Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions

Authors' objectives
To review the effectiveness of treatment for chronic stable angina which included the assessment of medical therapy and newer adjunctive technologies such as coronary stents; broader assessment of patient benefits; and consideration of costs and cost-effectiveness.

Searching
For the clinical effectiveness outcome, the authors searched the electronic databases of MEDLINE, Health Planning and Administration, BIDS, NHS CRD's DARE, Cochrane Library, Dissertation Abstracts Online, EMBASE, PsycINFO, and Social SciSearch.

For the health-related quality of life outcome, the authors searched the MEDLINE database.

For the cost and cost-effectiveness outcomes, the authors searched the databases of MEDLINE, Health Planning and Administration, the Office of Health Economics and the NHS CRD's NHS EED. The search terms used are listed in an appendix to the review. The authors search strategy was developed using standard systematic review techniques and had five components: sources of evidence (the databases searched); inclusion and exclusion criteria for studies; methods for data extraction; data synthesis; and assessment of quality of evidence.

Study selection
Study designs of evaluations included in the review
For non-drug clinical studies, included studies had to be either a randomised controlled trial (RCT), or a UK-based observational study with greater than 1,000 patients, or a North American, Australasian or European observational study with greater than 1,000 patients.

For drug clinical studies, studies were RCTs with a follow-up of at least 6 months with between-class comparisons. Comparisons between ordinary beta blockers and beta blockers with some other level of mode of activity such as a vasodilating beta blocker and a beta blocker with intrinsic sympathomimetic activity were included. Combinations of drugs were also included.

For cost and cost-effectiveness analyses, studies were either a comparative economic evaluation looking at costs and outcomes, or a comparative cost analysis looking at full range of costs, or a non-comparative cost analysis looking at full range of costs (UK only).

For analysis of health-related quality of life and patient preferences, studies were either an analysis of health-related quality of life using a formal quantitative instrument, or analyses of patients' preferences.

The authors also included good quality systematic reviews and meta-analyses.

Only English language publications were included in the review.

Specific interventions included in the review
Coronary artery bypass grafts (CABGs), percutaneous transluminal coronary angioplasty (PTCA), medical treatment, medical adjuncts to CABG (antithrombotics (aspirin/warfarin)) or medical adjuncts to PTCA (ACE inhibitors, antithrombotics and corticosteroids). Actual drugs examined by included studies were: beta blockers (propranolol, metoprolol, epanolol, atenolol, carvedilol and nadolol), nitrates (Isosorbide dinitrate (ISDN)), calcium channel antagonists (bepridil, diltiazem, nifedipine and amlodipine) and potassium channel activators (nicorandil).
Participants included in the review
Cardiac patients diagnosed with chronic stable angina.

Outcomes assessed in the review
Effectiveness of treatment, quality of life benefits for patients and cost and cost-effectiveness.

How were decisions on the relevance of primary studies made?
It is not stated how many reviewers performed the first trawl through the references obtained from the searches, however the second trawl was undertaken by two researchers with disagreements being settled by a third researcher. The extent to which acquired hard copies of primary studies satisfied the inclusion criteria was determined by one reviewer.

Assessment of study quality
The quality of two large prior reviews (RAND and SBU, see Other Publications of Related Interest no.1 and no.2) was assessed using six quality criteria (relating to the search, inclusion and exclusion criteria, methods of data extraction and synthesis, investigation of heterogeneity and assessment of validity of the primary studies). Trials not included in these two reviews were assessed for inclusion in this review using the following sets of quality assessment criteria.

RCTs were assessed for quality using a published checklist, see Other Publications of Related Interest no.3) covering the six dimensions of:

1. Randomisation.
2. Completeness of follow-up.
3. Withdrawals.
5. Comparable groups.

6. Were the groups treated identically, other than for the named interventions?

Observational studies were assessed for quality using a published checklist (see Other Publications of Related Interest no.3) covering the six criteria of:

1. Is the sample representative of the standard users of the intervention?
2. Are the criteria for inclusion in the sample clearly defined?
3. Did all the individuals enter the study at a similar point in their disease progression?
4. Was follow-up long enough for important events to occur?
5. Were outcomes assessed using objective criteria?
6. If comparisons of series are being made, was there sufficient description of the series and the distribution of prognostic factors?

Health-related quality of life studies were assessed at two levels:

1. The study itself was subjected to the same criteria for RCTs or observational studies.
2. An attempt was made to assess the quality of the instruments used in the studies.

Economic studies were assessed for quality using the 35-point checklist of Drummond and Jefferson (see Other
Publications of Related Interest no.4).

The authors have also summarised the perceived quality of the included studies in their narrative summary of the data. The authors do not state how the how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Data were extracted by one reviewer.

Methods of synthesis
How were the studies combined?
The studies were reviewed using a qualitative narrative synthesis.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
One hundred and ninety-seven studies were included in the review (148 on treatment effectiveness, 24 of patient quality of life benefits, and 25 on cost-effectiveness) although these figures do not match the numbers of included studies and participants in the appendices.

In studies of medical therapy, there were 2,981 participants in 11 studies for clinical effectiveness, 1,606 participants in 2 studies for health-related quality of life, and 1 study of a model for cost and cost-effectiveness in medical therapies.

In studies of medical therapy versus CABG, there were 7,040 participants in 9 studies of clinical effectiveness, 780 participants in 1 study of health-related quality of life, 1 study of cost and cost-effectiveness primary data and two studies of models for cost and cost-effectiveness in medical treatments versus CABG.

In studies of medical therapy versus PTCA, there were 2,736 participants in 5 studies of clinical effectiveness, 779 participants in 3 studies of health-related quality of life, and 1 study of a model for cost and cost-effectiveness in medical treatments versus PTCA.

In studies of PTCA versus CABG, there were 14,500 participants in 10 studies of clinical effectiveness, 2,379 participants in 4 studies of health-related quality of life, 9 studies of cost and cost-effectiveness primary data and 2 studies of models for cost and cost-effectiveness of PTCA versus CABG.

In non-comparative observational studies of CABG alone, there were 320,069 participants in 36 studies of clinical effectiveness, 3,751 participants in 12 studies of health-related quality of life, and 1 study of cost and cost-effectiveness primary data.

In studies of medical adjuncts to CABG, there were 2,120 participants in 9 studies of clinical effectiveness. There were no data reported for health-related quality of life, or for cost and cost-effectiveness.

In studies of non-comparative observational studies of PTCA alone, there were 108,315 participants in 25 studies of clinical effectiveness, and 303 participants in 3 studies of health-related quality of life.

In studies of non-medical adjuncts to PTCA, there were 4,535 participants in 12 studies of clinical effectiveness, 3,123 participants in 2 studies of health-related quality of life, 5 studies of cost and cost-effectiveness primary data and 1 study of a model for cost and cost-effectiveness in medical treatments versus CABG.

In studies of medical adjuncts to PTCA, there were 9,607 participants in 18 studies of clinical effectiveness, and 1 study of cost and cost-effectiveness primary data. No health-related quality of life studies were reported.
Medical treatment: few studies exist of long-term effectiveness, with little evidence of large differences between different classes of drug. There is little evidence on patients’ quality of life.

CABG versus medical therapy: CABG have mortality benefits for up to 5 years and possibly longer (up to 10 years) compared with medical therapy, particularly in patients with greater extent of disease. One study showed that the initial benefit to patients from CABG, in terms of extent of angina and activity limitation, disappeared by 10 years.

PTCA versus medical therapy: some evidence supports PTCA in terms of relief of angina but evidence on myocardial infarction (MI) rates is conflicting. Clinical benefit is apparently reflected in improved health-related quality of life, although information on long-term effects of revascularisation is lacking.

PTCA versus CABG: no differences emerged between PTCA and CABG in terms of mortality and non-fatal MI. CABG is likely to be associated with fewer additional procedures than PTCA in the first year post-surgery and appears to be more effective in relief of angina. CABG improves survival compared with PTCA in patients with severe disease. No differences were found between CABG and PTCA in terms of health-related quality of life largely due to methodological problems. Indirect assessment of health-related quality of life (via reductions in angina rates) shows a benefit for CABG over PTCA.

Non-comparative studies of CABG: CABG relieves angina in most patients undergoing surgery. Interior mammary artery (IMA) grafts appear to be associated with greater long-term patency and less angina at long-term follow-up than non-IMA grafts. Many outcomes appear to be slightly worse in women than men, and in older patients. There is a clear association between short- and longer-term mortality and disease severity (number of vessels diseased), ejection fraction and initial severity of angina. Health-related quality of life improves after CABG; physical, sexual and social functioning improve significantly in most patients.

Medical adjuncts to CABG: aspirin (with or without dipyridamole) appears to reduce occlusion following CABG. No evidence was identified on health-related quality of life.

Non-comparative studies of PTCA: there is some evidence of gender differences in long-term outcomes. Success of PTCA is influenced by the age of patient and angina class. PTCA can be effective in patients with left ventricular disease. Health-related quality of life improves after PCTA but no information is available on key sub-groups.

Non-medical adjuncts to PTCA: results on on-going trials with longer follow-up periods are awaited before conclusions can be drawn on effectiveness of elective stenting. At present, evidence is very limited, and few studies support the current opinion of cardiologists that stents are effective. Aspirin therapy as an adjunct to stenting results in a lower risk of MI, fewer repeat interventions and less occlusion of the stented vessel. There is no evidence that laser angioplasty or atherectomy add any benefit to conventional PTCA.

Medical adjuncts to PTCA: few trials detected any important benefits from the addition of drugs to PTCA. Some evidence supports the use of aspirin, in terms of reduced long-term MI and restenosis rates. There is some evidence that calcium antagonists are useful in reducing restenosis after coronary angioplasty. Patients benefited from a lower rate of in-hospital MI, CABG and repeat PCTA after a new glycoprotein IIb/IIIa receptor monoclonal antibody. However, the benefits came at the cost of an increased bleeding rate which may have been a function of the relatively high level of heparin administration. The platelet-derived growth factor antagonist trapidil has been shown to be more effective than aspirin in reducing stenosis after PTCA. Good quality meta-analyses showed the effectiveness of antiplatelet agents in reducing risk of MI and stroke in post-PTCA patients. One meta-analysis showed that supplemental fish oils reduce stenosis.

Cost information
In the medical treatment studies no UK cost or cost-effectiveness studies were identified.

CABG is most cost-effective where there is greatest incremental benefit (in patients with severe angina, left main disease, and multi-vessel disease.

In PTCA versus CABG, the relative cost of procedures depends on point of follow up. The most recent UK cost
analysis showed an initial mean cost for PTCA of 52% that for CABG, increasing to 81% at 2 years. No recent cost-effectiveness analyses were identified, and none relating to UK practice.

In medical adjuncts to CABG, no evidence was identified on cost-effectiveness.

In non-medical adjuncts to PTCA, cost studies undertaken in the USA showed that adjunctive technologies cost more than PTCA overall and their cost-effectiveness is doubtful.

In medical adjuncts to PTCA, a cost analysis of the new glycoprotein IIb/IIIa receptor monoclonal antibody showed a 6-month difference in costs between the new drug and placebo of $293 per patient.

**Authors’ conclusions**

The authors state that discussion of the conclusions of this review emphasise that, in some areas, firm clinical opinion exists which this review has found neither evidence to support nor to refute. Furthermore, it was considered that all drug regimens are effective in terms of symptom relief but only beta-blockers have been shown to improve prognosis (at least after MI). Despite the available number of studies in this area, the overall picture that emerges is not clear. The authors state that this serves to emphasise that they are still far from a firm unambiguous evidence-base for even this relatively well-researched area of medicine. Moreover, the results of the systematic review imply that, for many patients, a clear and unambiguous choice does not follow from the available evidence on clinical or cost-effectiveness. Rather, particularly in the case of the choice between PTCA and CABG, the evidence indicates that patient preference with regard to trade-offs between degree of symptom relief and severity of surgery may be the key factor determining appropriate choice at the individual level.

**CRD commentary**

This is a good quality review. The authors have stated their research question and the inclusion and exclusion criteria. The literature search appears very thorough. The quality of the included studies was assessed and the authors have reported on how the articles were selected, and how many of the reviewers were involved in the data selection and extraction.

The data extraction is reported extensively in tables and text, however the summary's details of studies and participants does not match the details of the individual studies listed in the text of the review or the appendices. The narrative synthesis was appropriate and heterogeneity was discussed narratively. The authors have also discussed several methodological and data limitations of the review. The authors conclusions appear to follow from the results and several detailed policy and research implications are stated for further investigation.

**Implications of the review for practice and research**

**Practice/policy:**

1. Healthcare purchasers and providers should consider local information, such as local epidemiological data, cost structures and available patterns of care.

2. The relative benefit of alternative forms of clinical management involves values or preference weightings being placed on a range of outcomes generated by an intervention. Decision-makers could consider local information on public or patients’ values.

3. For purchasers the evidence could imply that blanket decisions to provide only one form of intervention to patients should not be made. The various main forms of treatment for stable angina should be available and patients should be informed of the therapeutic options rather than offered a single therapy based on provider preferences.

4. The provision of local evidence-based guidance to general practitioners on smoking cessation may also help improve outcomes in smokers undergoing CABG or PTCA.

5. Local decisions about resource allocation should be informed by the use of decision analysis as a framework to
handle the multiple factors that need to be considered.

6. Formal evaluation of new technologies should be considered before they become widely diffused.

Research:

1. Adequately-powered, long-term studies are needed of costs and effects of rational combinations of medical treatment.

2. Cost and cost effectiveness of PTCA should be compared with medical therapy.

3. Relative cost-effectiveness of the new generation medical and non-medical adjuncts to PTCA and CABG, including stents, requires assessment.


5. In stable angina, studies of patients' treatment- and health-related preferences are required.

6. More economic evaluation of alternative treatments for stable angina is needed; it should cover a wider selection of technologies and reach higher methodological standards than those already published.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.