The Appropriate Role Of Cost-Effectiveness In Determining Device Coverage: A Case Study Of Drug-Eluting Stents

Cost-effectiveness analysis is not in itself sufficient for making major policy decisions.

by Brian Garriock Firth, Liesl M. Cooper, and Steve Fearn

ABSTRACT: The use of incremental cost-effectiveness ratios based on quality-adjusted life-years (QALYs) as a critical determinant of what should be covered by a health system is a growing trend. This presents challenges when applied to rapidly evolving technologies. The case study here focuses on the example of drug-eluting stents and the four-year change in cost-effectiveness as determined by the U.K. National Institute for Health and Clinical Excellence (NICE). We contend that classic cost-effectiveness as a blunt instrument for determining what should be covered may lead to erroneous conclusions when a broader perspective and the impact on health outcomes and costs are considered. [Health Affairs 27, no. 6 (2008): 1577–1586; 10.1377/hlthaff.27.6.1577]
It is important that other entities seeking to adopt an approach similar to that of NICE consider the limitations of cost-effectiveness for decision making and the wider impact of their policies on the provision of health care. In particular, there are some unique challenges associated with the use of classic cost-effectiveness methodology when applied to rapidly changing technologies such as many medical devices. The recent evaluation of drug-eluting stents (DESs) by NICE provides a pertinent illustration.

The sirolimus-eluting Cypher stent (Cordis) and paclitaxel-eluting Taxus stent (Boston Scientific) (both generically known as “drug-eluting stents”) have now come under scrutiny by NICE on two occasions. The initial determination in October 2003 was that DESs were recommended for use in patients with long-lesion (more than 15mm in length) or small-vessel (less than 3mm diameter) coronary artery disease and stable or unstable angina pectoris. A second evaluation that commenced in early 2005 resulted in a draft recommendation in August 2007 that “drug-eluting stents are not recommended for use in the treatment of patients with coronary artery disease.” This announcement has met with a major challenge based on disputed inputs into the cost-effectiveness model by cardiology specialty societies and industry alike. It also resulted in a series of questions being raised in the British House of Commons and House of Lords about the economic model for NICE and the validity of its conclusions. Highlighting a major limitation of models that do not weigh all treatment options, particular concern was expressed about the potential impact a shift back to less effective bare metal stents (BMSs) and coronary artery bypass graft (CABG) surgery would have on waiting times (a major policy focus for the U.K. government), as well as the associated potential for increased costs to the health care system, if DESs were removed from the market. Indeed, if revascularization and device costs are decreasing while evidence continues to show the efficacy of DESs is sustained over time, consideration of this broader context seems both wise and germane.

The focus of this case study is on (1) the limitations of cost-effectiveness analysis (CEA) for rapidly changing technologies, and (2) some concerns about the use of incremental cost-effectiveness ratios (ICERs) based on quality-adjusted life-years (QALYs) as the main or sole criterion for making health policy decisions.

**Background On Coronary Revascularization**

The surgical treatment of coronary arteries by CABG dates back to the initial work of René Géronimo Favolaro at the Cleveland Clinic in 1967. The first successful balloon angioplasty of a human coronary artery was performed in 1977 by Andreas Gruentzig. Percutaneous coronary angioplasty (PTCA), using just a balloon catheter, was associated with major limitations in terms of both effectiveness and safety. The introduction of stainless steel, balloon-expandable coronary artery stents in the mid-1990s in the United States (and a few years earlier in many countries) ushered in a new era: (1) the risk of abrupt vessel closure decreased
markedly due to vessel scaffolding and percutaneous coronary procedures became much safer; and (2) the risk of restenosis and a repeat procedure decreased 30–50 percent. The result was a progressive shift from coronary artery surgery to percutaneous coronary interventions (PCIs) using balloon angioplasty plus BMSs. However, as ever more complex lesions were being treated with stenting, the incidence of restenosis of the vessels began to climb back up toward 30–50 percent, and about half of patients required repeat revascularization. The reason for this restenosis was increased tissue proliferation through the struts of the stent despite the beneficial effects of the stent on vascular scaffolding. This led to the development of stents that would deliver antiproliferative drugs from a surface-coated polymer to the vessel wall over an extended period of months. The first of these DESs to be approved was the Cypher stent in 2002 in most of Europe and in 2003 in the United States, with the approval of the Taxus stent approximately one year later.

The two DESs mentioned above are arguably the most rigorously studied medical devices in history and have been the subject of a large number of randomized controlled trials (RCTs) with long-term follow-up, meta-analyses of these trials, a large number of registry studies of “real-world populations,” and well in excess of 400 scientific publications. The largest of these meta-analyses by Christoph Stettler and colleagues includes thirty-eight RCTs of the Cypher, Taxus, or BMSs and 18,000 patients. The reduction in restenosis, and in the resulting need for repeat revascularization, is striking for both DESs compared to BMSs. Their efficacy across a wide variety of populations has been demonstrated. During 2006 and early 2007, concerns were raised about a potential safety hazard with DESs. However, after extensive study, it seems clear that there is no increase in death or myocardial infarction with DESs, although there may be a very small ongoing risk of late stent thrombosis.

**NICE Recommendations: 2003 Versus 2008**

- **The 2003 guidance.** In 2003, NICE determined that DESs could be recommended for the treatment of patients with coronary artery disease and stable or unstable angina who had a vessel diameter of less than 3mm or a lesion more than 15mm in length, based on NICE’s assessment that DESs were cost-effective under these circumstances. Although the relative reduction in restenosis is fairly similar (60–75 percent) across widely different patient and lesion subsets with DES versus BMS, the absolute risk in terms of events avoided per 100 patients treated is greatest in smaller vessels, longer lesions, and diabetics. It is estimated that by 2007 approximately 63 percent of patients who underwent PCI in the United Kingdom received DESs and presumably met these criteria.

- **The 2007 guidance.** In August 2007, NICE issued draft guidance that “drug-eluting stents are not recommended for the treatment of patients with coronary artery disease,” thereby suggesting that what had become the standard of care for
higher-risk patients undergoing PCI should no longer be paid for by the National Health Service (NHS). This conclusion was based on new cost-effectiveness assessments performed by an external academic group, who had also performed the original analysis in 2003. This coverage decision was not the result of concerns about the device safety or efficacy—only its cost-effectiveness. This draft guidance was immediately challenged and was reissued in February 2008. NICE reinstated coverage of the same populations as in 2003 but specified that the difference in price between DES and BMS should not exceed £300.12 This decision was recently appealed, but NICE rejected the assertion that it was trying to establish a price control mechanism in setting a maximum price premium for DES over BMS.

**Implications of the NICE decision for health policy.** There are three broad issues relating to the NICE decision that have important health policy implications: (1) As a point estimate, the value of the ICER depends critically on the certainty of the values for outcomes and costs being input into the ICER equation. Ideally, inputs should also capture outcomes of real value to society. Both industry and physician specialty societies have challenged the validity of the inputs used and the issue of conflict of interest and bias by NICE’s academic advisers.13 (2) Even if good estimates of inputs are used, the sensitivity of the resulting point estimate should be examined to better understand the range within which the result holds true. This will be further discussed as it relates to the DES case. (3) The use of DESs has led to movement not only from the pool of patients who would have been treated with BMSs (a less expensive technology) but also from the pool of patients who would have been treated by CABG (a much more invasive therapy that costs the NHS 2.5 times more than a DES procedure).14 For the conclusions to be durable, it must be assumed that all patients who would have received DESs will instead be treated with BMSs at their average cost and outcomes—an unrealistic assumption. Furthermore, contrary to NICE’s own guidelines that call for the evaluation of new technologies to be made against “all relevant comparators,” the cost-effectiveness of DESs versus CABG has not been rigorously assessed.

**Potential Pitfalls In The Use Of ICERs**

The classic cost-effectiveness approach to assessing medical devices is fraught with some unique challenges. The ICER represents the ratio of the difference in costs between strategy A (new therapy) and strategy B (an older, established therapy) divided by the incremental improvement in outcomes of treatment A versus treatment B.15 Or, stated otherwise, ICER = (cost of strategy A – cost of strategy B)/(outcome of strategy A – outcome of strategy B). The costs in the numerator of this ratio include the costs of the device or treatment itself as well as the costs of downstream consequences of such treatment, both positive and negative. The derived ICER value is highly sensitive to even small changes in each of the four factors in the equation. Typically, only direct medical costs are included, because of measurement challenges.
The particular outcome of interest depends on the disease state and treatment provided. For PCI, the difference in reintervention rates between strategies A and B is germane, and it may be expressed in cost-benefit terms as “cost per reintervention avoided.” This is not as straightforward as it sounds, because there may be major disagreement about what constitute the correct values for numbers of reinterventions and the relevant observation period. Indeed, with respect to the NICE review of DESs, the British Cardiovascular Intervention Society (BCIS) objected not to the structure of the economic model used by NICE, but rather to several key inputs to the economic model. The BCIS highlighted the need to use contemporary U.K. cost data and case-mix, realistic absolute risk of repeat revascularization for BMSs, risk reduction based on the randomized trials, and contemporary market premiums for DESs over BMSs.17

Establishing the correct denominator for the cost-effectiveness ratio. The use of cost per reintervention avoided, although valuable, does not allow for comparison with other treatments for other disease states that society deems essential and payers use as a benchmark—for example, antihypertensive therapy or renal dialysis. Currently, the preferred unit of measurement of outcomes for such comparison across disease states is the utility-based QALY.

The majority of medical and surgical treatments are designed to improve the quality of life, and available data might not be sufficient to show whether or not they actually prolong life. This is the case for most coronary revascularization procedures, whether performed percutaneously or by CABG surgery. The primary objective is relief of limiting angina, and the only utility score applied in the CEA is a single estimate of time free of angina.18 Despite the vast body of evidence on PCI with stenting, there is a paucity of data on utility for the procedure, which leads to an analysis that assumes that the only benefit of avoiding a revascularization is avoiding the time with angina while waiting for treatment. Although mortality and morbidity associated with PCI with stenting as well as with a repeat procedure are low, they are not zero, and even if they do not differ between BMS and DES use, this oversimplified analysis should raise doubts about the value of the results. Given that emerging registry data are beginning to suggest that there may be reductions in myocardial infarction and mortality associated with DES use, one should consider what effect this could have on cost-effectiveness.

In addition to the issue of utility associated with the QALY assessment, other disputed variables raised by both industry and the BCIS affect the results and are worth mentioning here, including a dispute as to whether the absolute risk of revascularization in the United Kingdom is 11 percent or 13 percent and whether the relative risk reduction is 55 percent or 65 percent for DES versus BMS use.19

Establishing the correct numerator for the cost-effectiveness ratio. The costs of essentially every treatment, as well as their comparator treatments, vary widely from country to country and even from institution to institution within a given country.20 Thus, although it is not uncommon to hear otherwise well-
informed people talk about a certain therapy as being “cost-effective” or “not cost-effective,” the conclusions are in fact highly situational based on local prices. Furthermore, the threshold for what is considered cost-effective varies.

Some of the differences between medical devices and pharmaceuticals have been recognized (for example, the learning curve and the iterative nature of devices) as well as their potential impact on outcomes. However, there are other differences, which are not well appreciated. With pharmaceuticals, the prices of existing marketed products tend to remain stable despite the advent of new entrants until the time of patent expiration; this is not the case with medical devices. This is well illustrated by what has happened with BMSs following the introduction of DESs in many markets, including the United Kingdom and United States. In response to the introduction of DESs, manufacturers reduced the price of BMSs progressively over time. Based on the best available data, the initial average selling price of DESs at the time of launch in the United Kingdom in 2002 was around £1,500. By mid-2003, when NICE first appraised DESs, their average selling price had decreased to around £900, and the cost of BMSs was around £380. By the start of the second NICE review of DESs in 2005, these prices had fallen to approximately £820 for DESs and £280 for BMSs, as BMSs were being marginalized as a less effective therapy. The price of DESs has fallen significantly since 2002, but the price of BMSs has fallen faster than that of DESs, in absolute terms, resulting in a widening of the cost differential, for which DESs have now been penalized in terms of the ICER. Importantly, these costs are not independent of each other but rather are interdependent. The cost differential has further widened as a result of a recommendation for up to one year of dual antiplatelet therapy (aspirin and clopidogrel) in patients treated with DESs, although the optimal duration for both DES and BMS use is not fully understood. The price changes for BMSs would almost surely have been much less marked had the DESs not entered the market. A limitation of CEA is that it does not account for future market behavior relating to price that could result from a policy change. Policy changes should be made following careful assessment of all potential implications, whether or not they are measured by the CEA. Health technology assessment programs such as those operated by NICE need to understand and take into account the dynamics of the medical device market, where, unlike pharmaceuticals, prices of the “old technology” do not stay static when a new product is introduced.

Additionally, outcomes with medical devices, unlike those with pharmaceuticals, depend not just on the device but also on the skill of the operator and procedural technique. Initially, the outcomes and the total costs associated with the new therapy might not be favorable, but over time, with greater operator expertise and a fuller understanding of how best to use the device, this therapy may become cost-effective. The experience with BMS use is an apt example. When these devices were first approved, they required hospital admission for approximately one week (versus one to two days now), as patients had to be converted from intrave-
nous heparin to coumadin and stabilized to prevent thrombosis of the stents. Over several years, it became evident that an even more effective way to prevent stent thrombosis entailed better deployment of the stent (using high-pressure balloon inflation) and the use of dual antiplatelet therapy instead of prolonged heparin and coumadin therapy. The net result was a hospital stay of one to two days, fewer bleeding complications, and lower restenosis rates, with the associated beneficial effect on costs. Undue reliance on the ICER/QALY methodology can lead to premature rejection of a promising technology on the grounds of incomplete understanding of optimal patient selection and technique. The reality is that for a given technology, repeated application of this methodology at different points in time may yield different conclusions for one or more of the reasons discussed above.

ICERs As A Proxy For “Value”

- The fallibility of ICERs. To demonstrate the impact of the disputed inputs to the model, we provide sensitivity analysis in an economic model that reproduces the NICE model results within 1–4 percent depending on subgroup. The effects of these inputs on one-year cost-effectiveness, individually and in combination, are shown in Exhibit 1. By simply introducing a small number of changes in line with current literature, ICERs vary greatly, and in combination, results are well within the accepted range of £20,000–£30,000 per QALY.

There is also evidence from the NHS that the cost of PCI has remained essentially flat over many years and may in fact be decreasing, that the cost of CABG has increased, and that waiting times for both CABG and PCI procedures have fallen—an outcome desired by the NHS (Exhibit 2). Furthermore, several very well-conducted studies in large populations have shown that the mortality rate following treatment with DESs in the “real world” is actually lower than with BMSs. We estimate that one life saved has seven to ten times the QALY benefit of one revascularization avoided and will thus affect the ICER considerably if included. Just a 1 percent absolute reduction in mortality in combination with the alternative data inputs described reduces ICERs to £12,586, £13,105, and £5,875 for patients with long lesions, diabetes, and small vessels, respectively. This suggests that a decision based on a single estimate using widely disputed inputs should be very carefully considered. If data from payers themselves show that procedural costs remain stable or even decrease in the face of the introduction of new, more effective technology, as is the case in both the United Kingdom and the United States, this should surely call into question the infallibility of the ICER/QALY approach as a sole arbiter of economic value and support the real value of a technology such as the DES. Indeed, one may even ask why a repeat cost-effectiveness evaluation was performed under these circumstances.

- Cost and service impact of reducing DES use. One final, but important, consideration is the cost and service impact of a decision to reduce or eliminate DES use. Based on strong statements by the BCIS, we estimated that the cost of a 20 per-
cent shift from PCI revascularization back to CABG surgery would cost the NHS approximately £54.7 million per year, or £806 per patient undergoing PCI. If offset against the incremental cost of DESs in the economic model, these costs reduce the base-case ICERs in Exhibit 1 to £9,782, £8,232, and £35,483 for patients with long lesions, diabetes, and small vessels, respectively. Most decision analyses do not take into account the impact of the policy decisions they may ultimately drive, but, in this

EXHIBIT 1
Results Of Sensitivity Analysis Using Various Data Inputs, Effects On One-Year Cost-Effectiveness Of Drug-Eluting Stents Versus Bare Metal Stents

<table>
<thead>
<tr>
<th>Data input</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case (NICE model) ICER</td>
<td>Long lesions</td>
</tr>
<tr>
<td>Current cost data and case-mix</td>
<td>£179,755</td>
</tr>
<tr>
<td>13% absolute risk of repeat revascularization (instead of 11% in base case)</td>
<td>112,488</td>
</tr>
<tr>
<td>65% DES risk reduction (instead of 55% in base case)</td>
<td>145,790</td>
</tr>
<tr>
<td>£300 DES price premium (instead of £600 in base case)</td>
<td>145,210</td>
</tr>
<tr>
<td>Combination of case-mix, absolute risk, risk reduction, and price premium</td>
<td>83,962</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>£179,060</td>
</tr>
<tr>
<td></td>
<td>114,764</td>
</tr>
<tr>
<td></td>
<td>92,254</td>
</tr>
<tr>
<td></td>
<td>Small vessels</td>
</tr>
<tr>
<td></td>
<td>£144,693</td>
</tr>
<tr>
<td></td>
<td>114,215</td>
</tr>
<tr>
<td></td>
<td>58,495</td>
</tr>
<tr>
<td></td>
<td>8,792</td>
</tr>
</tbody>
</table>

SOURCE: Authors’ analysis of data inputs suggested by the British Cardiovascular Intervention Society (BCIS) and current literature.
NOTES: Data inputs include contemporary U.K. cost data, case-mix, absolute risk of repeat revascularization, risk reduction based on randomized trials, and current market premiums for drug-eluting stents (DESs) compared with bare metal stents (BMSs). NICE is National Institute for Health and Clinical Excellence. ICER is incremental cost-effectiveness ratio.

EXHIBIT 2
Inflation-Adjusted U.K. National Health Service Costs (Per Person) And Waiting Times For Percutaneous Coronary Intervention (PCI) And Coronary Artery Bypass Grafting (CABG), 1997–2006

NOTES: Costs and waiting times are averages and have been weighted according to the proportion of elective, nonelective, and day-case procedures. Inflation adjustment employed National Health Service (NHS) inflation statistics. The increasing use of stent technology is shown at three points. Costs are denoted by dashed lines (with squares) and relate to the left-hand y axis. Waiting times are denoted by solid lines (with circles) and relate to the right-hand y axis. BMS is bare metal stent. DES is drug-eluting stent.
case, the additional cost of bypass surgery that would result from a decision to not use DESs could be considered a legitimate health service cost that should be taken into account.

A Cautionary Tale On Cost-Effectiveness In Medical Device Evaluation

As Albert Einstein is reputed to have said, “We should strive to make things as simple as possible, but not more simple.” Given current pressures on health care spending, it may be reasonable to use cost-effectiveness as one component of the comprehensive evaluation of any new medical device or procedure. Nevertheless, the question of the full magnitude of the benefits provided and what the net budgetary impact of a new form of therapy is should be very carefully considered and play an appropriate role in these deliberations. If payers overzealously use flawed ICER/QALY methodology to the exclusion of other important inputs into their decision-making process, important opportunities to improve health outcomes at a similar or lower cost to society will be lost, and innovation in this field may be halted in its tracks. When overall revascularization costs are declining, waiting times have been virtually eliminated, and outcomes are well within expectations, the potential for the suggested policy change to negatively affect the NHS is very real. It is clearly important to appreciate that CEA used in the context of rapidly evolving technology, such as medical devices, is fraught with challenges, especially when the confidence intervals around the input values are in dispute. This case study sounds a note of caution to countries considering similar methods of medical technology assessment as used by NICE and emphasizes the importance of taking a broader economic view before making major policy decisions.

Brian Firth and Liesl Cooper were formerly employed in Medical Affairs and Health Economics at Cordis Corporation. Steve Fearn is currently employed in Health Economics at Cordis Corporation in the United Kingdom. Cordis Corporation manufactures the Cypher drug-eluting stent.

NOTES
10. See online Appendix Figure 1 at http://content.healthaffairs.org/cgi/content/full/27/6/1577/DC1.
11. See online Appendix Figure 2, as above; and Stettler et al., “Outcomes Associated with Drug-Eluting and Bare Metal Stents.”