noted that the prevalence of PTCA in The Netherlands is around half that in the USA. Appropriate comparisons were not made with others studies. The results were not presented selectively.

**Implications of the study**
When additional research is initiated, it would be worthwhile to incorporate quality of life measures in the measurement of the potential harms and benefits. Additional studies are required to elucidate the problem of avoiding bleeding complications and to define the optimal dose-body weight relationship for both c7E3, heparin, and the combination of both agents, alone and combined. In addition, a study employing a broader perspective than that of the hospital is needed.

**Bibliographic details**

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