Decision analytic models, sensitivity analysis and value of information in economic evaluations in health care

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Prof. Dr. Marcel Tanner, Prof. Dr. Heiner C. Bucher und PD Dr. Jean-Blaise Wasserfallen.

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To measure is to know.

If you cannot measure it, you cannot improve it.

Lord Kelvin

Contents

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ABBREVIATIONS

APDRG	All patients diagnosis related groups
BMS	Bare metal stent
CABG	Coronary artery bypass graft surgery
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CHF	Swiss francs
CUA	Cost-utility analysis
DES	Drug-eluting stents
DRG	Diagnosis related group
DVT	Deep vein thrombosis
ENBS	Expected net benefit of sampling
EVSI	Expected value of sample information
EVPI	Expected value of perfect information
EVPPI	Expected value of partial perfect information
HFS	Hip fracture surgery
ICER	Incremental cost-effectiveness ratio
INMB	Incremental net monetary benefit
LYG	Life-year gained
MI	Myocardial infarction
NB	Net benefit
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PES	Paclitaxel-eluting stent
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
QOL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
SES	Sirolimus-eluting stent
THR	Total hip replacement
VBA	Visual Basic for Applications
VOI	Value of information
VTE	Venous thromboembolic event

SUMMARY

Economic evaluations of health care technologies are now commonly carried out to assess the economic value of new pharmaceuticals, medical devices and procedures. The growing number of economic evaluations reflects both widespread interest in economic information for new technologies and the regulatory and reimbursement requirements of many countries. The aim of health economic evaluations is to measure, value and compare the costs and benefits of different health care interventions. To date, *cost-effectiveness analysis* (CEA) and *cost-utility analysis* (CUA) are the two types of economic evaluations that are applied in the vast majority of economic evaluation studies.

Cost-effectiveness estimates in CEAs and CUAs can either be derived from data collected alongside a randomized controlled clinical trial or by means of decision analytic modelling. In recent years, there has been a trend towards increasing incorporation of economic evaluations within randomized controlled trial. Trial-based economic evaluations will be efficient for answering economic questions for diseases or treatments where the bulk of costs derive from primary outcomes that are measured in the trial and for which the quality of life impacts are persistent, and thus can be measured infrequently.

In situations where evidence from a trial is insufficient to address a certain decision problem (e.g. short time horizon of the trial; small sample size), decision analytic modelling provides a structure within which evidence from a range of sources can be directed at a specific decision problem for a defined population and context. Decision analytic models use mathematical relationships to define a series of possible consequences. Based on the inputs into the model, the likelihood of each consequence is expressed in terms of probabilities. Costs and outcomes are linked to each consequence. It is thus possible to calculate the expected costs and expected outcome for different interventions analyzed in the model.

In the first study the cost-effectiveness of extended prophylaxis with fondaparinux of one month versus one week in patients undergoing hip fracture surgery and total hip replacement was analysed. The analysis was based on a

decision tree model that allowed to compare costs from a health care perspective and health effects for both strategies using a time horizon of 30 days and 5 years. In this *cost-effectiveness analysis* the health effect was measured in life-years gained. Depending on the patient population and the time horizon, the extended prophylaxis with fondaparinux was found to be cost-effective or cost-saving (i.e. the extended prophylaxis was more effective and less costly). Uncertainty in various clinical and cost input parameters was explored by univariate sensitivity analysis and showed that reasonable changes in the parameters' values had only a small effect on the cost-effectiveness estimates.

In the second study the cost-effectiveness of risedronate was examined for Swiss osteoporotic women. Several clinical trials and meta-analyses proved the efficacy of risedronate in reducing the number of fractures at the hip, wrist and vertebra. A limitation of the published trials is that the range of the age of the enrolled patients is relatively small and on average around 70 years. From epidemiological data it is well established, however, that for osteoporotic women, the fracture risk is strongly dependent on age. The fracture risk in women who had a previous fracture is further increased compared to the fracture risk in osteoporotic women without a previous fracture. In this study we developed a time-dependent Markov model to examine the cost-effectiveness of risedronate for women who start a 5 year risedronate therapy between 60 and 90 years of age. This cost-utility analysis was carried out from a Swiss health care perspective using a lifetime time horizon. For osteoporotic women or women with severe osteoporosis we found that risedronate treatment is cost-effective. As expected, the cost-effectiveness estimate is influenced by the patients' age and disease severity.

Two chapters of this thesis are based on a cost-utility analysis of 2 drug-eluting stents (the sirolimus- and the paclitaxel-eluting stent; DES) compared to bare metal stents (BMS). Since their approval in 2003, drug-eluting stents have revolutionized the care for patients with acute or symptomatic coronary heart disease. Clinical trials have demonstrated a striking reduction in angiographic restenosis and revascularization rates with drug-eluting stents. As a consequence the majority of coronary interventions are today performed with drug-eluting stents. Although DES are now used for several years, concerns remain about their

long term safety. Given the threefold higher acquisition costs, it was unclear whether DES are cost-effective when compared to BMS. Based on clinical data with 3-year follow-up we developed a Markov cost-utility model to shed light on this question. Both DES under analysis were found to not be cost-effective from a US Medicare payer's perspective. Although revascularisation rates were lower in DES patients, the gain in quality-adjusted life years was very small (for the sirolimus-eluting stent) or negative (for the paclitaxel-eluting stent). Given the uncertainty in the input parameters, the decision uncertainty is large.

In a further study the decision uncertainty was examined in full depth. With expected value of perfect information (EVPI) analysis total decision uncertainty was assessed. EVPI provides the value a rational decision maker should be willing to spend in order to acquire perfect information (i.e. to eliminate parameter uncertainty). Through expected value of partial perfect information analysis the contribution of groups of parameters towards total decision uncertainty was examined. The uncertainty in the cost-effectiveness estimate is largely driven by the uncertainty in the clinical model input parameters. More precise clinical parameter estimates could be derived from a future clinical trial. To assess the value of such a trial, analysis of expected value of sample information was performed. Although the value of a future trial would be enormous, we show diminishing marginal returns and a linear increase in the costs of the future trial per additional patient enrolled into the trial for sample sizes larger than 2000 patients. The optimal sample size was estimated to be 4700 patients for a 3 year time horizon.

To conclude, decision analytic models have a range of uses and are thus an important and powerful tool for economic evaluations in health care. Decision analytic models that incorporate probabilistic sensitivity analysis and closely related expected value of perfect information analysis are best suited to provide decision makers not only with a point estimate for the cost-effectiveness estimate but to quantify in addition decision uncertainty and the value of future research.

ZUSAMMENFASSUNG

Gesundheitsökonomische Evaluationen werden heutzutage standardmässig eingesetzt, um den ökonomischen Wert von neuen Arzneimitteln, medizinischen Geräten und Verfahren zu ermitteln. Die wachsende Anzahl von veröffentlichten gesundheitsökonomischen Evaluationen spiegelt sowohl das weitverbreitete Interesse an ökonomischen Informationen über neue Technologien wider, als auch die Notwendigkeit solcher Daten für die Zulassung und Erstattungsfähigkeit dieser Technologien. Das Ziel der gesundheitsökonomischen Evaluationen ist es, die Kosten und den Nutzen verschiedener Interventionen zu messen, zu bewerten und zu vergleichen. Die in ökonomischen Evaluationen am häufigsten verwendeten Studientypen sind die Kosten-Effektivitäts-Analyse (CEA) und die Kosten-Nutzwert-Analyse (CUA).

Für die CEA und die CUA werden Kosteneffektivitätsschätzer von Daten die in einer randomisierten klinischen Studie erhoben wurden oder mittels eines entscheidungsanalytischen Modells abgeleitet. In den letzten Jahren hat sich ein Trend zur vermehrten Integration von ökonomischen Evaluationen in randomisierte klinische Studien abgezeichnet. Studienbasierte ökonomische Evaluationen sind effizient, wenn ökonomische Fragen für Krankheiten oder Behandlungen beantwortet werden sollen, bei denen der Grossteil der Kosten durch Ergebnisse anfällt, die innerhalb der Studie gemessen werden können und bei denen gleichzeitig die Lebensqualität gleichbleibend ist.

In verschiedenen Situationen (z.B. kurzer Zeithorizont der Studie; kleine Anzahl an Studienteilnehmern) sind Daten von klinischen Studien unergiebig, um bestimmte Entscheidungsprobleme anzugehen. Hier, stellen entscheidungsanalytische Modelle eine Möglichkeit Daten aus verschiedenen Quellen für ein bestimmtes Entscheidungsproblem für eine definierte Population und einen bestimmten Kontext zu synthetisieren. Entscheidungsanalytische Modelle benutzen mathematische Zusammenhänge um die Konsequenzen verschiedener Behandlungsstrategien aufzuzeigen. Durch die Eingangswerte des Modells wird die Wahrscheinlichkeit des Eintretens dieser Konsequenzen durch Wahrscheinlichkeitswerte ausgedrückt. Für jede Konsequenz werden Kosten und

Effekte bestimmt. Dadurch ist es möglich, die erwarteten Kosten und die erwarteten Ergebnisse für verschiedene Interventionen, die mit dem Modell analysiert werden, zu bestimmen.

In der ersten Studie wurde die Kosteneffektivität von verlängerter Fondaprinux-Prophylaxe von einer Woche bis zu einen Monat für Patienten im Rahmen einer Enscheidungsanalyse untersucht, die sich einem chirurgischen Eingriff an der Hüfte unterziehen mussten oder bei denen die Hüfte komplett ersetzt wurde. Für beide Strategien wurden die Kosten aus der Krankenkassen-Perspektive sowie die Gesundheitseffekte bei einem Zeithorizont von 30 Tagen und 5 Jahren analysiert. In dieser *Kosten-Effektivitäts-Analyse* wurde der Gesundheitseffekt anhand gewonnener Lebensjahre gemessen. Abhängig von der Patientenpopulation und vom Zeithorizont war die verlängerte Prophylaxe mit Fondaparinux entweder kosteneffektiv oder kostensparend (d.h. die verlängerte Prophylaxe war gleichzeitig effektiver und günstiger). Mittels univariater Sensitivitätsanalyse wurde die Unsicherheit bezüglich verschiedener klinischer und kostenbezogener Eingangsparameter untersucht. Die Analyse zeigte, dass angemessene Veränderungen der Parameterwerte nur einen kleinen Effekt auf die Kosteneffektivitätsschätzer hatten.

In der zweiten Studie wurde die Kosteneffektivität von Risedronat für osteoporotische Frauen in der Schweiz untersucht. In mehreren klinischen Studien und Meta-Analysen konnte gezeigt werden, dass Risedronat ein effektives Mittel ist, um Frakturraten der Hüfte, des Handgelenks und der Wirbelsäule zu reduzieren. Durch epidemiologische Daten gilt als gesichert, dass das Frakturrisiko stark vom Alter der Patientinnen abhängt. Des Weitern ist das Frakturrisiko derjenigen Frauen mit einer vorausgegangenen Fraktur im Vergleich zu Frauen ohne vorausgegangene Fraktur deutlich erhöht. In dieser Studie wurde ein zeitabhängiges Markovmodell entwickelt, um die Kosteneffektivität einer 5-jährigen Risedronattherapie bei Frauen, die im Alter von 60 bis 90 Jahren mit der Therapie beginnen zu untersuchen. Für osteoporotische Frauen oder Frauen mit schwerer Osteoporose ist die Behandlung mit Risedronate kosteneffektiv. Wie zu erwarten, wurde der

Kosteneffektivitätsschätzer durch das Alter der Patienten und den Schweregrad der Erkrankung beeinflusst.

Zwei Kapitel dieser Dissertation basieren auf einer Kosten-Nutzwert-Analyse von Arzneimittel-freisetzende Stents (Sirolimus- und Paclitaxel-freisetzende Stents; DES) im Vergleich zu herkömmlichen Metallstents (BMS). Seit ihrer Zulassung im Jahr 2003 haben die Arzneimittel-freisetzenden Stents die Behandlung der akuten und symptomatischen koronaren Herzkrankheit revolutioniert. In klinischen Studien konnten beachtenswerte Verminderungen in angiographischen Restenose- und Revaskularisationsraten gezeigt werden. Dieser Ergebnisse haben dazu geführt, dass die Mehrzahl der Koronarinterventionen heutzutage mit Arzneimittel-freisetzenden Stents durchgeführt werden. Trotz des schon mehrjährigen Gebrauchs der DES gibt es jedoch immer noch Bedenken bezüglich ihrer langfristigen Sicherheit. Da zudem die Beschaffungkosten von DES im Vergleich zu BMS rund dreifach höher sind, wird die Kosteneffektivität von DES je nach Modellansatz in der Literatur kontrovers diskutiert. Wir entwickelten basierend auf klinischen Daten mit 3-jährigem Follow-up - ein Markov Kosten-Nutzwert-Modell um die Kosten-Effektivität von CES im Vergleich zu BMS für die US amerikanischen Verhältnisse zu untersuchen. Wir zeigen, dass aus Sicht der US amerikanischen Krankenkasse *Medicare* beide DES nicht kosteneffektiv sind. Obwohl die Revaskularisationsraten bei DES-Patienten niedriger waren, war schlussendlich der Gewinn an qualitätsadjustierten Lebensjahren sehr gering (für den Sirolimus-freisetzenden Stent) oder negativ (für den Paclitaxel-freisetzenden Stent). Aufgrund von hoher Unsicherheit bei den Eingangsparametern war die Entscheidungsunsicherheit in unserem Model jedoch gross.

In einer weiteren Studie wurde deshalb die Entscheidungsunsicherheit durch eine Analyse des *erwarteten Wertes von perfekter Information* (EVPI) weiter untersucht. EVPI bestimmt den Wert, den ein rationaler Entscheidungsträger zu zahlen bereit sein sollte, um perfekte Information zu erhalten (d.h. unter Ausschaltung von Parameterunsicherheit). Mittels einer Analyse des *erwarteten Wertes von partiell perfekter Information* wurde bestimmt, inwieweit einzelne Parametergruppen zur gesamten Entscheidungsunsicherheit beitragen. Die

Unsicherheit der Kosteneffektivitätsschätzer wird grösstenteils durch die Unsicherheit in den klinischen Inputparametern des Modells bestimmt. Präzisere Schätzer für die klinischen Parameter könnten prinzipiell durch eine zukünftige klinische Studie erlangt werden. Der Wert einer solchen Studie wurde durch eine Analyse des *erwarteten Wertes von Stichprobeninformation* ermittelt. Auch wenn der Informationswert einer zukünftigen Studie wichtig ist, zeigt sich bei abnehmendem Grenzertrag pro zusätzlich eingeschlossenem Patienten, den gleichzeitig linear ansteigenden Kosten der zukünftigen Studie bei Stichprobenzahlen von mehr als 2000 Patienten dass die optimale Stichprobenzahl, bei einem Zeithorizont von 3 Jahren 4700 Patienten beträgt.

Wir veranschaulichen, dass entscheidungsanalytische Modell eine Vielzahl von Anwendungen haben, und daher wichtige und nützliche Werkzeuge in gesundheitsökonomischen Analysen darstellen. Entscheidungsanalytische Modelle, welche probabilistische Sensitvitätsanalyse und eine Analyse des erwarteten Wertes von perfekter Information beinhalten, erlauben Entscheidungsträgern zudem die Entscheidungsunsicherheit und den Wert zukünftiger Forschung im Entscheidungsprozess zu berücksichtigen.

CHAPTER 1: INTRODUCTION

The introduction of new pharmaceuticals, medical devices or procedures in the last decades has lead to unprecedented improvements in health outcomes in many the northwestern hemisphere (1). Unfortunately the majority of advances in medical technology comes at higher costs than the currently used technologies, or add new costs to the health care budget for previously unavailable treatments (2; 3). As a consequence, spending on health care has been rising in many countries of the western world at a faster rate than the increase in the gross domestic product (4; 5).

Economic evaluations are now routinely used in many countries for the evaluation of health technologies and for decision making on reimbursement policy (6-8). This development has favored very important methodological advances in economic evaluation for health care decision making (9-12). The general concepts of modern economic health care evaluations and some of the advanced concepts are presented in this chapter and applications are shown in the following chapters.

The decision problem

In its simplest form, economic evaluations compare two treatments strategies against each other on the basis of expected costs (*C*) and expected health outcomes (*E*)(13). The ratio of the expected cost difference (incremental costs) over the expected difference in health effects (incremental effect) is termed the incremental cost-effectiveness ratio (ICER) and is a standard cost-effectiveness estimate that is presented in almost every economic evaluation published to date:

$$ICER = \frac{C_{treatment} - C_{control}}{E_{treatment} - E_{control}} = \frac{\Delta C}{\Delta E}$$

Types of economic evaluations

Different types of economic evaluations exist to date. The three most prominent types are *cost-benefit analysis*, *cost-effectiveness analysis* and *cost-utility*

analysis (13-17). All three analyses measure costs in monetary units (e.g. in US$ or CHF), but differ in the way health outcomes are measured. In a cost benefit-analysis, the oldest form of economic evaluations, health outcomes are measured in monetary units as are costs. In contrast, in a cost-effectiveness analysis (applied in chapter 2) health outcomes are measured in natural units (e.g. life-years gained, event prevented, mmHg blood pressure lowered). Although useful within disease areas, economic evaluation can only be applied to its fullest strength, if comparisons between disease areas are possible (13). This is not the case with cost-effectiveness analysis (with the exception of life-years gained as the unit of health outcome). For decision making purposes within the whole health care sector, a decision maker would for example need to know the relative value of preventing a hip fracture in osteoporotic patients (see chapter 3) compared to the value of avoiding the need for a repeat revascularisation procedure in interventional cardiology (see chapter 5). This problem can be avoided when health outcomes for all disease areas are measured in the same generic unit. Several different generic units have been proposed (e.g. healthy years equivalent (HYE), quality adjusted life years (QALY), disability adjusted life years (DALY)). QALYs are generally the most used generic measure (18).

Clinical trials vs. decision analytic models

Economic evaluations of health care interventions are usually based on data from a single randomized controlled trial (RCT) or use decision analytic modelling (13;19). Since 1994, approximately 30% of published economic evaluations have been based on data from a single RCT (19). It has been argued, that trial-based economic evaluation is a limited framework for cost-effectiveness analysis. Main concerns relate to the failure of most trials to compare all relevant options, the limited time horizon, the lack of relevance to the decision context, the failure to incorporate all evidence and the inadequacy to allow for the quantification of decision uncertainty (19). An alternative to trial-based economic evaluations are economic evaluations based on decision analytic modelling. The use of decision analytic models in economic evaluations is the only framework that has the

potential to meet all the requirements for economic evaluation for decision making (20).

Model types

The choice of the model type and structure used in an economic evaluation based on a decision analytic model is dependent on the features of the disease/technology under analysis (20; 21). These features include, for example, the timing of the occurrence of health-related events or whether the assumption of a constant effect of the intervention over time holds to be true. The two most prominent model types are decision trees and Markov models (see appendix) (13; 20-23).

Probabilistic sensitivity analysis

In probabilistic sensitivity analysis (PSA) the joint implication of parameter uncertainty on the cost-effectiveness estimate is analysed (24). Hence, in PSA, probability distributions are assigned to those parameters that could in principle be sampled. In decision analytic models, these parameters are often clinical parameters (e.g. relative risk estimates, transition probabilities), cost parameters or quality of life parameters (24-27). The assigned distribution should reflect the prior beliefs concerning the uncertainty in the parameters' uncertainty (20). Although numerous types of probability distributions exist, their choice is not arbitrary and should incorporate logical bounds on the parameter values. As for example cost parameters cannot be negative, a gamma distribution is an appropriate choice to reflect uncertainty in cost parameters, since the gamma distribution is bound to be non-negative. A beta distribution is a legitimate choice to reflect parameter uncertainty in (transition) probability parameters since both the beta distribution and probability parameters are bound to the interval zero to one. The most likely probability distribution (i.e. the distribution's hyperparameters) from the infinite number of beta, gamma or other probability distributions can be obtained by the method of moments fitting. When expected

values (i.e. mean values) and corresponding variances are known the equations below can be solved to obtain the hyperparameters α and β of a beta or gamma distribution (see appendix) (28).

The uncertainty of input values in a given model is then analyzed by means of Monte Carlo simulation, whereby random values of the model input parameters are simulated and the model is run for each simulated parameter set (29). The resulting sample of outputs (e.g. net monetary benefit of an intervention) characterizes the output uncertainty. In order to obtain accurate estimates, typically 1000 or more model runs (iterations) are necessary (30). The output of a probabilistic sensitivity analysis is often presented by the cost-effectiveness acceptability curve, that estimates the probability that the intervention under analysis is cost-effective for various willingness-to-pay values (31-33).

Value of information

Decisions should be based on expected cost-effectiveness given the existing information (i.e. on the mean value of the cost-effectiveness estimate) (34). Yet, decisions based on existing information will be uncertain, and there will always be a chance that the wrong decision will be made (i.e. an intervention will be adopted when in fact it is not cost-effective).

To reduce decision uncertainty, a rational decision maker may thus wish to base the decision on a more sound evidence base (35). Expected value of perfect information analysis (EVPI) and expected value of partial perfect information analysis (EVPPI) analysis provides information on the contribution of single parameters or groups of parameters towards total decision uncertainty (36-38). Hence, EVPPI allows to identify those parameters for which further information is of highest value to reduce total decision uncertainty. In many situations, further information will only be available from clinical trials. Given that the cost of conducting a clinical trial is large and increases with sample size, the net benefit of the future clinical trial will ultimately yield diminishing marginal returns with increasing sample size (34). The optimal sample size for the future

clinical trial can thus found by identifying the sample size that maximises ENBS (37).

Appendix

Markov models

A Markov model is a discrete-time stochastic process with the *Markov property* (39-41). The Markov property refers to the fact that future states in the model are independent of the present state.

	A	B	C	D	E
1	**cycle**	**well**	**sick**	**dead**	**sum**
2	**0**	100	0	0	100
3	**1**	89	10	1	100
4	**2**	79.21	18.4	2.39	100
5	**3**	70.4969	25.401	4.1021	100
6	**4**	62.742241	31.18064	6.077119	100
7	**5**	55.84059449	35.8958321	8.26357341	100
8					
9					
10	**cycle**	**well**	**sick**	**dead**	**sum**
11	**0**	100	0	0	=SUM(B11:D11)
12	**1**	=B11-B11*D22-B11*E22	=C11+B11*D22-C11*E23	=D11+B11*E22+C11*E23	=SUM(B12:D12)
13	**2**	=B12-B12*D22-B12*E22	=C12+B12*D22-C12*E23	=D12+B12*E22+C12*E23	=SUM(B13:D13)
14	**3**	=B13-B13*D22-B13*E22	=C13+B13*D22-C13*E23	=D13+B13*E22+C13*E23	=SUM(B14:D14)
15	**4**	=B14-B14*D22-B14*E22	=C14+B14*D22-C14*E23	=D14+B14*E22+C14*E23	=SUM(B15:D15)
16	**5**	=B15-B15*D22-B15*E22	=C15+B15*D22-C15*E23	=D15+B15*E22+C15*E23	=SUM(B16:D16)
17					
18					
19	transition				
20	probabilities		**to**		
21		**from**	**well**	**sick**	**dead**
22		**well**	0.85	0.1	0.01
23		**sick**	0	0.95	0.05

Figure 4. Example of a Excel worksheet with a simple Markov model. 100 patients are defined to be in the health state "well" at cycle zero. Based on the transition probabilities (cells C22 to D23) patients face the risk of moving to the health states "sick" or "dead" each cycle. Cells B11 to D16 contain the actual model. The numerical values of cells B11 to D16 are shown in cells B2 to D7. Column E was included to record the total number of patients in the model over time (which should remain constant).

Method of moments fitting

The method of moments fitting is used to derive hyperparameters for a given mean value and standard deviation (42). The hyperparameters define a unique probability distribution from the set of infinite probability distributions:

Beta

$$E(\theta) = \frac{\alpha}{\alpha + \beta}$$

$$var(\theta) = \frac{\alpha \cdot \beta}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

Gamma

$$E(\theta) = \frac{\alpha}{\beta}$$

$$var(\theta) = \frac{\alpha}{\beta^2}$$

Expected value of perfect information

In decision making under uncertainty with unknown parameters θ, a rational decision maker should adopt the intervention j that has the highest expected net benefit (20). The optimal decision is the one that has the highest expected net benefit:

$$max_j E_\theta NB(j, \theta)$$

Without parameter uncertainty, it true value of the unknown parameters θ would be known and thus the expected benefit of the adopted strategy would always be equal to the maximum net benefit:

$$E_\theta \, max_j NB(j, \theta)$$

The difference in expected benefit of the adopted decision without parameter uncertainty (i.e. perfect information) in parameters θ and the net benefit of the decision given current information with uncertainty in parameters θ is the expected value of perfect information:

$$\text{EVPI} = E_\theta \, max_j NB(j, \theta) - max_j E_\theta NB(j, \theta)$$

As the absolute value in net benefit of a strategy is dependent on the number of patients that were analysed, so EVPI is likewise dependent on the number of patients for whom EVPI is calculated (20). Although it may be useful to compare parameter uncertainty per single patient (or thousands of patients) across different decision problems, the absolute value of perfect information can only be obtained by multiplying the number of patients entering the decision problem with the EVPI per patient:

$$\text{population EVPI} = \text{EVPI} \cdot \sum_{t=1,2,\ldots,T} I_t/(1+r)^t$$

To account for the timing of the occurrence of new patients the incidence rate I has to be discounted at a discount rate r per period t.

Expected value of partial perfect information

In almost every situation a decision maker will encounter several unknown parameters (φ, ψ). To compare the relative impact the unknown parameters have

on overal decision uncertainty the expected value of *partial* perfect information can be calculated (36-38). This approach the yields the value of perfect information in one parameter φ (or one group of parameters) while the true values of the other parameters ψ will remain unknown. For a given value of φ, a rational decision maker would choose the intervention j that provides the highest expected net benefit:

$$max_j E_{\psi|\varphi} NB(j, \varphi, \psi)$$

Given perfect knowledge about parameter φ, the expected benefit of the decision taken can be obtained by averaging the maximum expected net benefits over the distribution of φ:

$$E\varphi \; max_j E_{\psi|\varphi} NB(j, \varphi, \psi)$$

The expected benefit of the decision given current information is the same as above:

$$max_j E_\theta NB(j, \theta)$$

Consequently EVPPI is obtained by calculating the difference between the expected value of the decision made with perfect information in parameter φ and the value of the decision given all the current level of uncertainty:

$$\text{EVPPI}_\varphi = E\varphi \; max_j E_{\psi|\varphi} NB(j, \varphi, \psi) - max_j E_\theta NB(j, \theta)$$

Although in principle the EVPPI calculation is similar to the calculation of EVPI, the computation of EVPPI is far more complex since there are two levels of uncertainty that have to be addressed simultaneously (36; 38). The first level of uncertainty arises from the imperfect knowledge about the parameter of interest φ. Even in light of perfect information in the true value of parameter φ it would still not be known how uncertainty in the other parameters ψ will resolve. Unfortunately EVPPI can thus only be calculated by using a 2-level sampling algorithm. In the outer loop simulation a value of φ is sampled from its prior distribution. Given this sampled values for φ, uncertainty in parameters ψ have to be assessed in an inner loop.

Calculation of Net Benefit of the baseline decision

1) set up a decision model that compares two strategies
2) characterize uncertain parameters with probability distributions
3) use Monte Carlo simulation with a large number of iterations (e.g. 10 000) to collect a sample set of the uncertain parameter values; the *baseline adoption decision* is the strategy that has the highest expected net benefit

2-Level EVPPI algorithm

4) sample the parameter of interest *once* from its prior distribution (outer-level simulation)
5) sample the remaining parameters with a Monte Carlo simulation multiple times (inner-level simulation; e.g. 1000 times), while holding the value of the parameter of interest fixed at its sampled value; calculate the conditional expected net benefit for the two strategies by averaging over the inner-level simulation values; the revised adoption decision is the one with the highest expected net benefit given the sampled value (outer-level simulation) of the parameter of interest
6) loop back and repeat steps 4 and 5 multiple times (e.g. 1000 times); then calculate the expected net benefit of the *revised adoption decision* (outer-level simulation) by averaging over the expected net benefit of the revised adoption decisions from the inner-level simulations
7) calculate EVPPI by subtracting the net benefit of the *baseline adoption decision* from the net benefit of the *revised adoption decision*:

$$\text{EVPPI} = NB|\text{perfect information} - NB|\text{current information}$$

Box 1. 2-Level EVPPI algorithm

Expected value of sample information

The expected benefit of sample information (i.e. the value of a future clinical trial) can be regarded as the resulting reduction in the cost of uncertainty surrounding the choice between different treatment alternatives. Given that incremental net benefit is normally distributed, the expected benefit of sample information can be calculated as follows (20):

$$\mathrm{EVSI}|n,n_{(2)} = \lambda \cdot \sqrt{(\mathrm{V}|n,n_{(2)} \cdot \sigma 0 \cdot L(D|n,n_{(2)})}$$

$$\mathrm{D}|n,n_{(2)} = |\eta 0|/(\sigma 0 \cdot \sqrt{(\mathrm{V}|n,n_{(2)})})$$

$$\mathrm{V}|n,n_{(2)} = \sigma_0^2/(\sigma_0^2 + \frac{\sigma_2^2}{n_{(2)}} + \sigma_2^2 + \frac{\sigma_1^2}{n\text{-}n_{(2)}})$$

n = total sample size of the future trial

$n_{(2)}$ = size of the 'new intervention' trial arm

λ = threshold value

L = unit normal loss integral

$\eta 0$ = prior mean net *health* benefit

σ_2^2 = variance of the net benefit of the new intervention

σ_1^2 = variance of the net benefit of the old intervention

Population EVSI

Similar to the calculation of population EVPI, the population EVSI is calculated by multiplying per patient EVSI with the incidence of patients (I) in each period (t) discounted at rate (r). Patients who are enrolled in the trial will not be able to benefit from the sample information (i.e. the gain in information obtained by the trial) (20):

$$\text{population EVSI} = \text{EVSI}|n,n_{(2)} \cdot \sum_{t=1,2,\ldots,T} (I_t - n_t)/(1+r)^t$$

Expected net benefit of sampling

Assuming that the trial costs comprise fixed costs (Cf; i.e. for the data analysis) and variable reporting costs (Cr), the costs of the future trial are calculated as follows:

$$\text{cost of sampling} = \text{Cs}|n,n_{(2)} = \text{Cf} + (C_2 - C_1) \cdot n_{(2)} + \text{Cr} \cdot n$$

The net benefit of sampling is the difference in the value of the future trial and its estimated costs (20):

$$\text{ENBS}|n,n_{(2)} = \text{EVSI}|n,n_{(2)} - \text{Cs}|n,n_{(2)}$$

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CHAPTER 2: FONDAPARINUX

Cost-effectiveness of extended venous thromboembolism prophylaxis with fondaparinux in hip surgery patients

Abstract

Summary background data: Extended prophylaxis with the synthetic pentasaccharide fondaparinux for one month versus one week in hip fracture surgery has been shown to reduce the risk of venous thromboembolic events (VTE) by 96% in the Penthifra Plus trial. The cost-effectiveness of extended prophylaxis with fondaparinux still remains to be determined.

Methods: We developed a decision analytic cost-effectiveness model comparing the use of fondaparinux for four weeks versus one week from a health care perspective. The analyses were performed for patients undergoing hip fracture surgery (HFS) and total hip replacement (THR). Efficacy data were extracted from published randomised controlled trials and natural history data after VTE from observational studies. Cost data were derived from the literature and other published sources. Costs were expressed in 2004 Swiss Francs (CHF) and effects as life-years gained (LYG).

Results: In patients undergoing HFS, the incremental cost-effectiveness ratio (ICER) of extended four-week fondaparinux prophylaxis versus a one-week regimen was CHF 2801/LYG after 30 days, with cost-savings after 5 years. In patients undergoing THR, the respective ICER of extended fondaparinux prophylaxis was CHF 20294/LYG after 30 days, with cost-savings after 5 years.

Conclusion: In our model, the substantial clinical benefit of extended thromboembolism prophylaxis with fondaparinux in major orthopaedic surgery translates into favourable cost-effectiveness figures in the short term and cost-savings when a 5-year time horizon is used.

Introduction

Patients undergoing major orthopaedic procedures such as hip fracture surgery (HFS) and total hip replacement (THR) are at increased risk of developing venous thromboembolic events (VTE)(1) such as deep vein thrombosis and (DVT) and pulmonary embolism (PE). Without prophylactic treatment, 36-60% of HFS patients and 47-57% of THR patients will develop a VTE . It has been estimated that 0,2% of PE following a DVT after surgery will lead to death. In addition, the long-term clinical course of DVT may be complicated by recurring episodes and post-thrombotic syndrome (PTS), which is associated with significant morbidity and costs (2;3). An estimated 20%-50% of patients with symptomatic DVT will develop a consecutive PTS within 1 to 2 years (4). Both DVT and PE may be silent and there may be no specific symptoms and signs, which may complicate the diagnostic work-up of patients.

Fondaparinux is a synthetic pentasaccharide that has been shown to be effective in preventing thromboembolic events in patients undergoing hip fracture surgery as compared to enoxaparin in the Penthifra trial (5). The majority of symptomatic VTEs occurs after hospital discharge. Since the risk of VTE persists for up to 3 months after surgery, patients may benefit from extended prophylaxis. The efficacy of extended antithrombotic prophylaxis with fondaparinux for four weeks versus one week was evaluated in the Penthifra Plus trial (6). Extended fondaparinux prophylaxis reduced the incidence of VTE from 35.0% to 1.4% (relative risk reduction of 95.9%, 95% CI:87.2%-99.7%). However, in times of increasing awareness about the scarcity of health care resources, considerations must also be given to whether extended fondaparinux prophylaxis represents value for money. The cost-effectiveness of extended prophylaxis with fondaparinux in major orthopaedic surgery in Switzerland still remains to be determined. We therefore estimated the cost-effectiveness of a four-week fondaparinux regimen versus a one-week regimen from a health care perspective using a decision analytic model.

Methods

An international decision analytic cohort simulation model developed in Microsoft Excel® was used to compare a four-week fondaparinux regimen with a

one-week regimen in patients undergoing THR or HFS in Switzerland. The model describes the clinical pathway in terms of conditional probabilities of events and the associated costs, and estimates the total effects and costs for each treatment option. The difference in costs between the two regimens (i.e., incremental costs) are then divided by the difference in effects (i.e., incremental effects) and expressed as costs per life-year gained (i.e., incremental cost-effectiveness ratio). The analysis was conducted from the Swiss health care perspective, only health care costs were therefore considered in our analysis. Future costs and health outcomes were discounted using an annual discount rate of 4% (7;8). We used a time horizon of 30 days and 5 years in our analysis. The shorter time horizon reflects the immediate benefit of extended fondaparinux prophylaxis and coincides with the time horizon of the Penthifra Plus trial. A longer time horizon of 5 years was used to reflect the long-term benefit of fondaparinux prophylaxis in terms of recurrent VTE and postthrombotic syndrome (PTS) prevented, a chronic disease associated with substantial costs.

Model structure

Patients undergoing HFS or THR are at risk of VTE. In the model, all patients are assumed to receive fondaparinux immediately after surgery. The prophylactic treatment is provided to all patients for 7 days. Only patients without symptomatic VTE events are eligible for extended prophylaxis with fondaparinux for an additional three weeks. Patients who receive prophylaxis during the entire extended period may experience a DVT until day 30. Between day 30 and day 90, a small proportion of DVT patients will have developed a symptomatic VTE (either DVT or fatal/non-fatal PE). Patients who do not receive extended fondaparinux prophylaxis (i.e., receive only a one week fondaparinux regimen) follow the same clinical pathways but are at increased risk of VTE. For the period after day 90 until the end of year 5, patients were assumed to be at risk of recurrent VTE and/or of post-thrombotic syndrome. Patients who experienced a clinically symptomatic DVT and PE are assumed to be at risk of recurrent VTE and PTS. Those with subclinical DVT are only assumed to be at risk of PTS.

Clinical model parameters

Event probabilities were derived from clinical trials and the published literature (see Table 1). Rates of subclinical DVT and PE at day 30 were taken from the Penthifra Plus trial (6). Rates of subclinical DVT for THR patients were taken from Eikelboom et al. (9). The risk of clinical VTE at day 7 was obtained from the Penthifra Plus trial for HFS patients (6). For THR patients a rate was obtained by using an estimated rate for enoxaparin treated patients (9) that was adjusted for the relative risk of fondaparinux by using the risk ratio published by Lassen et al. (10) and Turpie et al. (11). Rates for clinical VTE for the period from day 7 to day 30 for THR patients under short term and extended prophylaxis were also obtained from Eriksson et al. (6). Among THR patients, the rate of clinical VTE was derived from data published by Gordois et al. (12) and Eriksson et al. (6). Clinical rates of VTE for the time that falls beyond the time horizon of the published trials (30 days) were calculated by using a study that analysed the temporal pattern of VTE (13).

Although the event rates were reported as combined VTE rates (for DVT and PE together), the model was set up to differentiate between DVT and PE. Using data from Eriksson et al. (5;6), it was assumed for HFS patients with a VTE, that 62.5% will develop a DVT and 37.5% a PE. Similarly, 71.3% of the THR patients with a VTE were assumed to have a DVT, the remaining 28.7% were assumed to be PE cases (14;15). The risk of major bleeding following prophylaxis was taken from trial data (6). A false-positive rate was applied to assess patients incorrectly suspected of having a DVT or PE (16;17). The false-positive rates were assumed to be the same for both types of prophylaxis and both HFS and THR patients. The risk of recurrent VTE was estimated from a long-term follow-up study of patients with objectively verified symptomatic DVT (18). The risk of PTS for patients who developed a clinical VTE during the first 90 days was taken from Prandoni et al. (2). Among patients who had a subclinical VTE, the risk of PTS was based on the incidence of PTS among orthopaedic surgery patients with venographically detected DVT in two retrospective studies (19;20).

For HFS patients, the risk of death was taken from the Penthifra and the Penthifra Plus trial (5;6). The risk of death for THR patients was derived from

Probabilities	HFS	THR	Reference
All patients:			
Symptomatic VTE initial 7 day period	0.0068	0.0039	(6;9)
False-positive DVT	0.1	0.1	(16;17)
False-positive PE	0.02	0.02	(16;17)
Death due to fatal PE	0.64	0.0145	(5;6;14;15;21;22)
Death due to recurrent VTE	0.1231	0.0279	(2)
PTS pts. with clin. DVT or PE day 90 – year 1	0.1730	0.1730	(2)
PTS pts. with clin. DVT or PE year 2	0.0550	0.0550	(2)
PTS pts. with clin. DVT or PE year 3+	0.0173	0.0173	(2)
PTS pts. with subclin. DVT day 90 to year 1	0.0722	0.0722	(19;20)
PTS pts. with subclin. DVT year 2	0.0229	0.0229	(19;20)
PTS pts. with sublin. DVT year 3+	0.0072	0.0072	(19;20)
Recurrent VTE day 1 to day 30	0.0018	0.0018	(12;18)
Recurrent VTE day 31 to day 90	0.0036	0.0036	(12;18)
Recurrent VTE day 91 to year 5	0.0397	0.0397	(12;18)
Extended prophylaxis patients:			
Symptomatic VTE before day 30	0.0031	0.0028	(6)
Subclinical VTE day 7 to day 30	0.0114	0.0045	(6;12)
Symptomatic DVT day 30 to day 90	0.0388	0.1058	(13)
Bleeding index>2 day 1-7	0.018	0.026	(5;6;10;11)
Bleeding index>2 day 8-30	0	0	(5;6;10;11)
Major Bleeding day 1-7	0.004	0.003	(5;6;10;11)
Major Bleeding day 8-30	0.006	0.006	(5;6;10;11)
Patients without extended prophylaxis:			
Symptomatic VTE before day 30	0.0273	0.0252	(6)
Subclinical VTE day 7 to day 30	0.3227	0.1095	(6;12)
Symptomatic DVT day 30 to day 90	0.0388	0.1058	(13)
Bleeding index>2 day 1-7	0.018	0.026	(5;6;10;11)
Bleeding index>2 day 8-30	0.018	0.018	(5;6;10;11)
Major Bleeding day 1-7	0.004	0.003	(5;6;10;11)
Major Bleeding day 8-30	0.006	0.006	(5;6;10;11)

Table 1. Probabilities of events in the model (HFS=hip fracture surgery; THR= total hip replacement; VTE= venous thromboembolic event; DVT=deep vein thrombosis; PE=pulmonary embolism; pts.=patients; clin.=clinical; subclin.=subclinical).

published sources (14;15;21;22). The risk of death from other causes for THR patients was assumed to be the same as for the general population, adjusted for age and sex (23). The risk of death for HFS patients was estimated from Todd et al. (24).

For THR patients it was assumed that life expectancy would not differ from the life expectancy of the general population. Since hip fractures are associated with increased mortality, life expectancy for HFS patients was assumed to be 25% lower as compared to the general population (25).

The length of the initial prophylaxis was 7 days for both THR and HFS patients. Patients who received extended prophylaxis were modelled to receive prophylaxis for an additional 21 days. The average length of inpatient stay (LOS) was assumed to be 13.4 days for THR patients and 12.3 days for HFS patients based on the LOS of APDRG 209 (THR) and 211 (HFS)(26). The average age of patients of the cohort was modelled to be 65 for THR patients and 76.6 for HFS patients, based on values of the four trials that were mainly used as a source for the model input parameters (5;6;10;11). The average life expectancy was assumed to be 82.8 years for THR patients and 84 years for HFS patients (23;25).

Cost data

All costs were expressed in 2004 Swiss Francs (CHF). Table 2 shows a summary of the major cost parameters used in the model. Since Switzerland has a decentralized health care system, hospitalization costs may substantially differ between hospitals in the different Cantons in Switzerland, with in-patient costs often being reimbursed on a per diem basis independent of the disease category. Reimbursement schedules based on the DRG system are currently being considered, and further developed, as a method to more appropriately estimate resource consumption in Swiss hospitals, taking severity of disease and the disease category into account. We therefore estimated per diem hospitalisation costs using cost weights and average LOS data provided by APDRG Switzerland for each DRG (APDRG version 4.1 data)(26). The respective cost weight is then multiplied with CHF 9'041 for university hospitals or CHF 6842 for non-

Surgery	Event	Diagn.	Time of occurrence	Calculation	Total cost
THR	PE	Conf.	IP	THR with acute cor pulmonale (DRG 558) minus THR without complication (DRG 209); follow up costs	11'120
THR	PE	Conf.	PD	Assumption all patients hospitalised (DRG 78); follow up costs	11'753
THR	PE	Susp.	IP	Complete blood count; Prothrombin Time (PT) assay (Quick); blood chemistry; D-Dimer test; ultrasound scan of the leg; spiral CT scan	732
THR	PE	Susp.	PD	Complete blood count; Prothrombin Time (PT) assay (Quick); blood chemistry; D-Dimer test; ultrasound scan of the leg; spiral CT scan; hospitalisation	991
THR	DVT	Conf.	IP	Hip procedure with complications (DRG 210) minus hip procedure without complications (DRG 211); follow up costs	2125
THR	DVT	Conf.	PD	Assumption 50% hospitalised (DRG 128); outpatient treatment reduces costs by 64% (29)	5621
THR	DVT	Susp.	IP	Complete blood count; Prothrombin Time (PT) assay (Quick); blood chemistry; D-Dimer test; ultrasound scan of the leg	394
THR	DVT	Susp.	PD	Complete blood count; Prothrombin Time (PT) assay (Quick); blood chemistry; D-Dimer test; ultrasound scan of the leg; hospitalisation	653
HFS	PE	Conf.	IP	HFS with acute cor pulmonale (DRG 558) minus HFS without complication (DRG 211); follow up costs	13'832
HFS	PE	Conf.	PD	same as for THR patients	11'753
HFS	PE	Susp.	IP	same as for THR patients	732
HFS	PE	Susp.	PD	same as for THR patients	991
HFS	DVT	Conf.	IP	same as for THR patients	2125
HFS	DVT	Conf.	PD	same as for THR patients	5621
HFS	DVT	Susp.	IP	same as for THR patients	394
HFS	DVT	Susp.	PD	same as for THR patients	653
Both	PTS acute		PD	Data from Perone (29) for procedure; follow up costs	5056
Both	PTS chronic		PD	Data from Perone (29); costs as costs per 3 month	787
Both	BI>2		PD	Hospitalisation; Complete blood count; Prothrombin Time (PT) assay (Quick); Chemogramm; blood replacement (2 units)	736
Both	MB		PD	Data from Perone (29)	11'661

Table 2. Unit costs for the procedures. Costs in CHF (year 2004; adjustment to 2004 prices using the consumer price index for health care in Switzerland) per one procedure (THR=total hip replacement; HFS=hip fracture surgery; Diagn.=Diagnosis; Conf.=confirmed diagnosis; Susp.=suspected diagnosis; IP=inpatient; PD=post discharge; PE=pulmonary embolism; DVT=deep vein thrombosis; PTS=post thrombotic syndrome; MB=clinical relevant major bleeding).

university hospitals (26). The cost of treating THR and HFS patients with suspected or confirmed DVT or PE was calculated as described in Table 2.

Clinically relevant major bleeding was assumed to result in additional costs of CHF 11'661 (see table 2) for both patient groups. This figure was derived from the literature, and converted into 2004 Swiss Francs (CHF) using the consumer price index for health care.

The cost for PTS was divided up into an acute part and follow-up costs per three-month period. We used the proportion of acute and chronic costs associated with PTS in relation to the post-discharge costs after DVT as reported by Lundqvist et al. (27) to estimate the costs associated with PTS in Switzerland, using post-discharge DVT cost estimates as reported by Perone et al. (28).

The costs for diagnostic procedures (e.g. CT scans) and out-patient treatments were estimated using Tarmed version 1.1r (29). The required procedure for diagnostic workup was based on guidelines and expert opinion as shown in Table 2.

The price of fondaparinux (Arixtra®) was obtained from the Swiss Drugs Compendium (30) to estimate the daily cost of the fondaparinux prophylaxis. It was assumed that both HFS and THR patients would receive 2.5 mg as a single dose per day (CHF 16.7 per day). It was assumed that extended prophylaxis would impose additional costs of CHF 23 per day for administering the drug by an outpatient nurse to 7.7% of the patients, who would not be able to self-inject fondaparinux after discharge (29).

Sensitivity analysis

A one-way sensitivity analysis was performed on major model parameters. Since costs were calculated for university hospitals in Switzerland in the base case analysis, DRG cost estimates from non-university hospitals were used to calculate the lower bound of the incremental cost-effectiveness ratio in a sensitivity analysis. This difference in costs between the base case and lower bound estimate was added to the base case value of the respective model input parameter to estimate the upper bound of the incremental cost-effectiveness ratio. The ranges

used for the cost and clinical parameters in the sensitivity analyses are shown in Table 3 and Table 4.

The discount rate was also varied between 0% and 8% to assess the impact of different time preferences for costs and effects over time. The age of the patients was varied between 25-97 years for THR patients and 23-97 years for HFS patients (6). The percentage of patients that require a nurse visit after discharge to administer fondaparinux was varied between 0% and 100%. The impact of length of stay (LOS) on the results was analysed by varying LOS after HFS from 4-28 days, and after THR from 5-30 days, respectively. These ranges were obtained from the APDRG data (26). The values correspond to the upper and lower bounds for the length of stay when outliers are excluded.

Results

Given the results of the model, providing extended prophylaxis with fondaparinux to HFS patients avoids 9 DVTs, 5 non-fatal PEs and 10 fatal PEs per 1000 patients treated when a time horizon of 30 days is used. The incremental cost effectiveness ratio (ICER) at day 30 in these patients was CHF 2801 per LYG. Since the risk of a VTE is lower in THR patients, extended prophylaxis with fondaparinux avoids 16 DVTs, 5 non-fatal PEs, and one fatal PE per 1000 patients when a time horizon of 30 days is used. This translates into an ICER of CHF 20'294 per LYG.

In the analysis using a time horizon of 30 days, an estimated 135 of the 1000 THR patients and 346 of the 1000 HFS patients receiving a one-week fondaparinux regimen will have experienced a VTE, as opposed to 11 out of 1000 THR patients and 21 out of 1000 HFS patients in the extended prophylaxis arm. Looking at PE events only, at day 30 the event rate for HFS and THR patients is 21 out of 1000 and 8 out of 1000, respectively. Extended prophylaxis reduces these rates to 6 per 1000 for HFS patients and 1.9 per 1000 for THR patients. After 5 years, extended fondaparinux prophylaxis is cost saving compared to the one-week regimen for both HFS and THR patients.

Sensitivity analysis

Table 3 shows the results of the sensitivity analysis on costs. The ICER is most sensitive to the daily cost of fondaparinux as shown in the corresponding tornado diagrams (Figure 1 and 2). The two next most influential variables are the cost associated with PE treatment after hospital discharge and the cost for DVT treatment after hospital discharge in HFS patients. Other cost parameters do not have a major impact on the results (The ICER varies by less than CHF 250). Figure 2 shows the tornado diagram for costs in THR patients. The sensitivity of the ICER to variations in cost parameters are similar to HFS patients. Importantly, after 5 years, the results are robust to any substantial variations in model cost parameters and usually result in cost-savings.

A sensitivity analysis was also performed on major clinical model parameters as shown in Table 4. In HFS patients, the results were stable to variations in clinical model parameters at day 30 and after 5 years. However, in THR patients, the age of the patients has a substantial impact on the ICER. The ICER may vary between CHF 18'727 and CHF 125'353 per LYG at day 30. However, when a time horizon of 5 years is used, the results become stable to variations in age.

Discussion

In this paper we show that extending fondaparinux prophylaxis in major orthopaedic surgery from one week to four weeks may result in cost-savings after five years. When a shorter time horizon of 30 days is used, extended fondaparinux thromboprophylaxis costs CHF 2'801 per life year gained in HFS patients, and CHF 20'294 per life year gained in THR patients.

We used a time horizon of five years in our main analysis. The time horizon of the analysis should be long enough to reflect important differences between the long-run consequences and costs of alternative treatment options and strategies (31). A shorter time horizon of 30 days does not capture events that would occur after the initial four weeks of prophylaxis and underestimates the cost-effectiveness of the intervention. A time horizon of 5 years was chosen as a longer

One way sensitivity analysis on costs (Swiss Francs: CHF)

Variable	Baseline value	Range	ICER HFS (30 days) CHF/LYG	ICER HFS (5 years) CHF/LYG	ICER THR (30 days) CHF/LYG	ICER THR (5 years) CHF/LYG
Suspected DVT – before discharge	394	200-500	2774- 2816	cost saving	20'235-20'326	cost saving
Suspected DVT – after discharge	653	300-1000	2730-2871	cost saving	20'161-20'424	cost saving
DVT – before discharge	2125	1670-3021	2769-2817	cost saving	19'938-20'474	cost saving
DVT – after discharge	5621	1950-9750	2362-3191	cost saving	16'555-23'618	cost saving
Suspected PE – before discharge	732	500-1000	2795-2809	cost saving	20'280-20'310	cost saving
Suspected PE –after discharge	991	700-1200	2789-2810	cost saving	20'272-20'309	cost saving
PE – before discharge (HFS)	13'832	10'592-17'957	2554-2995	cost saving		
PE – before discharge (THR)	11'120	8539-14'585			19'740-20'706	cost saving
PE – after discharge	11'753	9018-15'372	2160-3286	cost saving	18'974-21'291	cost saving
Outpt. visit by nurse for injecting fondaparinux	23	23-46	2801-3236	cost saving	20'294-22'398	cost saving
fondaparinux daily cost	16.7	13 –20 (+/- 20%)	1586-3885	cost saving	13'964-25'938	cost saving
Bleeding – BI ≥ 2	736	300-1000	2676-2877	cost saving	19'641-20'689	cost saving
Major bleeding	11'661	9100-13'000	2800-2802	cost saving	20'286-20'298	cost saving
PTS acute (1st Quarter)	5056	1755-8775	2801	cost saving	20'294	cost saving
PTS chronic (quarterly)	787	273-1365	2801	cost saving	20'294	217- cost s.

Table 3. Results of the sensitivity analysis on costs for the two patient groups and at different points in time (ICER = incremental cost-effectiveness ratio; HFS = hip fracture surgery; THR = total hip replacement; LYG = life year gained; DVT = deep vein thrombosis; PE = pulmonary embolism; BI = bleeding index; PTS = post thrombotic syndrome).

One way sensitivity analysis on other major model parameters

Variable	Baseline value	Range	ICER HFS (30 days) CHF/LYG	ICER HFS (5 years) CHF/LYG	ICER THR (30 days) CHF/LYG	ICER THR (5 years) CHF/LYG
Discount Rate	4.0%	0%-8%	2478-3131	cost saving	14'893-26'332	cost saving
Age of patient THR	65	23-97	1297-8636	cost saving	18'727-125'353	cost saving
Age of patient HFS	76.6	23-97				
Outpatient visit by nurse	8%	0%-100%	2367-8010	cost saving	18'189-45'523	c. saving-10200
PE fatality rate HFS	64%	+/- 20%	2348-3522	cost saving		
PE fatality rate THR	15%	+/- 20%			16'409-24'613	cost saving
RR extended prophylaxis fondapar.	4.1%	+/- 20%	2816-2820	cost saving	20'373-20'378	cost saving
LOS HFS	12.3	4-28	2314-2999	cost saving		
LOS THR	13.4	5-30			19'906-21'636	cost saving

Table 4. Sensitivity analysis on other major model parameters (ICER=incremental cost-effectiveness ratio; HFS=hip fracture surgery; THR=total hip replacement; LYG=life year gained; PE=pulmonary embolism; RR=relative risk; LOS=length of stay).

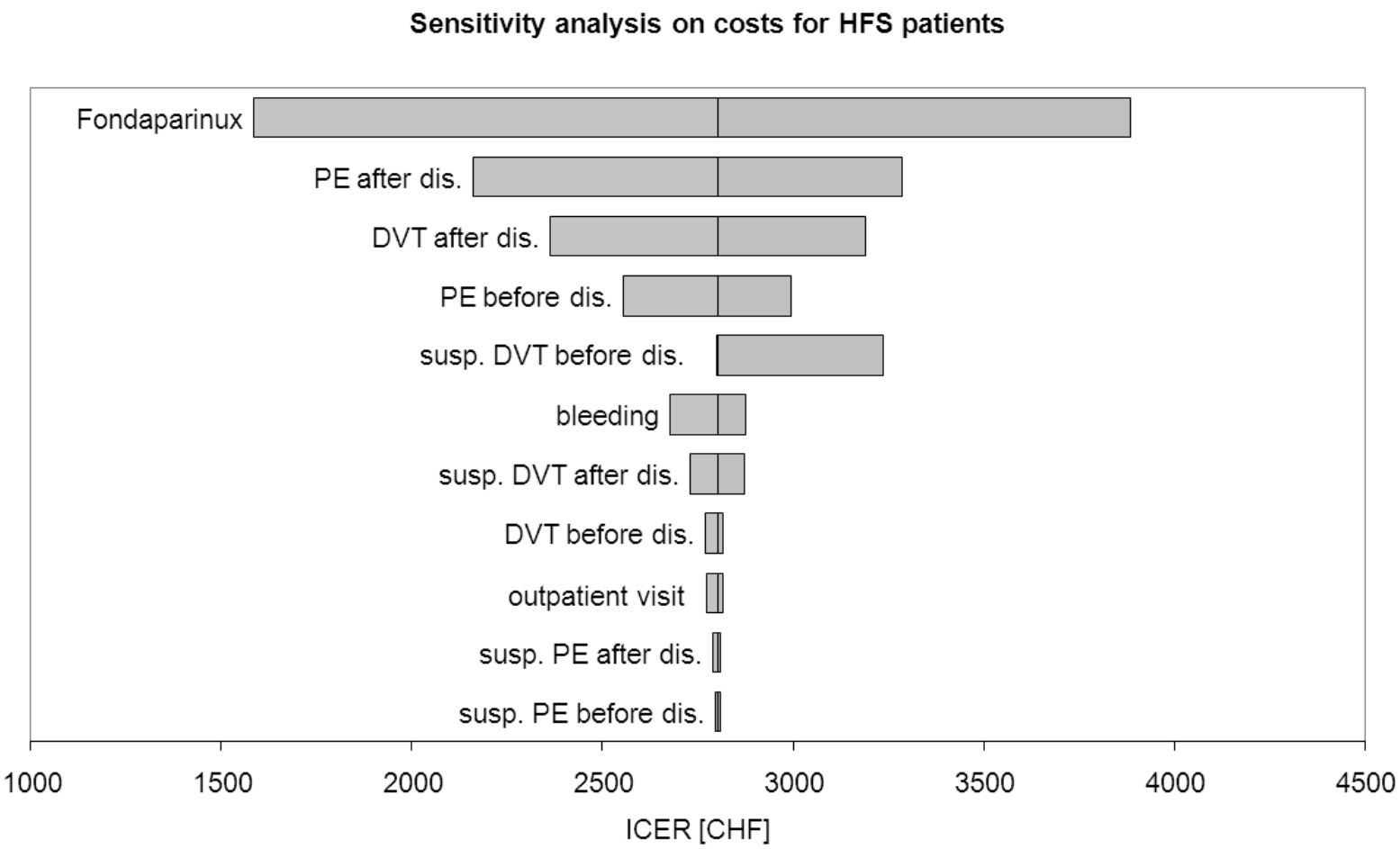

Figure 1. Sensitivity analysis on costs for HFS patients

Arixtra=cost of fondaparinux; PE=pulmonary embolism; dis.=discharge; DVT=deep vein thrombosis; bleeding=bleeding with bleeding index ≥ 2; susp=suspected

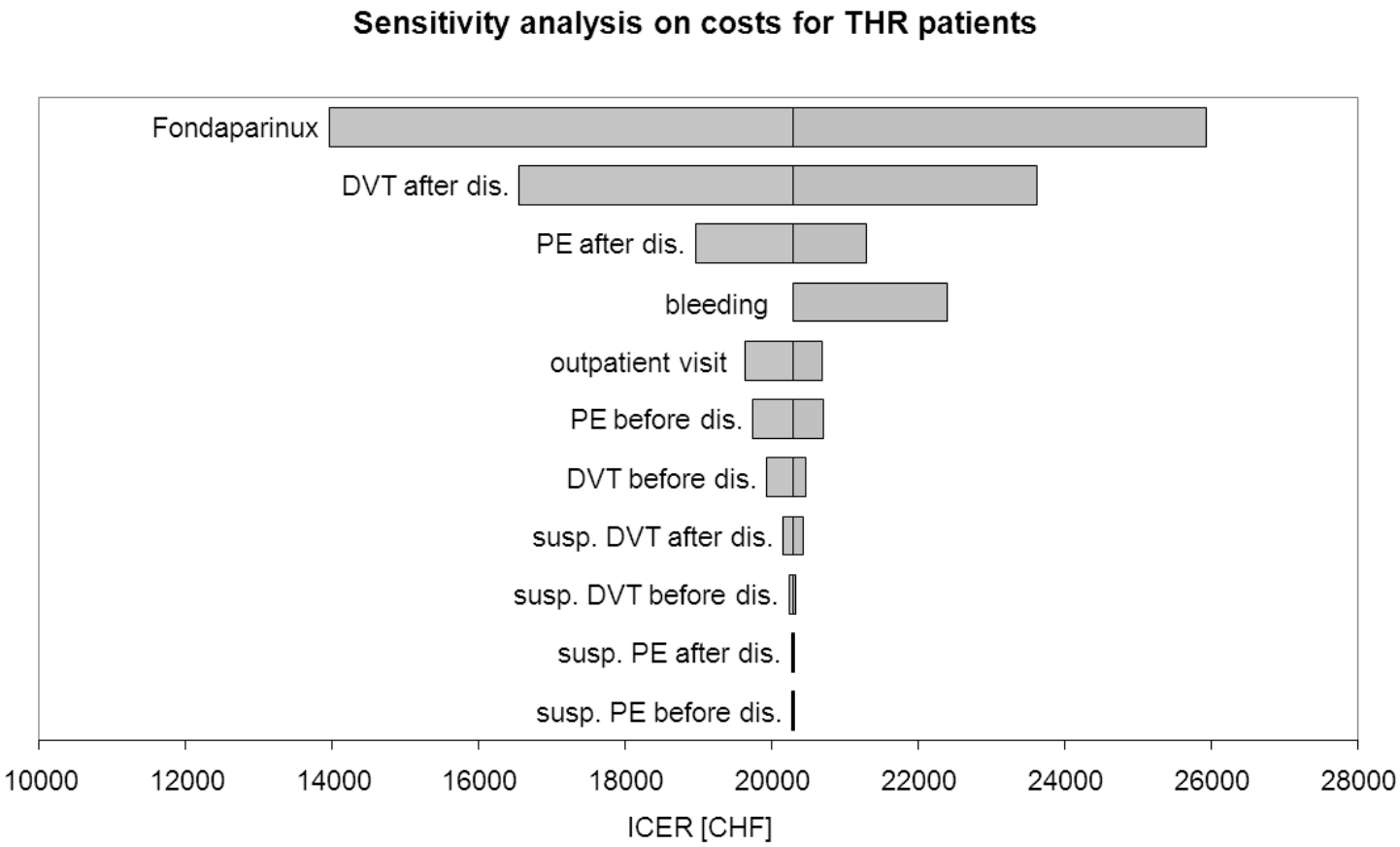

Figure 2. Sensitivity analysis on costs for THR patients

Arixtra=cost of fondaparinux; DVT=deep vein thrombosis; PE=pulmonary embolism; dis.=discharge; DVT=deep vein thrombosis; bleeding=bleeding with bleeding index ≥ 2; susp=suspected

time horizon better reflects the full value of this regimen in terms of complications and costs prevented.

As was also shown for enoxaparin, extending thromboprophylactic prophylaxis from one week to four weeks is likely to be cost-effective (32;33). In the study by Bergqvist et al. (32), based on a Swedish trial (34), extended prophylaxis with a low-molecular-weight-heparin (enoxaparin) was cost-saving under reasonable assumptions. In this trial, patients were hospitalised for 9 - 11 days and then received extended enoxaparin prophylaxis or placebo for another 19 - 23 days. Patients that received extended prophylaxis had significantly less VTE (most of which were asymptomatic). In addition, there was a significant reduction in the incidence of symptomatic thromboembolic events (34). Although extended enoxaparin was found to be cost-effective within this 4-week time horizon, important clinical benefits may have been omitted from the analysis by using a time horizon that is too short to capture the full clinical benefit of the extended prophylaxis regimen.

The substantial clinical benefit of extending thromboprophylaxis with fondaparinux from one week to four weeks translates into cost savings after five years. However, whether extended prophylaxis with fondaparinux compared to an extended enoxaparin regimen is cost-effective would need to be evaluated in an additional study. More evidence on the effectiveness and cost-effectiveness of extended fondaparinux treatment compared to enoxaparin would ideally be derived from a head-to-head randomised trial that is not yet available to date. However, the results of such a clinical trial would still need to be further evaluated within a modeling study to capture the long-term benefits of extended thromboembolic prophylaxis.

The treatment effect of extended fondaparinux prophylaxis was derived from the Penthifra Plus trial. This trial uses the same outcome measure as the Penthifra trial (5) whose results have been questioned since surrogate end points (venographically detected DVT) were used (35). However, asymptomatic, distal DVT is argued to be probably the only causal pathway that leads to proximal DVT and pulmonary embolism (36). In meta-analyses conducted on low-molecular-weight-

heparin administered to patients undergoing elective joint replacement surgery, it could be shown that a reduction of venographically detected DVT was associated with a proportional reduction in symptomatic VTE (9;37;38).

We used life years gained as the main outcome measure in our cost-effectiveness analysis. This allows decision makers to compare the results of this study with the results of other studies that have been conducted on other health technologies that mainly address survival. Preventing thromboembolic events that do not necessarily lead to death also results in gains in quality of life. Adjusting length of life for quality of life (i.e., quality-adjusted life-years) would have been an alternative outcome measure that would have also captured the benefit of extended prophylaxis with respect to the patient's quality of life. However, quality of life data were not available for this study. Our analysis therefore underestimates the cost-effectiveness of fondaparinux prophylaxis after 30 days and can be seen as a conservative estimate of the incremental cost-effectiveness ratio.

The age and life-expectancy of the patients may substantially affect the cost-effectiveness of the intervention. Preventing the death of a young patient will result in more life years gained than preventing the death of an older patient with a lower life expectancy. In our model the mean age of the population modelled was 65 years for THR patients and 76.6 years for HFS patients. These values have been derived from the four trials that were mainly used as a source for the model input parameters (5;6;10;11). In a sensitivity analysis the age of the patient substantially influenced the cost-effectiveness of extended fondaparinux prophylaxis after 30 days. However, using a five-year time-horizon, extended prophylaxis still results in cost-savings.

In the model it was assumed that eight percent of the extended prophylaxis patients would need to be cared of by a nurse in order to have fondaparinux injected after hospital discharge. This estimate was based on a published study by Spahn (39). Of the 207 patients who underwent knee arthroscopy, 8% rejected to self-inject a low-molecular-weight-heparin (LMWH). This estimate might be larger in other patient populations and settings. In a study by Harrison and colleagues (40) only 70% of patients felt comfortable with the self-injection of a LMWH. However, when we assumed that none of the patients would be able to self-inject fondaparinux in the sensitivity analysis, extended prophylaxis still resulted in cost savings in HFS patients

after 5 years and yielded a moderate incremental cost-effectiveness ratio for THR patients.

The results after 5 years depend on the inclusion of PTS into the analysis. In general PTS has not been well characterized and different definitions of PTS exist (2;41).

The uncertainty of including PTS into the analysis has partly been addressed by the sensitivity analysis on PTS costs (Table 3). The range of values used for the costs of treatment of acute PTS did not have any impact on the ICER after 5 years. The sensitivity analysis on costs for chronic PTS treatment showed only a marginal impact on the ICER.

Finally, the drug price of fondaparinux treatment influences the incremental cost-effectiveness ratio most. For the base case analysis, the daily cost of fondaparinux prophylaxis was based on the Swiss Drug Compendium 2004. The incremental cost-effectiveness ratios were recalculated in a sensitivity analysis when the drug price was lowered or increased by 20%. But even with 20% higher drug costs, extended fondaparinux VTE prophylaxis would result in cost savings after 5 years. On the other hand, health care providers that may eventually benefit from discounts when pharmaceuticals are purchased in large quantities (bulk discounts), would experience lower initial costs, resulting in even more favourable results for the cost-effectiveness of extended fondaparinux prophylaxis four weeks after orthopaedic surgery.

In conclusion, our results suggest that extending thromboprophylaxis with fondaparinux from one week to four weeks in patients undergoing hip fracture surgery and total hip replacement in Switzerland is likely to be cost-effective after 30 days and cost-saving after 5 years.

Expert opinion

In this study based on a decision analytic model it was shown that extending thromboprophylaxis from one week to four weeks is cost-effective in patients undergoing hip fracture surgery and total hip replacement. For a treatment to be cost-effective, clinical effectiveness is a prerequisite. The estimates of the increased effectiveness of extended fondaparinux treatment were derived from the Penthifra Plus study (6). Other input parameters were derived from published studies and the robustness of the model was evaluated in extensive one-way sensitivity analyses.

At the moment there is no accepted threshold value that defines the cut-off point between cost-effective and cost-ineffective treatments in Switzerland. The estimates of the cost-effectiveness for the prophylactic treatment with fondaparinux both in hip fracture surgery patients and total hip replacement surgery patients lie well below the frequently quoted 30'000 UK pounds per (quality adjusted) life year that are used in many cost-effectiveness studies (42;43). Assuming that the willingness to pay per unit of outcome is at least as high in Switzerland as it is in the UK, it can be concluded that extended thromboprophylaxis in those patients is cost-effective. Incorporating the full clinical benefit into the analysis by increasing the time horizon to five years shows that extended fondaparinux thromboprophylaxis is cost-saving.

Five-year view

The routine use of fondaparinux for thromboprophylaxis in hip fracture surgery patients is now recommended in the latest guidelines of the American College of Chest Physicians (44). The quality of the evidence that led to this recommendation is rated as being of grade 1A. The recommended duration of prophylaxis is a minimum of 10 days and 28 to 35 days for those patients who are considered to be at high risk for VTEs (grade 1A)(44).

Given the results of the Penthifra Plus trial (6) the use of extended thromboprophylaxis with fondaparinux in THR and HFS patients will increase. In order to ensure that all patients will receive appropriate care the prophylactic

regimens have to be standardized (45). This will also include a routine assessment of risk factors that will make it possible at least to provide extended prophylaxis to those patients that are at high risk of a VTE (46).

Key issues

- Patients undergoing major orthopaedic procedures (hip fracture surgery, total hip replacement) are at increased risk of developing venous thromboembolic events
- The most common complications in these patients are the deep vein thrombosis which can cause pulmonary embolism (mortality 0.2%) or the post-thrombotic syndrome
- Effective prophylactic agents exist and are routinely used (warfarin, LMWH, fondaparinux)
- The effectiveness of fondaparinux has been shown in the Penthifra trial; extending the treatment duration from one week to four weeks further improves the prophylactic potency of fondaparinux (Penthifra Plus trial)
- This cost-effectiveness analysis that is based on a decision analytic model shows that extending the treatment duration from one week to four weeks is cost-effective for both patient groups, using a longer time horizon of five years extended prophylaxis with fondaparinux becomes cost-saving

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CHAPTER 3: RISEDRONATE

Cost-effectiveness of risedronate treatment for preventing osteoporotic fractures in Swiss postmenopausal women

Abstract

Objective: Osteoporosis is a major public health concern in Switzerland and is associated with an increased rate of bone factures, health care costs, mortality and loss of quality of life. Risedronate has been shown to effectively prevent fractures in patients with osteoporosis. We examined the cost-effectiveness of risedronate from the Swiss health care perspective for the treatment of osteoporosis in elderly postmenopausal women.

Methods: A probabilistic Markov model was developed to address this issue. Data for the treatment effect was derived from a meta-analysis and quality of life estimates were extracted from a systematic review. Costs were identified by using Swiss sources and expressed in Swiss Francs (CHF) for the year 2007.

Results: Osteoporotic women 70 years of age with a T-score of -2.5 who are treated over 5 consecutive years with risedronate and vitamin D and calcium, experienced on average 0.064 additional QALYs (95% CI: 0.040 QALYs to 0.090 QALYs) compared to patients treated with vitamin D and calcium alone. Costs in the treatment group were CHF 4516 higher (95% CI: CHF 3668 to CHF 5264), yielding an incremental cost-effectiveness ratio (ICER) of CHF 70323/QALY. For women 70 years of age with a T-score of ≤-2.5 SD the ICER is CHF 16475/QALY.

Conclusions: Based on a decision analytic model the results of this study suggest that risedronate is cost-effective in the Swiss setting for the treatment of osteoporosis in 70-year-old females at the threshold of osteoporosis or with established osteoporosis.

Keywords: osteoporosis, risedronate, cost-effectiveness, decision analytic model, probabilistic sensitivity analysis

Introduction

Osteoporosis is a chronic disease which leads to low bone mass and increased bone fragility resulting in an increased risk of bone fractures. Osteoporosis is more than three times more common in postmenopausal women than in men and the risk of osteoporosis related fractures increases with age (1-3). The most common osteoporotic fractures are vertebral fractures, hip fractures and wrist fractures (1-3). Hip fractures are related to considerable morbidity and mortality (4-6) and reduced quality of life (7-9). As hip fractures generally require hospitalisation, surgery and subsequent rehabilitation, treatment costs are high and osteoporosis induced costs to the health care system are substantial. For Switzerland alone total costs due to osteoporosis and related fractures were estimated to be CHF 357 millions for the year 2000 (1). It was further estimated that total fracture-related first-year inpatient costs will rise by 31.5% to CHF 584 millions by the year 2020 (10). With rising expenditure on health care and limited budgets the value for money of interventions becomes increasingly important.

Pharmacologic treatment against osteoporosis consist of antiresorptive and anabolic agents that are combined with calcium and vitamin D (11; 12). Antiresorptive agents reduce bone remodelling and comprise bisphosphonates like risedronate, raloxifene a selective estrogen-receptor modulator, calcitonin and strontium ranelate. Bisphosphonates are the most commonly used agents today in the treatment of postmenopausal osteoporosis. In the US, risedronate is used in about 22% of patients receiving bisphosphonate (13). Several large clinical trials (14-17) and meta-analyses of randomised controlled trials (18-21) have shown that risedronate reduces vertebral and non-vertebral fractures in postmenopausal women with established osteoporosis.

Data on the cost-effectiveness of risedronate for the Swiss setting are sparse. (22).

Our study provides an economic evaluation of the cost-effectiveness of risedronate treatment (with calcium and vitamin D) compared to calcium and vitamin D intake alone in postmenopausal women with established osteoporosis in Switzerland from a third party payer perspective. Our cost-utility analysis is based on a decision analytic

model that allows to project the course of the disease and the corresponding costs over time.

Methods

The Model

We constructed a half-cycle corrected Markov model with Microsoft Excel and Microsoft Visual Basic 6.5 (Microsoft Corporation, Redmond, WA, USA). The model structure is based on a previously published reference model [Figure 1](23). We modelled a cohort of patients either receiving risedronate plus calcium and vitamin D or a basic treatment with calcium and vitamin D. The cohort was assumed to start in the well health state in cycle zero and face the monthly risk of experiencing a hip, wrist, vertebral or humerus fracture (cycle length = 1 month) and consequently move to one of the corresponding fracture specific health states.

Throughout the model patients are at an age specific risk of dying from a natural death (24). For the base case analysis the age of the cohort at treatment initiation is 70 years. The time horizon of the analysis is the patients' remaining lifetime.

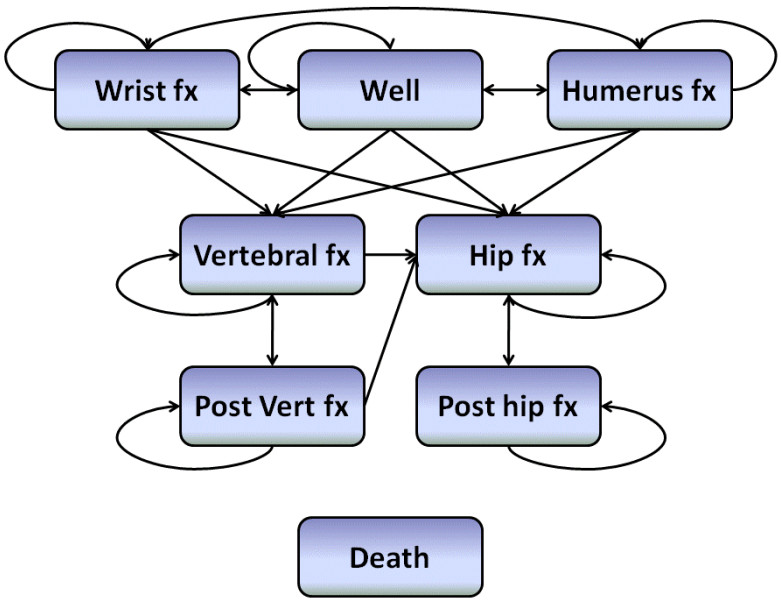

Figure 1. State transition diagram. Transitions to the death state not shown.

Legend: fx = fracture; vert = vertebral

Disease risk

Swiss fracture incidences for the four fracture sites were calculated from Swiss data for 10 age groups – each comprising 5 years – for the ages 50 years to 100 years. This was achieved by matching the number of cases with the number of women at risk for experiencing a fracture. The number of cases of the year 2005 (cases identified by ICD-10 code) per fracture site were obtained from the Medical Statistics of Hospitals, published by the Swiss Federal Statistical Office (24). Swiss age and gender specific population statistics data for the year 2005 was obtained from the same source. The quality of the Swiss Federal Statistical Office data is good – on average 98% of all cases are being recorded in the Medical Statistics of Hospitals (24). As not all fractures can be attributed to osteoporosis - it is estimated that only 91% of all hip fractures in 75-84 year old women can be attributed to osteoporosis - we adjusted the osteoporosis related fracture incidences accordingly with osteoporosis attribution rates published for Switzerland (1). All incidences (annual rates) were then transformed into monthly probabilities (25)[Table 1].

To account for the increased fracture risk in osteoporotic women with a T-score of either -2.5 SD or ≤-2.5 SD, baseline fracture incidences were adjusted using data published by Kanis et al. (26)[Table 2]. It should be noted, that based on the study by Kanis et al. osteoporotic women of any age with a T-score of ≤-2.5 SD have at least a 40% increased fracture risk at any site. In contrast, the relative risk of a fracture at the fracture sites under analysis decreases for women with a T-score of -2.5 SD and aged 80 years or older relative to the population at risk (26).

Increased mortality and increased fracture rates

Women who experience a hip or vertebral fracture are at increased risk of dying subsequent to the fracture or in the following year. Swiss age, gender and fracture specific data was used in the model to account for the increased mortality after hip and vertebral fractures (6; 22). Likewise, women with a prior fracture have an increased risk of any subsequent fracture. In the model we applied fracture site, age and gender specific relative risk data - obtained from a meta-analysis - to account for the difference in risk between women with or without a prior fracture (27).

T-score -2.5 SD

	Hip		Vert		Wrist		Humerus		Distribution
Age	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
60-64	0.0001385	0.0000088	0.0000783	0.0000052	0.0003646	0.0000112	0.0001466	0.0000055	beta
65-69	0.0002184	0.0000116	0.0001149	0.0000071	0.0004008	0.0000126	0.0001699	0.0000066	beta
70-74	0.0003470	0.0000135	0.0001429	0.0000076	0.0004236	0.0000127	0.0001796	0.0000066	beta
75-79	0.0007383	0.0000208	0.0002692	0.0000112	0.0004761	0.0000138	0.0002625	0.0000094	beta
80-84	0.0011305	0.0000250	0.0004068	0.0000141	0.0004719	0.0000144	0.0002599	0.0000098	beta
85-89	0.0013466	0.0000314	0.0004774	0.0000187	0.0004661	0.0000177	0.0002566	0.0000120	beta
90-95	0.0015069	0.0000417	0.0004579	0.0000242	0.0003877	0.0000217	0.0002144	0.0000148	beta
95+	0.0015463	0.0000765	0.0003547	0.0000386	0.0002840	0.0000337	0.0001587	0.0000231	beta

Table 1A. Monthly fracture probabilities for women with a T-score of -2.5 SD. Mean values and standard deviations for different age groups and fracture sites. SD = standard deviation

T-score <-2.5 SD									
	Hip		Vert		Wrist		Humerus		Distribution
Age	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
60-64	0.0002481	0.0000157	0.0001400	0.0000093	0.0006532	0.0000200	0.0002626	0.0000099	beta
65-69	0.0004212	0.0000224	0.0002222	0.0000137	0.0007752	0.0000243	0.0003285	0.0000127	beta
70-74	0.0007209	0.0000281	0.0002968	0.0000159	0.0008832	0.0000265	0.0003744	0.0000138	beta
75-79	0.0016163	0.0000456	0.0005959	0.0000249	0.0010509	0.0000305	0.0005793	0.0000207	beta
80-84	0.0027473	0.0000608	0.0009903	0.0000344	0.0011441	0.0000349	0.0006302	0.0000237	beta
85-89	0.0032645	0.0000760	0.0011603	0.0000453	0.0011361	0.0000430	0.0006255	0.0000292	beta
90-95	0.0040571	0.0001123	0.0012347	0.0000652	0.0010475	0.0000587	0.0005792	0.0000399	beta
95+	0.0041631	0.0002059	0.0009564	0.0001042	0.0007673	0.0000911	0.0004289	0.0000623	beta

Table 1B. Monthly fracture probabilities for women with a T-score of ≤-2.5 SD. Mean values and standard deviations for different age groups and fracture sites. SD = standard deviation

Age	RR with T-score of -2.5 SD			RR with T-score of <-2.5 SD		
	Vert	Hip	Wrist	Vert	Hip	Wrist
60	1.32	2.35	1.20	2.36	4.21	2.15
65	1.21	1.82	1.06	2.34	3.51	2.05
70	1.04	1.42	0.94	2.16	2.95	1.96
75	0.89	1.11	0.82	1.97	2.43	1.81
80	0.76	0.86	0.73	1.85	2.09	1.77
85	0.65	0.66	0.64	1.58	1.6	1.56
90	0.56	0.52	0.57	1.51	1.4	1.54

Table 2. Increased fracture risk for ostoeporotic women, as published by Kanis et al. (26)**.** RR = relative risk; SD = standard deviation

Treatment effects

We derived estimates for the treatment effects of risedronate from a meta-analysis of randomised placebo controlled trials (21) showing a reduced risk for fractures from all sites when compared to vitamine D and calcium: The relative risk (RR) was 0.63 (95% CI, 0.51 to 0.78) for vertebral fractures, 0.60 (95% CI 0.42 to 0.88) for hip fractures, 0.67 (95% CI 0.50 to 0.90) for humerus fractures, and 0.68 (95% CI 0.43 to 1.08) for wrist fractures, respectively [Table 3].

For the base case analysis we assumed a treatment duration of 5 years with full adherence, followed by 5 years of offset time. During the offset time, we assumed that risedronate's effectiveness declines linearly from full to no effectiveness.

Quality of life data

We use health state utility values as reported by Kanis et al. (28), age and gender specific UK baseline quality of life (QoL) values from the literature (29) and data provided by Paul Kind (University of York, UK, personal communication) because no Swiss quality of life data of sufficient quality was available. However, baseline health

Parameter	Mean	SD	Distribution	Source
Relative Risk				
RR hip	0.60	0.046	normal	(21)
RR wrist	0.68	0.092	normal	(21)
RR vert	0.63	0.107	normal	(21)
RR humerus	0.67	0.122	normal	(21)
Costs [CHF]				
hip fx	7232	2236	gamma	(30)
wrist fx	4336	830	gamma	(30)
vert fx	5456	1753	gamma	(30)
humerus fx	8505	2670	gamma	(30)
hip rehab	5508	1574	gamma	(33; 63)
wrist rehab	805	230	gamma	(36; 63)
vert rehab	1830	523	gamma	(34; 63)
humerus rehab	1647	471	gamma	(35; 63)
risedronate/month	62.75	-	-	(42)
GP visit/year	315	-	-	(41)

Table 3. Treatment efficacy and costs. SD = standard deviation; RR = relative risk; CHF = Swiss francs; fx = fracture; rehab = rehabilitation; GP = general practicioner

related quality of life is likely to be similar in the Swiss and UK populations as indicated by estimates from the 2002 Swiss Health Survey (24) that was based on telephone interviews.

To estimate age and health status specific quality of life values, the values of the general population were multiplied with the values for women with established osteoporosis for each health state. This assumes that the loss in quality of life due to

an event is dependent on the pre-event quality of life (e.g. younger people with higher pre-fracture QoL have more to loose)[Table 4].

Parameter	Age	Mean	SD	Distribution	Source
well	60-64	0.81	0.26	beta	(28)
well	65-74	0.78	0.25	beta	(28)
well	75+	0.71	0.27	beta	(28)
hip	60-64	0.65	0.22	beta	(28)
hip	65-74	0.62	0.22	beta	(28)
hip	75+	0.56	0.23	beta	(28)
wrist	60-64	0.81	0.26	beta	(28)
wrist	65-74	0.78	0.25	beta	(28)
wrist	75+	0.71	0.27	beta	(28)
humerus	60-64	0.74	0.24	beta	(28)
humerus	65-74	0.71	0.23	beta	(28)
humerus	75+	0.65	0.25	beta	(28)

Table 4. Quality of life data. SD = standard deviation

Cost data

Costs for the treatment of fractures were obtained from the Swiss All Patient Diagnosis Related Groups (APDRG) version 5.1 (30)[Table 3]. For fractures where more than one diagnosis related group (DRG) was available (i.e. cases with and without complications) we combined the costs from all relevant DRGs weighted by the number of cases in 2005. As treatment costs in Switzerland differ between university and non-university hospitals, we weighted the different costs by the number of total cases treated in university and non-university hospitals. Fracture patients will require musculoskeletal rehabilitation after discharge from hospital (31-33). Duration and intensity of rehabilitation was taken from the literature (33-37). Costs per physiotherapy sessions were estimated from the cost data for rehabilitation from the association of Swiss hospitals and rehabilitation clinics (38): hip fracture

CHF 12813, wrist fracture CHF 5141, vertebral fracture CHF 7286 and humerus fracture CHF 10152.

To account for complications in hip fracture surgery (e.g. bacterial infections, loosening of the prosthesis) we conservatively estimated in hospital treatment costs to increase by 1% (39; 40).

Patients in the post-hip and post-vertebral fracture health states are assumed to have impaired physical functioning and consequently are in need of home care (e.g. help with personal hygiene). Costs for this were obtained from Spitex, a large Swiss home care organization (Spitex, Basel, personal communication). Monthly home care costs were conservatively estimated at CHF 1314 [Table 3].

Patients under risedronate treatment will need at least one annual visit at their general practitioner. Costs for this visit are assumed to amount to CHF 315 (41). Monthly costs for risedronate were obtained from the Swiss Drug Compendium (42)[Table 3].

Analysis

The estimate of the cost-effectiveness of risedronate therapy compared to no therapy is presented as the incremental cost-effectiveness ratio (ICER; i.e. the ratio of incremental costs over incremental effects)(43) and as the incremental net monetary benefit statistics (44). We calculate the total health effect and obtain the corresponding resource use for each treatment strategy. The health effect is measured in quality adjusted life years to incorporate any differences in mortality and morbidity into the analysis (45).

All costs in the model are in Swiss Francs (CHF) of the financial year 2007. Costs and health effects are discounted with monthly compounding at an annual discount rate of 3%.

Sensitivity analysis

Parameter uncertainty is addressed by probabilistic sensitivity analysis (PSA) with 10 000 Monte Carlo simulations (46-48). Hence, parameters in the model are assigned individual probability distributions by the method of moments fitting (49). We used normal distributions for the RR parameters, gamma distributions for the cost parameters, and beta distributions for the quality of life and fracture incidence parameters. Uncertainty in all model parameters was based on the same source as for the mean values without any further assumptions.

We explore with extensive one-way sensitivity analyses the effect of different values for parameters that may vary but are not subject to parameter uncertainty and may therefore not naturally be ascribed a probability distribution (i.e., starting age, treatment duration, offset time and discount rate).

Results

Base case analysis

Results for the base case analysis (women starting treatment at age 70) are shown in Tables 5 and 6. Females with postmenopausal osteoporosis, aged 70 years with a T-score of -2.5 SD, and 5 year consecutive treatment with risedronate will experience 8.686 QALYs (95% CI 7.205 QALYs to 9.939 QALYs) compared to 8.621 QALYs (95% CI 7.161 QALYs to 9.861 QALYs) experienced by individuals without risedronate treatment when assuming 100% drug adherence. The average total treatment costs under risedronate therapy are CHF 22 369 (95% CI CHF 19 935 to CHF 25 280) compared to CHF 17,952 (95% CI CHF 15 017 to CHF 21 284) for the no treatment strategy. This yields an incremental cost-effectiveness ratio of CHF 70,323 per QALY.

Women aged 70 years with a T-score of ≤-2.5 SD gain 0.121 QALYs compared to untreated women (95% CI 0.074 QALYs to 0.171 QALYs) [Tables 5 & 6]. Total costs are CHF 38 141 (95% CI CHF 32 913 to CHF 43 911) for women treated with risedronate and CHF 36 139 (95% CI 30 096 QALYs to 42 857 QALYs) for women with no therapy. With incremental costs of CHF 2 001 (95% CI CHF 322 to CHF 3 429) the ICER then is CHF 16 475/QALY.

Age at initiation of therapy

The age of the patients at which the treatment is initiated has a large impact on the estimated cost-effectiveness of risedronate. Figure 4 shows the ICER when treatment for osteoporotic women with a T-score of -2.5 SD and ≤-2.5 SD is initiated at different ages. For both patient populations, the ICER decreases until a starting age of 80 years. For women with a T-score of <-2.5 SD who start treatment at age 74 or later, risedronate treatment becomes cost-saving (i.e. more effective and less costly than no treatment).

Treatment duration and length of offset time

Using a shorter treatment duration of one year (and assuming an offset time of one year) the ICER is CHF 310 427/QALY for 70-year-old women with a T-score of -2.5 SD (for women with a T-score ≤-2.5 SD: CHF 141 888/QALY). Extending the treatment duration to 10 years lowers the ICER to CHF 39 872/QALY for women with a T-score of -2.5 SD (CHF -333/QALY for women with a T-score of ≤-2.5 SD).

Assuming no treatment effect during the offset time increases the ICER to CHF 146 969/QALY for 70-year-old women with a T-score of -2.5 SD (women with a T-score ≤-2.5 SD: CHF 57 291/QALY). Extending the offset time to 10 years lowers the ICER to CHF 42 767/QALY (women with a T-score ≤-2.5 SD: CHF 1524/QALY).

Time horizon and discount rates

Using a shorter time horizon of increases the ICER for both patient population, as not all treatment benefits are captured in the analysis. Applying different discount rates to the analysis yields the expected results.

Probabilistic sensitivity analysis and value of information analysis

Probabilistic sensitivity analysis provides an estimate of the cost-effectiveness of risedronate for different willingness to pay values [Table 6, Figures 2 & 3]. The

applied threshold value is crucial in the decision whether risedronate is cost-effective or not. At a threshold value of CHF 50 000/QALY the probability that risedronate is cost-effective for osteoporotic women with a T-score of -2.5 SD is 7%, at the higher threshold value of CHF 100 000/QALY, however the corresponding probability is 90%. The probability that risedronate is cost-effective is much larger and approaches 100% for women with a T-score ≤-2.5 SD who are at the highest fracture risk.

Depending on the applied threshold value, the decision uncertainty varies from large to small values [Figure 2]. Decision uncertainty can be expressed as the expected value of perfect information (EVPI)[Figure 3]. For both patient populations EVPI reaches a maximum of more than CHF 350 per patient. In practice EVPI is negligible for women with a T-score of ≤-2.5 SD and a willingness to pay of at least CHF 50 000/QALY. For women with a T-score of -2.5 SD total EVPI per patient is CHF 30 at a decision maker's willingness to pay of CHF 50 000/QALY and increases to CHF 60 per patient when a willingness to pay of CHF 100 000/QALY is assumed [Table 6].

Discussion

Based on a decision analytic model we analysed the cost-effectiveness of risedronate treatment in osteoporotic women in a Swiss setting. For a variety of scenarios we have shown that the treatment of osteoporosis with risedronate is cost-effective. The cost-effectiveness of risedronate is dramatically influenced by the age of patients at treatment initiation. Older patients are at higher risk for any of the modelled fractures (hip, wrist, vertebral and humerus fractures) and thus will have a larger treatment benefit at the same treatment costs. If we assume a constant relative risk reduction from risedronate over age, the treatment prevents more fractures when the treated population is older. Risedronate therefore is more likely to be cost-effective in older patient populations. This general finding is supported by various cost-effectiveness analyses (26; 50-52).

Age	Population	Costs comp. [CHF]	Effects comp. [QALYs]	Costs risedronate [CHF]	Effects risedronate [QALYs]	Incremental costs [CHF]	Incremental effects [QALYs]	ICER [CHF/QALY]
70	-2.5 SD	17952 (15017 to 21284)	8.621 (7.161 to 9.861)	22369 (19935 to 25280)	8.686 (7.205 to 9.939)	4516 (3668 to 5264)	0.064 (0.040 to 0.090)	70323
70	<-2.5 SD	36139 (30096 to 42857)	8.224 (6.862 to 9.371)	38141 (32913 to 43911)	8.346 (6.947 to 9.525)	2001 (322 to 3429)	0.121 (0.074 to 0.171)	16475

Table 5. Base case results. Costs, effects and ICER (mean values and 95% confidence intervals). ICER = incremental cost-effectiveness ratio; comp. = comparator; CHF = Swiss francs; QALYs = quality adjusted life years; SD = standard deviation

Age	Population	INMB [CHF] @ CHF 50000/QALY	INMB [CHF] @ CHF 100000/QALY	P (INMB>0) @ CHF 50000/QALY	P (INMB>0) @ CHF 100000/QALY	EVPI [CHF/patient] @ 50000/QALY	EVPI [CHF/patient] @ 100000/QALY
70	-2.5 SD	-1305 (-2942 to 457)	1906 (-903 to 4857)	0.069	0.904	30	60
70	<-2.5 SD	4072 (913 to 7498)	10146 (4772 to 15901)	0.995	1	2.2	0

Table 6. Probabilistic sensitivity analysis. Incremental net benefit and expected value of perfect information (mean values and 95% confidence intervals). INMB = incremental net monetary benefit; CHF = Swiss francs; P = probability; QALY = quality adjusted life year; EVPI = expected value of perfect information; SD = standard deviation

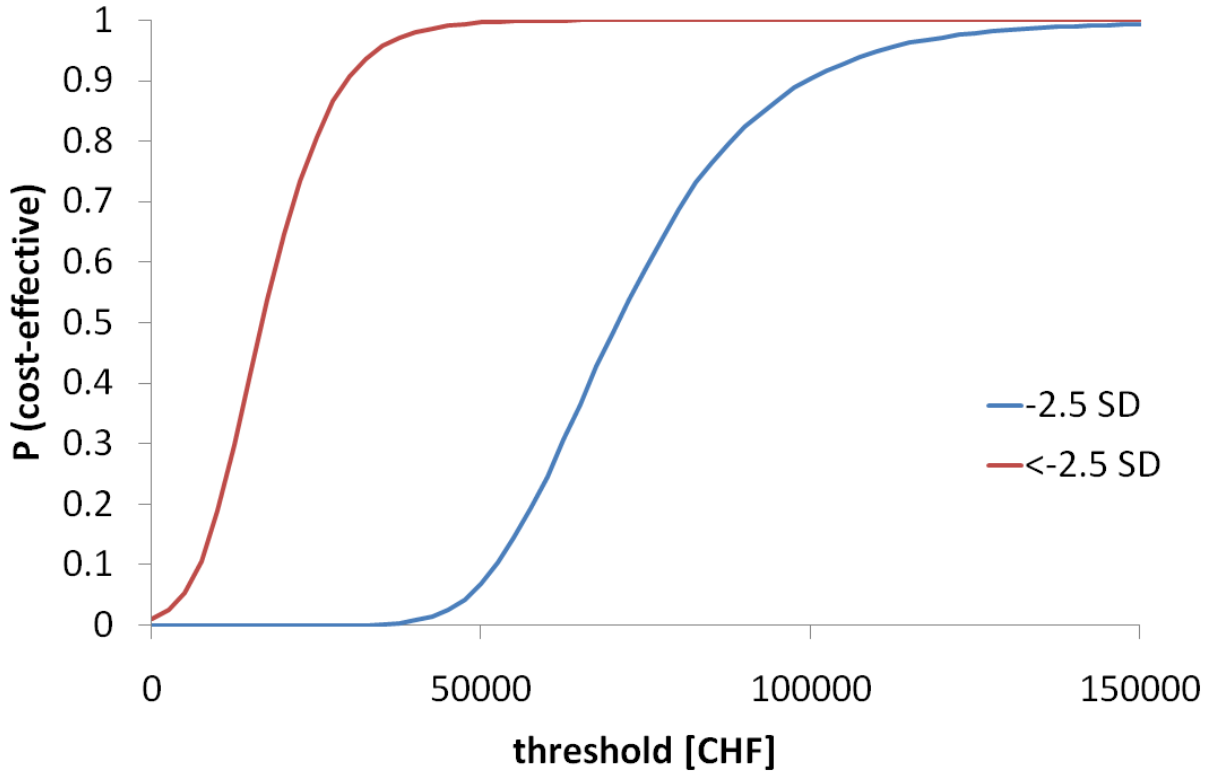

Figure 2. Cost-effectiveness acceptability curves (starting age 70 years). P = probability; CHF = Swiss francs; SD = standard deviation

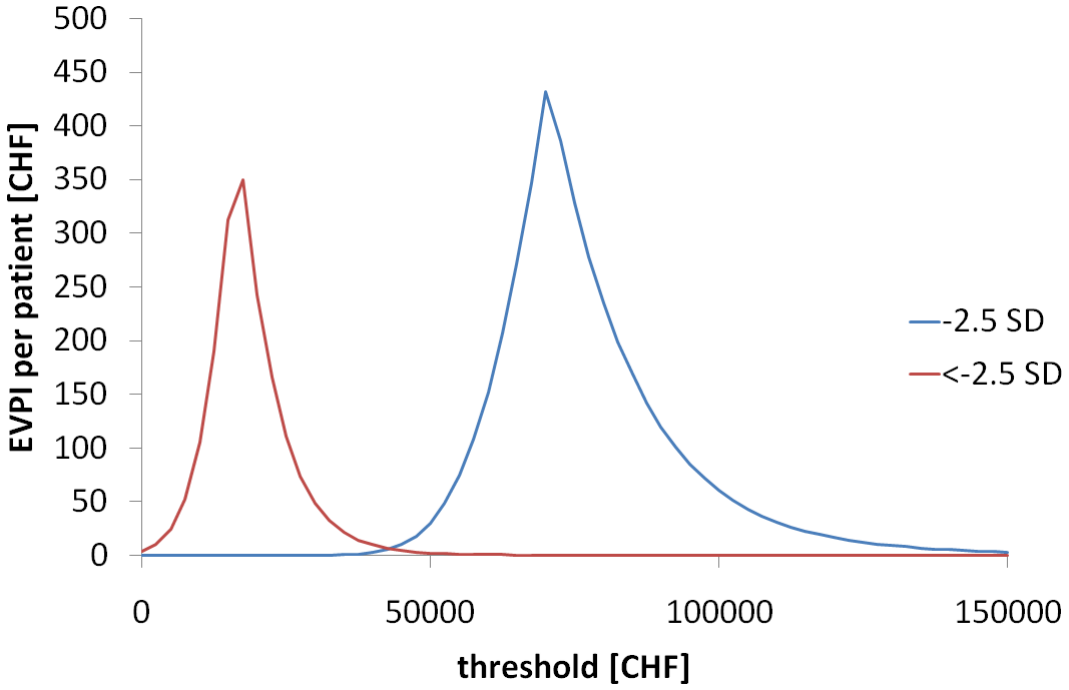

Figure 3. Expected value of perfect information per patient (starting age 70 years). CHF = Swiss francs; SD = standard deviation

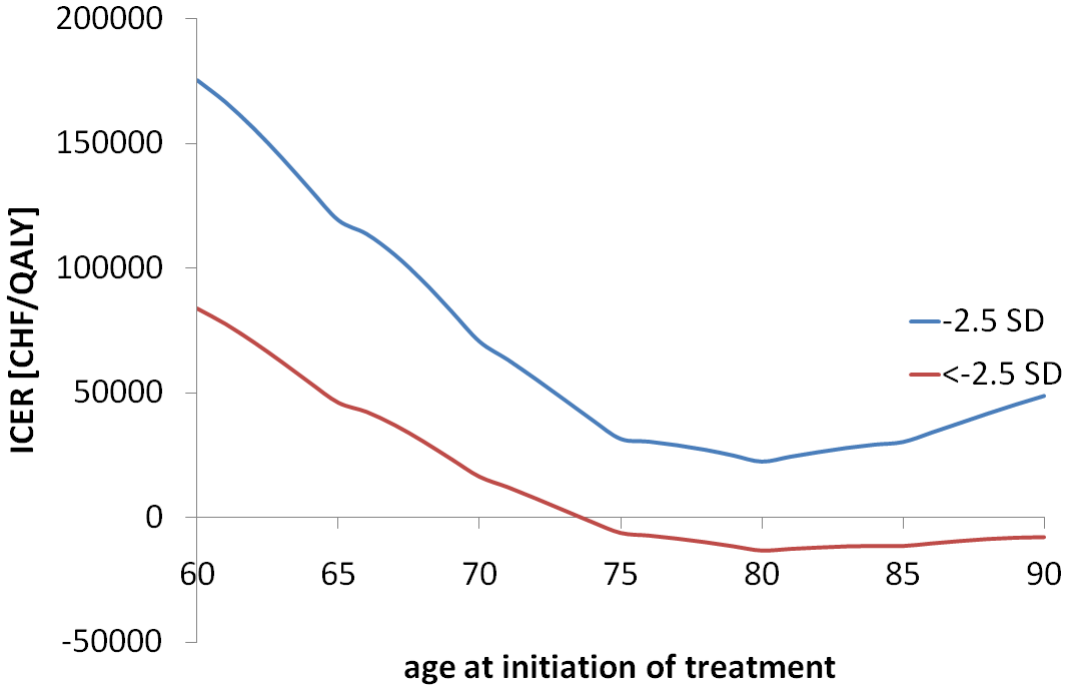

Figure 4. Univariate sensitivity analysis on starting age. ICER = incremental cost-effectiveness ratio; CHF = Swiss francs; QALY = quality adjusted life year; SD = standard deviation

Although for Switzerland there is no official data on the decision makers' willingness to pay value per quality adjusted life year, using a threshold level of CHF 100 000/QALY risedronate treatment is cost-effective for postmenopausal osteoporotic women with a T-score of ≤-2.5 SD and an age of 58 years or older (data not shown). For women with a T-score of -2.5 SD risedronate treatment becomes cost-effective for women 68 years or older, assuming the same threshold value.

In a recently published review, Fleurence and colleagues (53) found in most analysed studies from Denmark, USA, UK and Sweden)that bisphosphonates are unlikely to be cost-effective in women younger than 50 years of age. Bisphosphonate therapy is most cost-effective in women at 70 years of age or older. For the age group 60 to 69 years the authors found uncertainty concerning the cost-effectiveness of bisphosphonate therapy. A cost-utility analysis for alendronate in 9 European countries reported incremental cost-effectiveness ratios of cost saving to € 46 326/QALY (for Italy) depending on the country, women's age at baseline, bone mineral density and status regarding previous fractures (54). For Germany the estimate was € 33 079/QALY. These values correspond to estimates of the ICER of about CHF 89 000/QALY (Italy) and CHF 52 000/QALY (Germany) in 2007 Swiss francs. Compared to these two countries, our estimate of CHF 82 682/QALY for 69-year-old women lies in between these values. This is in line with the findings by Ström et al. (54) who report a general pattern of smaller cost-effectiveness estimates for countries at higher latitude and larger ICERs for countries located further south. A reason for this may be the varying pattern of fracture incidences across different countries (54).

Our study has several strengths such as the rigorous way we set up and populated our model with data. Using a previous published model structure, the results of our analysis are more easily comparable to other studies, although generalisability may still be limited since we applied our analysis to a Swiss setting. To date there exist only two other cost-utility analysis of a bisphosphonate that have been published for a Swiss setting (22; 41). Krieg et al. found that treating postmenopausal women with risedronate for 5 years is associated with an incremental cost-effectiveness ratio between CHF 77 276/QALY and CHF -15 098/QALY, depending on the age of women at treatment initiation (numbers shown for ages 65 to 75 years) and their fracture

risk. The study is difficult to assess since the presentation of model inputs and outputs is sparse. Schwenkglenks et al.'s study (41) analysed the cost-utility of a mass screening programme followed by 5 years of alendronate treatment. This approach is different to ours and the ICERs are not comparable, since with Schwenkglenks et al.'s screening approach, women with T-scores of -2.5 SD and ≤-2.5 SD would be identified and subsequently treated. Thus, patient populations with different fracture risks cannot be distinguished anymore.

One of the limitations of our analysis is, that we assumed full drug compliance throughout the 5 years treatment period. It is known that in actual practice, compliance with bisphosphonate treatment is suboptimal (55-57). Modelling the impact of less than full compliance in decision analytic models has been discussed previously, but ultimate recommendations for handling this issue are inconclusive (58; 59). Hence, we assumed full compliance and may thus underestimate the ICER, but we are in line with a variety of cost-effectiveness analyses published to date (23; 26; 54; 60; 61) using the same approach.

Apart from the usual probabilistic sensitivity analysis, we calculated the expected value of perfect information (EVPI) for our base line scenarios for two willingness to pay values. Expected value of perfect information places a monetary value on the opportunity loss that will arise both in monetary units and health benefits foregone, when the wrong decision is adopted (62). For osteoporotic women with a T-score of ≤-2.5 SD the EVPI is at a threshold level of CHF 50 000/QALY very small and approaches zero for larger threshold values. This means that the decision uncertainty is too small, that further information (that could inform the decision of whether risedronate is cost-effective for 70-year-old women with a T-score of ≤-2.5 SD) will be of any value. In contrast, EVPI for 70-year-old women with a T-score of -2.5 SD is relatively large for potentially relevant threshold values between CHF 50 000/QALY and CHF 100 000/QALY. Collecting new data could be cost-effective in order to be able to put this decision on a more sound evidence basis.

Conclusion

The results of our study suggest that risedronate treatment for preventing osteoporotic fractures in Swiss postmenopausal women is cost-effective for women with a T-score of ≤-2.5 SD. Risedronate treatment is cost-effective for osteoporotic women with a T-score of -2.5 SD at age 70 years or older. For younger women risedronate may be cost-effective, depending on the decision maker's willingness to pay value per QALY.

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CHAPTER 4: COMPLIANCE IN OSTEOPOROSIS DECISION ANALYTIC MODEL

How much bone for the buck? On the importance of addressing compliance issues in economic evaluations of bisphosphonates.

Medical care usually entails careful consideration of benefits, risks and costs. Bisphosphonate therapy for the prevention and treatment of osteoporosis has significant benefits at moderate risks that come at costs that are somewhat higher than the price of a box of calcium tablets . Prescription rates from the US show the increased acceptance of bisphosphonate therapy. 97% of all osteoporosis patients will leave their physician's practice with a prescription, 73% of which will be for a bisphosphonate. Recent economic evaluations of bisphosphonate therapy have shown that these antiresorptive drugs are cost-effective for certain patient populations .

Is this really always the case? How cost-effective is a treatment that may not be taken but instead takes up space in the bathroom cabinet (where drugs shouldn't be stored in the first place anyway)? Did we forget about compliance? It is known that compliance with bisphosphonate therapy is often suboptimal. The results of a recent analysis by McCombs and colleagues show that the mean unadjusted duration of continuous therapy is 245 days for bisphosphonates . Further, we know that high compliance with bisphosphonate therapy reduces the risk of a fracture by 16% . Or to put in another way: low compliance will reduce the effectiveness of the intervention and consequently its cost-effectiveness.

The vast majority of all economic evaluations of bisphosphonate therapy (or of interventions for the prevention or treatment of osteoporosis in general) are studies that make use of decision-analytic models. Based on the results of a recent review on economic evaluations for the prevention and treatment of osteoporosis, published between 1980 and 2004, 41 out of 42 studies were model-based . This is not surprising. Osteoporosis is a chronic disease, the event rate (fracture rate) is relatively small, and the beneficial effects of therapy will not be effective until months after the onset of therapy. Decision-analytic models like the frequently used Markov models provide the possibility of easily projecting the course of a chronic disease over time, including the respective number of events and resource use. However, because the model structure depends on the research question (and research group) and is naturally not predefined, it is up to the analyst to build a model in such a way that it

reflects clinical reality or the „real world." As compliance may substantially jeopardize effectiveness, this should clearly be taken into account when a decision analytic model is constructed .

How has compliance been dealt with hitherto in published models? The striking result is: almost not at all, at least not explicitly. In a review of decision analytic modeling studies of the cost-effectiveness of interventions for the prevention of osteoporosis published in the years 2001 to 2004 (unpublished data, available on request from the authors), only 4 out of 17 studies addressed compliance issues either in the base-case analysis or in the sensitivity analysis. However, the majority of these studies addressed the problem of poor compliance in the discussion sections of the papers. Frequently, it was stated that poor compliance may influence the result of the analysis and would lower the effectiveness of the intervention. It was then further argued that such reduced effectiveness would „to some extent" be offset by lower treatment costs . This sounds intuitively right, but we should be interested in total health care costs and not just treatment costs. A recent study by Sokol et al. has shown that for four chronic conditions (diabetes, hypertension, hypercholesterolemia and congestive heart failure) compliance is negatively correlated not only with hospitalization risk, but also with total health care costs. So although medical costs may be lower because of poor compliance, overall health care costs might be larger. This is because of a larger hospitalization risk in patients that comply poorly with their therapy. However, McCombs and colleagues do not find such a strong relationship between patient compliance with osteoporosis prevention/treatment and fracture risk. The additional drug costs of US$266 for one year, when the patient does fully comply with therapy, is only partly offset by the reduced costs for physicians (- US$56), hospital outpatient services (- US$38) and laboratory use (- US$9) and other hospital costs of - US$155 (total reduction of non-drug costs in case of compliance: US$258). But it should be noted that a higher fracture rate is also associated with productivity costs and a reduced quality of life. It is very likely that when the full societal economic consequences are considered, the impact of compliance on cost-effectiveness would be even larger.

But even if we exclude total health care costs from our analysis, there is something odd about stating that lower effectiveness through lower compliance is

partly offset by lower treatment costs. Why don't we just simply say that we may overestimate the intervention's cost-effectiveness (i.e., report too low incremental cost-effectiveness ratios) if compliance is suboptimal? The majority of researchers are aware of the problem of poor compliance. So why don't we find more studies that properly deal with it? The answer to this can be found in a recent study on the cost-effectiveness of the bisphosphonate alendronate, which stated that „compliance is not an easy issue to handle in economic evaluations“ .

It is difficult to estimate the level of compliance with bisphosphonates over time and it is even more difficult to estimate the effect of poor compliance on the amount of relative risk reduction associated with bisphosphonate therapy. In order to be able to discuss the influence of poor compliance, we first need to establish what we mean by compliance or being compliant. One possible way that is frequent in the medical literature is to consider patients compliant if they have medication available during a certain duration of treatment time (e.g., prescriptions are obtained to cover 80% of treatment time) . As we don't know whether the patients are actually using the drugs they obtained, using this definition will overestimate the level of compliance, yielding a conservative estimate of patients‘ actual compliance. Some patients will have their tablets ready but then simply forget to take them or intentionally decide to stop taking their medication for whatever reason (e.g., side effects or costs of medication).

In the end, it comes down to the question „how much compliance is sufficient for full effectiveness?“ This is determined by the drug‘s pharmacodynamics, i.e., the drug's dose-response relation. There are drugs which require either substantially more or less than 80% of prescribed doses taken for full effectiveness. Although bisphosphonates have now been used for many years, their complex pharmacokinetic/pharmacodynamic relationship is not yet fully understood. Having said this, we should have a closer look at the data from McCombs et al. again.

McCombs et al. show that 42.7% of all patients in the first treatment year take their medication for less than 90 days and only 31% of all patients in their initial year of therapy have a level of compliance above 80%. These figures are based on prescription data of 3720 Californian patients who were prescribed bisphosphonates. In light of these data, it seems to be quite a strong assumption that a cohort of say

5000 patients would take their weekly (or even daily) dose of bisphosphonates for 5 years without any interruption or break of therapy.

Another problem arises because we don‘t really know how patients do not comply. Some patients will just switch to other therapies, others will refuse to take any medication and a third group of patients will have an intermittent therapy that is just a little bit more intermittent than originally intended by the treating physician (i.e. they will forget to take their medication every now and then). One way to take these latter patients‘ lower compliance into account is to assume that a reduced level of compliance of for example 80% will result in only 80% of the drug’s full effectiveness (e.g., 80% compliance to a treatment with a relative (fracture) risk of 0.6 under a level of compliance of 100% will result in an (increased) relative risk of 0.68 (compliance adjusted relative risk = 1 – ([1-0.6]*0.8) = 0.68). Admittedly, assuming a linear relationship between relative risk reduction and compliance is fairly arbitrary, but the analyst may also want to explore alternative relationships in a sensitivity analysis if pharmacodynamic considerations do not clearly suggest how compliance and hence drug plasma levels may affect effectiveness.

At the moment, we don’t have data to provide a standard prescription for how compliance should be technically dealt with in analyses, but neither do we think that omitting compliance issues from the analysis is the way to go. The absence of data is not in itself a justification for simplification . Patients who switch therapies accrue no further costs and likewise obtain no further benefits if we do not assume the presence of any positive effect during the „offset time.“ This seems to be a reasonable assumption since 37% of bisphosphonate patients switch to a second medication within their initial treatment year, which is a short time period for any clinical effect to become significant and large enough to have an effect during the „offset time.“ Patients who just „store“ their medication at home probably do not make for the largest part of patients.

In the end, what we have tried to emphasize in this editorial is that compliance may have a substantial impact on how much bone we get for the buck, and we therefore recommend its formal implementation in economic evaluations of bisphosphonates.

CHAPTER 5: DRUG-ELUTING STENTS

Cost-Effectiveness of Drug-eluting Stents in a US Setting: A Cost-Utility Analysis with 3 Year Clinical Follow-up Data

Abstract

Background: The cost-effectiveness of drug-eluting compared to bare metal stents over a time horizon of more than one year is unknown.

Methods: We developed a Markov model based on clinical outcome data from a meta-analysis including 17 randomized controlled trials (RCTs) comparing drug-eluting versus bare metal stents with a minimum follow-up of one (n = 8221) and a maximum follow-up of 3 years (n = 4105) in patients with chronic coronary artery disease. Costs were obtained as reimbursement rates for diagnosis related groups (DRGs) from the US Centers for Medicare and Medicaid Services. All costs and effects were discounted at 3% annually. All costs are reported in US dollars of the financial year 2007.

Results: The incremental effects are 0.001 (95% CI -0.032 to 0.038) QALYs for the sirolimus-, and -0.002 (95% CI -0.049 to 0.047) QALYs for the paclitaxel-eluting stents. The incremental costs are $1953 for the sirolimus- and $4329 for the paclitaxel-eluting stents. The incremental cost-effectiveness ratio is > $1 000 000 per quality adjusted life year for the sirolimus-eluting stent. The paclitaxel-eluting stent is dominated by bare metal stents (i.e. less effective and more costly). Among various sensitivity analyses performed, the model proved to be robust.

Conclusions: Our analysis from a US Medicare perspective suggests that DES are not cost-effective compared to BMS when implanted in unselected patients with symptomatic ischemic coronary artery disease.

Introduction

The economic burden of cardiovascular disease is substantial. In the year 2006, health care spending and lost productivity from cardiovascular disease exceeded $400 billion in the US (1). Among patients with coronary artery disease, stent implantation has become the treatment of choice in the last decade (2; 3). Currently, nearly 80% of all inserted stents in the US are drug-eluting stents (DES) (4). It is estimated that the world market for DES sums up to $6 billion annually (5).

In recently published meta-analyses of randomized controlled trials (RCTs) comparing bare metal to drug-eluting stents, drug-eluting stents were found to reduce restenoses and the need for revascularization procedures, but not overall mortality or the incidence of myocardial infarction (6-12).

As with many new interventions, there is a significant price premium on drug-eluting stents when compared to conventional bare metal stents (BMS). Limited health care budgets increase the incentive to not only look at the clinical effectiveness of an intervention but also to take into account the cost-effectiveness of a novel therapy.

Several economic evaluations of DES exist to date, some of which are directly based on clinical trials and others on model-based economic evaluations (9; 13-18). However, there still remains a considerable controversy about the cost-effectiveness of DES when compared to BMS for all patients undergoing percutaneous coronary interventions (19; 20).

In a recent systematic review, Lightart and colleagues identified 19 cost-effectiveness studies of DES that were published between January 2000 and July 2006 (5). In their conclusions 10 studies were in favour whereas 9 studies were not in favour of widespread use of DES. Five of the 19 studies were performed from a US third party payer perspective, and favoured the widespread use of DES (21-25). All studies from the US used a short time horizon with maximum clinical follow-up of one year, and thus disregarded potential differences in other patient-relevant outcomes as well as quality of life estimates that may arise beyond the first year after stent implantation. Other studies used a single trial as a vehicle for the economic evaluation which will often lead to a partial and limited analysis (26).

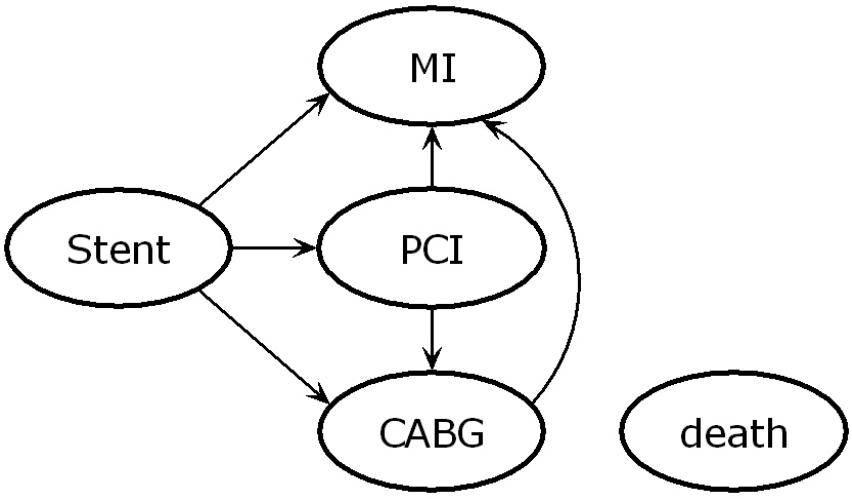
To provide a more thorough answer to the question whether the routine use of DES is cost-effective for the treatment of coronary artery disease from a US Medicare payer's perspective, we developed a decision analytic model based on recently published data of long-term outcomes of randomized controlled trials comparing DES to BMS. We developed a model that allows for a probabilistic sensitivity analysis to address the joint implications of parameter uncertainty (i.e. uncertainty about the input data) on the uncertainty relating to the decision whether a novel technology is cost-effective (26).

Methods

A half-cycle corrected Markov cohort simulation model with the 5 mutually exclusive health states stent, non-fatal myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), and death was developed (Figure 1) (27). We compared two strategies: SES versus BMS and PES versus BMS. The transition probabilities from the index procedure to death, non-fatal myocardial infarction, clinically driven percutaneous coronary intervention, and coronary artery bypass grafting were derived from an updated, previously published meta-analysis of randomized controlled trials comparing SES or PES to BMS in patients with coronary artery disease (11). Briefly, trials were required to report mortality data after at least one year of follow-up. Trials exclusively including patients with acute coronary syndromes or trials focussing on interventions in non-native coronary arteries were excluded since these trials evaluate a different patient population. We conducted a systematic literature search of Medline, Embase, Web of Science, the Cochrane Library, websites dedicated to the dissemination of results from cardiovascular trials from January 1980 up to April 2006 and contacted the manufacturers of SES and PES. We identified 17 trials including 8221 patients that fulfilled inclusion criteria. Seven trials used SES (n=2487), 9 trials (n=4908) PES, and one trial (15) used (n=826) both DES. Twelve trials including 4631 patients reported outcome data after 2 years, 9 trials including 4105 patients reported outcome data after 3 years. Details on the selection process for potentially eligible trials, the characteristics and quality of included trials and on the generation of

summary estimates are provided in the appendix and have been published elsewhere (11).

The cycle length in the model is one month to allow for a precise estimation of the timing of events and related cost. The study's perspective is a US Medicare payer's perspective. Estimates for all parameters where there was no data available from our meta-analysis were derived from a systematic search of the medical literature. All costs and effects were discounted at 3% annually using monthly compounding.



Clinical parameters

Transition probabilities are of central importance in a Markov model. The transition probabilities from the stent state to the health states MI, PCI, CABG and death were obtained by transforming point estimates for event rates and their corresponding standard deviations into monthly probabilities (for 0 to 30 days after the index procedure, for 30 days to one year, for year 1 to 2 and for year 2 to 3; for details see appendix [tables 1A, 1B and 2]) (27). PCI was defined as any percutaneous target vessel revascularization. From the meta-analysis, outcome data were available for the time period 30 days following the initial stenting procedure, and for the years 1, 2, and 3 after the index procedure. Likewise we obtained values for the relative risks for the same transitions. We used the method of moments fitting (28) to fit beta distributions to the transition probabilities derived from the meta-analysis, and fitted lognormal distributions to all relative risk parameters in the model. The remaining transition probabilities were taken from published studies (29-34) and are provided

in Table 1. We assumed that the transition probabilities from the PCI-state to the health states MI, CABG and death were the same as for patients in the "stent" state.

Costs

All costs in the model were obtained as reimbursement rates for diagnosis related groups (DRGs) from the US Centers for Medicare and Medicaid Services (35). We used reimbursement rates for the DRGs 121 and 122 (circulatory disorders with acute myocardial infarction with/without major complications discharged alive), 547-550 (coronary bypass with/without cardiac catheterization with/without major CV DX), 556 (PCI with non-DES without CV DX), and 557 and 558 (PCI with DES with/without major CV DX). Reimbursement rates for DES are independent of the type of DES used. For events where more than one diagnosis related group (DRG) was available (i.e. cases with and without complications) we combined the costs from all relevant DRGs weighted by the number of cases in 2006 (35). We assumed that physician fees would account for the same percentage share per event as reported by Mahoney et al. (36). For our base case we used average Medicare reimbursement rates of 10 top-rated cardiology hospitals in the United States (37), in a sensitivity analysis we used average reimbursement rates from a random sample of 10 US hospitals from the same source (35). Costs are provided in Table 1. We assumed that there would be no difference in resource use for antiplatelet medication because clopidogrel or ticlopidine were used for the same time period in patients treated with DES and BMS in all trials of the meta-analysis. Thus, costs for medications and follow-up visits were not included into the model.

We fitted gamma distributions to reflect parameter uncertainty of the unit costs of the procedures. All costs are reported in US dollars of the financial year 2007.

Outcomes

The outcome of the two strategies was measured in natural units and quality adjusted life years (QALYs). This generic instrument weighs the length of life by the quality of life a patient has while being in a specific health state. QALYs combine both,

Parameter	Mean (SD) base case†	Dist.	Source	Mean (SD)	Source SA
Transition probabilities*					
MI -> death (30 days)‡	0.13	-	(30)	-	-
MI -> death (after 30 days)‡	0.00569	-	(30)	-	-
CABG -> death (30 days)§	0.015	-	(36)	-	-
CABG -> death (after 30 days)§	0.00255	-	(36)	-	-
CABG -> MI (first 30 days)§	0.0276	-	(32)	-	-
CABG -> MI (after 30 days)§	0.00077218	-	(32)	-	-
Disutilities [QALYs]					
MI‡	0.0104 (0.00047)	**beta**	(3)	0.00658	(39)
PCI‖	0.0104 (0.00047)	**beta**	(3)	0.00658	(39)
CABG§	0.0208 (0.00063)	**beta**	(3)	0.00658	(39)
Costs [US dollars]					
PCI with BMS‖	18469 (3781)	**gamma**	(35)	14609 (2602)	(35)
PCI with DES‖	24536 (5042)	**gamma**	(35)	18429 (2910)	(35)
Acute MI‡	15999 (3851)	**gamma**	(35)	11150 (1704)	(35)
CABG§	51050 (10972)	**gamma**	(35)	37576 (5882)	(35)

Table 1. Model parameters

*Transition probabilities are shown as monthly probabilities
†standard deviation
‡nonfatal myocardial infarctions
§coronary artery bypass graft
‖percutaneous coronary intervention

Table 1 continued

Cost data for the base case represent average DRG reimbursement rates for the following 10 **top-rated US hospitals**:

Cleveland Clinic, Cleveland, OH,
Mayo Clinic, Rochester, MN
Brigham and Women's Hospital, Boston, MA
Massachusetts General Hospital, Boston, MA
Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, TX
Duke University Medical Center, Durham, NC
Stanford Hospital and Clinics, Stanford, CA
Barnes-Jewish Hospital/Washington University, St. Louis, MO
UCLA Medical Center, Los Angeles, CA
William Beaumont Hospital, Royal Oak, MI

Cost data for the base case represent average DRG reimbursement rates for the following 10 **randomly chosen US hospitals**:

Northern Michigan Hospital, Petoskey, MI
Manchester Memorial Hospital, Manchester, CT
Reynolds Memorial Hospital Inc., Glen Dale, WV
Metrowest Medical Center, Natick, MA
Saint Luke's Hospital of Kansas City, Kansas City, MO
Whittier Hospital Medical Center, Whittier, CA
Sumter Regional Hospital, Americus, GA
St. Mary's Hospital, Centralia, IL
Alexian Brothers Medical Center, Elk Grove Village, IL
Madison County Hospital, London, OH

morbidity and mortality into a single parameter and therefore allow comparing the effect of treatments across different disease areas.

We calculated QALYs using the approach by Bagust et al. (14). We assumed a baseline quality of life value of 0.86 for patients without an event. We estimated disutility values (i.e. a short term drop in patients' quality of life) for patients with

PCI and CABG (Table 1) based on the results of the ARTS trial. In this trial quality of life values were obtained based on the EQ-5D questionnaire at baseline and 1, 6 and 12 months after stenting or coronary artery bypass graft surgery for coronary artery disease (3). We calculated the disutility values by taking the difference in health related quality of life values between a patient with and without an event. Thus, the calculated disutility values reflect the loss in patients' quality of life for up to 6 months after the event. No loss in quality of life was assumed to occur 6 months after the event. For patients experiencing a myocardial infarction we attributed an ongoing disutility of 0.01 per month starting at the time of the event until end of follow-up based on a community-based study reporting self-perceived quality of life after myocardial infarction (38). In a sensitivity analysis we used disutility values per event as reported in a health technology assessment from the United Kingdom on the use of coronary artery stents (39) disregarding the patients' loss in quality of life due to long waiting time (which generally does not apply to patients in a US Medicare setting).

Analysis

Total costs of the two strategies and the corresponding outcomes as number of quality adjusted life years experienced were recorded. The result of the analysis is expressed as the incremental net monetary benefit (INMB) for drug-eluting stents when compared to bare metal stents for 2 different threshold values ($50 000 and $100 000) (40). The INMB is calculated by the following standard equation:

$$INMB = \Delta \text{ effect} * \text{threshold value} - \Delta \text{ costs}$$

INMB is therefore the difference in treatment effect of DES (incremental effect) multiplied by the willingness to pay (i.e. threshold value) per one unit of outcome gained (i.e. per QALY) minus the incremental (i.e. additional) net total health care costs for providing DES. By multiplying the incremental effect with the threshold value, the effect is transformed into a monetary unit. For the base case analysis, we assumed an arbitrary decision maker's willingness to pay of $100 000 per QALY. A

positive INMB reflects that the intervention under analysis is cost-effective. The INMB approach yields the same results as when calculating the incremental cost-effectiveness ratio. However, the INMB approach avoids the potential problem of averaging over positive and negative incremental effects and costs that may arise when performing a probabilistic sensitivity analysis with multiple iterations.

We performed a probabilistic sensitivity analysis with 5 000 Monte Carlo simulations (41; 42) to account for parameter uncertainty that relates to the uncertainty in the analysis arising from the lack of definite knowledge about a parameter's true value. We tested the robustness of the model towards model assumptions with univariate sensitivity analysis on estimates of clinical effectiveness, on different time horizons, on the difference of DRG reimbursement rates for BMS and DES, on health state utilities, on costs of PCI, MI and CABG, and on discount rates for costs and health effects. Since published data on the need for percutaneous coronary re-interventions report censored data after one event, but some patients have multiple interventions, we conducted an additional sensitivity analysis on the number of patients undergoing multiple percutaneous coronary reinterventions. Based on data from the BASKET trial (15), we assumed that there are about 5% more percutaneous interventions due to multiple interventions in individual patients. The model was developed with Microsoft Excel and Microsoft Visual Basic 6.5.

Results

In the comparison of SES to BMS, 23.09% of BMS patients require a repeat PCI, compared to 8.72% of SES patients. The incidence of MIs over the 3 year time horizon is 4.38% in BMS patients and 3.35% in SES patients. Likewise the incidence of CABG is lower in the DES group (BMS: 3.18%; SES: 2.19%). Mortality is slightly increased in SES patients (BMS: 2.62%; SES: 2.66%). Results for the PES to BMS comparison are similar (not shown), with the only marked difference being the smaller difference between the number of PCI events in the PES and BMS groups (14.95% in BMS versus 10.18% in PES patients).

Costs , effects, INMB and ICER*							
stent type†	**Costs [US$]**	**Effects [QALYs]‡**	**Incremental costs [US$]**	**Incremental effects [QALYs]**	**INMB [using $50 000 as threshold]**	**INMB [using $100 000 as threshold]**	**ICER [US$/QALY]**
BMS	26253 (24615 to 28085)	2.358 (2.324 to 2.378)					
SES	28206 (27513 to 29014)	2.359 (2.334 to 2.376)	1953 (-14 to 3779)	0.001 (-0.032 to 0.038)	-1914 (-4442 to 795)	-1875 (-5646 to 2496)	➢ 1000000
BMS	24243 (23150 to 25478)	2.362 (2.318 to 2.385)					
PES	28571 (27851 to 29409)	2.360 (2.321 to 2.383)	4329 (2914 to 5700)	-0.002 (-0.049 to 0.047)	-4409 (-7102 to -1654)	-4490 (-7102 to -1654)	PES dominated

Table 2. Costs , effects, INMB and ICER.

*INMB=incremental net monetary benefit; ICER=incremental cost-effectiveness ratio; mean values and 95% confidence intervals, time horizon 3 years

†BMS=bare metal stent, SES=sirolimus-eluting stent, PES=paclitaxel-eluting stent

‡QALYs=quality adjusted life years

Costs , effects, INMB and ICER, assuming no difference in event rates for deaths between BMS and DES*							
stent type†	**Costs [US$]**	**Effects [QALYs]‡**	**Incremental costs [US$]**	**Incremental effects [QALYs]**	**INMB [using $50 000 as threshold]**	**INMB [using $100 000 as threshold]**	**ICER [US$/QALY]**
BMS	26272 (24651 to 28124)	2.356 (2.324 to 2.376)					
SES	28203 (27510 to 29020)	2.359 (2.335 to 2.376)	1931 (-45 to 3757)	0.003 (-0.029 to 0.039)	-1785 (-4211 to 843)	-1640 (-5384 to 2364)	662581
BMS	24208 (23147 to 25441)	2.360 (2.319 to 2.384)					
PES	28569 (27865 to 29415)	2.361 (2.323 to 2.384)	4360 (2955 to 5762)	0.001 (-0.043 to 0.047)	-4324 (-7019 to -1554)	-4289 (-9004 to 650)	➢ 1000000

Table 3. Costs , effects, INMB and ICER, assuming no difference in event rates for deaths between BMS and DES

*INMB=incremental net monetary benefit; ICER=incremental cost-effectiveness ratio; mean values and 95% confidence intervals, time horizon 3 years

†BMS=bare metal stent, SES=sirolimus-eluting stent, PES=paclitaxel-eluting stent

‡QALYs=quality adjusted life years

The incremental effects of the DES are 0.001 (95% CI -0.032 to 0.038) QALYs for SES and -0.002 (95% CI -0.049 to 0.047) QALYs for PES. The incremental costs are $1953 for SES and $4329 for PES. This yields an incremental cost-effectiveness ratio of > $1 000 000 for SES. PES are dominated by bare metal stents (i.e. PES less effective and more costly). Table 2 provides the expected costs and health effects for the base case analysis.

The uncertainty for the decision is graphically represented on the cost-effectiveness plane [Figure 2]. Cost-effectiveness acceptability curves provide an estimate of the probability that DES are cost-effective for a range of different willingness to pay values [Figure 3]. At an arbitrary willingness to pay of $100 000 per QALY, SES have a 16% probability, and PES a 3.5% probability of being cost-effective.

Univariate sensitivity analysis

In individual patient data meta-analyses comparing DES to BMS (6;8) there were no significant differences in the rates of death and myocardial infarction. Given the uncertainty around the point estimates of the relative risks for these outcomes in our meta-analysis, we conducted a sensitivity analysis assuming no difference in the number of deaths between patients treated with BMS and DES [Table 3]. Both DES then yield a small positive incremental effect, but the INMBs still remain negative. At an arbitrary willingness to pay of $100 000 per QALY, the INMB is then $-1640 for SES and $-4289 for PES, respectively. Accounting for multiple percutaneous coronary interventions in individual patients had no qualitative effect on the overall cost-effectiveness estimates, neither for SES nor for PES. To explore the effect of different time horizons, we calculated the incremental effect and the incremental net monetary benefit of DES for time horizons up to 3 years [Figures 4 and 5]. Both DES provide positive incremental effects (in QALYs) over a time horizon up to ~2.5 years of follow-up. Only SES, however, yield a small positive incremental effect over the full time horizon of the analysis (i.e. 3 years). After 2 years there is a decline in incremental effects for both DES, which seems to be driven by a trend towards increased mortality in patients treated with DES [Figure 4]. Both DES yield a negative incremental net monetary benefit for time horizons ranging from 0 to 3 years, assuming a decision maker's willingness to pay of $100 000/QALY [Figure 5]. The INMB is relatively stable for both DES for time horizons of 1 year and longer.

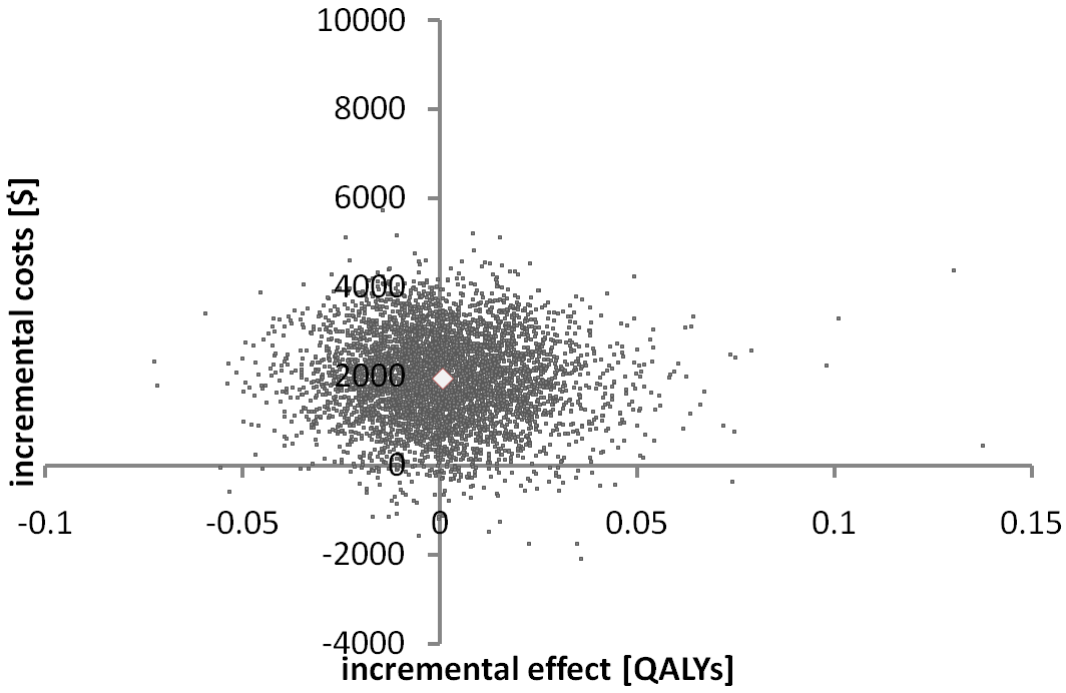


Figure 2A. Cost-effectiveness plane. Incremental costs and effects of the **sirolimus-eluting stent** are based on 5 000 Monte Carlo simulations. The point estimate (incremental costs $1953; incremental effect 0.001 QALYs) is highlighted.

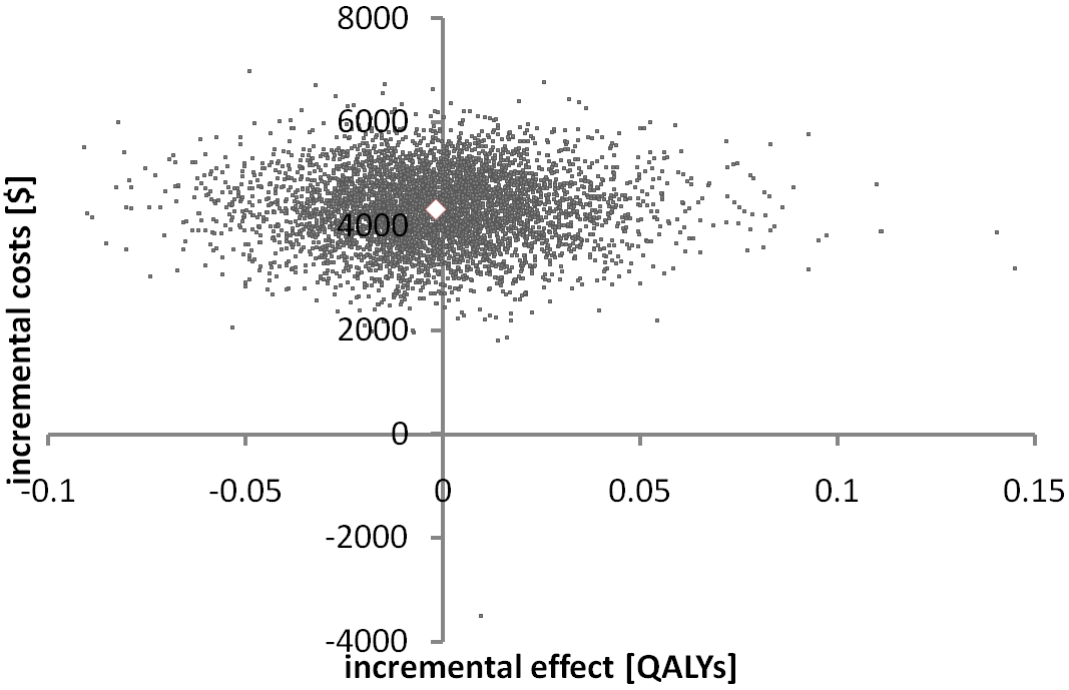


Figure 2B. Cost-effectiveness plane. Incremental costs and effects of the **paclitaxel-eluting stent** are based on 5 000 Monte Carlo simulations. The point estimate (incremental costs $4329; incremental effect -0.002 QALYs) is highlighted.

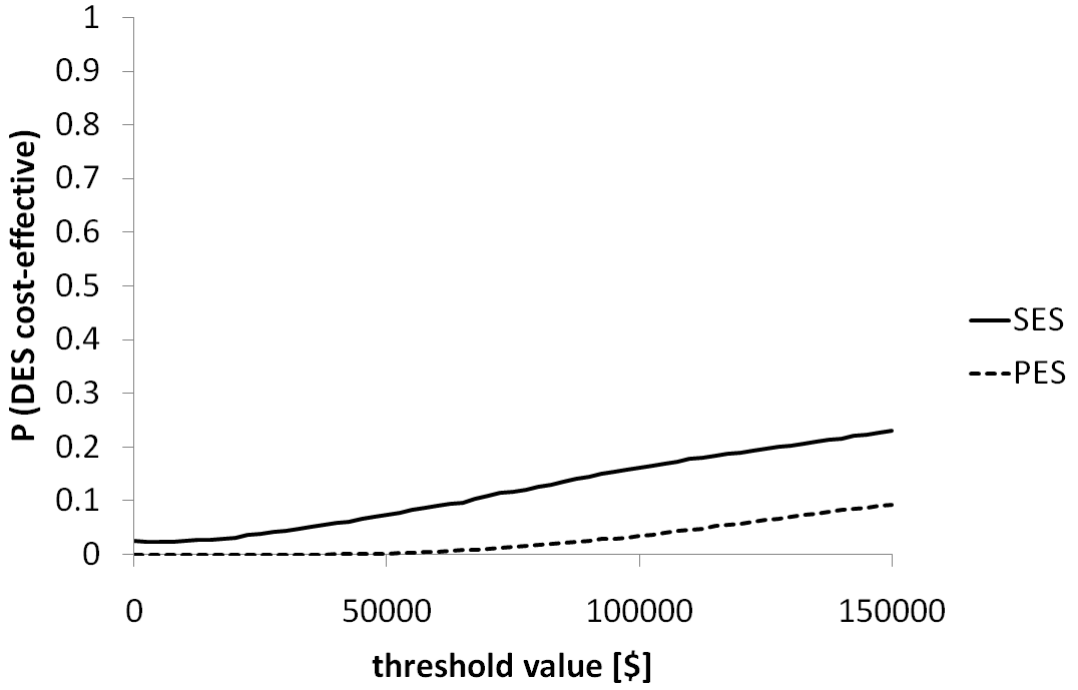


Figure 3. Cost-effectiveness acceptability curves. BMS vs. DES. Base-case analysis with a time horizon of 3 years. Results are based on 5 000 Monte Carlo simulations. SES = sirolimus-eluting stent, PES = paclitaxel-eluting stent

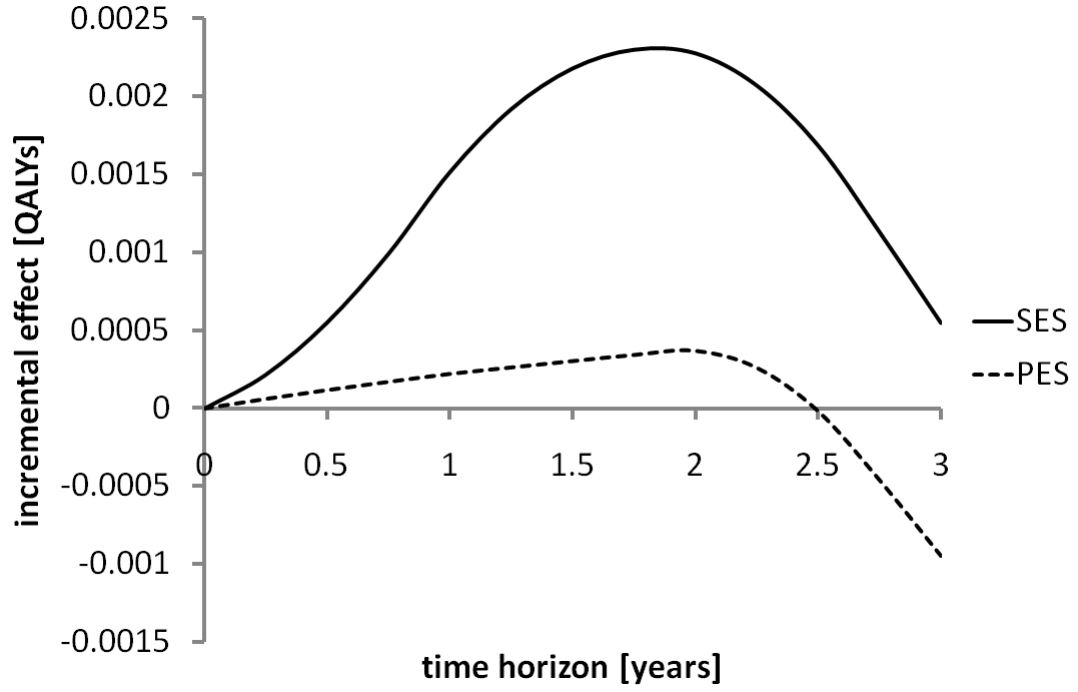


Figure 4. **Time horizon and incremental effect [QALYs] of DES**. SES = sirolimus-eluting stent, PES = paclitaxel-eluting stent

The DRG reimbursement rates for BMS and DES clearly influence the result. At a difference in DRG reimbursement rates of less than $3863 (current difference $6760) between BMS and DES, SES yield a positive INMB (at a willingness to pay of $100 000/QALY) and would therefore be superior to BMS. At the same threshold level, PES yield a positive INMB when the difference in reimbursement rates is less than $1400. DES are then likely to be cost-effective.

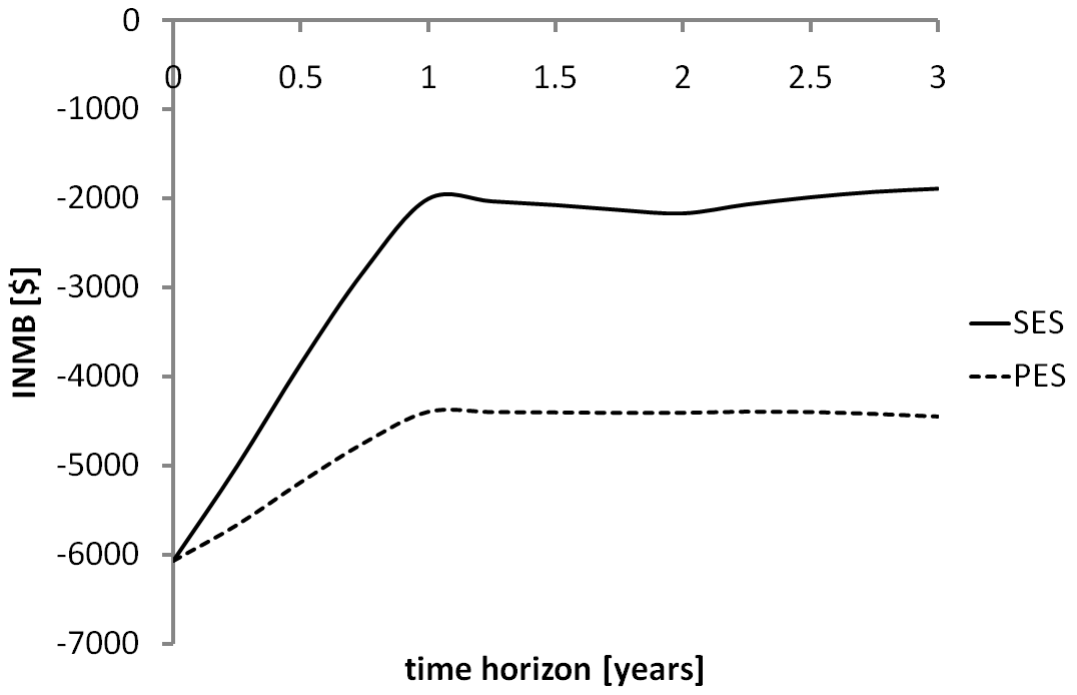


Figure 5. Incremental net monetary benefit (INMB) of DES with different time horizons. SES = sirolimus-eluting stent, PES = paclitaxel-eluting stent

In our base case analysis we used average DRG reimbursement rates for 10 top-rated US hospitals. In a sensitivity analysis using average DRG reimbursement rates derived from a random sample of 10 US hospitals with lower reimbursement rates (Table 1), there was no qualitative change in our results.

We also explored the robustness of the model towards changes in quality of life and used the disutility values for PCI and CABG form a recent health technology

assessment report in the United Kingdom (39) disregarding long waiting times that are not existent in the United States. In this sensitivity analysis, model results did not change the conclusion that would be drawn from the analysis.

When we applied different commonly used discount rates for both health effects and costs ranging from zero to ten percent or when we used differential discounting (i.e. using a different discount rate for health effects and costs), we found no major impact on the results.

Discussion

Our results demonstrate that the wide use of DES is not cost-effective and cannot be advocated for patients with coronary artery disease similar to those evaluated in the pivotal randomized controlled trials comparing BMS to DES. Interestingly, both types of evaluated DES showed very small (for SES) or no positive incremental effects (for PES) when compared to bare metal stents. At the same time, costs associated with DES are higher than costs associated with BMS, and consecutively DES can not be considered to be cost-effective.

The strength of our model is the probabilistic approach and the use of clinical effectiveness data from a large comprehensive meta-analysis of 17 trials including 8221 patients. The effectiveness part of our analysis is supported by the recent publications of individual patient data meta-analyses of trials comparing DES to BMS (6). No other cost-effectiveness analysis on DES used data from such a large number of patients. By relying on clinical effectiveness data from such a large number of patients, our model is more precise in predicting clinical outcome events than other models relying on smaller number of patients. Furthermore, we integrated 3 years follow-up data into our model. This is important since differences in need for target vessel revascularizations between patients treated with DES and BMS become smaller after the first year of stent implantation, whereas the risk of late stent thrombosis remains constant at a rate of 0.6% per year in patients treated with DES (43). Therefore, any cost-effectiveness analysis restricting the time horizon to one year or calculating the cost per revascularizations avoided in the first year clearly results in a biased assessment of the cost-effectiveness of DES. Many of the included

trials intend to follow-up patients for 5 years after the index procedure. Our analysis based on 3 years follow-up data may not necessarily be extrapolated to an extended time horizon since the clinical effectiveness of DES may differ with longer follow-up.

In our analysis we explicitly took parameter uncertainty into account by fitting individual probability distributions to all cost-, quality of life- and epidemiologic parameters in the model. This allowed us to perform a Monte Carlo simulation which results in an estimate of the probability that DES are cost-effective for a given willingness to pay value. The uncertainty concerning the estimates of total health care costs and total health effects for both BMS and DES is large. As a consequence, the decision uncertainty (i.e. the confidence interval for the estimate of the incremental net monetary benefit) is large as well. However, this has no direct influence on the conclusion whether DES are cost-effective or not. In a situation where a decision has to be taken, the only rational way for a risk-neutral decision maker is to adopt the strategy with a positive incremental net monetary benefit. In our analysis DES provided a negative INMB and were thus not cost-effective when compared to BMS at a willingness to pay up to at least $150 000 per QALY (Figure 3).

Further uncertainty arises through methodological and modelling structure uncertainty which can be addressed with univariate sensitivity analysis. To assess the influence of various other parameters and assumptions on the cost-effectiveness estimate we performed univariate (i.e. one-way) sensitivity analyses on various parameters and assumptions. Various sensitivity analyses did not result in qualitative changes of our results and the model proved to be rather robust. Only marked reductions in the difference of DRG reimbursement rates for BMS and DES influenced the decision in favour of DES.

Our analysis has several limitations. Quality of life data were not directly obtained from patients enrolled in comparative trials of DES and BMS, but was derived from the medical literature. In order to evaluate the importance of these parameters, we conducted a sensitivity analysis to evaluate the impact of uncertainty around quality of life parameters. Using disutility values per event from a different data source (39), did not change the conclusion of our analysis. In our base case, we used the average Medicare reimbursement rates and physician fees of ten top-rated cardiology hospitals. For this reason, the results of our analysis may seem limited to patients

treated in leading cardiology clinics where treatment costs are usually higher than in other hospitals. However, sensitivity analysis using lower reimbursement rates of a random sample of 10 US hospitals did not lead to a qualitative different conclusion of our analysis and the INMB of DES versus BMS remained negative, thus increasing the credibility of our analysis.

Our analysis was mainly based on effectiveness data from original pivotal trials comparing DES to BMS in patients with symptomatic ischemic discrete de novo lesions of ≤ 30 mm length in native coronary arteries with reference vessel diameters of 2.5 to 3.75 mm ("on-label use"). However, it is estimated that 60% of current DES use in the United States is off-label (44). Thus, our findings can not easily be generalized to these more complex patients including patients with acute myocardial infarction, multiple vessel disease, long lesions, lesions involving arterial bifurcations or the left main coronary artery. The lack of individual patient data precluded the conduct of subgroup analyses in patients with diabetes or small vessel disease. Cost-effectiveness analyses in these subgroups should definitely be conducted in the future.

Patients enrolled in the SES and PES trials reflect patient populations with different baseline risks. In addition, the choice of control stents used in these trials was different, and restenoses rates in the control arms of the paclitaxel-eluting stent trials were lower than in the control arms of the sirolimus-eluting stent trials. Our analysis does therefore not allow any conclusion as to whether the incremental cost-effectiveness of one of the DES is more favourable than the other. Meta-analyses of randomized controlled trials in mixed populations of patients with acute MI and coronary heart disease based on direct and indirect comparisons (45) or head to head comparisons (46) indicate that SES compared to PES are associated with fewer late stent thromboses and revascularisations. Evidence from indirect comparisons, however, must be interpreted with care in particular in situations where baseline risks in control groups are different between compared pairs (47). Given the higher baseline risk and absolute risk reduction from comparative trials of SES to BMS versus PES to BMS and considering the caveat expressed above, we do not feel comfortable in incorporating evidence form indirect comparisons into our model. Furthermore, in light of the results from our study where neither of the 2 DES can be

considered cost-effective compared to BMS, the question which of the two DES may be the preferred strategy can be considered futile from a decision maker's perspective.

Our study is the first cost-effectiveness analysis from a US third party payer's perspective to conclude that the broad use of DES in patients with coronary artery disease is not cost-effective. Our findings are in conflict with at least five cost-effectiveness analyses from the US which concluded that DES are attractive economic interventions (5). Our results are likely to differ for mainly two reasons. Our model is the first to incorporate data from a large meta-analysis including trials identified by a systematic, unbiased literature search. In addition, previous studies have not used a time horizon that is long enough to take into account the reduced absolute difference in need for target vessel revascularizations after the first year of stent implantation.

Recently, two cost-effectiveness analyses of DES have been published from a Swiss and a United Kingdom perspective. Yet, both of these analyses have their limitations. In the BASKET trial, a single center trial with 18 months of follow-up the incremental cost-effectiveness ratio of DES was € 40'467 per QALY gained (48). The authors concluded that "DES are not good value for money" if implanted in unselected patients, but may be cost-effective in patients with small vessel disease or bypass graft stenting. This conclusion was based on a subgroup analysis of only 268 patients deemed to be at high risk with a limited follow-up of 18 months.

In a health technology assessment report from the United Kingdom using 12-month clinical follow-up data, DES were not cost-effective in a typical NHS population, but were considered to be potentially cost-effective in high risk subgroups (39). In their analysis the authors assumed no difference in mortality between all stent types under analysis. However, from a decision analytic point of view, even statistically non-significant differences of effects should be incorporated into an analysis (49). As mentioned above, lack of individual patient data precluded us from conducting cost-effectiveness analyses in high risk subgroups.

Conclusion

Contrary to other cost-effectiveness analyses conducted from a US health care perspective, our analysis from a US Medicare perspective suggests that DES are not cost-effective compared to BMS when implanted in unselected patients with symptomatic ischemic coronary artery disease. Only if the difference of DRG reimbursement rates for BMS and DES is markedly reduced, the wide use of DES can be recommended to a large patient population with symptomatic ischemic coronary artery disease.

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Appendix

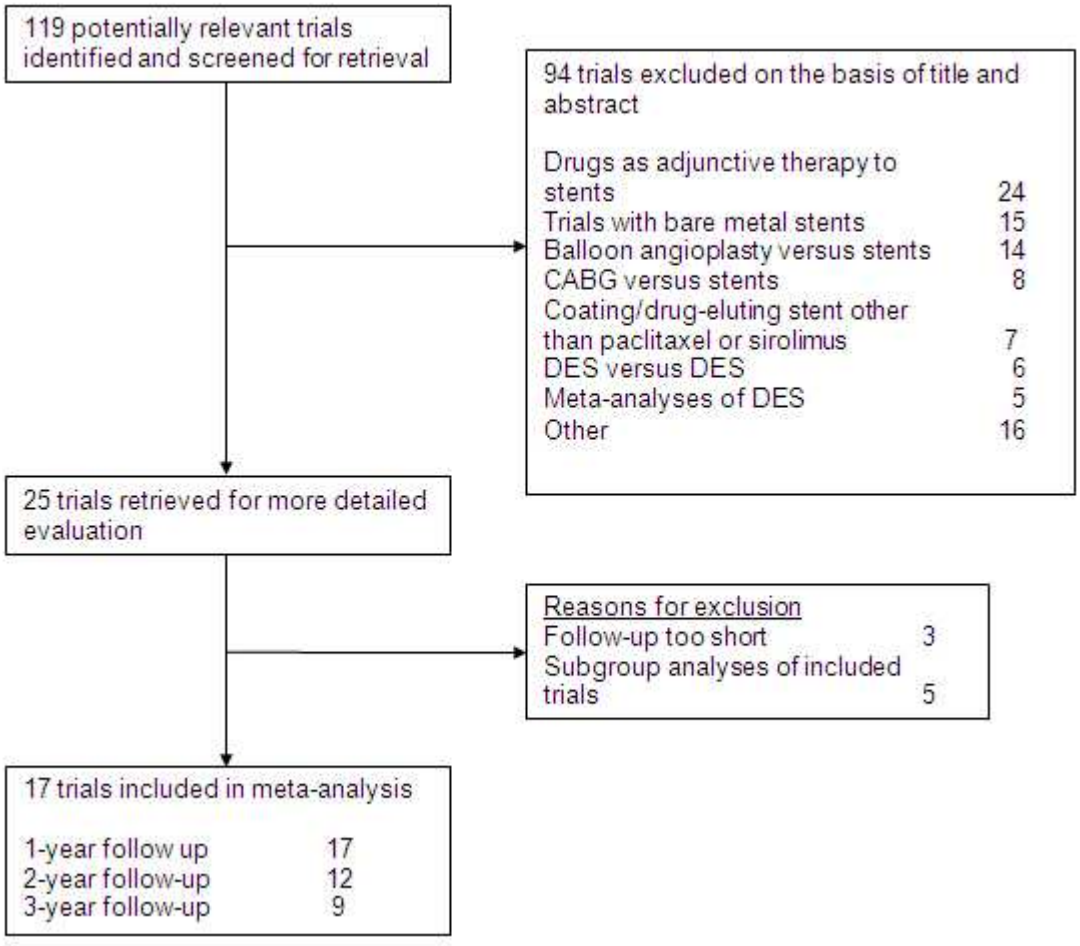

Figure 1

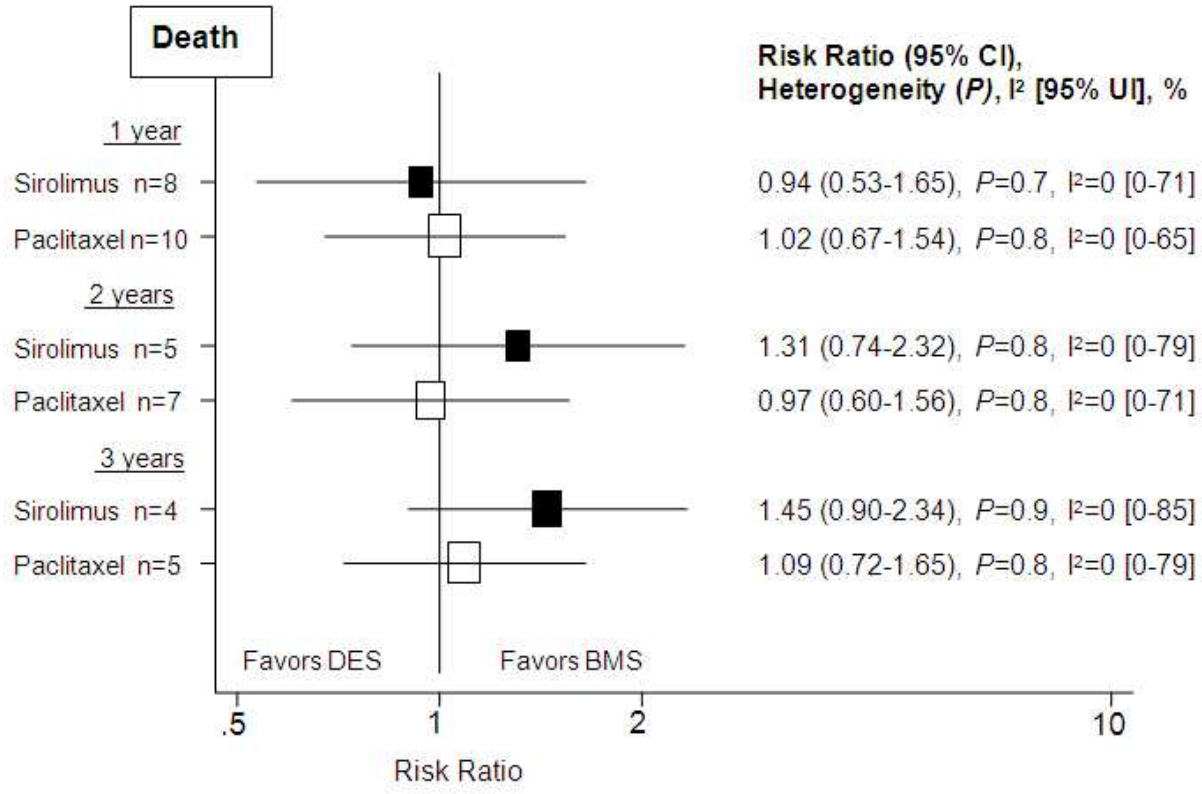

Figure 2A.

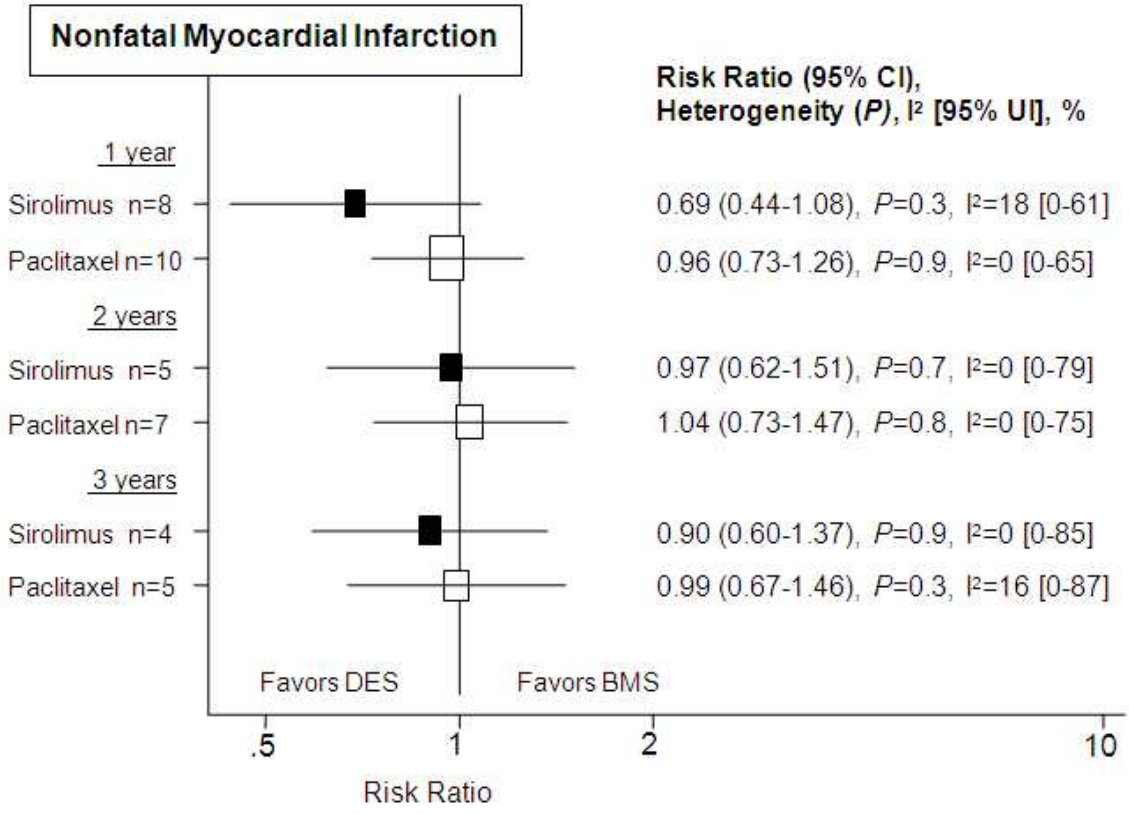

Figure 2B.

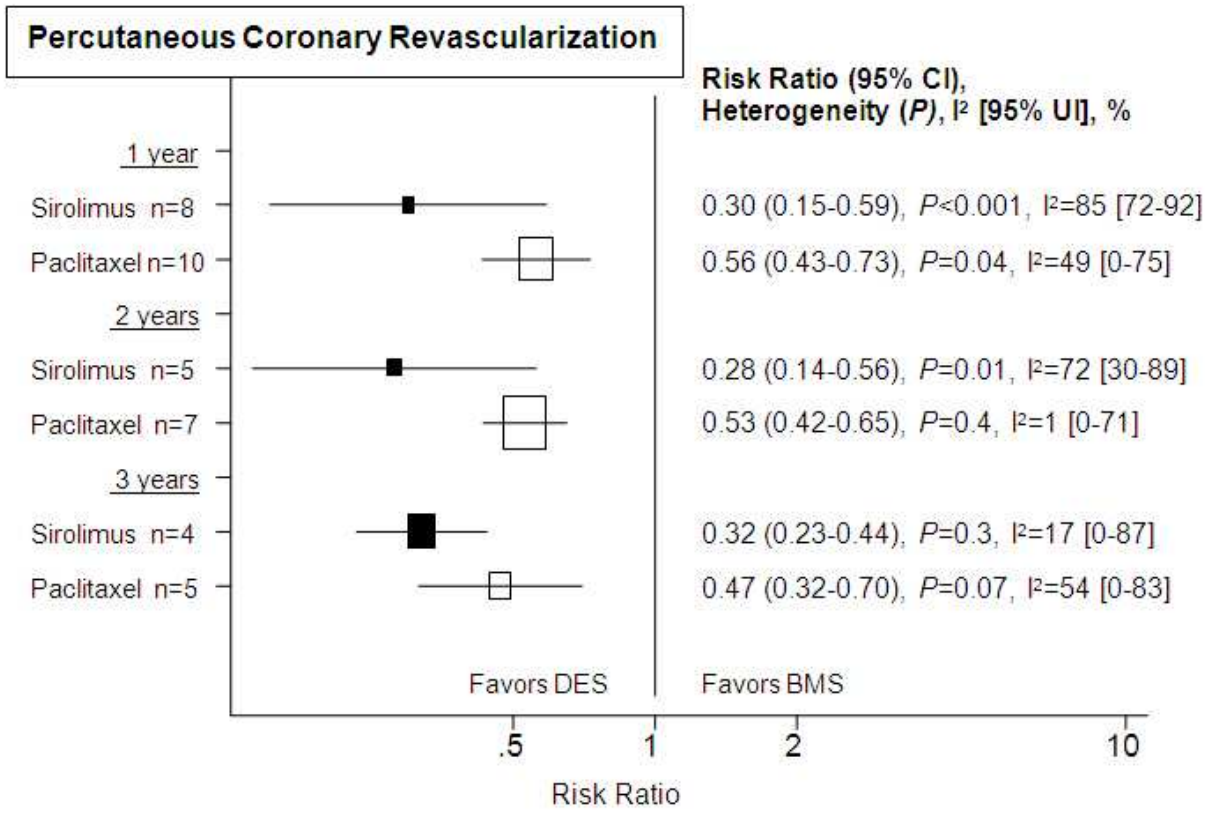

Figure 2C.

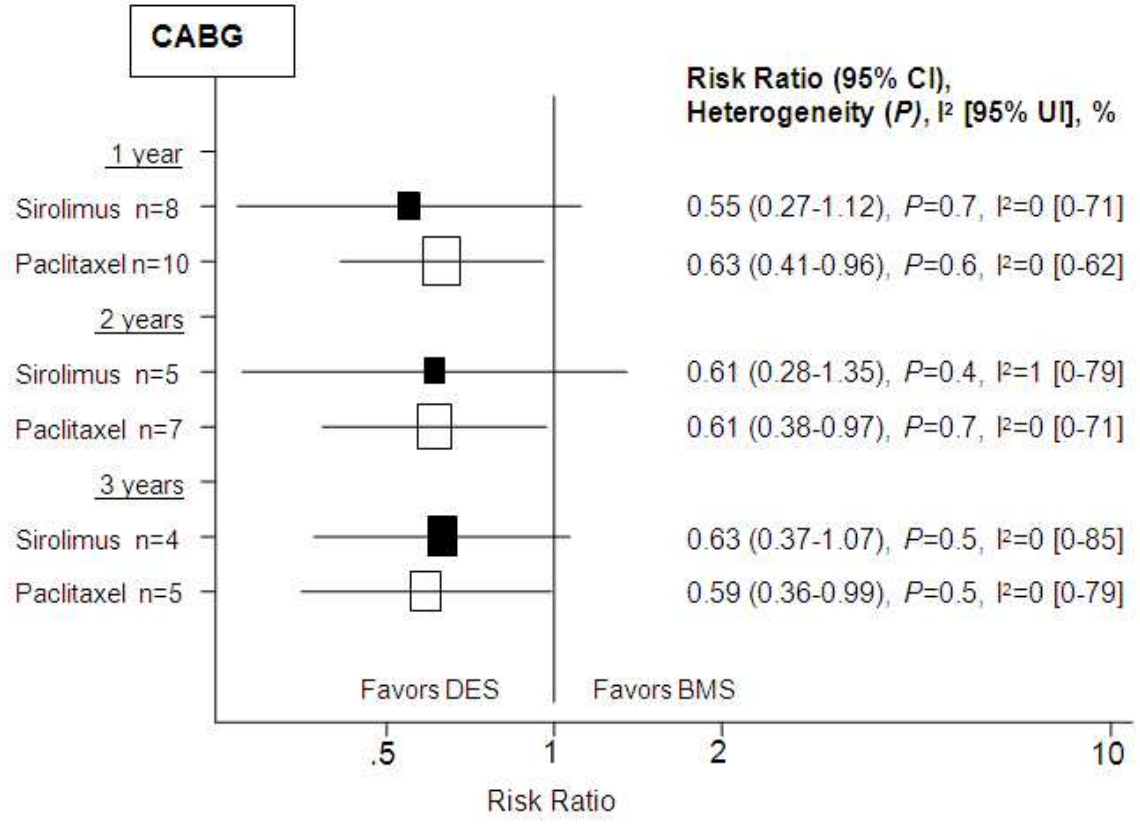

Figure 2D.

Cumulative event rates

Trial	N	Follow-up (years)	Data Source*		Cumulative event rates in patients treated with SES and BMS† (%)			
					Death	MI‡	PCI§	CABG¦
RAVEL, 2002 (50)	120 118	1	P	SES BMS	1.7 1.7	3.3 5.1	0 13.6	0.8 0
		2	CP/PI	SES BMS	5.0 2.5	4.2 5.1	1.7 13.6	1.7 0
		3	CP/PI	SES BMS	7.5 4.2	5.0 6.8	3.3 14.4	1.7 0
SIRIUS, 2003 (51)	533 525	1	CP/PI	SES BMS	1.3 0.8	3.0 3.4	3.6 6.7	0.9 1.7
		2	P	SES BMS	2.1 1.3	3.6 3.4	4.9 6.9	1.1 2.1
		3	M	SES BMS	3.9 2.9	4.3 4.8	11.6 30.1	3.0 5.1
E-SIRIUS, 2003 (52)	175 177	1	P	SES BMS	1.1 0.6	4.0 2.3	5.1 26.0	0.6 2.3
		2	PI	SES BMS	2.3 2.8	5.1 3.4	5.7 28.2	0.6 2.8
		3	M	SES BMS	5.1 4.0	5.1 5.1	6.9 31.1	1.1 2.8
C-SIRIUS, 2004 (53)	50 50	1	CP/PI	SES BMS	0 0	4.0 4.0	4.0 22.0	2.0 2.0
		2	CP/PI	SES BMS	2.0 0	4.0 4.0	6.0 22.0	4.0 2.0
		3	M	SES BMS	2.0 0	6.0 6.0	6.0 22.0	4.0 4.0
SES SMART, 2004 (54)	129 128	1	PI	SES BMS	0.8 3.9	1.6 10.2	28.7 42.2	0.8 4.7
DIABETES, 2005 (55)	80 80	1	P/PI	SES BMS	3.8 5.0	2.5 7.5	6.3 33.8	0 1.3
		2	PI	SES BMS	6.3 6.3	3.8 8.8	7.5 33.8	0 1.3
BASKET, 2005 (15)	264 281	1	P/PI	SES BMS	3.0 3.6	4.2 5.3	8.0 6.4	1.1 1.1
SCANDSTENT, 2006 (56)	163 159	1	CP/PI	SES BMS	0.6 0.6	1.2 3.1	2.5 30.0	NA¶ NA¶

Table 1A. Cumulative event rates.
*CP=conference proceeding; M=manufacturer; P=publication; PI=principal investigator
†SES=sirolimus-eluting stent; BMS=bare-metal stent
‡nonfatal myocardial infarctions
§percutaneous coronary intervention
¦coronary artery bypass graft
¶not available

Cumulative event rates

Trial	N	Follow-up (years)	Data Source*		Cumulative event rates in patients treated with SES and BMS† (%)			
					Death	MI‡	PCI§	CABG¦
TAXUS I, 2003 (57)	31 30	1	P	PES BMS	0 0	0 0	0 10.0	0 3.3
		2	M	PES BMS	3.2 0	0 0	3.2 10.0	0 3.3
		3	M	PES BMS	3.2 0	0 0	3.2 10.0	0 3.3
TAXUS II MR, 2003 (58)	135 134	1	P	PES BMS	0.7 0.7	3.7 5.2	5.2 18.7	0.7 3.0
		2	CP/M	PES BMS	3.0 1.5	4.4 6.0	6.7 17.2	2.2 3.0
		3	CP/M	PES BMS	3.7 2.2	5.2 6.7	6.7 20.9	2.2 3.0
TAXUS II SR, 2003 (58)	131 136	1	P	PES BMS	0 1.5	2.3 5.1	6.9 15.4	3.1 0.7
		2	M	PES BMS	1.5 2.2	3.8 5.1	7.6 19.1	3.8 2.2
		3	M	PES BMS	4.6 2.9	3.8 5.9	9.2 21.3	3.8 2.9
ASPECT, 2003 (59)	117 59	1	P/PI	PES BMS	0.9 0	2.6 1.7	12.0 8.5	0.9 0
		2	PI	PES BMS	0.9 0	2.6 1.7	12.0 10.2	0.9 0
DELIVER, 2004 (60)	517 512	1	M	PES BMS	1.0 1.4	1.4 1.0	5.4 6.8	0.6 0.8
ELUTES, 2004 (61)	152¶ 38	1	P	PES BMS	0.7 0	1.3 0	5.9 13.2	0.7 2.6
		2	PI	PES BMS	0.7 0	1.3 0	7.9 13.2	1.3 2.6
TAXUS IV, 2004 (62)	662 652	1	P	PES BMS	2.1 1.7	3.3 4.0	5.3 13.5	1.5 3.8
		2	M	PES BMS	3.6 3.7	4.2 4.6	8.2 17.2	2.1 4.6
		3	M	PES BMS	4.2 4.1	5.0 5.7	10.3 18.6	2.9 5.1
TAXUS V de novo, 2005 (63)	577 579	1	P/CP/M	PES BMS	2.1 1.7	4.9 4.5	13.9 18.8	1.4 2.6
TAXUS VI, 2005 (64)	219 227	1	P/M	PES BMS	0 1.8	8.2 6.2	9.6 18.9	1.8 2.2
		2	CP	PES BMS	0.5 2.2	9.1 5.7	12.8 19.4	1.8 3.1
		3	M	PES BMS	2.3 3.1	9.1 5.7	15.5 19.4	2.3 3.1
BASKET, 2005 (15)	281 281	1	P/PI	PES BMS	3.6 3.6	3.9 5.3	4.3 6.4	1.8 1.1

Table 1B. Cumulative event rates.

*CP=conference proceeding; M=manufacturer; P=publication; PI=principal investigator, †SES=sirolimus-eluting stent; BMS=bare-metal stent, ‡nonfatal myocardial infarctions, §percutaneous coronary intervention

¦coronary artery bypass graft; ¶ all DES with various doses of paclitaxel pooled

Baseline event rates and relative risks with standard deviation (SD)

SES – baseline monthly event probabilities*

from	**stent**		**stent**		**stent**		**stent**	
to	**death**		**MI**†		**PCI**‡		**CABG§**	
	mean	SD	mean	SD	mean	SD	mean	SD
30 days	0.002639	0.003079	0.018972	0.007175	0.003955	0.005335	0.000660	0.000382
1st year	0.001141	0.000864	0.001018	0.000880	0.005631	0.003137	0.000660	0.000377
2nd year	0.001159	0.000878	0.000625	0.000302	0.001696	0.000768	0.000266	0.000437
3rd year	0.001747	0.000646	0.000487	0.000332	0.000975	0.000340	0.001066	0.000781

PES – baseline monthly event probabilities¦

from	**stent**		**stent**		**stent**		**stent**	
to	**death**		**MI**†		**PCI**‡		**CABG§**	
	mean	SD	mean	SD	mean	SD	mean	SD
30 days	0.0028309	0.0035681	0.026917	0.02066	0.006358	0.00881	0.0008905	0.002169
1st year	0.0011920	0.0008671	0.000707	0.000743	0.006333	0.003136	0.0011593	0.000454
2nd year	0.0009359	0.0006428	0.000643	0.000392	0.001931	0.000916	0.0004106	0.000263
3rd year	0.0009388	0.0007865	0.00044	0.00034	0.001525	0.000848	0.0004379	0.000306

SES – relative risk for BMS (SES baseline)¶

from	**stent**		**stent**		**stent**		**stent**	
to	**MI**†		**PCI**‡		**CABG§**		**death**	
	mean	sd	mean	sd	mean	sd	mean	sd
30 days	1.08	0.2639	0.86	0.5707	1.75	0.926	1.12	0.6497
1st year	1.724	0.43465	3.846	0.85917	1.851	0.4155	1.075	0.250144
2nd year	0.575	0.207755	0.524	0.142096	1.02	0.391797	0.725	0.2128
3rd year	2.174	0.673777	2.22	0.594536	1.538	0.404037	0.676	0.175134

PES – relative risk for BMS (PES baseline)¶

from	**stent**		**stent**		**stent**		**stent**	
to	**MI**†		**PCI**‡		**CABG§**		**death**	
	mean	sd	mean	sd	mean	sd	mean	sd
30 days	0.91	0.2191	0.76	0.3875	1.61	0.7469	1.22	0.4798
1st year	1.493	0.322771	1.887	0.208206	1.587	0.283296	0.952	0.174795
2nd year	0.541	0.172268	0.909	0.279675	1.429	0.441276	1.031	0.25909
3rd year	1.449	0.457121	0.943	0.363275	1.563	0.47847	0.556	0.169068

Table 2. Baseline event rates.

***** SES=sirolimus-eluting stent

† nonfatal myocardial infarctions

‡ percutaneous coronary intervention

§ coronary artery bypass graft

¦PES=paclitaxel-eluting stent

¶ BMS=bare metal stent

CHAPTER 6: VALUE OF INFORMATION ANALYSIS IN DRUG-ELUTING STENTS

Abstract

Introduction: Currently published studies on the cost-effectiveness of drug eluting stents (DES) have not sufficiently addressed parameter uncertainty. In an economic evaluation based on a decision analytic model that accounts for uncertainty in input parameters we analysed the cost-effectiveness of the sirolimus-eluting Cypher stent (SES) and estimated whether the benefit of a future clinical trial would offset its estimated costs.

Methods: Based on a decision-analytic Markov model cost-effectiveness estimates were derived for SES. Total decision uncertainty was assessed by expected value of perfect information (EVPI) analysis. The value of a future clinical trial was analysed by means of expected value of sample information analysis. The optimal sample size for a future clinical trial was determined by finding the sample size that maximizes the expected net benefit of sampling.

Results: Sirolimus-eluting stents are more costly and slightly more effective than bare metal stents. At a decision maker's willingness to pay of $100 000 per quality-adjusted life year gained, SES have a 16% probability of being cost-effective. The corresponding total decision uncertainty expressed as the EVPI is large, at $205 per patient. Clinical parameters that include the baseline event rates and the relative risk of events in patient receiving DES contibute most to total decision uncertainty. Perfect knowledge of these parameters has an expected value of $7.3 millions per 100 000 patients. Given the large population size, the expected value of a future trial is enormous. The costs of a future trial are by far offset by the value of a trial. The optimal sample size for a future trial that would provide more precise clinical parameter estimates is 4700 patients over a time horizon of 3 years.

Conclusion: Based on currently available evidence and the used willingness to pay threshold SES have a low probability of being cost-effective. The value of a future trial to provide more precise parameter estimates is larger than the costs of conducting such a trial.

Introduction

Numerous clinical trials have shown that drug-eluting stents (DES) reduce in patients with symptomatic coronary heart disease restenosis and revascularization rates when compared to bare metal stents (BMS)(1). These remarkable achievements have lead to dramatic changes in the management of coronary heart disease since the approval of DES in April 2003 (1) and DES adoption rates quickly rose to more than 90% in some US hospitals (1;2). However, recent reports of late adverse events and stent thrombosis prompted caution from regulators and physicians (1-4). It was further criticized that the randomized controlled trials on the efficacy of DES have been underpowered (3; 5-7).

Acquisition costs of DES are large and therefore, a potential clinical benefit of DES may be overshadowed by these costs (8). A review of the literature from 2007 (9) identified five cost-effectiveness studies comparing DES to BMS for the United States (10-14). Two of the studies are based on randomized controlled trials (10;12), in 3 studies a decision analytic model was used (11; 13; 14).

Given these limitations and concerns, uncertainty in clinical and cost parameters, cost-effectiveness analysis of DES must be scrutinized. However, none of the five mentioned US studies explored the decision uncertainty in full depth. In particular, none of the decision analytical studies accounted for the uncertainty regarding the true value of the input parameters. The two economic analyses (15; 16) that were based on a clinical trial used bootstrap resampling methods to assess parameter uncertainty.

In this study we examined the cost-effectiveness of the sirolimus-eluting stent (SES) compared to BMS with a decision analytic model. We explicitly took parameter uncertainty in model input parameters into account and performed a probabilistic sensitivity analysis (PSA). PSA provides an estimate of the probability that SES are cost-effective for various threshold levels (i.e. willingness to pay values per unit of outcome gained)(17-20). A rational risk-neutral decision maker will then adapt the strategy with the higher probability of being cost-effective at the decision maker's

threshold value. For any adoption decision that is based on a probability (*P*) of less than 100% (i.e. decision uncertainty is present), there is a 1-*P* chance that the adopted strategy or decision is not cost-effective. The adopted strategy will then lead to a loss in monetary terms, health outcomes or both.

To examine the total decision uncertainty we calculated the *expected value of perfect information* (i.e. no uncertainty in model input parameters)(21; 22). The decision model has a large number of uncertain input parameters which all can be assigned to one of three groups (cost data, clinical data, quality of life data). These groups of parameters do not necessarily contribute equally to the overall decision uncertainty. In order to identify the magnitude of the individual contribution of groups of parameters to the overall decision uncertainty, the *expected value of partial perfect information* (EVPPI) was calculated in a further step for these three groups of parameters (23-25). EVPPI places an upper boundary on the value of perfect information for groups of parameters.

Usually, more precise parameter estimates will in practice be derived from a clinical trial (26; 27). Although very large trials are desirable to obtain very precise parameter estimates, the marginal gain in precision may be small at very large sample sizes while the marginal costs increase linearly per additionally enrolled patient (28). To obtain from a decision maker's point of view the optimal sample size for a future trial, the expected value of the future trial needs to be offset by the costs of the trial. The expected net benefit of sampling (ENBS) provides a net monetary value of the future trial by subtracting the trial's costs from its expected value (22). The optimal sample size of the future trial can then be estimated by calculating the ENBS for different sample sizes.

Methods

The decision model

For this study a previously developed decision analytic model was used. The model is presented in detail elsewhere (see chapter 5). In short, the model is a probabilistic,

half-cycle corrected Markov model with 5 health states, a cycle length of 1 month and a time horizon of 3 years (29; 30). Initially all patients start in the health state "stent" – representing patients after the insertion of either a DES or BMS. Every cycle patients are at risk of moving to the health states *myocardial infarction (MI), coronary bypass surgery (CABG), percutaneous coronary intervention or death*. Age-dependent utility values are assigned to the patients in the model. The decrease in health related quality of life in patients with an event is modelled by assigning disutility values to patients in an event health state. Quality of life values are derived from the ARTs trial (31). Clinical effectiveness data was derived from a large meta-analysis comprising 17 randomized controlled trials with a follow-up of 3 years (32). Unit costs for hospitalizations and surgeries and initial stenting procedures are derived from US Medicare diagnosis-related groups (33). The studies perspective is the US Medicare payer's perspective. Costs are in US$ of the financial year 2007. Both health effects and costs are discounted at 3% annually (34; 35). For the purpose of this study we only focus on the cost-effectiveness of sirolimus eluting stents because in our previous analyses these stents were shown to be slightly more advantageous than paclitaxel eluting stents when both were compared to BMS.

Analysis of cost-effectiveness

In this cost-utility analysis, health outcomes were measured in terms of quality-adjusted life years (QALYs). The incremental net monetary benefit statistics were used to analyse cost-effectiveness (36).

Probabilistic sensitivity analysis

Beta distributions were assigned to the quality of life and the baseline transition probabilities. Truncated normal distributions were used to reflect parameter uncertainty in relative risk parameters. Gamma distributions were used for cost parameters. The baseline decision was calculated by averaging over 10 000 Monte Carlo simulations (20).

Expected value of perfect information

The contribution of groups of parameters towards total decision uncertainty was calculated with a two-level algorithm for the analysis of expected value of partial perfect information (23; 25). Given the two levels of uncertainty (uncertainty in the parameters of interest and in the remaining parameters) a two-level Monte Carlo simulation was applied with 400 inner level and 400 outer level simulations.

Estimation of the value of the future trial

The value of the future trial is calculated as the expected value of sample information (EVSI)(37). Detailed descriptions of the method can be found elsewhere (22; 37). EVSI is measured by the reduction in expected opportunity loss and can be calculated for a particular sample size from the prior information used to calculate EVPI and an estimate of the sample variance. Assuming that the net health benefit of the SES and the BMS is normally distributed, the unit normal loss integral can be used for the calculation. To obtain the population EVSI, EVSI per patient for a particular sample size is multiplied by the incidence of patients entering the decision problem.

Costs of the future trial and optimal sample size

The costs of the future trial comprise fixed costs (e.g. for data management and analysis) and variable reporting costs. Fixed costs were estimated to be $700 000 for a NIH-sponsored clinical trial carried out in an academic medical center (28). Reporting costs depend on the number of patients enrolled and were estimated to be $700 per patient.
The sample size for the future trial will be optimal where the marginal benefit of additional sample information is equal to the marginal cost of sampling (i.e. the optimal sample size is found by identifying the sample size that maximizes ENBS)(22).

The model was developed and analysed with Microsoft Excel and Visual Basic 6.5. For all analyses a threshold level of $100’000/QALY was assumed.

Results

Cost-effectiveness analysis

Total health related costs were higher in DES patients than in BMS patients (Table 1). At the same time DES are slightly more effective than BMS. The incremental cost-effectiveness ratio (the incremental costs over the incremental effect) is > 2 millions. $ per QALY. For threshold values of $50 000 and $100 000 this yields a negative incremental net monetary benefit. However, the results are far from being significant. The decision uncertainty is large as can be seen from the spread of the joint density distribution over the four quadrants and from the relatively large 95% confidence intervals (Figure 1, Table 1).

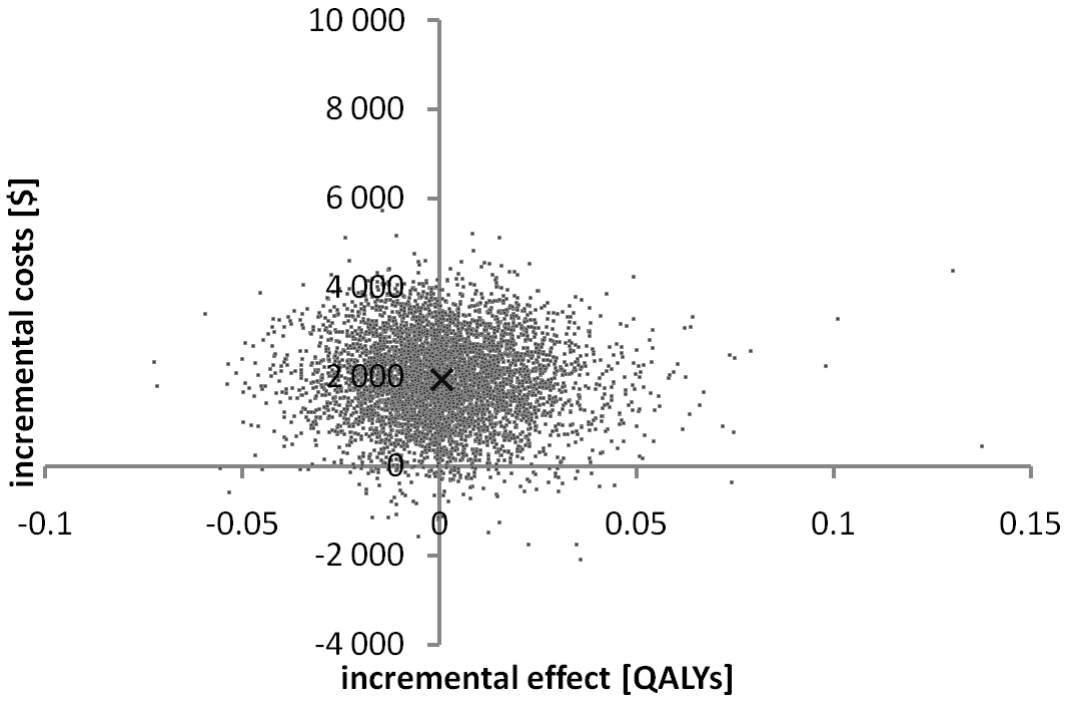

Figure 1. Cost effectiveness plane. Shown are 5 000 incremental cost/effect pairs derived from a Monte Carlo simulation. The point estimated ($1953, 0.001 QALYs) is highlighted.

Results (mean values and 95% confidence intervals)

BMS* costs [$]	BMS* effect [QALYs†]	DES‡ costs [$]	DES‡ effect [QALYs†]	Δcosts [$]	Δeffect [QALYs†]	ICER§ [$/QALY†]
26253 (24615 to 28084)	2.358 (2.324 to 2.378)	28207 (27513 to 29015)	2.359 (2.334 to 2.376)	1953 (-14 to 3779)	0.001 (-0.032 to 0.038)	> 2 000 000

INMB¶ @ $50 000 [$]	INMB¶ @ $100 000 [$]	P (INMB>0) @ $50 000	P (INMB>0) @ $100 000	EVPI¤ per patient @ $50 000 [$]	EVPI¤ per patient @ $100 000 [$]
-1914 (-4442 to 795	-1875 (-5646 to 2497)	7.5%	16.2%	53	205

Table 1. Results. * BMS = Bare metal stent; † QALY = quality-adjusted life year; ‡ DES = drug-eluting stent; § ICER = incremental cost-effectiveness ratio; ¶ INMB = incremental net monetary benefit; ¤ EVPI = expected value of perfect information

Total decision uncertainty

If we assume the decision maker's willingness to pay (i.e. threshold value) is $50 000 or $100 000 per quality-adjusted life year, DES have a probability of being cost-effective of 7.5% and 16.2%, respectively (Table 1). Thus, given the higher threshold value, the chance of making the wrong decision by adopting a strategy that is not cost-effective is 16.2%. The cost-effectiveness acceptability curve (Figure 2) provides further probability values for threshold values ranging from $0 to $150 000. Additionally, figure 2 shows the total expected value of perfect information per patient. As for the threshold values that were analysed, the probability that DES are cost-effective increases, but never reaches a value of more than 50%, likewise the expected value of perfect information increases over the range of threshold values

analysed. At a threshold value of $100 000/QALY total EVPI per patient is $205 (Table 1).

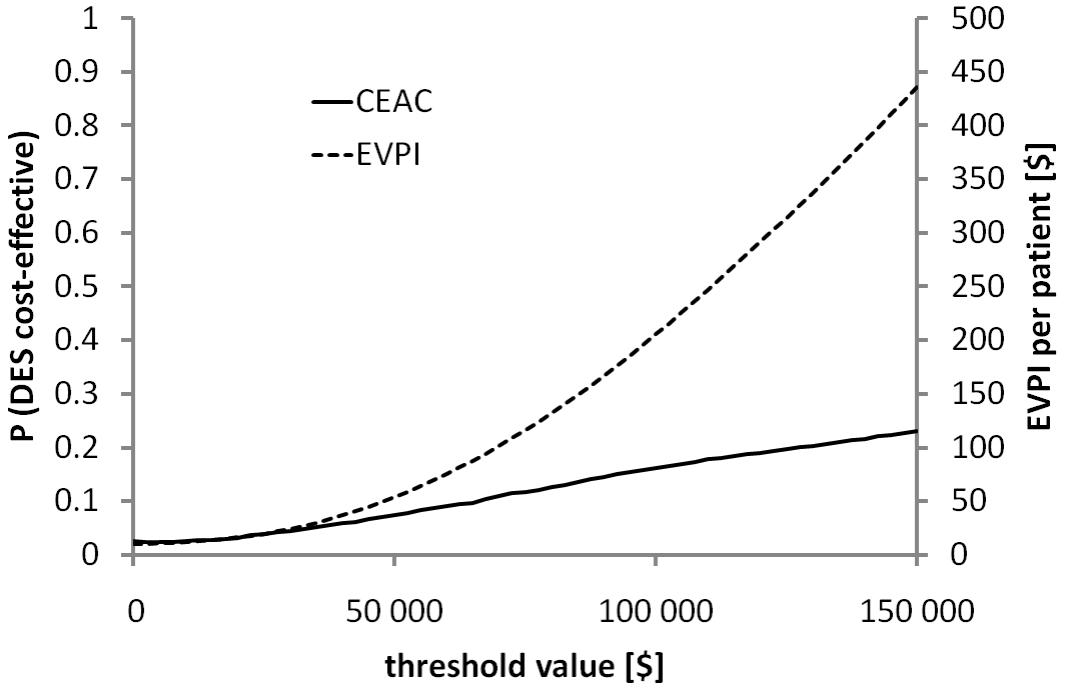

Figure 2. Cost-effectiveness acceptability curve (CEAC) and expected value of perfect information (EVPI) per patient. P = probability that DES are cost-effective

Expected value of perfect information for parameter groups

Figure 3 shows the expected value of partial perfect information for 3 groups of parameters. Clinical parameters that include the baseline event rates and the relative risk of events in patient receiving SES contibute the most to total decision uncertainty. Perfect knowledge of these parameters has an expected value of $7.3 millions per 100 000 patients. EVPPI for the quality of life parameters is $3.1 millions per 100 000 patients and $0.56 millions per 100 000 patients for the cost parameters.

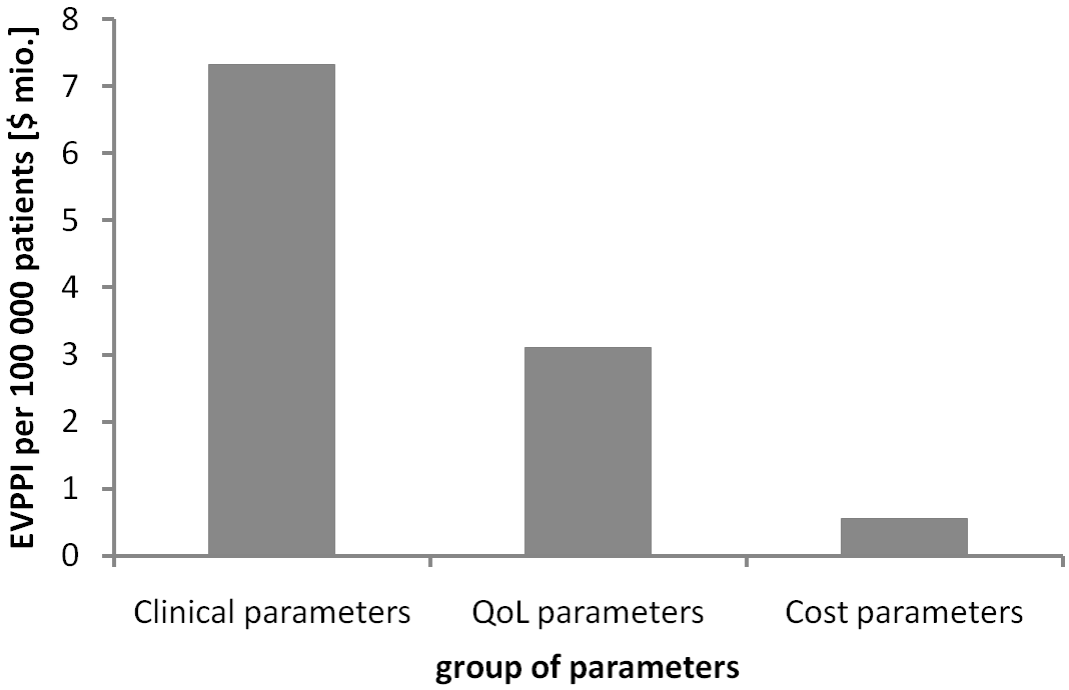

Figure 3. Expected value of partial perfect information for three groups of parameters.

Value of a future clinical trial

The expected value of sample information is enormous. Even for a small trial with less than a thousand patients, the expected value of that trial is more than $40 billions (Figure 4). This value exceeds by far the costs of conducting a trial for all sample sizes that were analyzed. The optimal sample size of the future clinical trial is found by calculating the sample size that maximises the expected net benefit of sampling (i.e. the difference between the value of the trial and its costs). For sample sizes larger than 2000 patients (1000 patients per arm) the marginal gain in sample information per additional patient is small and diminishing. Thus, ENBS already reaches a maximum at 4700 patients which would be the optimal sample size for a future clinical trial.

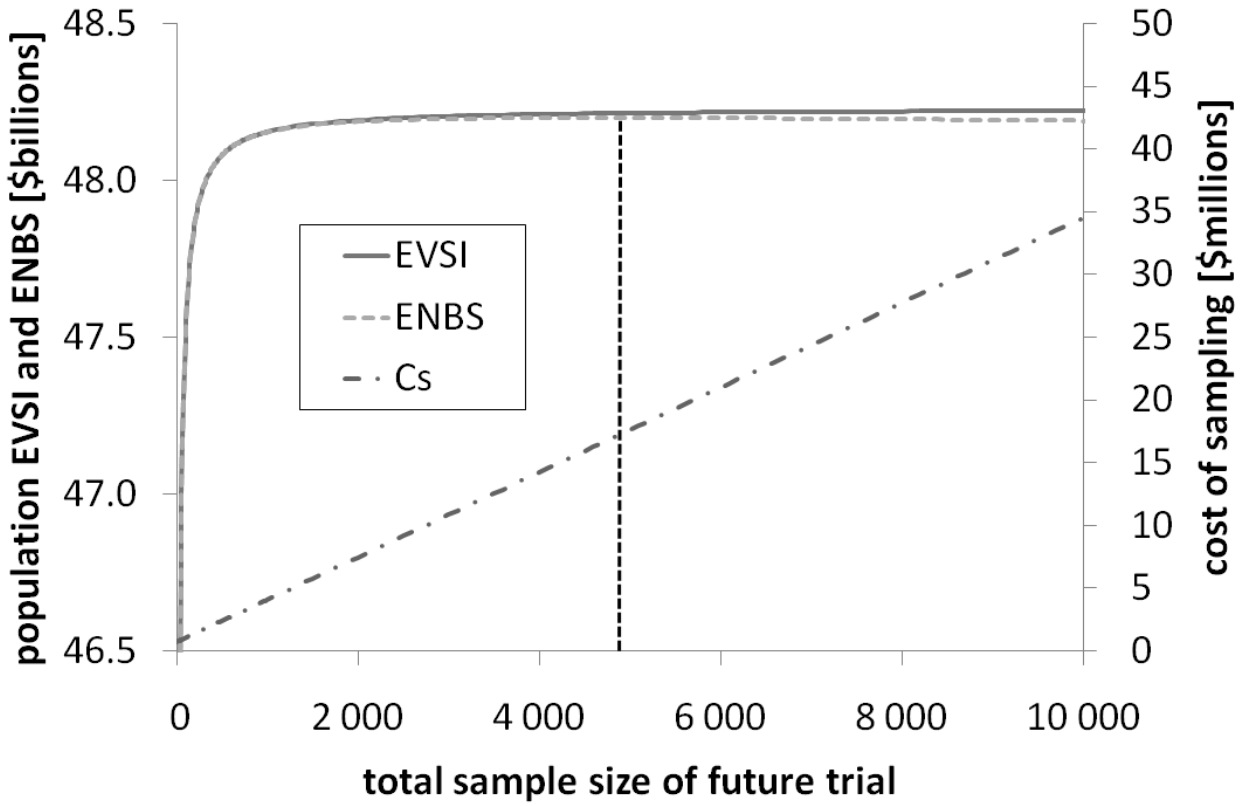

Figure 4. Population EVSI and expected costs and benefits of sampling. EVSI = expected value of sample information (value of the trial); ENBS = expected net benefit of sampling (EVSI – Cs); Cs = cost of sampling (cost of the trial). The optimal sample size of 4700 patients is highlighted through the horizontal dashed line.

Size of the population

The base case analysis was calculated for 554 400 patients eligible for stenting per year and a time horizon of 3 years based on data from the Centers for Disease Control. Because the population size directly influences the value of a future trial, the optimal sample size also depends on the population size. Figure 5 shows the optimal sample size for a population sizes up to 2 million patients per 3 years (the time horizon of the study). As expected, a larger population size increases the optimal sample size for the future trial.

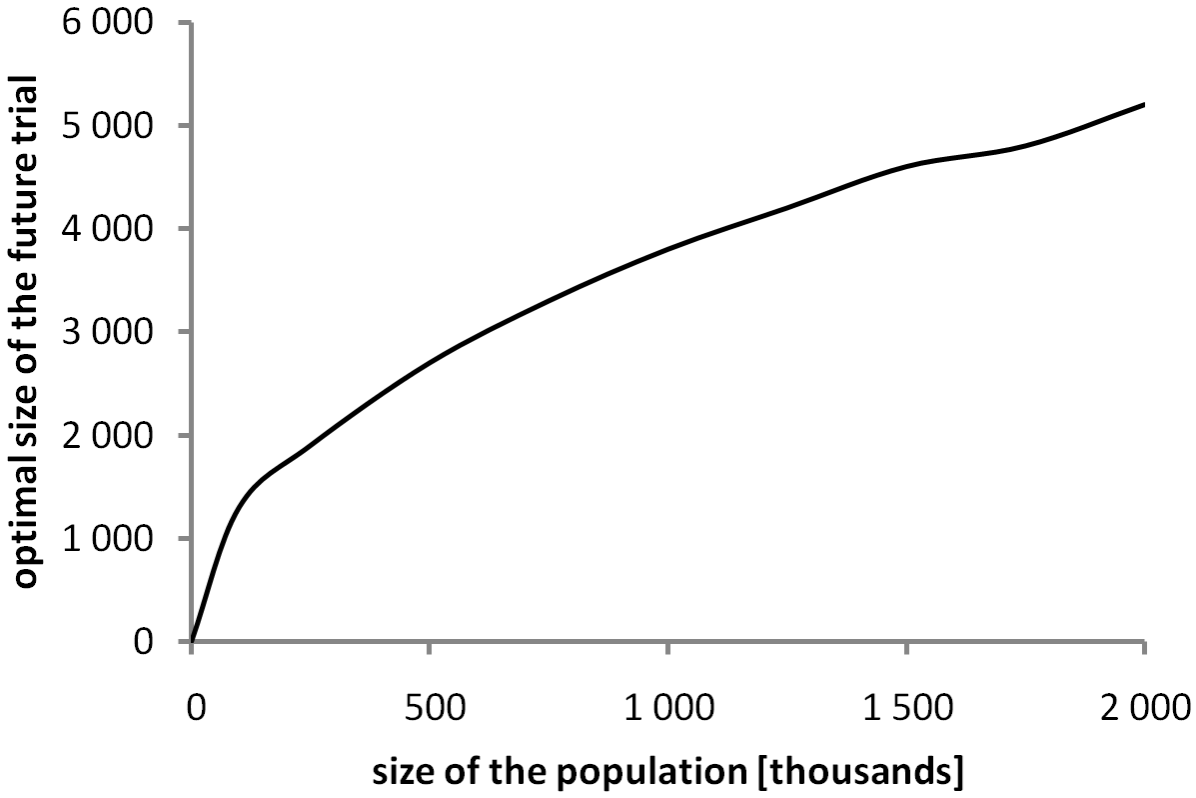

Figure 5. Population size and corresponding optimal sample size of the future clincal trial. Size of the trial shown as total number of enrolled patients

Discussion

Within this study the cost-effectiveness of the sirolimus-eluting stent compared to bare metal stents was analysed from a US Medicare payer's perspective. Although the clinical input data used for this study was based on data from a meta-analysis with more than 8 000 patients, the question of the cost-effectiveness of the sirolimus-eluting stent cannot be answered satisfactorily due to the large decision uncertainty. At a decision maker's willingness to pay value of $100 000 per quality-adjusted life year gained, the optimal decision would be not to adopt drug-eluting stents from a health economic perspective. Still, there remains a chance of about 16% that this decision would be wrong. Although a 84% chance of making the right decision may seem acceptable, this value in itself is insufficient for rational decision making. In an economic evaluation usually data from bootstrap analysis or a Monte Carlo simulation are presented on the cost-effectiveness plane and summarized by the cost-

effectiveness acceptability curve (Figure 2). The CEAC provides information on the probability of making the wrong decision but not about the consequences of making the wrong decision (38). Given a potentially harmful intervention that increases patients' mortality or an intervention that is very costly, the resulting loss in monetary terms and/or health outcome that would arise by making the wrong decision may be substantial.

To reduce decision uncertainty, a rational decision maker may thus wish to base the decision on a more sound evidence base. EVPPI analysis provides information on the contribution of single parameters or groups of parameters towards total decision uncertainty. Hence, EVPPI allows to identify those parameters for which further information is of highest value to reduce total decision uncertainty. In many situations, further information will only be available from clinical trials. Given that the cost of conducting a clinical trial is large (28) and increases with sample size, the net benefit of the future clinical trial will ultimately yield diminishing marginal returns with increasing sample size. The optimal sample size for the future clinical trial is thus found by identifying the sample size that maximizes ENBS.

In this evaluation on the cost-effectiveness of the SES we estimated the optimal sample size for a future clinical trial that would inform this decision is 4700 patients. The time horizon of this analysis was identical with the time horizon of the decision analytic model (3 years). Although in future the second generation of drug-eluting stents will likely dominate the market, SES may well be used for many years to come. Consequently the eligible patient population would increase manyfold, thus yielding a larger optimal trial size for the future clinical trial.

Although this study showed that conducting a future clinical SES trial is worthwhile given the positive ENBS, this does not necessarily mean that this trial should be carried out. Given the limited amount of resources for clinical research, the net benefit of the proposed trial needs to be compared to the net benefit of other proposed trials with a potentially higher ENBS (26). Furthermore the proposed trial may exceed the budget available for clinical research. The proposed trial with 4700 patients would cost close to $17 millions.

EVPPI and ENBS analyses are new techniques that build on currently employed methods for the analysis of parameter uncertainty (39). Whether the concept of EVPPI and ENBS will be understood and adopted by decision makers and agencies that decide on the reimbursement of health care technologies and on funding of future clinical research has to be seen and investigated. To date, only very few studies have been published that employ these methods. Therefore, important aspects of these methods are not yet fully established. It is probably possible to predict the number of patients eligible for stenting in the year 2018, but whether these patients will then receive a first-generation sirolimus-eluting stent is unknown. ENBS analysis that employs a long time horizon may thus overestimate the optimal sample size for a future clinical trial to inform sirolimus-eluting stents' cost-effectiveness.

Nevertheless, even for a short time horizon – as applied in this study - ENBS analysis showed that conducting a future DES clinical trial will be worth its cost in light of the uncertainty of cost-effectiveness estimates for DES and of long-term safety and efficacy data. However, we would like to stress that the results of our ENBS analysis should not be interpreted *'to halt expediting the approval of novel products but to require larger, longer-term post-marketing studies, particularly for permanent medical-device implants'* (40). In conclusion, value of information analysis offers a framework to support decision maker's in identifying the right trial size for future studies seen worthwhile to be pursued.

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CHAPTER 7: DISCUSSION

A detailed discussion of the findings of each study and its implications for clinical practice and medical decision making have been given at the end of each chapter. Here, a more general discussion of the methods and findings will be given.

Within this thesis the cost-effectiveness of three different health care interventions has been assessed in economic evaluation studies. Economic evaluations provide information on the expected health benefit and expected costs of novel interventions and are, thus of interest to decision makers, reimbursement and health technology assessment agencies.

Since the seminal study by Neuhauser and Lweiki published in the New England Journal of Medicine in 1975 (1), the progress in methodology and the number of economic evaluations published has increased enormously. Although the basic methodology did not change over time, numerous analytical and statistical techniques have been developed – and some of them abolished – since then.

The development of the methodology of health economic analyses and its rigorous application was also supported by the rise of evidence based medicine that underwent a similar development at the same time (2).

The widespread use of computer technology and the continuous improvement in computer software and hardware can also be attributed to the progress of economic evaluation methodology and the position economic analyses have reached to day (3). Advanced Bayesian statistical techniques, on which probabilistic sensitivity analysis and value of information analysis are based, have contributed significantly to feel and go back to the original ideas of reverend Thomas Bayes more than 200 years ago (4). But only now, with the availability of modern computers and standard spreadsheet packages, these methods are within reach for many scientists.

Although trial-based economic evaluations are still carried out, many economic evaluations published to date are now based on decision analytic models (5). Given

the complexity of decision problems, the variety of available data and the truncated time horizon of randomized controlled trials, only decision analytic models meet all requirements for economic evaluation for decision making (5). Further, by univariate and probabilistic sensitivity analysis, decision analytic models allow to truly address methodological and parameter uncertainty. Different types of decision analytic models exist to date, but all models rely on decision analysis, probability theory and expected utility theory (6).

The model type is in principle determined by the research question that the model is set up to inform. For evaluations of interventions and therapies for which the timing of events and effects is fully captured within a short period of time, decision trees are the appropriate model type. A decision tree model was used in the study of chapter one, to analysis the cost-effectiveness of extending prophylactic fondaparinux treatment for patients undergoing hip fracture surgery and total hip replacement . An adverse event that may result from such a surgical procedure is deep vein thrombosis. As a thrombosis caused by the surgical intervention will only be expected within the first 30 days after the initial intervention, the timing of events in the fondaparinux cost-effectiveness analysis is largely irrelevant. This provided the rational for using a decision tree model in the fondaparinux study.

In contrast, the exact estimation of the timing of events was an important part of the Markov models developed for the risedronate and the drug-eluting stents cost-effectiveness analyses (see chapter 3 and 5). It is well established that the bisphosphonate risedronate is effective in preventing fractures in osteoporotic women of older age with a reduced bone density. From epidemiological data it is also well known, that the fracture risk at different fracture site (e.g. at the hip, vertebra, wrist) increases with the patients' age. Many of the clinical trials that analyzed the efficacy of bisphosphonates had inclusion criteria that only allowed to enroll women from a certain age range.

In order to model the effectiveness of risedronate treatment and to assess risedronate's cost-effectiveness a Markov model was the appropriate choice. The model allowed to model time-dependent characteristics of the patients (risk of

natural death, baseline quality of life; disutility per fracture), the treatment (offset time) and the disease (fracture rates). Because the time horizon for this analysis was a lifetime time horizon, also costs in later years could be discounted and thus estimated by their net present value.

Timing did also play an important role in the economic evaluation of the sirolimus- and the paclitaxel-eluting stent (chapter 5). Although the actual time horizon in the analysis was short, the Markov model structure was useful to not only examine the cost-effectiveness of drug eluting stents 3 years after stent implantation, but also allowed to calculate the incremental effect for every time horizon between zero and 3 years. In a sensitivity analysis, the model thus confirmed the expected decline in the effectiveness of drug eluting stents 2 to 3 years following the initial stent insertion (7-10).

The use of decision analytic models in economic evaluations has another advantage over the use of trials as the vehicle for an economic evaluation. Probabilistic decision models allow to calculate the expected value of partial perfect information. Hence, it is possible to identify the contribution of individual parameters towards total decision uncertainty. Based on the cost-utility model for drug-eluting stents, presented in chapter 5, the value of perfect information to inform the adoption decision of sirolimus-eluting stents was calculated (see chapter 6).

Unsurprisingly, given the ongoing debate about the safety and efficacy of drug-eluting stents, it was found that uncertainty in the clinical model input parameters contributes most to total decision uncertainty. In an extension of this analysis it was estimated by means of expected net benefit of sampling analysis, that a future clinical trial would provide valuable information.

In conclusion, economic evaluations based on decision analytic models represent a systematic approach to decision making under uncertainty, and provide decision makers with relevant information on cost-effectiveness estimates and the value of further research (6; 11-13).

The classical conclusion "*further research is needed*" is often found in the discussion section of many research papers. In economic evaluations with expected net benefit of sample information analysis and positive expected net benefit of sampling, such statements in the future may well be extended by the quote "*and will most likely be cost-effective.*"

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APPENDIX

Useful Excel functions

Function and syntax	Description
abs (number)	returns the absolute value of a number
average(number1; number2;...)	returns the arithmetic mean
betainv(probability; alpha; beta)	returns the inverse of the cumulative beta prob. function
exp(number)	returns e raised to the power of number
gammainv(probability; α;β)	returns the inverse of the gamma cumulative distribution
if(logical test; value if true; v. if false)	returns value based on logical test
indirect(reference text; A1)	returns the reference specified by a text string
large(array;k)	returns the k-th largest value in a data set
ln(number)	returns the natural logarithm of a number
max(number1; number2;....)	returns the largest value in a set of values
min(number1; number2;...)	returns the smallest number in a set of values
norminv(probability; mean; SD)	returns the inverse of the normal cumulative distribution
rand()	returns an evenly distributed random real number
round(A1;2)	rounds a number to a specified number of digits
small(array;k)	returns the k-th smallest value in a data set
sqrt(number)	returns a positive square root
stdev(number1; number2;...)	estimates standard deviation based on a sample
sum(A1:A5)	adds all the numbers specified as arguments
var(number1; number2;...)	returns the variance of a set of values

VBA code for EVPPI calculation

```
Public Sub EVPPI_two_level()

Worksheets("evppi").Range("g4:g1010").Clear
noofouterruns = 5
noofinnerruns = 1000

For outer = 1 To noofouterruns

'clear results
Worksheets("evppi").Range("c4:d1010").Clear
Worksheets("evppi").Range("c1:d2").Clear

'sample parameter of interest
Worksheets("qol").Range("d1").Value = "on"
calculate
Worksheets("qol").Range("d1").Value = "off"

'sample other parameters
Worksheets("costs").Range("g1").Value = "on"
Worksheets("rr").Range("ak1").Value = "on"
Worksheets("transp").Range("ai1").Value = "on"

    For i = 1 To noofinnerruns
      calculate
      nbbms = Worksheets("results").Range("d26").Value
      nbdes = Worksheets("results").Range("d28").Value
      Worksheets("evppi").Range("c" & i + 3).Value = nbbms
      Worksheets("evppi").Range("d" & i + 3).Value = nbdes
    Next i

'calculate average
Worksheets("evppi").Range("c1").Value = "=average(c4:c1003)"
Worksheets("evppi").Range("d1").Value = "=average(d4:d1003)"
calculate

'choose highest and record
highestinner = Worksheets("evppi").Range("e1").Value
Worksheets("evppi").Range("g" & outer + 3).Value = highestinner
Next outer

calculate

End Sub
```

SELECTED ABSTRACTS

Bischof M, Lim M, Ferrusi I, Burke N, Blackhouse G, Goeree R, Tarride JE. R there any differences between Excel and R? Comparison of ICER estimates and CEACs obtained from a model implemented in Microsoft Excel and R. ISPOR 12th Annual European Congress, October 2009, Paris, France

Bischof M, Lim M, Ferrusi I, Burke N, Blackhouse G, Goeree R, Tarride JE. Some results are more equal than others: comparison of ICER estimates and CEACs obtained from a model implemented in Microsoft Excel and TreeAge. 31st Annual Meeting of the *Society for Medical Decision Making*, October 2009, Hollywood, California

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CURRICULUM VITAE

EDUCATION

10/03 – 09/04	**MSc Health Economics**, University of York, England. Thesis title: "Cost-effectiveness of neonatal ECMO based on seven year results from the UK Collaborative ECMO Trial", published in *Pediatrics* 2006
09/95 to 03/02	**Pharmacy degree (equivalent MPharm)**, Westfaelische-Wilhelms-University, Muenster, Germany, and professional licence as a pharmacist (Approbation)

MILITARY SERVICE

07/94 to 06/95	German Armed Forces

LICENSURE

03/02	Pharmacist (German license)

FIELDS OF INTEREST

Economic Evaluations
Decision Analytic Modelling
PSA & Value of Information Analysis
Evidence Synthesis
Clinical Epidemiology
Resource Allocation

WORK EXPERIENCE

09/08 to present	**Post-doctoral Research Fellow**, Programs for Assessment of Technology in Health (PATH) Research Institute, McMaster University, Hamilton, ON, Canada
11/04 to 06/08	**Research Fellow**, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland
05/02 – 08/03	**Pharmacist**, Apotheke des Westens (community pharmacy), Berlin, Germany
04/02	**Pharmacist**, Barbara Apotheke (community pharmacy), Kamen, Germany
11/00 – 10/01	**Junior Pharmacist**, Panorama Apotheke (community pharmacy), Berlin, Germany

OTHER PROFESSIONELL EXPERIENCES

07/08 to present	Associated Research Fellow, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland
07/08 to 08/08	Visiting Fellow, Programs for Assessment of Technology in Health (PATH) research institute, McMaster University, Hamilton, ON, Canada
04/06 to 06/08	Research Fellow, Swiss Tropical Institute, University of Basel, Switzerland
2006	Investigator, *European network for Health Technology Assessment*
2005	Health economic reviewer for *Swiss Medical Weekly*
07/04 – 09/04	Research Fellow, National Perinatal Epidemiology Unit, University of Oxford, England
12/03, 05/04	York Health Economics Consortium Ltd., York, England
09/03	Summer Session in Microeconomics, University of York, England
08/99	3M Health Care, Loughborough, England
11/98 – 12/98	Institute for Pharmaceutical Technology, University of Muenster, Germany

MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

International:	iHEA, International Health Economics Association, since 2005 ISPOR, International Society for Pharmacoeconomics & Outcomes Research, since 2005 SMDM, Society for Medical Decision Making, since 2005
National:	GMDS, Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie, since 2005 DPhG, Deutsche Pharmazeutische Gesellschaft, since 2000

PEER-REVIEWING FOR SCIENTIFIC CONFERECES

Judge for poster sessions and oral presentations, 2009 ISPOR 12th Annual European Congress

Abstract reviewer, 2010 *ISPOR* 15th Annual International Meeting
Abstract reviewer, 2010 *ECHE* 8th European Conference on Health Economics
Abstract reviewer, 2009 *ISPOR* 14th Annual International Meeting
Abstract reviewer, 2008 *ECHE* 7th European Conference on Health Economics
Abstract reviewer, 2007 *ISPOR* 10th Annual European Congress
Abstract reviewer, 2007 *ISPOR* 12th Annual International Meeting
Abstract reviewer, 2006 *ISPOR* 9th Annual European Congress

EDITORIAL POSITIONS

Member of the Editorial Board, Medical Decision Making, 3 years term, since 2009

Reviewer, Archives of Internal Medicine, since 2010
Reviewer, Canadian Journal of Cardiology, since 2009
Reviewer, PharmacoEconomics, since 2008
Reviewer, Journal of the American College of Radiology, since 2008
Reviewer, Value in Health, since 2007
Reviewer, Medical Decision Making, since 2007

PUBLICATIONS

Bischof M, Kraenzlin M, Bucher HC, Sendi P. Cost-effectiveness of risedronate for the prevention and treatment of osteoporosis in Swiss postmenopausal women. *The Open Pharmacoeconomics & Health Economics Journal.* 2010. 2, 25-33.

Tarride JE, Hopkins R, Blackhouse G, Bowen JM, **Bischof M**, Von Keyserlingk C, O'Reilly D, Xie F, Goeree R. Economic evaluations of treatments for diabetes mellitus. A review of methods used in long-term cost-effectiveness models of diabetes treatment. *PharmacoEconomics.*28(4):255-277, April 1, 2010

Tarride JE, Burke N, **Bischof M**, Hopkins R, Goeree L, Campbell K, Goeree R. A review of health utilities across conditions common in pediatric and adult poplulations. *Health and Quality of Life Outcomes.* 2010 Jan 27;8(1):12.

Tarride JE, Blackhouse G, **Bischof M**, McCarron EC, Lim M, Ferrusi I, Xie F, Goeree R. Approaches to economic evaluations of healthcare technologies. *J Am Coll Radiol*. 2009 May;6(5):307-16.

Goeree R, Levin L, Chandra K, Bowen JM, Blackhouse G, Tarride JE, Burke N, **Bischof M**, Xie, F. O'Reilly D. Health technology assessment and primary data collection for reducing decision making uncertainty. *J Am Coll Radiol*. 2009 May;6(5):332-42.

Bischof M, Briel M, Bucher HC, Nordmann A. Cost-effectiveness of drug eluting stents in a US setting: a cost-utility analysis with 3 year clinical follow-up data. *Value in Health*, 2009,12(5):649-656.

Petrou S, **Bischof M**, Bennett C, Elbourne D, Field D, McNally H. Cost-effectiveness of neonatal ECMO based on seven year results from the UK Collaborative ECMO Trial. *Pediatrics*, 2006 May; 117(5):1640-9

Bischof M, Leuppi JD, Sendi P. Cost-effectiveness of extended venous thromboembolism prophylaxis with fondaparinux in hip surgery patients. *Expert Review of Pharmacoeconomics & Outcomes Research*, April 2006, Vol. 6, No. 2

Bischof M, Sendi P. How much bone for the buck? The importance of compliance issues in economic evaluations of bisphosphonates. *Expert Review of Pharmacoeconomics & Outcomes Research*, Aug 2005, Vol. 5, No. 4

PEER-REVIEWED ORAL PRESENTATIONS

Bischof M, Lim M, Ferrusi I, Burke N, Blackhouse G, Goeree R, Tarride JE. R there any differences between Excel and R? Comparison of ICER estimates and CEACs obtained from a model implemented in Microsoft Excel and R. ISPOR 12th Annual European Congress, October 2009, Paris, France

Bischof M. Expected Value of Partial Perfect Information: Application of a 2-level algorithm in a drug-eluting stent decision analytic model. 29th Annual Meeting of the *Society for Medical Decision Making*, October 2007, Pittsburgh, USA

Nordmann A**, Bischof M**, Briel M, Bucher HC. Cost-effectiveness of drug eluting stents in a US setting: cost-utility analysis with a decision analytic model using meta-analysis data with 3 year follow-up. *European Society of Cardiology* Congress 2007, September 2007, Vienna, Austria

Bischof M. Expected Value of Perfect Information Calculations in Health Economics. 51. Jahrestagung der *Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie*, September 2006, Leipzig, Germany

Bischof M, Sendi P. Choice of parametric distributions in decision analytic models and expected value of perfect information. Accepted oral presentation. *iHEA* 6th European Conference on Health Economics, July 2006, Budapest, Hungary

INVITED PRESENTATIONS

Bischof M, Blackhouse G, Goeree R, Xie F. Value of Information: Vision of Ingenuity or Venture of Icarus? Workshop at the 2010 Canadian Agency for Drugs and Technology in Health Symposium, 18 – 20 April 2010, Halifax, Canada

POSTERS

Bischof M, Lim M, Ferrusi I, Burke N, Blackhouse G, Goeree R, Tarride JE. Some results are more equal than others: comparison of ICER estimates and CEACs obtained from a model implemented in Microsoft Excel and TreeAge. 31st Annual Meeting of the *Society for Medical Decision Making*, October 2009, Hollywood, California

Bischof M, Brogan A, Cavassini M, Bernasconi E, Furrer H, Vernazza P, Hirschel B, Weber R, Battegay M, Bucher HC and the Swiss HIV Cohort Study. Cost-effectiveness of first line antiretroviral backbone therapies in combination with efavirenz in HIV-infected patients in Switzerland. 5th *International Aids Society's* Conferecence on HIV Pathogenesis, Treatment and Prevention, July 2009, Cape Town, South Africa

Bischof M, Briel M, Bucher HC, Nordmann A. Drug-eluting stents from a medicare payer perspective: cost-utlility analysis with 4-year clinical meta-analysis data. *ISPOR* 13th Annual International Meeting, May 2008, Toronto, Canada

Bischof M. Analysis of uncertainty in economic evaluations in health care: expected value of perfect information for drug-eluting stents. *BioValley Science Day*, October 2007, Basel, Switzerland

Leuppi J, **Bischof M.** Cost-effectiveness of eNO measurements in chronic asthma management. *European Respiratory Society's* 17th Annual Congress, September 2007, Stockholm, Sweden

Bischof M. Expected value of perfect information: an application to a decision analytic cost-utility model for a novel therapy in cardiology. *European Association of Decision Making 21st* conference on Subjective Probability, Utility and Decision Making , August 2007, Warsaw, Poland

Bischof M. Expected value of perfect information: an application to a decision analytic cost-effectiveness model for drug eluting stents. Accepted for *iHEA* 6th World Congress on Health Economics, July 2007, Copenhagen, Denmark

Bischof M, Briel M, Bucher HC, Nordmann A. Economic evaluation of drug eluting stents: cost-utility analysis. *ISPOR* 9th Annual European Congress, October 2006, Copenhagen, Denmark

Bischof M. "Expected Value of Perfect Information" for osteoporosis cost-utility analysis. Would it pay off to know more? *European Science Foundation – The Kiel Institute for the World Economy* Conference on the Global Health Economy, October 2006, Salzau, Germany

Bischof M, Kraenzlin M, Sendi P. Cost-effectiveness of risedronate for the treatment of osteoporosis in Swiss postmenopausal women. *iHEA* 6th European Conference on Health Economics, July 2006, Budapest, Hungary

Bischof M, Sendi P, Leuppi J. Cost-effectiveness of an extended four-week fondaparinux prophylaxis regimen for the prevention of thromboembolic events in patients undergoing major orthopedic surgery. *ISPOR* 8th Annual European Congress, November 2005, Florence, Italy

ELECTRONIC LETTERS

Bischof M, Certainty about uncertainty. http://www.bmj.com/cgi/eletters/334/7594/621#163441. 4 April 2007

PRESENTATIONS

Some results are more equal than others: comparison of Excel, R and TreeAge for decision analytic modelling, Centre for the Ecaluation of Medicine, Hamilton, December 2010

Modelling in economic evaluation: an unavoidable fact of life. McMaster University, Hamilton, December 2010

VBA programming in Microsoft Excel. PATH Research Institute, September 2009

The things they don't teach you at grad school: getting the most out of TreeAge and Excel. PATH Research Institute, September 2009

(Almost) all you need to know about cost-effectiveness analysis. Basel Institute for Clinical Epidemiology, February 2008

Expected value of perfect information: the example of drug-eluting stents, McMaster University, Canada, November 2007

Probabilistic Sensitivity Analysis: Initial results from the malaria model, Technical Advisory Group for the *Malaria Modelling Project*, Swiss Tropical Institute, June 2007

Cost-utility analysis of eNO measurements in chronic asthma management, 2nd *SWISS NO MEETING*, University Hospital Basel, May 2007

Limitations of the Acceptability Curve, Basel Institute for Clinical Epidemiology, May 2007

Cost-effectiveness of drug-eluting stents in a US setting: cost-utility analysis with a decision analytic model using meta-analysis data with 3 year follow-up, Swiss Tropical Institute, February 2007

Gesundheitsökonomische Evaluationen [Health economic evaluations], Department of Philosophy, University of Basel, January 2007

Cost-effectiveness of eNO measurements in chronic asthma management, Pneumology Department, University Hospital Basel, November 2006

Evaluating Uncertainty, Training workshop on the *Manual of Implementation,* Intermittent Preventive Treatment in Infants (IPTi) Cost-Effectiveness Working Group (CEWG), Swiss Tropical Institute, November 2006

Probabilistic Sensitivity Analysis and Value of Information, Technical Advisory Group for the *Malaria Modelling Project*, Swiss Tropical Institute, November 2006

Economic Evaluation of Drug Eluting Stents, *European Network for Health Technology Assessment*, Working Package 4 meeting, Basel, November 2006

A decision analytic model for the evaluation of the cost-effectveness of drug eluting stents, *European Network for Health Technology Assessment*, Working Package 4 meeting, Helsinki, September 2006

Expected Value of Perfect Information Calculations in Health Economics, Swiss Tropical Institute, Basel, May 2006

Expected Value of Perfect Information Calculations in Health Economics, Basel Institute for Clinical Epidemiology, University Hospital Basel, Basel, December 2005

Interpreting the Cost-Effectiveness Acceptability Curve, Basel Institute for Clinical Epidemiology, University Hospital Basel, January 2005

TEACHING

Clinical Epidemiology (to 3rd year medical students), University of Basel, May 2008
Calculations with a scientific calculator, HCMTC 2008, STI, February 2008
Diagnostic Tests (to 6th year medical students), University of Basel, December 2007
Meta-Analysis (to 6th year medical students), University of Basel, November 2007
Clinical Epidemiology (to 3rd year medical students), University of Basel, June 2007
Meta-Analysis (to 6th year medical students), University of Basel, November & December 2006
Critical Appraisal, European Center of Pharamceutical Medicine, University of Basel, July 2006
Clinical Epidemiology (to 3rd year medical students), University of Basel, June 2006
Clinical Epidemiology (to 3rd year medical students), University of Basel, June 2005

GRANTS

Travel Grant, Canadian Agency for Drugs and Technologies in Health, April 2010

Post-doctoral research grant, Amgen Canada Inc., direct funds: CAN$ 75 000, September 2009
Post-doctoral research grant, Amgen Canada Inc., direct funds: CAN$ 75 000, September 2008
Travel Grant, *European Network for Health Technology Assessment*, 2006
Conference Grant, *European Science Foundation*, 2006
Travel Grant, University of Basel, 2006