Drug-eluting stents: a systematic review and economic evaluation

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Executive summary

Health Technology Assessment 2007; Vol. 11: No. 46
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Objectives

The objectives were to assess the effectiveness and cost-effectiveness of the use of drug-eluting coronary artery stents in percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD).

Specifically, the clinical review compares the use of:

- drug-eluting stents (DES) versus non-drug-eluting bare metal stents (BMS)
- drug-eluting stents of different design (DES versus DES).

A technology assessment was completed in 2003, early in the introduction of DES. Continued, rapid development of DES suggests that it is appropriate to explore the current evidence base on DES in order to inform the development of National Institute for Health and Clinical Excellence (NICE) guidance for the NHS in England and Wales.

Background

PCI with the use of stents has become an established means for treating CAD. Although PCI is considered effective, re-narrowing (restenosis) in and around implanted stents can occur, which may require repeat treatment. Drugs released from DES aim to reduce the need for repeat intervention by limiting the processes underlying restenosis.

Methods

The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and economic evaluations.

Evidence on clinical effectiveness and cost-effectiveness of DES was identified using a comprehensive search strategy of bibliographic databases from December 2002 to August 2005 and included the Cochrane Library, EMBASE and MEDLINE and also handsearching activities. Unpublished evidence was considered for inclusion in the assessment.

Assessment of health economics evidence included review of published economic evaluations, critique of manufacturer submissions to NICE and our own economic evaluation in the form of cost-utility analysis.

Inclusion criteria

Primarily, randomised controlled trials (RCTs) comparing DES with BMS or DES with DES were considered for inclusion, but other designs of study were considered where no RCT evidence was available. Non-controlled clinical studies of DES were only considered in the absence of data from comparative studies.

The assessment was restricted to adults with CAD, undergoing treatment of native and intervention naïve vessel(s) by PCI with the use of stents. Only studies of DES awarded CE Marking [indicating European Union (EU) conformity and authorisation to market within the EU] at or around the time of this assessment were eligible for inclusion. Eleven distinct DES designs were considered: AXXION™, CoStar™, Cypher™, Cypher Select™, Dexamet™, Endeavor™, Janis™, Liberté™, Taxus™, Xience V™ and Yukon™.

Clinical outcomes included death, myocardial infarction (MI), target lesion revascularisation (TLR), target vessel revascularisation (TVR), composite event rate (major adverse cardiac event and/or target vessel revascularisation), binary restenosis rate and late luminal loss.

Full economic evaluations that compared two or more options and considered both costs and consequences were eligible for inclusion in the economics review.

Results

Clinical findings

A total of 25 RCTs were included in the review of clinical effects. These included 17 RCTs of DES versus BMS and eight RCTs of DES versus DES. For some DES, no data from RCTs were available (in some cases, RCTs were in progress).

Handsearching and utilisation of unpublished data made an important contribution to the review.
Meta-analysis of RCTs of DES versus BMS
All 17 RCTs identified were included for at least one outcome in the meta-analysis. A range of eluting agents were studied: paclitaxel \( (n = 11) \), sirolimus \( (n = 5) \), everolimus \( (n = 1) \) and ABT-578 \( (n = 1) \). One study included three arms, comparing paclitaxel, sirolimus and non-eluting stents. Follow-up extended to 3 years for paclitaxel and sirolimus-eluting stents.

No statistically significant differences in mortality or MI were identified up to 3 years. Significant reductions in repeat revascularisations were determined for DES compared with BMS (for example, at 1 year: TLR relative risk 0.24; 95% confidence interval (CI) 0.19 to 0.31; and TVR relative risk 0.43; 95% CI 0.33 to 0.55). This estimated benefit appears to be stable from 1 to 3 years. Binary restenosis and late luminal loss also favoured DES.

DES without RCTs
For six of the 11 DES designs there were no RCTs available for assessment. Reporting of data after completion of this assessment may assist in evaluating these DES in the near future.

Meta-analysis of RCTs of DES versus DES
All eight RCTs identified were included for at least one outcome in the meta-analysis. Six of these compared Taxus (paclitaxel-eluting) and Cypher (sirolimus-eluting) directly. Follow-up was limited to 9 months, except for a single study.

No statistically significant differences in mortality or MI were detected between DES designs. In meta-analyses of TLR, TVR and composite event rate, marginal improvement in efficacy of Cypher over Taxus was observed. These results await confirmation beyond 1 year and differences in study design may have influenced reporting of outcomes.

Economic evaluation
Ten full economic evaluations were included in the review. In general, the balance of evidence indicated that DES are more cost-effective in higher risk patients.

In the review of submitted models, when more realistic assumptions and data values were used they confirmed the view that DES may be cost-effective only under very limited circumstances.

A cost–utility analysis of DES versus BMS was undertaken from the perspective of the NHS. For the purposes of our base case evaluation, it was assumed that all DES are clinically equivalent. The costs and benefits of DES versus BMS were identified, measured and valued.

Compared with BMS, the use of DES appears to reduce the rate of repeat revascularisations; benefit estimates used in the economic assessment are defined as ‘broad’ (i.e. cases involving any TLR/TVR irrespective of any other lesions/vessels undergoing revascularisation) and ‘narrow’ (i.e. cases involving TLR/TVR only). The incremental benefit to the patient is therefore described as the loss of quality-adjusted life-years (QALYs) avoided by not having to undergo a repeat revascularisation.

Univariate sensitivity analysis and extreme values analysis indicate that the price premium, numbers of stents used in the index procedure and absolute risk reduction in repeat interventions most significantly influence the cost-effectiveness ratios. Sensitivity analyses also permit a range of values for efficacy and effectiveness to be considered for individual designs of DES.

The cost-effectiveness results reveal that, all patients considered together, the calculated cost per QALY ratios are high (£183,000–562,000) and outside the normal range of acceptability. Cost-effectiveness is only achieved for those non-elective patients who have undergone a previous coronary artery bypass graft and have small vessels. ‘Real-world’ data show that patient numbers in this latter group are very small (one in 3100 of all patients treated with PCI).

Additional research and analysis were undertaken to support the NICE Appraisal Committee. Information on evidence sources considered for the report and range of post hoc sensitivity analyses are presented within the full monograph.

Conclusions
The conclusions of the assessment are that the use of DES would be best targeted at the subgroups of patients with the highest risks of requiring reintervention, and could be considered cost-effective in only a small percentage of such patients. This is similar to the conclusion of our previous assessment.

Implications for the NHS
Assessment of budgetary impact of DES on the NHS involved investigation of purchase cost and trends in DES usage. On the basis of assumptions in the NHS Tariff Prices and 50% use of DES,
the annual volume of DES purchased by the NHS in England (assuming 5% wastage) is estimated to be between 35,000 and 42,000 units, costing an additional £21–25 million.

If anecdotal evidence of 70% current DES usage is accepted, the estimated total cost of purchasing DES rises to £30–36 million; if 100% DES usage is assumed the projected cost would be around £42–51 million.

**Recommendations for further research**

This assessment was able to utilise long-term follow-up from trials of DES, head-to-head studies of DES versus DES and more real-world data from registries and the NHS. However, further research would be useful in the following areas:

- trials of DES compared with new generation BMS
- trials of DES compared with DES
- further evaluation of newer BMS in combination with drug administration.

**Publication**

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care. The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/42/01. The protocol was agreed in March 2005. The assessment report began editorial review in May 2006 and was accepted for publication in May 2007. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.

Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.