Advanced coronary artery disease: appropriate end points for trials of novel therapies

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
Two alternative strategies for the treatment of patients with coronary artery disease (CAD) were examined. One strategy was medical treatment, including new therapies such as vascular growth factors and myocardial laser perforation. The other strategy was revascularisation procedures, including percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients undergoing cardiac catheterisation for suspected CAD. In particular, eligible patients included those found to have at least 1-vessel CAD at the time of diagnostic catheterisation: at least 70% stenosis in the left anterior descending, left circumflex, or right coronary artery; or at least 50% stenosis in the left main coronary artery. Patients with prior revascularisation within 90 days, congenital heart disease, primary valve disease, or prior cardiac transplantation were excluded from the study. Also excluded were patients with ongoing illicit drug use and those with altered mental status.

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

Dates to which data relate
The effectiveness and resource use data were gathered from August 1992 to July 1997. The price year was 1997.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the clinical study.

Study sample
Power calculations were carried out after sample selection in order to identify the appropriate sample size for each outcome measure. Patients were prospectively enrolled from August 1992 to January 1996. Of all eligible patients, the advanced CAD group included all patients with significant 3-vessel or left main disease and left ventricular ejection fraction...
fraction less than 50% or severe angina (rest, nocturnal, progressive, or unstable) who did not undergo coronary revascularisation procedures (angioplasty or surgery) within 30 days of catheterisation. The reference (control) group included patients undergoing PTCA or CABG within 30 days of diagnostic catheterisation during the same time period. Overall, 1,189 patients were identified. Of these, 487 were included in the advanced CAD group (age 66.5 years; 32.7% women) and 702 underwent revascularisation procedures, of which 125 were in the PTCA group (age 63.8 years; 29.6% women) and 577 in the CABG group (age 64.2 years; 29.5% women).

Study design
This was a prospective cohort study that was carried out at a single centre, the Duke University Medical Center at Durham (NC). The average length of follow-up was 2.2 years (range: 3 months - 3.6 years). At the end of the follow-up period, there were 357 patients in the advanced CAD group, 98 patients in the PTCA group, and 310 patients in the CABG group.

Analysis of effectiveness
The analysis of the clinical study was restricted to those patients whose data were available at the follow-up assessment. The outcome measures used were:

- the rates of death, myocardial infarction (MI), catheterisation, CABG, PTCA and re-hospitalisation;
- length of stay (LOS);
- the use of medications at discharge;
- the proportion of patients reporting chest pain; and
- changes in health status, which was estimated using the Short Form-36 (SF-36) and the Duke activity status index (DASI).

The SF-36 comprised 36 items scored in 8 scales, while the DASI was a 12-item questionnaire in which patients ranked the ease with which they were able to perform 12 common activities of daily living. Higher scores reflected improved health status. Both measures were estimated in patients surviving to complete each stage of follow-up. Finally, the sample sizes needed for an 80% and 90% power to detect significant differences in health status (DASI, SF-36 General Health Perception, SF-36 Physical Function, SF-36 Bodily Pain), chest pain and mortality were estimated. The two groups of patients differed substantially at baseline in almost all sociodemographic and clinical characteristics. The authors pointed out that no attempt was made to balance comparisons since reference patients should not be considered to represent control groups.

Effectiveness results
The rates of death were 3% in both the advanced CAD group and the CABG group, and 0% in the PTCA group within the first 30-day period. The difference was not statistically significant. However, by the end of the study period, the rates of death were 37.8% in the advanced CAD group, 15.3% in the PTCA group, and 19.4% in the CABG group, (p<0.01).

The rates of MI were 10% in the advanced CAD group, 13.2% in the PTCA group, and 4.5% in the CABG group, (p<0.01).

The rates of catheterisation were 33% in the advanced CAD group, 69.5% in the PTCA group, and 28.7% in the CABG group, (p<0.01).

The rates of CABG were 17.1% in the advanced CAD group, 12.2% in the PTCA group, and 1% in the CABG group, (p<0.01).

The rates of PTCA were 8.1% in the advanced CAD group, 33.8% in the PTCA group, and 10.3% in the CABG group.
The rates of re-hospitalisation were 88.8% in the advanced CAD group, 83.7% in the PTCA group, and 91.7% in the CABG group. (p<0.05).

The mean number of re-hospitalisations was 2.3 (+/- 2.1) in the advanced CAD group, 2.4 (+/- 2.3) in the PTCA group, and (2 +/- 1.7) in the CABG group. The difference was not statistically significant.

The LOS was 17.4 (+/- 26.2) days in the advanced CAD group, 13 (+/- 20.5) days in the PTCA group, and 16.7 (+/- 54) days in the CABG group. The difference was not statistically significant.

The use of some medications (aspirin, nitrates, calcium-channel blockers, statin) at discharge differed across groups.

The proportions of patients reporting chest pain surgery were 95% in the advanced CAD group, 97% in the PTCA group, and 95% in the CABG group, at baseline. At 1 year, the corresponding values were 47% (advanced CAD), 43% (PTCA) and 27% (CABG), respectively, and at 2 years, 51% (advanced CAD), 50% (PTCA) and 27% (CABG).

DASI scores improved in all groups, but significantly better outcomes were observed only in the CABG group.

For the SF-36, similar patterns were observed in all three groups. The few significant differences found were only between the advanced CAD group and the CABG group.

The sample size needed to detect an 80% significant difference was 4,276 for the DASI, 1,115 for SF-36 General Health Perception, 734 for SF-36 Physical Function, 371 for SF-36 Bodily Pain, 130 for chest pain, and 188 for mortality.

The sample size needed to detect a 90% significant difference was 5,714 for the DASI, 1,493 for SF-36 General Health Perception, 977 for SF-36 Physical Function, 495 for SF-36 Bodily Pain, 170 for chest pain, and 247 for mortality.

**Clinical conclusions**

The effectiveness analysis showed that the advanced CAD cohort had exceedingly high mortality at 2 years in comparison with patients receiving revascularisation procedures within the first 30 days after catheterisation. However, most measures of health status, especially those related to general health, were comparable between the groups.

**Measure of benefits used in the economic analysis**

The health outcomes were left disaggregated and no summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was carried out.

**Direct costs**

Discounting was not relevant since the costs per patient were incurred during less than 2 years. The unit costs were not presented separately from the quantities of resources used. A breakdown of the cost items was not provided and only the total costs were reported. The cost/resource boundary of the hospital appears to have been adopted. The resource use data were derived from a sub-sample of patients included in the effectiveness study. The costs came from the Duke Hospital accounting system. A department-specific Medicare cost-to-charge ratio was applied to estimate the true costs of the services. The price year was 1997.

**Statistical analysis of costs**

The costs were presented as mean and median values +/- standard deviation. The costs were related to other measures of resource use (LOS, major procedures and death) by linear regression models. Statistical analyses were carried out to test the statistical significance of differences in the estimated costs.
Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean (median, standard deviation) baseline costs (within 30 days of catheterisation) per patient were $11,501 ($8,413, $12,267) in the advanced CAD group, $17,343 ($16,810, $10,536) in the PTCA group, and $31,604 ($25,905, $18,526) in the CABG group.

The mean (median) costs per patient during the follow-up period were $62,627 ($40,741) in the advanced CAD group, $54,277 ($34,785) in the PTCA group, and $43,580 ($24,005) in the CABG group, (p<0.05).

The mean (median) costs per patient from baseline to the last follow-up assessment were $74,128 ($49,140) in the advanced CAD group, $71,620 ($49,252) in the PTCA group, and $75,184 ($49,927) in the CABG group, (p<0.05).

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since a cost-consequences analysis was performed.

Authors' conclusions
Advanced coronary disease not managed using revascularisation procedures was associated with high mortality and economic burden. However, patients perceived their health status comparable to that of patients who had undergone revascularisation procedures. The authors noted also that their results showed that the most recent published studies had enrolled a too limited number of patients to show statistically significant differences in the main outcome measures.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as it reflected the alternative treatment strategies after catheterisation for patients with CAD. However, the authors reported that a large proportion of patients in the advanced CAD group were not selected for revascularisation therapy for unsuitable coronary anatomy or excess procedural risk. Therefore, it was unclear whether the interventions under examination were suitable for all patients. In fact, it would appear that for such patients, CABG or PTCA were not relevant comparators. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a prospective observational study. The method of allocating the patients to the study groups appears to have been based on clinical risk factors for the revascularisation procedures. The evidence came from a single centre and it was unclear whether the study sample reflected the patient population. The study groups were quite unbalanced at baseline since, as the authors noted, patients in the revascularisation groups did not represent a true control group. Power calculations showed that the study was barely powered to detect statistically significant differences in most clinical outcomes. The reasons for the loss to follow-up assessment were not reported.
The analysis was restricted to those patients with complete follow-up data. These issues tend to limit the internal validity of the study.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The perspective adopted in the study was not explicitly reported and only the hospital costs were included in the analysis. No details of the unit costs and quantities of resources used were provided, and a breakdown of the cost items was not given. In fact, only the total costs were reported. This limits the possibility of replicating the results of the analysis. The source of the data was given, and a cost-to-charge ratio was applied to derive the true costs of the services. The price year was reported, which will simplify reflation exercises in other settings. The cost estimates were specific to the study setting and sensitivity analyses were not carried out.

Other issues
The authors made some comparisons of their findings with those from published studies, and discussed potential reasons for some conflicting results. The issue of the generalisability of the study results to other settings was not addressed, which limits the external validity of the analysis. The authors attempted to identify the reasons of some improvements observed in the advanced CAD group. The study referred to patients with advanced CAD and this was reflected in the authors' conclusions.

Implications of the study
The study results suggested that revascularisation procedures led to significant reductions in mortality and costs for patients with advanced CAD in comparison with medical therapies. The authors pointed out that economic evaluations of new therapies should focus on a long-term time horizon. It was also noted that future studies should consider angina status and mortality as primary end points.

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None stated.

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Other publications of related interest


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