

Modelling the cost-effectiveness of cardiac interventions: the case of sirolimus-eluting stents

NEIL HAWKINS, MARK SCULPHER, MARTIN ROTHMAN

Abstract

This article aims to provide a primer on decision modelling to assess the cost-effectiveness of interventions in cardiology. The paper uses a cost-effectiveness model developed to compare alternative coronary stents. This decision analytic model assesses costs to the UK health service and health benefits in terms of quality-adjusted life-years (QALYs). Data were taken from a range of sources, including 12-month follow-up data from three important double-blind randomised controlled trials: RAVEL, SIRIUS and E-SIRIUS. Methods are employed to show the uncertainty in cost-effectiveness.

Sirolimus-eluting stents were compared to 'bare metal' stents in constructing this decision model. The patients included were those individuals with stable coronary disease randomised to the three trials.

The main outcome measures were: mean QALYs, mean health service costs, incremental cost per additional QALY, and the probability that sirolimus-eluting stents are more cost-effective than bare metal stents.

Mean QALY gains per patient from the sirolimus-eluting stent range from 0.017 to 0.017 over 12 months. Although the list price of the sirolimus-eluting stent is £617 more than the bare metal stent, its additional total mean cost per patient, including 'cost offsets' from a lower rate of subsequent events, ranges from £53 to £166. The incremental cost of the sirolimus-eluting stent per additional QALY ranges from £3,181 to £15,198. The probability that the sirolimus-eluting stent is less costly than the bare metal stent ranges from 0.13

to 0.34. If the health service is willing to pay up to £40,000 per additional QALY, the probability of the newer stent being the more cost-effective ranges between 0.8 and 1.0. These results are sensitive to assumptions about the price differential between the two forms of stent.

Cost-effectiveness analyses based on models are used increasingly as a basis for decision making. It is essential that these models are developed with clinical input regarding appropriate assumptions and interpretation of evidence.

Key words: decision analysis, cost-effectiveness, quality-adjusted life years, coronary stents.

Br J Cardiol (Acute Interv Cardiol) 2005;**12**:AIC 83–AIC 91

Introduction

Healthcare systems in most developed countries are increasingly interested in whether new healthcare interventions represent value for money, as well as improve patients' health. The National Institute for Health and Clinical Excellence (NICE) in England and Wales is an example of an organisation charged with assessing the cost-effectiveness, as well as clinical effectiveness, of healthcare technologies.¹ In the field of cardiology, new medical technologies are rapidly developing, and it is to be expected that healthcare systems will look closely at their effectiveness and cost-effectiveness. NICE has considered a number of cardiac interventions, including coronary stents and implantable cardioverter defibrillators, as well as pharmaceutical products in the field such as the glycoprotein IIb/IIIa receptor antagonists and clopidogrel (see www.nice.org.uk).

Technology assessments undertaken for bodies such as NICE often have limited evidence to draw upon. For some technologies (e.g. new diagnostic tests), there may be no trial data upon which to base an assessment. For the purpose of addressing issues of cost-effectiveness, trials that were designed to assess the efficacy and safety of interventions often have limitations. These include short follow-up, which precludes the estimation of changes in quality-adjusted life expectancy, failure to compare directly the new technology against current clinical practice and the absence of the measurements necessary for a full economic assessment, including impact on health-related quality of life and costs.² These features of the evidence base relating to new inter-

Centre for Health Economics, University of York, Heslington, York, YO10 5DD.

Neil Hawkins, Research Fellow

Mark Sculpher, Professor of Health Economics

Barts and the London NHS Trust, The London Chest Hospital, Bonner Road, London, E2 9JX.

Martin Rothman, Consultant Cardiologist

Correspondence to: Professor M Sculpher
(email mjs23@york.ac.uk)

ventions have resulted in the use of decision modelling techniques to estimate cost-effectiveness. Such methods incorporate a wide range of existing data rather than relying solely on information from clinical trials. Decision models represent the various clinical pathways along which patients may pass following alternative treatments and quantify the probability of a patient following each pathway. Conditional on a patient following a given pathway, the range of possible costs and health-related outcomes that a patient may experience is defined. In analysing the model, the objective is to calculate the expected (equivalent to mean) costs and health outcome of competing interventions together with the uncertainty in those estimates. Detailed introductions to decision modelling can be found elsewhere.³

A growing number of modelling studies are being undertaken on cardiac interventions to inform decisions about their value for money.^{4,5} It is important that these analyses characterise the clinical issues associated with the alternative treatments as accurately as possible, so it is crucial for clinicians to be fully involved in their development. This requires an understanding of the methods used in these studies. The aim of the paper is to provide insight into how decision models are developed and, in particular, how the results and the uncertainty surrounding them are presented. The paper uses a cost-effectiveness model developed to compare sirolimus-eluting stents versus 'bare metal' stents using data from a range of sources including three important double-blind randomised controlled trials: the randomised study with the sirolimus-eluting Bx Velocity™ balloon expandable stent (Cypher®) in the treatment of patients with *de novo* coronary artery lesions (RAVEL),⁶ the sirolimus-eluting stent in *de novo* native coronary artery lesions trial (SIRIUS)⁷ and the European multi-centre, randomised, double-blind study of the sirolimus-coated Bx Velocity™ balloon-expandable stent in the treatment of patients with *de novo* coronary artery lesions (E-SIRIUS).⁸ These trials provide strong evidence that sirolimus-eluting stents reduce revascularisation rates relative to bare metal stents, but are they cost-effective given their additional acquisition cost?

Methods

Study question

The purpose of the model is to assess the differential impact of sirolimus-eluting and bare metal stents on costs to the UK health service and on patients' survival duration, adjusted for their health-related quality of life (HRQL). In 'base-case' analysis, separate sets of results are presented relating to three relevant patient groups. The groups are defined according to the trials from which the clinical data are largely taken.

The characteristics of these three trials, and of their patients, are summarised in table 1. It can be seen that, in terms of mean age and sex, the trials are similar. There are, however, some differences between the studies: RAVEL had a smaller proportion of diabetics and patients with, on average, shorter lesions; in SIRIUS there was a higher proportion of diabetic patients and, on average, patients had larger diameter vessels and longer lesions; and in E-SIRIUS patients had a combination of characteristics of both RAVEL and SIRIUS, with small vessels and longer lesions.

Table 1. Details of the randomised controlled trials of sirolimus-eluting versus standard stents used to provide data for the cost-effectiveness model. Data relate to all patients in the trials

Trial characteristic	RAVEL ⁶	E-SIRIUS ⁸	SIRIUS ⁷
Sample size	238	352	1,058
Age in years (mean ± SD)	60.7±10.4	62.3±10.9	62.3±11.1
Men (%)	76	71	71
Diabetes mellitus (%)	19	23	26
Multi-vessel disease (%)	30	36	42
Diameter of reference vessel (mm, mean ± SD)	2.62±0.53	2.55±0.37	2.80±0.47
Length of lesion (mm, mean ± SD)	9.58±3.25	15.0±6.0	14.4±5.8

Defining benefits and costs

For the base case analysis, it is assumed that the two types of stent do not differ in their effect on mortality. This can be justified on the basis that coronary restenosis is not *per se* predictive of increased risk of death. This has been shown in randomised trials comparing coronary artery bypass grafting (CABG) and balloon angioplasty⁹ where, despite the significantly increased rate of restenosis following the angioplasty, there is no commensurate elevated mortality risk. Furthermore, Weintraub *et al.* found no differences in six-year mortality between patients with and without restenosis.¹⁰ The model also assumes that differential effects of the alternative stents on further revascularisation, mortality and myocardial infarction (MI) only occur during the period of measurement in the relevant trial in which the effects are estimated (i.e. 12 months).

The measure of health benefit used is quality-adjusted life years (QALYs). Given the assumption of no differential effect on mortality, these will reflect the decrement to HRQL associated with the symptoms that prompt further revascularisation. To implement this, only further revascularisations driven by patients' symptoms (rather than by angiography alone) are included to reflect the occurrence of such revascularisation in routine clinical practice. It is assumed that, at the onset of symptoms, patients will have to wait before they undergo further revascularisation and, during this period, they will experience the HRQL decrement. After their procedure, they will return to an average HRQL associated with successful revascularisation. HRQL is measured on a 'utility' scale which runs from 0, representing the value of health states considered equivalent to death, to 1, representing good health.¹¹

The cost side of the evaluation includes the additional cost of the sirolimus-eluting stents in the initial procedure, and the full cost of any further percutaneous coronary intervention (PCI) or CABG. The cost of further revascularisation procedures incorporates the cost of a prior angiography, the procedure, drug use

Table 2. Inputs into the cost-effectiveness model taken from the specific trials. Unless otherwise stated, data are events / those at risk (probabilities)*

Input	RAVEL ⁶		E-SIRIUS ⁸		SIRIUS ⁷	
	Sirolimus	Bare metal	Sirolimus	Bare metal	Sirolimus	Bare metal
Stents implanted (mean) [†]	1.03	1.04	1.22	1.19	1.30	1.30
All deaths	2/120 (0.017)	2/118 (0.017)	2/175 (0.011)	1/177 (0.006)	7/533 (0.013)	4/525 (0.008)
Cardiac deaths	0/120 (0.000)	1/118 (0.008)	1/175 (0.006)	1/177 (0.006)	3/533 (0.006)	2/525 (0.004)
Target vessel revascularisation with [‡] :						
- PCI	1/120 (0.008)	18/118 (0.153)	8/175 (0.046)	42/177 (0.237)	40/533 (0.075)	130/525 (0.248)
- CABG	1/120 (0.008)	0/118 (0.000)	1/175 (0.006)	4/177 (0.023)	8/533 (0.015)	16/525 (0.030)
Myocardial infarction	4/120 (0.033)	6/118 (0.051)	8/175 (0.046)	4/177 (0.023)	16/533 (0.030)	18/525 (0.034)

Key: * Where patients experience more than one event, all events are reported here; [†] These mean stent numbers are based on currently available stent lengths rather than those in the trials. This has been estimated using mean lesion lengths in the trials, so no standard errors are presented; [‡] Clinically-driven events only; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

Table 3. Inputs in the cost-effectiveness model taken from non-trial sources and used in all analyses

Input	Value	Source
Unit costs (2003 prices)		
Sirolimus-eluting stent	£1,762*	Cypher™, Cordis Ltd
Bare metal stent	£1,145*	Bx Velocity™, Cordis Ltd
Angiography	£372	NHS Reference Costs ¹²
PCI	£2,984	NHS Reference Costs ¹²
CABG	£6,450	NHS Reference Costs ¹²
Myocardial infarction	£1,055	NHS Reference Costs ¹²
Quality of life weights (mean ± standard deviation)		
Without symptoms	0.84±0.16	ARTS Trial ¹³
With symptoms	0.69±0.20	ARTS Trial ¹³
Waiting times for revascularisation (Days)	196 [†]	Target maximum waiting time in the NHS National Service Framework ¹⁴

Key: * Including value added tax (VAT); [†] Referral from GP to consultant appointment = four weeks, decision to investigate to angiography = three months, decision to do procedure to revascularisation = three months; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

event, all events are included. All three trials showed a marked reduction in revascularisation rates with sirolimus-eluting stents, although rates of death and MI are relatively low.

Unit costs are used to estimate the monetary cost of clinical events (table 3). The costs of the two forms of stent are taken from a manufacturer's 2003 list prices. In practice, hospitals may pay lower prices, and sensitivity analysis is used to explore the implications of price discounts for cost-effectiveness. All other costs are taken from routine NHS sources.

The HRQL associated with and without symptoms is taken from the Arterial Revascularisation Therapies Study (ARTS) Group trial.¹³ This trial used the EuroQol (EQ)-5D instrument at baseline and follow-up. The EQ-5D asks patients to categorise their health, using one of three levels (no problems, moderate problems and severe problems) on five dimensions – mobility, self-care, ability to undertake usual activities, pain and depression/anxiety – thereby defining themselves in one of 245 possible health states.¹⁵ Each of these states has been scored as a utility based on interviews with 3,395 members of the UK public.¹⁶ The mean HRQL score associated with symptoms (0.69) is assumed to apply throughout the period the patient waits for revascularisation. This is taken to be 196 days, which is the NHS' target waiting time and does not distinguish between initial and repeat procedures.¹⁴ When not in need of revascularisation (i.e. when without symptoms), patients' HRQL is assumed to be the same as the mean HRQL in patients undergoing PCI in the ARTS trial one month after revascularisation (0.84).¹³

and hospitalisation. The cost of MI is also incorporated into the analysis.

Data inputs

As with most decision models, the data inputs into the model are taken from several sources (tables 2 and 3). Inputs relating to the number of stents used in the initial procedure are estimated based on the lesions in trial patients and the lengths of stents currently available. Data on the rate of further revascularisations and MIs are taken directly from the RAVEL, E-SIRIUS and SIRIUS trials and based on data collected up to 12-month follow-up (table 2). For trial patients who experienced more than one

Analysis

The expected cost of managing a patient with one of the two types of stent is calculated in a series of steps. The first step involves defining the alternative events that a patient may experience: MI, further revascularisation with PCI and further revascularisation with CABG. The second step is to attach a probability and a cost to each of these events (tables 2 and 3). The probabilities detailed in table 2 allow for the fact that some patients may have two revascularisation procedures. The third step is to

Table 4. The cost-effectiveness of sirolimus-eluting versus standard stents: base-case results using data from the three trials

Input	RAVEL ⁶		E-SIRIUS ⁸		SIRIUS ⁷	
	Sirolimus	Bare metal	Sirolimus	Bare metal	Sirolimus	Bare metal
Total cost	£5,282	£5,116	£5,746	£5,692	£6,033	£5,920
Difference in costs		£166		£53		£113
Total reduction in QALYs	-0.001	-0.012	-0.004	-0.021	-0.007	-0.022
Difference in QALYs		0.011		0.017		0.015
ICER		£15,198		£3,181		£7,461

Key: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life-years

sum the cost of each event weighted by the probability of it occurring. This expected cost is analogous to a mean cost from sampled data and provides the best estimate of the cost that a patient will incur. The expected QALYs associated with the two forms of stent are calculated on a similar basis. Given the base-case assumption of equal mortality with both devices, differential QALYs are simply the difference in quality-adjusted time spent with symptoms.

An important aspect of decision models is how the uncertainty in the estimates of clinical inputs and costs going into the model are reflected in the results. To handle this 'parameter uncertainty', probabilistic sensitivity analysis is undertaken, which involves defining the model inputs as probability distributions rather than as point estimates.¹⁷ This reflects the imprecision of the model inputs which is usually reflected, for example, in terms of confidence intervals. A process known as Monte Carlo simulation is used: this effectively re-runs the model a large number of times, each time randomly picking from the probability distributions representing the parameter uncertainty. In effect, this produces a large number of sets of results. The means of these alternative results are the 'best' (expected) estimate of differential costs and QALYs between the stents. These are used to establish whether one type of stent 'dominates' the other; that is, whether it has higher expected QALYs and lower expected costs. If neither stent dominates, then the incremental cost per additional QALY of the more effective stent – that is, the additional cost divided by the additional QALYs – is calculated. This ratio represents the extra amount the health service would have to pay to generate an additional unit of health for the relevant population. Organisations such as NICE make a judgement regarding whether, compared to other uses of resources, this incremental cost-effectiveness ratio (ICER) represents good value for money.

The variation around that mean result is also important as it shows the uncertainty in cost-effectiveness. This uncertainty is presented using a cost-effectiveness acceptability curve.¹⁸ In our model, the curve shows the probability that sirolimus-eluting stents are more cost-effective than standard stents for a range of levels that the health service might be willing to pay for an additional QALY. NICE has indicated that it is willing to pay £20,000–£40,000 for an additional QALY associated with the

technologies it appraises.¹⁹ Finally, to assess how results might change if the differential price of the stents were different, the model is re-run under alternative price assumptions.

Results

Expected mean results

The expected costs and QALY reductions are shown in table 4, based on data from the three trials. The QALY reductions are based on estimates of decrements in HRQL during the time spent waiting for further revascularisation. As such, they are directly proportional to the subsequent revascularisation rates observed in the trials, which were always lower in patients randomised to sirolimus-eluting stents. The greater QALY advantage for sirolimus-eluting stent patients based on E-SIRIUS data reflects the higher baseline revascularisation rate (i.e. the rate with bare metal stents) in that trial compared with RAVEL, and the greater relative reduction in revascularisations compared with both RAVEL and SIRIUS.

Table 4 also shows that sirolimus-eluting stents result in an additional overall cost to the health service compared to standard stents. This incremental cost ranges from £54, based on E-SIRIUS data, to £166 using data from RAVEL. These added costs are less than the additional acquisition cost of the sirolimus-eluting stent itself because, in each of the trials, the new stent, on average, results in 'downstream' cost savings due to a lower incidence of further revascularisation. The extent of the cost saving with the sirolimus-eluting stent in the three trials is again directly proportional to the reduction in subsequent revascularisations.

Given the higher overall costs but QALY gains associated with sirolimus-eluting stents, it is appropriate to calculate the incremental costs per extra QALY associated with the new stent, and these are also shown in table 4. The lower additional cost and greater QALY gain associated with data from E-SIRIUS results in the incremental cost-effectiveness ratio being lower (£3,181) than those based on SIRIUS (£7,461) and RAVEL (£15,198).

Uncertainty

The expected costs and QALYs in table 4 are, however, measured imprecisely. Figure 1 shows how the uncertainty in cost-effectiveness can be represented in terms of cost-effectiveness accept-

