Clinical effectiveness and cost effectiveness of intracoronar brachytherapy and drug eluting stents

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English.

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Report

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We would like to thank all contributers for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, 2004

7 English summary

Background

Restenosis is one of the most important problems limiting the long-term success of coronary angioplasty. Use of stents has successfully reduced the problem of restenosis, on average from 22 % to 32 %, although with higher values for patients in high risk groups. The use of stents however, has led to the challenge of handling in-stent restenosis.

In-stent restenosis is the result of a process called intima hyperplasia whereby local cell activation and inflammation stimulates growth of smooth muscle cells and deposition of extracellular matrix within the vessel lumen. Approaches to combat the problem of restenosis such as systemic or local drug administration or intracoronar brachytherapy have had modest success. A recent approach is the use of drug eluting stents (DES) that may interfere with the proliferative response leading to in-stent restenosis. Drug-eluting stents provide a local drug reservoir that is released within a time period of 10-30 days, with no detectable systemic drug levels. Several antiproliferative agents added to different stents are under clinical investigation. Rapamycin, which includes the drugs Sirolimus, Everolimus and Tacrolimus, are immunosuppressive agents that inhibit proliferation of smooth muscle cells. Taxol-based drugs, such as 7-hexaonyltaxol or paclitaxel are cytotoxic drugs that interfere with cell proliferation, and are currently used in cancer chemotherapy.

Following the recent approval of two types of drug eluting stents in Europe and North America, drug eluting stents are rapidly disseminating throughout the health care systems in several countries. The uptake is advocated by great enthusiasm following positive results from randomised controlled trials.

Objectives

- To assess the clinical effectiveness and cost effectiveness of intracoronar brachytherapy and drug eluting stents

- To discuss possible implications of these findings for the Norwegian health care setting

Search strategy

Eligible studies were identified by searches in Medline for the period from 1966 until March 1st 2004 with the search profile: (intracoronar* or vascular or coronar*) and (radiotherapy or radiation or brachytherapy or coat* or eluting or tacrolimus or paclitaxel or sirolimus or taxol or everolimus) and stent*. Additional searches for unpublished studies and presentations from ongoing trials were undertaken at the following web-sides: TCTmd (http://www.tctmd.com/), American college of cardiology http://www.acc.org/ and Euro PCR (http://www.europcr.com/). In addition information and results from ongoing trials were kindly provided by Johnson and Johnson and Boston Scientific.

The systematic search yielded 641 references and 57 conference presentations. 24 publications and nine conference presentations were included for drug eluting stents and 29 publications for intracoronar brachytherapy.

Inclusion criteria
Population: patients with angina, ischemia, stenosis, restenosis, in-stent restenosis or graftstenosis
Intervention: intracoronary brachytherapy or drug eluting stents
Outcomes: mortality, myocardial infarction, revascularisation
Angiographic measures: restenosis, diameter stenosis and late loss
Study design: RCT, controlled trial, case series

Exclusions:
Stents with heparin, radioactive stents, liquid-balloon based brachytherapy

Data collection
All articles were independently reviewed by at least two authors. The final set was agreed by consensus. Methodological quality was assessed according criteria used by the Norwegian Centre for Health Technology Assessment (based on Cochrane reviews handbook and CRD guidelines) supplemented with clinical criteria defined by the review group.

Results
Evidenstables with data from included studies and results of assessment are shown in attachment 4 (in English).

Intracoronar brachytherapy
We identified nine RCTs comparing intracoronar brachytherapy with placebo treatment for patients with in-stent restenosis.

- Intracoronar brachytherapy (beta- or gamma radiation) reduced the risk for revascularisation by 34-44 % compared with placebo after 1 year follow up. The effect was maintained also after 5 years follow up in two gamma brachytherapy studies.

- The evidence regarding effect on death or myocardial infarction was insufficient for conclusions. No study or the metaanalysis of these studies had sufficient statistical power to analyse effect on clinical outcomes.

- Brachytherapy was associated with an increased risk of late thrombosis RR 2.18 (1.00-5.33) after 9-12 months follow up.

Drug eluting stents

We identified 13 RCTs that compared drug eluting stents with bare metal stents with over 5 000 patients included. All studies were randomised placebo controlled clinical trials. Six trials evaluated paclitaxel-eluting stents (42-47), and six trials evaluated rapamycin-eluting stents (53-56,66,67).

Most studies included patients with short lesions (< 15 mm) in large vessels (> 2.8 mm) in native coronary arteries, although three RCTs included patients with long lesions and / or small coronary arteries. Except for one small study (66) all studies included patients with diabetes. Patients with thrombus, acute myocardial infarction were excluded in these studies.

Seven non-controlled trials were identified that evaluated drug eluting stents for indications not included in RCTs.

- Mortality is a rare event following PCI, and none of the included studies had statistical power to assess effect on mortality.

- The combined estimate for all-cause mortality after 9-12 months follow up was 1.1 % in DES group and 0.7 % in the BMS group, with a combined RR of 1.56 (95 % CI 0.63-3.87). After two years follow up the RR for all cause mortality was 1.39 (0.75-2.58) (Fig 8).

- The combined rates for cardiac mortality was 0.8 % in DES group and 0.9 % in BMS group after 9-12 months follow up, RR 0.88 (95 % CI 0.39-1.95), with similar rates also after 2 years follow up. The relative risk for cardiac mortality was 0.83 (0.41-1.69) after 2 years follow up based on data from almost 2 000 patients.

- While all sirolimus trials reported all cause mortality, most paclitaxel trials reported cardiac mortality only. We do not know how paclitaxel eluting stents impact on all-cause mortality, or whether the direction of effect is confirmative or opposite to what has been reported in sirolimus trials. Thus we do not have sufficient data for conclusions regarding the long term safety of drug eluting stents with respect to mortality.

- There was no effect on rates of myocardial infarction. The combined risk estimate for paclitaxel studies after 1 year follow up was RR 0.94 (95 % CI 0.62-1.44) and for rapamycin studies RR 0.98 (95 % CI 0.58-1.66) after 1 year follow up, with similar figures for 2-3 years follow up in rapamycin studies.

- Thrombosis has been a concern because of the increased risk of thrombosis following intrakoronar brachytherapy. Thrombosis was a rare event and the metaanalysis of these studies showed apparently no difference between groups: late thrombosis was reported for 0.6 % of patients treated with DES and 0.8 % of patients given BMS, RR 0.98 (95 % CI 0.46-2.06).

- Drug eluting stents, whether rapamycin or paclitaxel, reduced rates of revascularisation for a follow up of 6 to 36 months. The combined results

from all studies showed an absolute reduction in retintervention of 9.4 %, RR 0.37 (0.24-0.56). Importantly, this effect was shown to be maintained also after 2 years follow up. There were 147 reintervention in the DES group (n=1801) compared with 373 reinterventions in the BMS group (n=1727), (RR 0.36 (0.25-0.50) p< 0.0001). Reintervention was reported for restenosis in the stent, lesion or target vessel, and were clinically driven according to FDAs criteria in five trials but not stated in seven trials.

- Several studies report subgroup analysis, with stratification of patients with diabetes, lesions in small vessel or long lesions. No study had power to analyse effect in subgroups. All studies showed reduced rates of revascularisation for patients with diabetes given DES compared with BMS with combined RR 0.37 (95 % CI 0.25-0.54) for 9-12 months follow up.

- Two studies stratified on lesion length and vessel diameter. Taxus IV found significantly reduced rates of restenosis for patients with lesions in vessel <3.0 mm RR 0.29 (95 % CI 0.19-0.52) but not for vessel ≥3.0 mm RR 0.43 (95 % CI 0.16-1.16) (48). Sirius reported comparable results for small and large vessels with stratification on 2.75 mm (54). Similarly good results were reported for patients with long lesions in Taxus IV and Sirius (47,54).

- MACE was reported as a composite outcome of death (cardiac or all cause), myocardial infarction and revascularisation. Most studies reported significant reduction in MACE with combined RR estimated for paclitaxel studies of 0.58 (95 % CI 0.47-0.72) and rapamycin studies RR 0.34 (95 % CI 0.27-0.45) after 1 year follow up.

- Several ongoing or planned trials are expected to make important contributions that may influence the findings in this review. At present results from studies with approximately 5 000 patients have been included in this review, in the next few years results from additional 8 000 patients is expected.

Comments

Two main findings emerged from the systematic review and metaanalysis of these trials. Drug eluting stents and intracoronar brachytherapy reduced rates of revascularisation. However, possible effect on clinical outcomes such as mortality is at present insufficiently addressed.

When new technologies are introduced into clinical practice, the question of clinical effectiveness and the safety of the technology need to be adressed, to ensure that patients are given efficient and safe treatment. This is especially challenging when considering fast evolving technologies such as drug eluting stents. The past history of abandoned studies calls for caution regarding the potential offset between benefit and harm.

The life-span of a systematic review in a fast evolving field such as drug eluting stents is short. Several ongoing trials accounting for over 8 000 patients will make important contributions regarding clinical effectiveness of this technology.

The results from this systematic review may also have implications for the future reporting of outcomes from ongoing and planned clinical trials, especially the use of composite endpoints. Use of MACE as the hierarchical combination of death, myocardial infarction and revascularisation is misleading, both due the possibility of divergent effects of individual outcomes, and due to the fact that revascularisation counts equally with mortality.