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# Costs and effects of c7E3 in high risk PTCA patients

## An indirect analysis for The Netherlands

B. A. VAN HOUT AND M. L. SIMOONS

*Institute for Medical Technology Assessment, Erasmus University Rotterdam, The Netherlands*

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*A cost effectiveness study is presented on the use of c7E3 in high risk patients undergoing percutaneous coronary angioplasty (PTCA). The results from the EPIC study have been combined with cost data from The Netherlands.*

*The study took account of the number of survivors without ischaemic events, and the number with neither ischaemic events nor bleeding (both measured after 6 months). It is estimated that the initial costs of c7E3 and the additional costs due to the increased risk of bleeding are almost entirely counterbalanced by the savings, as a result of fewer myocardial infarctions and revascularizations. The additional costs per additional patient without ischaemic events are approximately DFL 5235. The additional costs per additional patient with neither ischaemic events nor bleeding are estimated at DFL 15 685. Both figures are less than the average for similar procedures without c7E3. Sensitivity analysis supports the conclusion that c7E3 treatment is efficient. However, cost effectiveness could be further improved if patients are carefully selected.*

### Introduction

Recently, favourable results have been published with respect to the efficacy and safety of the use of c7E3, a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor, in patients with unstable angina or high risk coronary angioplasty[1–3]. The EPIC study, a prospective, randomized, double-blind trial, demonstrated a significant 35% reduction in the combined endpoints: death, myocardial infarction and urgent revascularization at one month. In addition, the 6-month follow-up showed a sustained benefit in terms of a decreased need for revascularization. Despite these favourable results, caution seems required before they can be extrapolated to standard clinical practice, because although the patient group was carefully selected c7E3 treatment was associated with an increase in the number of bleedings. Furthermore, treatment with c7E3 is costly. In The Netherlands, the drug is now commercially available at DFL 2250 (approximately $1500) per patient. Currently it could not be used on a large scale in hospitals, without exceeding their budgets. Thus structured information is necessary so that the balance between costs and benefits can be maintained.

Economic evaluation aims to provide such a balance. Depending on the outcome, a distinction can be made between cost-benefit analysis, costs-effectiveness analysis and cost utility analysis. In the latter, effects are integrated and measured, combining survival and quality of life (quality-adjusted life years gained, healthy years equivalents). In a cost-effectiveness analysis, effects are measured in terms of life years gained, lives saved or by some other measure. In a cost-benefit analysis, both costs and effects are expressed in terms of money[4].

*Correspondence*: Ben A. van Hout, Institute for Medical Technology Assessment, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

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Since health care varies from country to country, assessment of costs and effects should be based on trials from the country requiring the information. Unfortunately, while requests for additional budgets have already been submitted in the Netherlands, no structured large scale data are available. Accordingly, in order to support decisions in The Netherlands, an indirect analysis has been carried out by combining the efficacy results from the EPIC study with patient-specific data on costs from the Thorax Centre in Rotterdam. The analysis can best be characterized as a cost effectiveness analysis from the hospitals' perspective. No other areas of health care or non-medical costs have been included. The analysis is restricted to 6 months.

### Methods

#### THE EPIC STUDY

The EPIC study is a prospective, randomized, double-blind, placebo-controlled trial of 2099 patients at 56 centres. Patients were allocated to three treatment arms: 708 patients received c7E3 bolus and a 12 h infusion (bolus plus infusion); 695 patients received c7E3 bolus and placebo infusion (bolus) and 696 patients received placebo bolus and placebo infusion (placebo).

The primary endpoint of the trial includes any of the following events over the first 30 days after randomization: death from any cause, non-fatal myocardial infarction, emergency coronary artery bypass grafting (CABG), emergency PTCA, stent placement because of treatment failure, balloon-pump insertion to relieve refractory ischaemia. In addition, the risk of bleeding was taken into account, with a distinction being made between major, minor and insignificant bleedings. The first publication on the EPIC study comprises results of the first 30 days after treatment[1]. The second paper presents the results of the 6 months follow-up[2].

EFFECTS

The analysis of cost effectiveness is based on the assumption that the results from the EPIC study can be related to The Netherlands. In the EPIC study, c7E3 was significantly effective in decreasing the number of myocardial infarctions and re-PTCAs, and the number of CABGs was reduced. Unfortunately, c7E3 also increased the risk of bleeding. Thus, c7E3 is associated with beneficial as well as harmful effects. The standard technique used to assess both is an analysis of the quality of life of the patients. However, no such data have been gathered and so another approach has been followed. Noting that no systematic angiographic follow-up was performed in EPIC, one may assume that the revascularization procedures were driven by complaints (recurrent ischaemia) and that therefore the number of ischaemic events (including myocardial infarctions) could be used as a proxy for the quality of life of the patients. Consequently, it may be possible to measure the effects as a combination of various events, expressed as 'event-free survival'. Two definitions of event-free survival were introduced. The first was defined as the percentage increase in the number of patients surviving 6 months without ischaemic events. The second was the percentage increase in the number of patients surviving 6 months with neither ischaemic events nor major bleeding.

COSTS

Costs were calculated by linking the various events to estimates of cost. The marginal costs per event were estimated on the basis of all hospital costs from 119 patients treated in the Thoraxcentre of the University Hospital Dijkzigt between 1992 and 1994. These patients previously participated in the HELVETICA trial or in the CAPTURE study, both studies having patient selection criteria and complications similar to the EPIC study.

The costs per patient were estimated by multiplying resource used with unit costs. Four components were taken into account. The first three concern (1) in-hospital days, distinguishing between intensive care, coronary care and non-intensive/non-coronary care (2) laboratory tests and (3) all therapeutic and diagnostic procedures within the department of cardiology. The fourth component concerns the remaining diagnostic and therapeutic procedures.

For the first three, component unit cost estimates were based on the internal cost information system of the University Hospital Dijkzigt, applying a similar approach as in former studies[5,6]. For the last component, Dutch tariffs were used.

After estimation of the costs per patient, a stepwise procedure was followed to estimate the marginal costs of each event. First, the costs of a single PTCA without any additional events were estimated. Thereafter, the costs of CABG were estimated by subtracting the average costs of a PTCA from the average costs of patients who also had a CABG. The same procedure was followed for bleedings, for re-PTCAs and a similar procedure was applied with respect to myocardial infarctions.

COST EFFECTIVENESS

The estimates of costs were combined with those of effects to find out whether treatment with c7E3 is cost effective. In the absence of an established yardstick, the marginal cost effectiveness ratio was compared with the average cost effectiveness ratio. The average cost effectiveness ratio was defined as the costs of therapy divided by the effects of therapy. The marginal cost effectiveness ratio was defined as the difference in costs between two therapies divided by the difference in effects. c7E3 treatment could be labelled cost effective, or efficient, if the average cost effectiveness ratio of c7E3 treatment was smaller than the average cost effectiveness ratio of placebo treatment. This is equivalent to a marginal cost effectiveness ratio, wherein c7E3 compared with placebo is lower than the average cost effectiveness ratio of the placebo.

SENSITIVITY ANALYSIS

Finally, a sensitivity analysis was performed to assess whether other assumptions would lead to other conclusions and whether subgroups of patients might be identified for whom different conclusions should be drawn.

## Results

EFFECTS

The results from the EPIC study for both definitions of efficacy are presented in Table 1. The estimates were obtained by combining the 1- and 6-month results published in two major articles[1,2] and presented in the papers by Coller and Califf in this issue. It is noted that to be able to combine the figures, the assumption had to be made that the percentages published in Table 2 (taken from reference [2]) concern all patients and not just those mentioned in the Table. If this assumption were not made, the results from both papers could lead to different numbers of myocardial infarctions and deaths during the first 30 days! To prevent double counting, account was taken of the bleeding that occurred during bypass surgery, and it was assumed that all 'other' major bleeding occurred independently of other procedures.

The data in Table 1 confirm that a bolus plus infusion is superior to both other treatment options. Therefore, 'bolus

*Table 1 Effectiveness measures as drawn up for the EPIC study*

| | Survival with no ischaemic events (%) | | |
|---|---|---|---|
| Time | Placebo | Bolus c7E3 | Bolus + infusion c7E3 |
| 0 | 100·00 | 100·00 | 100·00 |
| 2 days | 90·37 | 91·65 | 92·23 |
| 30 days | 84·20 | 87·63 | 88·28 |
| 6 months | 64·94 | 67·34 | 73·02 |

| | Survival with neither ischaemic events nor bleeding (%) | | |
|---|---|---|---|
| Time | Placebo | Bolus c7E3 | Bolus + infusion c7E3 |
| 0 | 100·00 | 100·00 | 100·00 |
| 2 days | 88·88 | 88·03 | 87·48 |
| 30 days | 81·41 | 80·69 | 79·17 |
| 6 months | 62·80 | 62·01 | 65·49 |

*Table 2 Costs after 6 months*

| | Volume of events | | Marginal unit costs | Costs per patient | |
|---|---|---|---|---|---|
| | Placebo | c7E3 | | Placebo | c7E3 |
| Initial PTCA | 100·00% | 100·00% | 14 281 | 14 281 | 14 281 |
| c7E3 | 0·00% | 100·00% | 2250 | 0 | 2250 |
| Death | 3·4% | 3·1% | 5159 | 178 | 160 |
| MI | 10·5% | 6·9% | 19 874 | 2084 | 1375 |
| CABG | 10·9% | 9·5% | 29 882 | 3263 | 2828 |
| PTCA | 20·8% | 14·4% | 12 796 | 2666 | 1844 |
| Coronary bleeding | 3·3% | 3·7% | 2131 | 70 | 78 |
| 'Other' bleeding | 3·3% | 10·3% | 2131 | 70 | 220 |
| Average costs per patient | | | | 22 613 | 23 036 |

only' was not used clinically. Accordingly, this option was not addressed in the cost effectiveness analysis.

COSTS

The costs after 6 months, including the marginal costs per event, are presented in Table 2. The costs of the initial PTCA without complications were estimated on the basis of 70 patients, as described in the Methods section. The costs of bleeding were estimated using the data from 20 patients, the costs of a re-PTCA on the basis of 17 patients and the costs of CABG on the basis of eight patients. Six patients developed myocardial infarction, of whom two patients also underwent PTCA and one CABG. The costs of dying have been estimated independently and have been set at 7 days in hospital. The number of patients used to assess these costs are relatively small. Nevertheless the results were in the same order as estimates published recently[7–11]. Only the costs of bleedings seem relatively low. This may be explained by the absence of patients in our database who needed long-term intensive care for such complications.

It is apparent that a substantial part of the additional costs that arose due to the use of c7E3 and the associated bleeding complications were compensated for by savings as a result of a decrease in revascularization procedures and myocardial infarctions. After 6 months the initial difference of DFL 2250 decreased to DFL 423 per patient.

COST EFFECTIVENESS

From the above results, it may be concluded that the use of c7E3 is not expected to be cost saving within the first 6 months. Thus, the increase in costs should be weighed against the increased effectiveness. One way to demonstrate this is to compare the average costs per effect and to calculate the marginal cost effectiveness ratios (Table 3). The additional costs per additional patients without ischaemic events were estimated at DFL 5235, while the average costs per patient without c7E3 were DFL 34 821. Moreover, it appears that when bleeding complications are taken into account, the marginal costs effectiveness ratio of using c7E3 was below the average cost effectiveness ratio without c7E3. Both results support the conclusion that c7E3 in high risk PTCA patients represents an efficient treatment option. This implies that, if a hospital has a fixed budget and if it wants to maximize one of the two outcome measures introduced here, treatment with c7E3 leads to a better results than treatment without c7E3.

SENSITIVITY ANALYSIS

The conclusion that treatment of high risk PTCA patients with c7E3 is efficient is conditional on the correctness of all underlying estimates and assumptions. To analyse to what extent the conclusions depend on the underlying assumptions, all estimates have been changed. In Table 4 the cost-effectiveness ratios are presented as if all estimates of costs were increased by 20% and as if all differences in effects were subsequently decreased by 20%. The largest differences from the baseline are seen when the estimates concerning myocardial infarctions and re-PTCAs are changed. This implies that the estimates are most sensitive to these two variables. Overall, the changes do not affect the conclusion that c7E3 offers an efficient treatment option in the sense that the marginal cost effectiveness ratio is under the current average.

Additionally, when it was noticed that the estimate of the costs of bleeding complications was relatively low, a calculation was made to show how high the costs of bleeding complications needed to be to show c7E3 in an inefficient light. This was calculated as DFL 9863 when bleeding complications were included in the outcome measure and at DFL 38 619 when bleedings were not included in the outcome

*Table 3 Average and marginal cost effectiveness ratios*

| | Placebo | c7E3 | c7E3 versus placebo |
|---|---|---|---|
| Costs | 22 613 | 23 036 | 423 |
| % without ischaemic events | 64·94% | 73·02% | 8·08% |
| % without ischaemic events or bleedings | 62·80% | 65·49% | 2·70% |
| Costs per survivor without ischaemic events | 34 821 | 31 547 | 5235 |
| Costs per survivor without ischaemic events or bleedings | 36 011 | 35 174 | 15685 |

*Table 4 Univariate sensitivity analysis*

| | Costs per additional survivor without ischaemic events | | Costs per additional survivor without ischaemic events or bleedings | |
|---|---|---|---|---|
| | Costs + 20% | Effects − 20% | Costs + 20% | Effects − 20% |
| Death | 5192 | 5310 | 15 555 | 16 065 |
| MI | 3480 | 7441 | 10 427 | 25 009 |
| CABG | 4158 | 6472 | 12 458 | 20 256 |
| PTCA | 3200 | 8160 | 9587 | 30 807 |
| Coronary bleeding | 5255 | 5216 | 15 743 | 15 627 |
| 'Other' bleeding | 5605 | 4866 | 16 792 | 10 568 |

*Table 5 Marginal cost effectiveness ratios per subgroup*

| Group | Costs per additional survivor without ischaemic events | Costs per additional survivor without ischaemic events or bleedings |
|---|---|---|
| Average | 5235 | 15 685 |
| <76·8 kg | 5949 | 23 877 |
| 76·8–89·9 kg | 2092 | 2890 |
| >89·9 kg | −1604 | −2158 |
| Unstable angina or MI | 1263 | 1909 |
| High risk anatomy | 7243 | 18 994 |

measure. Thus, overall, it may be concluded that c7E3 is cost effective and robust, with respect to alternative estimates.

Finally, attention must be drawn to five subgroups. The first three concern a breakdown of patients according to their weight, the fourth patients with unstable angina or MI at entry. The fifth are patients with high risk anatomy. For all these groups, differences are published concerning the composite endpoints and the number of blood transfusions during the first month after randomization. Assuming that the number of blood transfusions reflects the differences in bleeding and using the published information about the other event rates, the outcome measures during the first month could be recalculated. Additionally, assuming that no other differences occur after the first month, the events over the first 6 months could be calculated. By multiplying the events with the costs per event, estimates of total costs were obtained and group-specific cost effectiveness ratios were estimated (Table 5). The most favourable results were obtained in the group of patients above 90 kg. For this group, characterized by less bleeding complications, savings were expected. The results suggest 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 can be reached.

## Discussion

While the favourable results from various trials may create optimism among patients, cardiologists and the pharmaceutical industry, hospital administrators may not respond so optimistically when confronted with the budgetary consequences. Every patient treated with c7E3 will cost an additional DFL 2250 and, depending on the budgetary constraints, choices have to be made. In order to inform the relevant protagonists in the decision process an economic evaluation has been carried out combining the results from a trial carried out in the U.S.A. with costs from The Netherlands. It is apparent that treatment with c7E3 is expected to increase expenditure but also that it will be an efficient choice when resources are scarce.

In the analysis, a number of assumptions have been made. Most notably, it has been assumed that the results from the EPIC trial can be reproduced in The Netherlands. This assumption may not be correct, especially when certain treatment decisions affect the costs and effects. For example, it should be appreciated that the average number of PTCAs per 100 000 citizens is between 115 and 143 in the United States while it is only about 70 inThe Netherlands[12]. However, it seems realistic to assume that once a decision to perform PTCA has been made procedures and follow-up will be similar between the two countries.

A second concern is the definition of effectiveness. The analysis includes revascularization procedures and bleeding complications in the outcomes measure without any distinction with respect to the severity of the various events. This can only be labelled as a very rough approach. The question may be raised whether the emergency procedures during the first 24 h should be included in the outcome measure. However these procedures, which might be better labelled as an input rather than as an output measure, have already been included in the calculation of costs. Thus, double counting may occur in favour of the use of c7E3. However, the same is true with respect to most bleeding complications and taking these into account is unfavourable as regards the use of c7E3. Therefore, it is assumed that the combination of both outcome measures, with and without bleeding complications, does allow for a

balanced view. However, especially when additional research is initiated, it would be worthwhile to incorporate quality of life measures in the assessment of the potential harms and benefits.

A third concern may be the selection of patients to be treated with c7E3. The sub-group analysis shows that some patients benefit more and others less. Greatest benefit is achieved in patients with unstable angina or myocardial infarction, whether direct or rescue PTCA. Additionally, both univariate and multivariate analyses revealed low body weight to be an independent prediction of bleeding risk in EPIC (see also Califf in this issue). Due to this increased bleeding risk, costs per additional survivor without ischaemic events or bleeding were high in patients less than 77 kg! It should be appreciated that patients in the U.S.A. are on average 10 kg heavier that in The Netherlands! However, while administration of c7E3 was related to body weight, heparin was given in fixed dosages. It is possible that the combined effect of c7E3 and heparin resulted in excessive bleeding risk in patients of low body weight. In order to avoid bleeding complications it may be prudent to adjust heparin dosing in combination with c7E3 in patients with body weight below 77 kg. Additional studies are required to elucidate this problem and to define the optimal dose–body weight relationship for both c7E3, heparin and the combination of both agents.

As a consequence, it is possible to improve efficiency by more restricted use of c7E3, while continued research is warranted to define the potential gains and harms of c7E3 more specifically. It may thus be worthwhile to follow patients more closely, and also to assess the costs in other areas of health care and the costs due to absence from work. These costs have not been taken into account in the present analysis, while it may be expected that these are positively related to the costs of the various events. In consequence, it might be expected that broadening the perspective would improve the cost effectiveness of c7E3.

At present, 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). c7E3 should not be used yet in patient groups other than those included in EPIC, since the efficacy of therapy in those patients is uncertain, and costs are not negligible.

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