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RA Hill,[1] A Boland,[1] R Dickson,[1*] Y Dündar,[1] A Haycox,[2] C McLeod,[1] R Mujica Mota,[1] T Walley[1] and A Bagust[2]

[1] Liverpool Reviews and Implementation Group, University of Liverpool, UK
[2] The University of Liverpool Management School, UK

* Corresponding author

Executive summary

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Executive summary

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 Unpublished evidence was considered for inclusion in the assessment.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 patents. 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

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NIHR Health Technology Assessment Programme

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