Expert Opinion

Cost-effectiveness of drug-eluting stents: real-world scrutiny of the BASKET trial of real-world usage

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This editorial examines incremental cost-effectiveness analysis as a decision-making tool to guide the allocation of scarce financial resources. BASKET (Basel Stent Kosten Effektivitats Trial) evaluated the cost-effectiveness of drug-eluting stents in a real-world setting. Results of this study are examined in relation to similar assessments and alternative plausible assumptions are explored and presented in the context of real-world sensitivity analysis.

Keywords: coronary disease, cost analysis, cost-effectiveness, drug-eluting stents

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1. Introduction

The purpose of cost-effectiveness analysis (CEA) is to inform decision making regarding the allocation of scarce financial resources. When cost-effectiveness is obvious, because a treatment is equally or more effective and less expensive than alternative treatments (e.g., generic drugs), there is no need for formal analysis. Comparisons in which costs and relevant outcomes differ, however, require more consideration. The introduction of drug-eluting stents (DES) as an alternative to bare-metal stents (BMS) in the treatment of coronary lesions is such a situation. DESs are more effective at preventing restenosis in treated lesions than BMS but have a higher acquisition cost. Are DES good value for the price? This question has been explored in a number of different settings using different data sources and key assumptions but, despite numerous publications, the answer remains elusive. With 2 million patients receiving percutaneous coronary intervention with stenting worldwide each year and the use of DES approaching US$6 billion in 2005 [1], this question is important for decision makers.

2. Cost-effectiveness analysis

A common tool that is used in economical analysis is the incremental cost-effectiveness ratio (ICER), which allows for the application of a common scale to quantities for practical comparison. It is defined as the ratio of incremental cost divided by the incremental improvement in relevant outcomes. Whilst the preferred common ratio is the cost per quality-adjusted life year (QALY) gained, other ratios are often chosen that do not allow direct comparison across disease states. However, describing the cost per revascularisation that is avoided for DES compared with BMS reflects the disease- and treatment-specific parameters that may be more informative to a buyer. Because mortality is not known to differ between DES and BMS, the cost per QALY comparisons of these treatment options are dependent on health-related quality of life differences that are associated with treatment failure (e.g., angina or reintervention); available instruments may not be able to measure these differences with adequate sensitivity. Nevertheless, regulatory and technology assessment groups often focus almost exclusively on the cost per QALY in CEA.

In economic evaluations of DES compared with BMS, the most common ICER is the cost to avoid a major adverse cardiac event (MACE), defined as cardiac

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death, non-fatal acute myocardial infarction or target vessel revascularisation. Whilst CEA distils diverse measures into a single number, the usefulness of this number depends on the relevance of the components to a particular situation. For this reason, a well-reported CEA includes transparent accounting of all of the assumptions and a thorough sensitivity analysis to aid the reader in applying the results for decision making.

2.1 Cost-effectiveness of drug-eluting stents compared with bare-metal stents

A full description of the principles of CEA is beyond the scope of this editorial but has been well reported elsewhere [2-4]. Instead, the authors will illustrate how certain nuances in CEA comparing DES with BMS may have a significant impact on the results.

CEA that are based on randomised trials have the obvious advantage of random treatment assignment and resource-use estimates are more clearly related to actual outcomes of interest, but may include limited data on populations with certain types of patients or lesions. This bias may affect both costs and outcomes, as MACE rates (particularly restenosis rates) may vary greatly depending on the complexity of the lesions treated. Protocol-driven care that is associated with clinical trials may also create treatment patterns that are not expected in clinical practice. In the case of stent trials, routine angiographic follow up has been shown to lead to higher rates of recognised restenosis due to the 'oculostenotic reflex' [5]. Depending on clinical practice, these additional costs and events may limit the applicability of these ICER results.

By contrast, decision analytical models use inputs from independent sources to model the effects of joint uncertainty. A common problem is the difficulty of interpretation due to a lack of transparency. These studies often include large numbers of model inputs with uncertain importance and weighting to produce answers requiring considerable faith. In addition, population characteristics, treatment effects and resource inputs often come from different sources, again requiring robust sensitivity analyses to determine the stability of model inputs.

Finally, there are factors that are important in all CEA of DES. The first is overall generalisation. A well-constructed CEA may meet all of the requirements for a particular country or healthcare provider, but provide a limited value in other environments. Clinical decision making or model inputs may be sufficiently different rendering a well-constructed CEA difficult to interpret in an alternative context. Again, the best way to resolve issues of generalisability is to perform robust sensitivity analysis of assumptions that include additional plausible scenarios. The time horizon of an analysis is of great importance but may be overlooked. It must be long enough for both benefits and adverse consequences to be accrued. Too short a time horizon could artificially inflate the ICER and cause a cost-effective therapy to seem economically unattractive. Multiple trials of angioplasty with stenting suggest that MACE events, particularly related to restenosis and the need for reintervention of the treated lesion, continue to increase until 1 year [6-8]. Events beyond 1 year may be associated with disease progression in the same or a different vessel. Finally, the measurement of gains in QALYs presents a challenge in performing CEA for stent comparisons. If DES use does not extend the survival relative to BMS, the contribution to QALYs that is gained must come from improved quality of life, ostensibly due to avoidance of the pain that is associated with angina and repeat interventions. These effects may be difficult to measure with existing health-related quality of life instruments. In addition, the results may vary according to the treatment protocols. For example, routine angiography with reintervention may preclude angina symptoms.

2.2 Examples from the current drug-eluting stent cost-effectiveness analysis literature

An examination of recently published CEAs comparing DES with BMS illustrates the points discussed above. Cohen *et al.* examined the cost-effectiveness of sirolimus-eluting stents using data from the SIRIUS (Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients with *de novo* Native Coronary Artery Lesions) trial, including single-vessel interventions and not adjusting for protocol-driven angiography [9]. The sirolimus-eluting stent is shown to be highly cost-effective; however, limited sensitivity analysis is presented. Shrive *et al.* conducted a decision analytical model using trial-based efficacy data and population characteristics from a Canadian database [10]. Unlike other studies, this group adopted a lifetime perspective. Unfortunately, the model is so complicated that it is difficult to understand how treatment effects enter the model. In addition, the only ICER is cost per QALY using external utilities at 1-year post-catheterisation. Bagust *et al.* also constructed a decision analytic model using trial-generated data from a single centre [11]. Methods are difficult to assess and the model predicts an overall revascularisation rate of only 8.8% in the BMS group but fails to report actual rates. Costs per QALY for the population are also not reported, so without the benefit of sensitivity analysis the generalisability of these results is uncertain. This study rigorously assesses the health utility benefits of DES, the decreased exposure to revascularisation procedures and the elimination of time with angina. Van Hout *et al.* conducted an analysis based on the RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with *de novo* Native Coronary Artery Lesions) trial, adding to the literature an assessment of an arm with no planned angiography [12]. However, the population is atypical with 98% of the patients having a single stent placed. This has the effect of reducing the DES cost by 30% compared with most studies, limiting the direct use of results. Sensitivity results are not reported. More details from these studies are presented in Table 1.

The first results from BASKET (Basel Stent Kosten Effektivitats Trial) are reported by Kaiser *et al.* [13]. This single-centre

Table 1. Summary of drug-eluting cost-effectiveness literature.

CE study	CEA country	Time horizon	Transparent methods	CEA type	Sensitivity analysis	Adjustment for planned angiography	Selection bias	Definition of QALY	Reported incremental CE ratio
Cohen *et al.* [9]	USA	1 year	Yes	Trial	Limited	None	Only single-vessel disease	From reference, value not provided in report	US$1650/RV US$27,540/ QALY
Shrive *et al.* [10]	Canada	Lifetime	No	Decision model	Extensive	None	None	External, mean utility 1-year post-catheterisation	CA$58,721/ QALY
Bagust *et al.* [11]	UK	1 year	No	Decision model	None	Used target vessel RV in place of target lesion RV	Single centre 8.8% BMS RV	Time in low-use state, EQ-5D	None reported for full population, only subgroups
van Hout *et al.* [12]	Belgium Netherlands	1 year	Yes	Trial	None	Included arm without angiography	98% received only one stent	Not used	235/MACE avoided with angiography 1495/ MACE avoided without angiography
Kaiser *et al.* [13]	Switzerland	6 months	Yes	Trial	None	No planned angiography	Single centre	Baseline and month 6, EQ-5D	€18,311/ MACE avoided €73,283/ QALY

BMS: Bare-metal stents; CE: Cost-effectiveness; CEA: Cost-effective analysis; EQ-5D: EuroQol utility survey score; MACE: Major adverse cardiac event; QALY: Quality adjusted life year; RV: Revascularisation.

study built on the experience from prior work and benefited from randomisation, clinically rather than angiographically driven revascularisations, enrolment of a broad representative cohort (including a significant number of high-cost, multi-vessel and multi-stent cases) and resource use and health utility measurements on the same population. These factors are important and would be expected to yield reliable estimates of cost-effectiveness. However, the unfortunate choice of a 6-month time horizon may significantly underestimate the revascularisation events and resultant MACE rates. No known published data support 6 months as an appropriate time point to capture the majority of MACE events. Sensitivity analyses of BASKET assumptions show the potential impact of these choices and help to put the results in context.

Many published studies evaluating the cost-effectiveness of DES were performed in a short period of time. These studies employ different techniques and evaluate data from varied sources. Despite these differences, each provides a valuable insight regarding the cost implications of DES in certain populations. Because CEA are a decision-making tool, improved reporting of sensitivity analyses is warranted. Whilst issues such as angiographically driven effects on MACE rates and device costs have been explored and continue to be of interest, there remains a paucity of data regarding the quality of life effects of stent procedures, rendering the cost per QALY results of a questionable accuracy. Overall, the results suggest that use of DES across diverse populations is cost-effective, particularly in those with complex lesions.

3. Expert opinion

To illustrate the importance of assumptions that were selected in BASKET, Cooper and Linde-Zwirble constructed a sensitivity analysis from the information in the report and from the plausible assumptions about the occurrence of restenosis in months 7 – 12 from other studies [12,14]. For this, these authors assumed a 1-year time frame with a base model, including no additional restenosis events in months 7 – 12. In addition, an extended event model assuming that the relative ratio of restenosis events remained the same between the treatment groups, but the number of events occurring in months 7 – 12 was three-quarters the number occurring in the first 6 months, was assumed. As only summary data were available, the change in the cost to avoid one major event was calculated assuming the

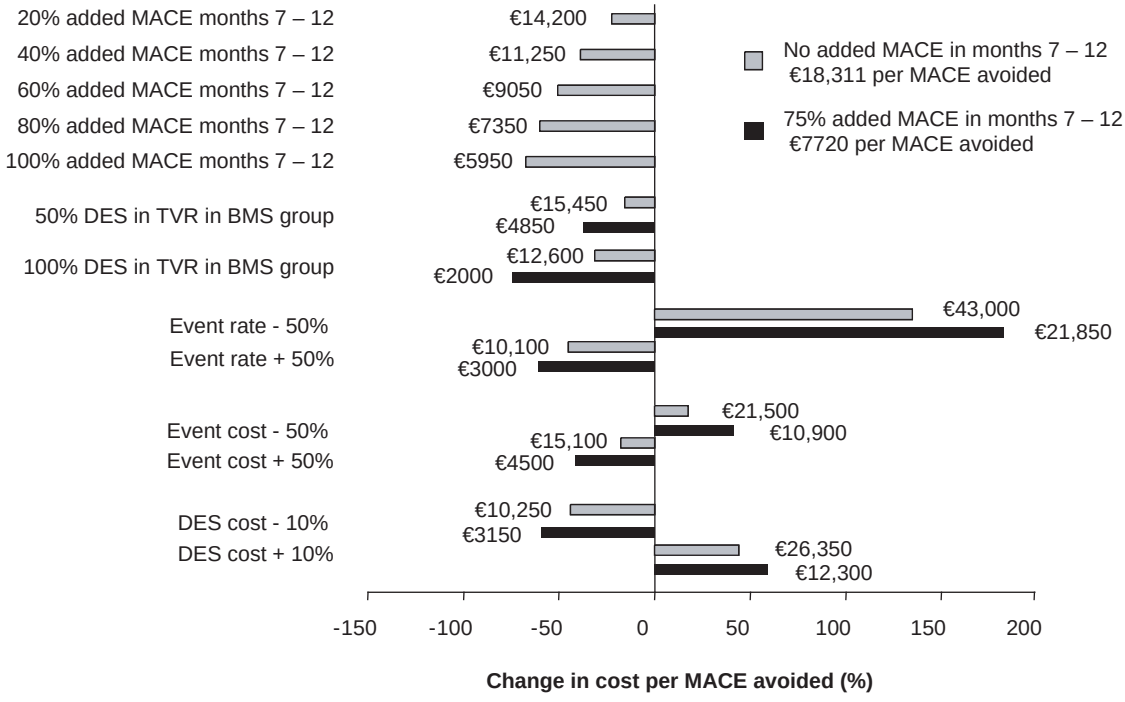

Figure 1. Sensitivity of 1-year incremental cost-effective ratio to changes in model assumptions. The figure shows the relative and absolute change in the cost per major event avoided when varying model input parameters for two different scenarios. The first (light bars) is the perspective from the published BASKET cost-effectiveness carried out to 1 year, assuming no added major events beyond month 6. The second (dark bars) assumes that the relative number of events in the BMS and DES groups remains the same, but that the added number of events in months 7 – 12 is 75% of the number that occur in months 1 – 6. The ICER for the extended event model was 58% less than the base model. The ICER was most sensitive to added events and least sensitive to event cost. The cost differential between BMS and DES was responsible for most of the incremental cost and resulted in the model being sensitive to the price used for each type of stent.

BASKET: Basel Stent Kosten Effektivitats Trial; BMS: Bare-metal stent; DES: Drug-eluting stent; ICER: Incremental cost-effectiveness ratio; MACE: Major adverse cardiac event; TVR: Target vessel revascularisation.

following alternative outcomes: added events in months 7 – 12 (20 – 100%, base model only); use of DES in target vessel revascularisation in the BMS group (50%, 100%); overall rate of major events (± 50%); cost of a major event (± 50%); and cost of DES (± 10%). Because the authors constructed the analysis from reported summary data, the results using actual data may vary. However, as the purpose of the sensitivity analysis is to gain an appreciation of the factors that drive the economics of an intervention, this limitation is minor.

The ICER for the base model as reported in BASKET was €18,311 per event avoided. This was reduced by 58% to €7720 in the extended event model by Cooper and Linde-Zwirble, with a 12-month follow up and was most sensitive to changes in the overall event rate (Figure 1), with decreases in the overall event rate reducing the cost-effectiveness of DES. The ICER decreased quickly with the addition of events in the second 6 months, falling below €10,000 per event avoided, as long as the number of events in months 7 – 12 was at least 50% of the number in the first 6 months. The model is much less sensitive to the cost of an event, primarily because a majority of the costs (~ 90%) occur during the initial hospitalisation. The ICER is also very sensitive to the cost of the DES. This is not surprising as all of the added costs in the initial hospitalisation were due to the cost of the DES. As the purpose of CEA is to inform decision making between alternate strategies, the authors evaluated a clinically plausible scenario using DES in 50 or 100% of the target vessel revascularisations in the BMS group given the known efficacy of DES for treating in-stent restenosis [15]. With this assumption, the ICER for the use of DES in all stent placements would be < €5000 per event avoided in the extended event model: a highly cost-effective treatment. A second point worth noting is that two different DESs were used in this study with substantially different outcomes. Thus, it follows that the cost-effectiveness of these two devices is also likely to be different and this point should be addressed more clearly.

Because the most sensitive assumption in BASKET is the overall event rate, the literature suggests that there is as much as a 75% increase in events in months 7 – 12, and the study is performed in a single institution; we look forward to the 18-month follow up. As interested readers of cost-effectiveness analyses, it is hoped that the authors will provide a comprehensive sensitivity analysis of the results of this very valuable study.

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