Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II)


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Using elective stenting with heparin-coated stents plus antiplatelet therapy in selected patients with stable or stabilised unstable angina, with one or more de-novo lesions, less than 18mm long, in vessels of diameter 3mm or more.

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with stable or stabilised unstable angina, with one or more de-novo lesions, less than 18mm long, in vessels of diameter 3mm or more.

Setting
The study setting was hospital. The economic study was carried out in the Netherlands.

Dates to which data relate
Effectiveness and resource use data were collected between September 1995 and March 1996. The price year was not explicitly specified.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Costing was prospectively conducted on subgroups of the patient sample and not on the whole patient sample used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size (in the main randomisation, with an assumption of a clinical event rate of 30% in the control group versus 20% in the intervention group and a two-sided type I error level of 0.05, a sample size of 412 patients in each group was required to reach a power of 0.90; in the subrandomisation, based on an assumption of 0.15mm difference between the stent and balloon-angioplasty groups in terms of minimum lumen diameter at 6 months in patients with angiographic follow-up, the same sample size would reach a power of 86%). A total of 827 patients were randomised to either the stent group (n=414) with an average (SD) age of 50 (10)
years or to the balloon-angioplasty group (n=413) with an average (SD) age of 59 (11) years. One patient from the intervention group and three from the control group were excluded. A one-to-one subrandomisation was conducted in each study group in order to assess the natural course of the treatment and the rate of restenosis by angiographic evaluation, according to which patients were allocated to either clinical follow-up alone or angiographic and clinical follow-up (n=209 in the balloon-angioplasty group and n=207 in the stent group).

**Study design**
The study design was a randomised, controlled trial carried out in 53 centres. The follow-up period was 12 months. The loss to follow-up (patients treated by alternative methods other than that assigned by randomisation) was 3.4% in the stent group and 13.4% in the balloon-angioplasty group. There were two patients in each group who were treated by coronary-artery bypass graft (CABG). The blockwise randomisation was performed from a central office by a computer-generated list of random numbers. The randomisation could not be performed in a blinded fashion, due to the nature of the intervention.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness was intention to treat. A composite measure of death, myocardial infarction, bypass surgery or a repeat percutaneous intervention of previously treated lesion was used as the primary clinical outcome of the study. In the analysis of subgroups, the mean minimum lumen diameter corresponding to a specific restenosis rate was chosen as the clinical outcome. The study groups were found to be comparable in terms of baseline characteristics or angiographic and procedural characteristics.

**Effectiveness results**
In terms of the composite measure of clinical events at 6 months, the stent group had a rate of 12.8% of cases versus 19.3% in the balloon-angioplasty group (relative risk 0.67; 95% CI: 0.48 - 0.92; p=0.013).

The difference between the groups remained significant at 12 months.

The stent subgroup with angiographic follow-up had a mean minimum lumen diameter of 1.89mm (SD, 0.65) versus 1.66mm (SD, 0.57) in the corresponding balloon-angioplasty subgroup, (p=0.0002).

The corresponding restenosis rates (diameter of stenosis greater or equal to 50%) were 16% and 31%, respectively, (p=0.0008).

The stent subgroup with clinical follow-up alone had an event-free survival rate of 0.89 at 12 months versus 0.79 in the corresponding balloon-angioplasty subgroup, (p=0.004).

**Clinical conclusions**
This study confirms that stenting has a preventive effect on restenosis. It also confirms that the combined use of two antiplatelet drugs, aspirin, and ticlopidine, is safe and effective in preventing stent thrombosis.

**Measure of benefits used in the economic analysis**
The benefit measure was event-free survival after 1 year for the patients assigned clinical follow-up alone.

**Direct costs**
Costs were not discounted due to the short timeframe of the study (less than one year). Quantities of resource use were reported separately from the costs. Unit costs were also reported separately. The cost analysis covered the direct medical costs of the initial procedure, hospital admissions, and major curative and diagnostic procedures after the initial procedure. The perspective adopted in the cost analysis was that of the hospital. The case record forms and specific patients' passports were used to collect the resource use data. The cost data were estimated based on the
detailed information from the Dijkzigt Hospital in Rotterdam. The date to which the price data referred was not explicitly specified.

**Statistical analysis of costs**
Unpaired Student t test was used to compare the groups in terms of the mean cost.

**Indirect Costs**
Indirect costs were not included.

**Currency**
Dutch guilders (Dfl). A conversion to US dollars was carried out based on an approximate exchange rate of US$1 = Dfl 2.045.

**Sensitivity analysis**
Confidence ellipses (based on 95%, 50%, and 5% probabilities) were employed to tackle the uncertainties surrounding the point estimates of both average costs and effects.

**Estimated benefits used in the economic analysis**
The stent subgroup with clinical follow-up alone had an event-free survival rate of 0.89 at 12 months versus 0.79 in the corresponding balloon-angioplasty subgroup, (p=0.004).

**Cost results**
The stent subgroup with clinical follow-up alone had an average total direct medical cost of Dfl 18,812 versus Dfl 16,727 in the corresponding balloon-angioplasty subgroup, leading to a difference of Dfl 2,085, (p=0.068).

**Synthesis of costs and benefits**
An incremental analysis was performed. The additional cost per additional event-free survival was used as the main measure of cost-effectiveness, which resulted in Dfl 19,358 for the stent implantation as compared to the balloon angioplasty. The balloon angioplasty had an average cost-effectiveness ratio of Dfl 21,073 (95% CI: 18,348 - 24,105, using Fieller’s approximation) versus Dfl 21,073 (95% CI: 18,638 - 23,263) for the stent implantation.

**Authors’ conclusions**
Over 12-month follow-up, a strategy of elective stenting with heparin-coated stents is more effective but also more costly than balloon angioplasty.

**CRD COMMENTARY - Selection of comparators**
No explicit justification was provided for the choice of the comparator, although balloon angioplasty seemed to be the standard practice in the authors’ setting. You, as a user of the database, should decide if this is a widely used health technology in your own setting.

**Validity of estimate of measure of benefit**
In general, this was a very well reported and thorough study and the validity of the measure of benefit is likely to be high. The analysis was based on a randomised-controlled trial, which was appropriate for the study question. Blinding was not possible due to the nature of the intervention, but the study was designed to minimise the potential bias that could arise from this. The study sample was representative of the study population. The authors of the study attempted...
to use broader inclusion criteria in order to capture real life effectiveness. The patient groups were shown to be comparable at analysis. The analysis of effectiveness was conducted credibly on an intention to treat basis and with the use of appropriate statistical techniques. The measure of health benefit was proxied directly by a single effectiveness estimate and this choice was justified.

Validity of estimate of costs
The analysis of costs was thorough and well conducted. The strengths of the analysis were the inclusion of all relevant categories of costs from the perspective adopted and the inclusion of all relevant costs within each category. Furthermore, quantities of resources were reported separately from the costs, a statistical analysis of costs was performed, and adequate details of methods of cost estimation were given. Discounting was, appropriately, not conducted due to the short time frame of the study. The costing was conducted on patients who underwent clinical follow-up alone so as to follow real life clinical practice as much as possible. One weakness was that the price year was not explicitly reported.

Other issues
Regarding the generalisability of the cost-effectiveness results, it was emphasised that it relied on the quite high costs of one selected Dutch university hospital. Some comparisons with other studies in the literature were made. The study considered patients with stable angina and this was reflected in the conclusions of the study. The authors acknowledged some limitations of the study. First, ticlodopine has been shown to significantly reduce the rate of acute complications after balloon angioplasty so the trial could be criticised for not having incorporated ticlodopine in the protocol. However, the authors mentioned that this treatment was not standard when the protocol for the trial was being designed, and the question still remains as to whether there are more potent antiplatelet agents available. The authors also acknowledged that a long-term follow up would be required to determine the cost-effectiveness of the interventions.

Implications of the study
It was suggested that "whether coating can be used as the only strategy for the prevention of thrombosis, without the adjunctive use of aspirin and ticlopidine, is still to be established". Furthermore, it was suggested that the concept that "the tendency to reintervene on the basis of the angiographic appearance might have long-term therapeutic value, should be prospectively investigated".

Source of funding
Supported by a grant from CORDIS/Johnson & Johnson Interventional Systems, Warrent, New Jersey, USA and Sanofi, Paris, France.

Bibliographic details

PubMedID
9728982

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Angina Pectoris /mortality /therapy; Angina, Unstable /mortality /therapy; Angioplasty, Balloon, Coronary; Anticoagulants /therapeutic use; Aspirin /therapeutic use; Coronary Angiography; Equipment Design;