Nitroglycerin is preferable to diltiazem for prevention of coronary bypass conduit spasm

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
The study focused on the use of two conduit vasodilators in the prevention of arterial conduit spasm after coronary bypass grafting (CABG). Patients received a 24-hour intravenous infusion of either nitroglycerin (0.1 microgram.kg-1.min-1) or diltiazem (0.1 mg/kg during 20 minutes and then 0.1 mg.kg-1.min-1), followed by 6 months of treatment with a daily dose of isosorbide mononitrate or diltiazem.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients undergoing isolated CABG using the radial artery. Those undergoing concomitant valve or other procedures were excluded.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were gathered between January 1998 and May 1999. The dates to which the resource use data and prices referred were not stated.

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

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
Power calculations were carried out to determine the present study sample size. These were based on a prior observational study, and an 80% power to detect an increased need for cardiac pacing (postoperatively) from 20 to 40% in diltiazem-treated patients. One hundred and sixty-one consecutive patients undergoing isolated CABG using the radial artery were recruited to the study. Four patients (2.5% of the sample) declined enrolment over the study period. Eighty-four patients were randomised to receive nitroglycerin and 77 to receive diltiazem. The majority were men (67 and 62, respectively) with a mean average age of 59 years (standard deviation, SD=11 and SD=9, respectively).
Study design
This was a prospective, single-centred, randomised controlled trial. The patients were randomised to study groups using the last digit of their medical record number. Follow-up was conducted postoperatively for 30 days (or within the same admission if the patients remained in hospital for longer than 30 days) and in the longer term at 2 months, 6 months and 1 year postoperatively. Two-month follow-up was obtained in 145 (90%) patients (nitroglycerin 80, diltiazem 65), 6-month follow-up in 100 (62%) patients (nitroglycerin 56, diltiazem 44), and 12-month follow-up in 61 (38%) patients (nitroglycerin 35, diltiazem 26).

Analysis of effectiveness
The analysis was conducted on an intention to treat basis. The short-term outcome measurement (using the Society of Thoracic Surgeons guidelines) included mortality, postoperative myocardial infarction, atrial fibrillation, cerebral vascular accident, re-operation for bleeding, and the use of cardiac pacing and inotropic drugs. Other outcomes measured were the duration of ventilator support, the length of stay in the hospital or intensive care unit, and total serum levels. Data on long-term outcomes included mortality, operative-related complications, myocardial infarction, angina class (Canadian Cardiovascular Society), cardiac re-intervention, and a thallium-201 stress test (investigator blinded). These data were collected by direct telephone contact with the patients, families and primary care physicians. There were no significant differences between the groups in demographic or clinical variables that might influence the outcomes, nor in operative profile.

Effectiveness results
Five patients (3% of the sample) crossed over from the diltiazem group because of haemodynamic or conduction side effects in the immediate postoperative period. Two patients with low left ventricular ejection fraction had low cardiac output requiring inotropic drugs. The remaining three patients required sustained cardiac pacing because of heart block (2 patients) or severe sinus bradycardia (1 patient). The problems were resolved when the patients were treated with nitroglycerin.

The two groups were generally statistically comparable on all short-term outcomes. The exception was the requirement for cardiac pacing (28% in the diltiazem group versus 13% in the nitroglycerin group; p=0.01).

There were no significant differences between the groups in any of the long-term outcomes.

Clinical conclusions
The authors concluded that nitroglycerin is as effective as diltiazem in the prevention of coronary bypass conduit spasm, but it is preferred on account of increased patient tolerability.

Measure of benefits used in the economic analysis
The authors did not derive a summary measure of benefits. In effect, a cost-consequences analysis was performed.

Direct costs
Actual hospital pharmacy costs based on 6 months of drug treatment were included in the analysis. The costs for 24-hour intravenous administration were reported. No other details were provided. The price year was not given.

Statistical analysis of costs
The cost data were deterministic.

Indirect Costs
In line with the adopted perspective, the indirect costs were not included.
Currency
US dollars ($).

Sensitivity analysis
There was no sensitivity analysis of the costs.

Estimated benefits used in the economic analysis
Owing to the cost-consequences approach, see the ‘Effectiveness Results’ section.

Cost results
The cost of a 24-hour intravenous infusion of diltiazem was $3,312. This was followed by 6 month' oral treatment costing $13,340.

The cost of a 24-hour infusion of nitroglycerin was $340. This was followed by 6 months' oral treatment costing $756.

The total cost was $16,652 for diltiazem (although the authors reported $16,340) and $1,096 for nitroglycerin.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Nitroglycerin compared favourably with diltiazem in the prevention of radial artery spasm after coronary artery bypass grafting (CABG). It is safe, effective, better tolerated, and less costly than diltiazem.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was provided for the choice of the comparators, it appears that the drugs have been chosen on the basis of their common use as conduit vasodilators. You should decide if these represent widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based upon a randomised controlled trial, which was appropriate given the study question. It seems likely that the study sample was representative of the study population, and the patient groups were shown to be comparable during the analysis. Some aspects of the study procedure demonstrated good internal validity. In particular, the adoption of power calculations in determining the sample size and the intention to treat analysis represented significant strengths. However, as the authors acknowledged, the method of randomisation (and consequent imbalance of numbers between the groups) and the lack of reported blinding during the assessment of most outcomes presented potential limitations to the reliability of the findings. In addition, the authors reported that the size of the study population was based on the risk of cardiac pacing and, therefore, it is possible that the study population was too small to detect small but significant differences in clinical outcomes between the groups.

Validity of estimate of measure of benefit
No summary measure of benefits was derived. The comments in the 'Validity of estimate of measure of effectiveness' field (above) therefore apply.

Validity of estimate of costs
Although the cost analysis was performed from a narrow perspective, it appears that the costs relevant to the hospital pharmacy have been included. It was possible to separate the costs and the quantities, thus enhancing the reproducibility of the study findings in other settings. The lack of a statistical analysis on the potential variance in resources and costs (taken from a single study and the authors' setting, respectively) means that possible uncertainty is contained within the results. The absence of a reported price year will preclude any future reflation exercise. Discounting was, appropriately, not conducted since the time horizon of the model was less than one year.

Other issues
The authors compared their clinical findings with those of other studies, demonstrating agreement that nitroglycerin is the preferred drug of choice. The issue of the generalisability of the results to other settings was not directly addressed. The authors do not appear to have presented their results selectively and the scope of the analysis was clearly reflected in their conclusions. In addition to the method of randomisation (mentioned already), the authors acknowledged further study limitations. For example, the non-blinded concomitant treatment decisions, the substantial loss to follow-up at 12 months, and the narrow study population. Also, the lack of a 'gold' standard graft patency test and potential issues arising from nitrate tolerance.

Implications of the study
The authors recommended that nitroglycerin should be the drug of choice in the prevention of radial artery spasm after CABG. There were no recommendations for future research.

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